**Summary Basis for Regulatory Action**

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|---|---|
| **Date:** | June 29, 2023 |
| **From:** | Andrew Harmon PhD, Chair of the Review Committee,<br>Office Therapeutic Products (OTP)<br>Office of Gene Therapy (OGT) |
| **BLA STN:** | 125720 |
| **Applicant:** | BioMarin Pharmaceutical Inc. |
| **Submission Receipt Date:** | Original submission: December 23, 2019<br>Resubmission: September 29, 2022 |
| **Action Due Date:** | June 30, 2023 |
| **Proper Name:** | valoctocogene roxaparvovec-rvox |
| **Proprietary Name:** | ROCTAVIAN |
| **Indication:** | For the treatment of adults with severe hemophilia A (congenital factor VIII deficiency with factor VIII activity <1 IU/dL) without pre-existing antibodies to adeno-associated virus serotype 5 (AAV5) detected by an FDA approved test. |

**Recommended Action:** The Review Committee recommends approval of this product.

**Acting Director, Office of Clinical Evaluation, Office of Therapeutic Products**

| Discipline Reviews | Reviewer / Consultant - Office/Division |
|---|---|
| **CMC**<br>• CMC Product (Product Office and OCBQ/DBSQC)<br>• Facilities review (OCBQ/DMPQ)<br>• Establishment Inspection Report (OCBQ/DMPQ and Product Office)<br>• QC, Test Methods, Product Quality (OCBQ/DBSQC) | Andrew Harmon, CBER/OTP/OGT<br>Emmanuel Adu-Gyamfi, CBER/OTP/OGT<br>Mikhail Ovanesov, CBER/OTP/OPPT<br>Y Nguyen, CBER/OTP/OGT<br>Andrey Sarafanov, CBER/OTP/OPPT<br>Arifa Khan CBER/OVRR/DVP<br>Bradley Dworak, CBER/OCBQ/DMPQ<br>Laura Fontan, CBER/OCBQ/DMPQ<br>Kula Jha, CBER/OCBQ/DMPQ<br>Thomas Ryan Withers, ORA/OMPTO/OBPO<br>Marie Anderson, CBER/OCBQ/DBSQC<br>Simleen Kaur, CBER/OCBQ/DBSQC<br>Varsha Garnepudi, CBER/OCBQ/DBSQC |
| **Clinical**<br>• Clinical (Product Office)<br>• Postmarketing safety/Pharmacovigilance review (OBPV/DE)<br>• BIMO | Kavita Natrajan, CBER/OTP/OCE<br><br>Bethany Baer, CBER/OBPV/DPV<br><br>Peter Lenahan, CBER/OCBQ/DIS/BMB |
| **Statistical**<br>• Clinical data (OBPV/DB) | Yuqun Abigail Luo, PhD, CBER/OBPV/DB |
| **Non-clinical/Pharmacology/Toxicology**<br>• Toxicology (Product Office)<br>• Developmental toxicology (Product Office)<br>• Animal pharmacology | Feorillo Galivo, CBER/OTP/OPT |
| **Clinical Pharmacology** | Xiaofei Wang, CBER/OTP/OCE |
| **Labeling**<br>• Promotional (OCBQ/APLB)<br>• PNR | Ben Cyge, PhD, CBER/OCBQ/DCM/APLB<br>Leyish Minie, CBER/OTP/ORMRR<br>Oluchi Elekwachi, CBER/OCBQ/DCM/APLB |
| **Other Review(s) not captured above categories, for example**:<br>• Consults-CDRH<br>• Devices<br>• Software<br>• Human Factors<br>• FONSI | Natasha Thorne, CDRH/OPEQ/OHTVII/DIHD |
| Advisory Committee Summary | N/A |

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## 1. Introduction

BioMarin Pharmaceutical Inc. submitted a Biologics License Application (BLA), STN 125720, for licensure of valoctocogene roxaparvovec-rvox, with a proprietary name of ROCTAVIAN. ROCTAVIAN is an adeno-associated virus vector-based gene therapy indicated for the treatment of adults with severe hemophilia A (congenital factor VIII deficiency with factor VIII activity <1 IU/dL) without pre-existing antibodies to adeno-associated virus serotype 5 (AAV5) detected by an FDA approved test.

Deficiency of the essential blood coagulation protein Factor VIII results in impaired hemostasis and increased bleeding tendency. ROCTAVIAN is designed to deliver a copy of a gene encoding a B domain-deleted (BDD) version of human coagulation Factor VIII to patients with hemophilia A to restore Factor VIII activity.

This document summarizes the basis for regular approval of ROCTAVIAN. One Phase 3 clinical trial provides the primary evidence of effectiveness and safety for the treatment of adult patients with severe hemophilia A. One Phase 1/2 clinical trial adds supporting evidence demonstrating the product's biological effect. Our recommendation for approval is based on the reduction in annualized bleeding rate (ABR), demonstrated in the Phase 3 clinical trial. The serious risks of ROCTVIAN include infusion-related reactions and hepatotoxicity [elevation of liver enzymes (e.g., alanine aminotransferase (ALT)].

The Applicant has provided substantial evidence of effectiveness and safety based on a single adequate and well controlled clinical investigation providing compelling evidence of clinical benefit, supported by the initial clinical investigation and preclinical studies. The review team recommends approval of this BLA.

## 2. Background

Disease Background

Hemophilia A is a recessive X-linked congenital bleeding disorder, caused by mutations in the factor VIII (FVIII) gene. It is the most common coagulation factor deficiency, occurring in 1:5000 live male births. This clotting factor (FVIII) deficiency occurs mostly in males as expected for an X-linked disease, but rarely the severe clinical form can occur in females also. About 30% of all patients with hemophilia A have no known family history of the disease, and these are called sporadic cases. Deficiency or absence of FVIII results in impaired hemostasis, spontaneous and prolonged bleeding, and rebleeding, if not corrected by providing the missing FVIII.

The severity of bleeding manifestations in hemophilia A generally correlates with the degree of deficiency of the clotting factor, and bleeding can be life-threatening. About 60%-70% of individuals with hemophilia A have a severe disorder that becomes apparent early in life and is characterized by functional FVIII levels that are less than 1% (1 IU/dl) of normal. Individuals with severe hemophilia A have at least monthly spontaneous bleeds, most frequently into joints or muscles without preceding trauma. Repeated bleeding into the joints can be debilitating and results in the development of hemophilic arthropathy with repeated hemarthroses, "target joints" (a joint that has more than 3 bleeds in a 6-month period), and chronic synovitis. Moderate and mild hemophilia A, with 1 to 5% or 5 to <40% of normal FVIII activity level, are each observed in about 15% and 25% of individuals with this condition, respectively. Subjects with moderate hemophilia A have less frequent and spontaneous bleeds compared to subjects with severe hemophilia and usually present with bleeds associated with minor trauma or surgery. Subjects with mild Hemophilia A rarely bleed spontaneously but have prolonged bleeding due to major trauma or surgery. Females with severe hemophilia have the same manifestations as males, but excessive bleeding may also be seen with menstruation and after giving birth.

A goal of modern hemophilia management is to prevent spontaneous bleeds by providing FVIII replacement therapy to maintain higher FVIII activity levels, i.e., in the range of subjects within the moderate/mild form of the disease at a minimum. This approach is known as routine prophylaxis. Routine prophylaxis treatment has limitations including the need for regular intravenous (IV) administration and risk of infection. In

addition, infusions may lead to variable FVIII activity resulting in breakthrough bleeding episodes. There are several plasma-derived and recombinant FVIII products, with standard or extended half-lives, that are approved for routine prophylaxis in hemophilia A subjects.

The most serious complication of replacement therapy is inhibitor development. FVIII inhibitors are allogenic antibodies to FVIII that reduce or eliminate the activity of FVIII. Approximately 30%-40% of patients with hemophilia A develop inhibitors following exposure to exogenous FVIII products.

Emicizumab, a bispecific monoclonal antibody, mechanistically bridges clotting factors IXa and X, thus bypassing the need for FVIII in clot formation. Emicizumab is approved by FDA for routine prophylaxis in hemophilia A subjects; it can be given subcutaneously once a month (after initial loading dose) and can be used in individuals with inhibitors to FVIII. However, emicizumab cannot be used to treat acute bleeding episodes. Rare instances of anti-emicizumab antibodies have also been reported.

Product Description

ROCTAVIAN (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 vector DNA 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 domain-deleted (BDD) human factor VIII (hFVIII) gene, under the control of a hybrid human liver-specific promoter (HLP). The (b) (4) B domain (b) (4) of hFVIII is replaced by a (b) (4) "SQ" linker sequence, from the (b) (4) B domain sequence. The resulting amino acid sequence is identical to that of the human FVIII reference sequence (b) (4) .

The regulatory history of ROCTAVIAN is outlined in Table 1.

The original Biologics License Application (BLA) submission (125720/0) of ROCTAVIAN was received on December 23, 2019. The clinical data from an interim analysis of Study 270-301 submitted in the BLA were not sufficient to provide substantial evidence of the effectiveness of ROCTAVIAN to support its approval. A surrogate endpoint of median FVIII activity level of (b) (4) IU/dL between weeks 23 and 26 post-administration of ROCTAVIAN, as assessed by the chromogenic substrate assay (CSA), was used as the primary endpoint to support the accelerated approval. However, in clinical study this endpoint was not demonstrated to be predictive of the clinically meaningful endpoint of annualized bleeding rate (ABR).

A Complete Response (CR) letter was issued August 18, 2020; the Applicant was requested to provide data on 134 subjects treated in Study 270-301 with a minimal follow-up of 2 years and at least 1 year of follow-up after cessation of immunosuppressive treatment (IS) in subjects who received it. The primary endpoint was revised to ABR (all bleeds). The Applicant was also requested to address several other concerns raised upon review of the original BLA.

In the current Class 2 resubmission, the Applicant submitted data to address all the deficiencies listed in the CR letter. Additional clinical data with a longer follow-up of a minimum of 3-years for subjects in the licensing trial were submitted in February 2023, for which a Major Amendment to the BLA was issued.

**Table 1. Regulatory History**

| Regulatory Events / Milestones | Date |
|---|---|
| 1. Pre-IND meeting | March 17, 2017 |
| 2. IND submission | September 1, 2017 (STN IND 17659) |
| 3. Fast Track Designation Granted | October 24, 2017 |
| 4. Orphan Drug Designation Granted | February 29, 2016 (Orphan Designation #15-5109) |
| 5. Breakthrough Therapy Designation Granted | October 24, 2017 |
| 6. Pre-BLA Meeting | July 26, 2019 |
| 7. BLA 125720/0 Submission | December 23, 2019 |
| 8. BLA Filed | February 20, 2020 |
| 9. Mid-Cycle Meeting | April 20, 2020 |
| 10. Late-Cycle Meeting | June 1, 2020 |
| 11. Complete Response | August 18, 2020 |
| 12. Regenerative Medicine Advanced Therapy Designation Granted | March 4, 2021 |
| 13. Re-submission After Complete Response | Sept 29, 2022 |
| 14. Major Amendment | February 15, 2023 |
| 15. Action Due Date | June 30, 2023 |

## 3. Chemistry Manufacturing and Controls (CMC)

### a. Product Quality

The CMC review team concludes that the ROCTAVIAN manufacturing process and controls can yield a product with consistent quality attributes, and the CMC review team recommends approval.

**Manufacturing Summary**

ROCTAVIAN is produced using a baculovirus (b) (4) insect cell line (Sf9) derived from Spodoptera frugiperda cells. The baculovirus (b) (4) serve to deliver the essential components (hFVIII transgene, AAV rep and cap genes) to produce AAV5 containing the hFVIII- transgene (AAV5-hFVIII) in the Sf9 cells. After the baculovirus (b) (4) the ROCTAVIAN vector is (b) (4) drug product (DP) and may be stored (b) (4) or at (b) (4)

The DP is manufactured by (b) (4) The DP manufacturing process does not include any additional (b) (4) manufacturing steps to further remove impurities. After sterile filtration, the DP is filled aseptically into vials and 100% visually inspected before being stored frozen (≤ -60°C). Frozen vials are (b) (4) for labeling and packaging. The (b) (4) DP are manufactured at BioMarin Pharmaceutical Inc.'s Novato facility (Novato, CA).

The DP has a nominal concentration of 2 x $10^{13}$ vector genomes (vg)/mL. Each vial of DP contains an extractable volume of not less than 8 mL. DP formulation consists of (b) (4) sodium phosphate (b) (4) sodium chloride, (b) (4) mannitol, and (b) (4) Poloxamer 188. The DP is sterile and contains no preservative. Each vial of DP is packaged into an individual finished good (FG) secondary carton. FG cartons are (b) (4) the cartons are stored frozen (≤ -60°C) and protected from light until ready for use. 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).

**Manufacturing Control Strategy**

Manufacturing process consistency is controlled by (b) (4) . The manufacturer accepts (b) (4) based on specified (b) (4) DP, and (b) (4) materials for (b) (4) , identity, purity, strength, and potency. (b) (4) DP quality are controlled and characterized by several release tests (see Table 2). These tests include a (b) (4)

Process Validation

The validation of the process for manufacturing of ROCTAVIAN (b) (4) was conducted by (b) (4) .

Process validation for the DP manufacturing process was conducted by manufacturing (b) (4) PPQ DP lots at commercial scale, at BioMarin Pharmaceutical Inc. (Novato, CA). The data demonstrate that the (b) (4), filtration, filling, and storage steps of the manufacturing process are controlled effectively to produce DP that consistently meets the established product quality acceptance criteria. The labeling and final packaging processes were also validated. Additional validation studies, including aseptic process simulation and shipping validation studies, were also performed.

Impurity Profile

Impurities can be classified into product-related and process-related impurities. Product-related impurities include (b) (4) Process-related impurities may include (b) (4) used for product manufacturing that are not intended to be present in the final product. Most process-related impurities are removed, however, (b) (4) The levels of these (b) (4) impurities are controlled by lot release acceptance limits. The typical level of (b) (4) in the (b) (4) is approximately (b) (4) of the (b) (4), the typical level of (b) (4) is approximately (b) (4) and the typical level (b) (4) is approximately (b) (4).

Manufacturing Risks

The risk of product contamination with other adventitious agents is minimized by ensuring adequate control of raw materials. Additionally, no raw materials derived from animals or humans are used in the generation of (b) (4) or in product manufacturing. In addition to routine testing of (b) (4) (b) (4) for adventitious agents, robust (b) (4) by the (b) (4) process was demonstrated.

Stability

The FBDS is stable for (b) (4) months when stored (b) (4) and (b) (4) days when stored at (b) (4) The DP is stable for 36 months when stored frozen (≤-60°C). 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 drug product 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 used to support licensure and is the commercial process.

## b. Testing Specifications

The analytical methods and their validations and/or qualifications reviewed for the ROCTAVIAN drug substance and drug product were found to be adequate for their intended use.

**Table 2. Drug Product Specifications**

| Attribute | Method | Acceptance Criteria |
|---|---|---|
| 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) | |
| Extractable Volume | (b) (4) | NLT 8.0 mL/vial |
| | (b) (4) | |
| (b) (4) | | |
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| | | |
| | | |
| Sterility (see template for details) | (b) (4) | No growth |
| Endotoxin (see template for details) | (b) (4) | |
| Poloxamer 188 Content | (b) (4) | |
| | | |
| | | |

## c. CBER Lot Release

The lot release protocol template for ROCTAVIAN was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

**d. Facilities Review/ Inspection**

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of ROCTAVIAN are listed in the table below. The activities performed and inspectional histories are noted in the table.

**Table 3. Manufacturing Facilities Table for ROCTAVIAN (valoctogene oxaparvovec-rvox)**

| Name/Address | FEI Number | DUNS number | Inspection/ waiver | Justification/ Results |
|---|---|---|---|---|
| BioMarin Pharmaceutical Inc. (b) (4)<br>Novato Campus<br>Novato, California, 94949<br>U.S.A., *DS manufacturing, DP manufacturing, DP release testing* | 3004079983 | 10004135 | PLI | CBER/DMPQ<br>(b) (4)<br>VAI |
| (b) (4)<br>*DP labeling and packaging* | (b) (4) | | Waiver | (b) (3) (A) VAI<br>ORA/OPQO<br>PAI and surveillance<br>(b) (3) (A) VAI |
| (b) (4)<br>*DP release testing* | (b) (4) | | Waiver | ORA/OPQO<br>surveillance<br>(b) (4) VAI |
| (b) (4)<br>*DP release testing* | (b) (4) | | Waiver | ORA/OBPO<br>surveillance<br>(b) (4) NAI |
| (b) (4)<br>*DP release testing* | (b) (4) | | Waiver | (b) (3) (A) VAI<br>ORA/OBPO<br>Surveillance<br>(b) (4) VAI |

Acronym key: DS – drug substance; DP – drug product; (b) (3) (A) OBPO – Office of Biological Products Operations; OPQO – Office of Pharmaceutical Quality Operations; ORA – Office of Regulatory Affairs; NAI – No Action Indicated; PAI – Pre-approval Inspection; PLI – Pre-license Inspection; VAI – Voluntary Action Indicated.

CBER/DMPQ conducted a PLI at BioMarin Pharmaceutical Inc. in (b) (4). A Form FDA 483 list of observations was issued at the end of the inspection. The firm responded to the observations and the corrective actions were reviewed. All inspectional issues were resolved, and the inspection was classified as VAI.

(b) (3) (A), (b) (4)

. Also, ORA/OPQO conducted a combination

Surveillance and PAI in (b) (4) . An FDA Form 483 was issued and was classified as VAI. This facility has experience in labeling and packaging activities.

ORA/OPQO conducted a routine surveillance inspection of the (b) (4) . facility in (b) (4) . An FDA Form 483 was issued, and the inspection was classified as VAI. This facility has experience in laboratory testing activities.

ORA/OBPO performed a surveillance inspection of the (b) (4) . facility in (b) (4) . No deficiencies were identified, and the inspection was classified as NAI. This facility has experience in laboratory testing activities.

ORA/OBPO completed a routine surveillance inspection of the (b) (4) facility in (b) (4) . An FDA Form 483 was issued, and the inspection was classified as VAI. (b) (4)

**e. Container/Closure System**

The drug product is filled into 10-mL (b) (4) vials, manufactured by (b) (4) with (b) (4) chlorobutyl rubber stoppers and crimped flip-off type aluminum seals both manufactured by (b) (4) . Each vial contains a single 8-mL dose. BioMarin conducted the container closure integrity testing at their Novato Campus facility, employing the (b) (4) test method. All acceptance criteria were met.

**f. Environmental Assessment**

The applicant submitted an environmental assessment (EA) pursuant to 21 CFR part 25.20(l). The EA provided an assessment of ROCTAVIAN environmental exposure based on known biology of the parental virus (adeno-associated virus serotype 5; AAV5), genetic modifications made to the vector, data from biodistribution and shedding studies, lot release testing, and related nonclinical studies, and a worst-case assumption in each case. The Agency determined that approval of ROCTAVIAN will not result in any significant environmental impact. A Finding of No Significant Impact memorandum has been prepared.

**4. Nonclinical Pharmacology/Toxicology**

In vivo pharmacology studies of ROCTAVIAN were conducted in an immunodeficient mouse model of hemophilia A ($Rag2^{-/-}$ × $FVIII^{-/-}$ double knockout mice). Intravenous (IV) administration of ROCTAVIAN at dose levels ranging from $1.81 \times 10^{13}$ to $1.77 \times 10^{14}$ vector genomes (vg)/kilogram (kg) in adult male hemophilia A mice resulted in dose-dependent vector transduction and hFVIII RNA expression in the liver, along with increases in plasma human FVIII-SQ (hFVIII-SQ) protein levels, and plasma hFVIII activity.

In single-dose toxicology studies conducted in adult male (b) (4):CD1 (b) (4) mice with study durations up to 6 months, the IV administration of ROCTAVIAN at dose levels of $6.53 \times 10^{13}$ vg/kg and higher resulted in dose-dependent adverse histopathologic findings in the heart that included epicardial hemorrhage, myocardial necrosis, fibrosis, inflammation, and vascular/perivascular necrosis that were generally minimal to moderate in severity. Additional cardiac findings included minimal to mild mesothelial hypertrophy/hyperplasia, fibroplasia, myocardial atrophy, and vascular/perivascular mixed cell infiltrates. In the lung, moderate to marked hemorrhage, and minimal to mild edema, vascular/perivascular necrosis, and mesothelial hypertrophy were observed. Additional ROCTAVIAN-related findings included mild fibrosis, hemorrhage, and pigmented macrophages in the epididymis, and moderate to marked hemorrhage and hypocellularity of the thymus. ROCTAVIAN-related mortality, adverse clinical observations, and changes in gross pathology were observed at dose levels of $6.53 \times 10^{13}$ vg/kg and higher, and were associated with fibrosis, hemorrhage, and necrosis in the heart. Development of high anti-AAV5 capsid antibody titers and variable levels of anti-hFVIII-SQ antibodies were observed through 6 months.

In a toxicology study in adult male (b) (4) monkeys evaluating the safety of ROCTAVIAN through three months, IV administration of $1.58 \times 10^{13}$ vg/kg and $5.44 \times 10^{13}$ vg/kg resulted in a dose-dependent prolongation of activated partial thromboplastin time (APTT). Histopathology findings included minimal to mild mononuclear/mixed infiltration in the lung at 3 months. ROCTAVIAN administration at both dose levels induced variable anti-AAV5 and dose-dependent anti-hFVIII-SQ total antibody titers through 3 months.

The biodistribution and hFVIII-SQ transgene expression profile of ROCTAVIAN was evaluated in adult (b) (4) mice. Following IV administration of $2.13 \times 10^{14}$ vg/kg ROCTAVIAN, the highest vector DNA concentration was detected in the liver, followed by the lung, heart, lymph nodes, kidney, spleen, bone marrow, testis, and brain through 6 months post-administration. The hFVIII mRNA transcripts were primarily detected in the liver, with no or minimal expression in extrahepatic tissues.

The risk of germline transmission of ROCTAVIAN was evaluated in (b) (4) mice. Adult male mice were administered $6.66 \times 10^{13}$ vg/kg ROCTAVIAN and mated with naïve female mice on Day 37 post-administration. At Day 50. ROCTAVIAN vector copies in the testes ranged between $1.87 \times 10^3$ and $6.88 \times 10^4$ vg/µg DNA. F0 female tissues were not evaluated for vector DNA. There were no ROCTAVIAN-related adverse changes on mating rates, maternal behavior, and fertility indices. All offspring of ROCTAVIAN-administered animals were negative for vector DNA in the liver.

Vector DNA integration site analysis was conducted in liver samples of nonhuman primates administered with ROCTAVIAN at dose levels $1.58 \times 10^{13}$ vg/kg or $5.44 \times 10^{13}$ vg/kg and collected at 13- and 26-weeks post-administration. ROCTAVIAN vector DNA was mostly detected in the form of episomal DNA that were not integrated into the host genome. Vector integration events were observed at low frequencies with an overall average of $1.55 \times 10^{-3}$ integration sites per cell. Overall, the integration events were broadly distributed across the host genome without any preference to specific sites, including genes associated with malignant transformation in humans. There was no

indication of clonal expansion or enrichment of insertion sites. The ROCTAVIAN vector integration profile did not change with immunosuppression and was stable between 13- and 26-weeks post-administration.

Studies to evaluate the safety pharmacology, developmental and reproductive toxicity, carcinogenicity/tumorigenicity of ROCTAVIAN were not conducted. These studies were not warranted based on the product characteristics, results from the toxicology studies, and target patient population.

## 5. Clinical Pharmacology

The clinical pharmacology section of this BLA includes one *in vitro* drug-drug interaction study and two clinical studies: a Phase 1/2, dose-escalation study evaluating the safety, tolerability, and efficacy of ROCTAVIAN in patients with severe hemophilia A, and one a Phase 3 study evaluating the efficacy and safety of ROCTAVIAN in hemophilia A patients with residual FVIII ≤ 1 IU/dL receiving prophylactic FVIII infusions. In both studies ROCTAVIAN was administered as a single intravenous infusion.

ROCTAVIAN vector DNA biodistribution and shedding:

- Following administration of ROCTAVIAN, vector DNA was detected in blood and all matrices evaluated (saliva, semen, stool, and urine). The peak concentrations of ROCTAVIAN vector DNA were observed between 1-9 days post-dose. The highest peak concentrations were in blood, followed by saliva, semen, stool, and urine. Following peak concentration, vector DNA steadily declined in all matrices. The peak levels and duration of detection of ROCTAVIAN vector DNA increased in a dose-dependent manner within the doses ranging from 6E12 vg/kg to 6E13 vg/kg. After administration of ROCTAVIAN at the dose of 6E13 vg/kg, the peak concentration observed to date in blood across both clinical studies was $2 \times 10^{11}$ vg/mL. The maximum concentration observed in any shedding matrix was $1 \times 10^{10}$ vg/mL.

- AAV capsids encapsidate the vector genome, transport it, and subsequently release the vector genome inside another host cell. To further address vector-shedding related safety concerns, the potentially transmissible form of ROCTAVIAN vector DNA, encapsidated vector DNA, was monitored. In subjects treated in both Phase 1/2 and Phase 3 studies, encapsidated (potentially transmissible) vector DNA was detectable in plasma up to 10 weeks after ROCTAVIAN administration.

- All subjects treated in clinical studies achieved the first of 3 consecutive measurements below the lower limit of quantification (LLOQ) for vector DNA in semen by 36 weeks, and all except one subject achieved 3 consecutive measurements below limit of detection (BLOD) or negative by the time of the data cutoff. The maximum time to the first of 3 consecutive measurements BLOD for encapsidated (potentially transmissible) vector DNA in semen was 12 weeks.

- In clinical studies, all subjects achieved 3 consecutive measurements below the LLOQ for vector DNA in urine and saliva, and 126 (89%) subjects achieved 3

consecutive measurements below the LLOQ for vector DNA in stool by the time of the data cutoff date. The maximum time to the first of 3 consecutive LLOQ measurements was 8 weeks for urine, 52 weeks for saliva, and 131 weeks for stool. All subjects in Phase 1/2 study achieved 3 consecutive measurements BLOD or negative in urine, saliva, and stool by five-year post-dosing. All subjects in Phase 3 study achieved 3 consecutive measurements BLOD or negative in urine, and saliva; 85 (63%) subjects achieved 3 consecutive measurements BLOD or negative in stool by three-year data cut.

ROCTAVIAN transgene produced hFVIII-SQ (FVIII activity and hFVIII-SQ Protein); results from Phase 3 study:

- FVIII activity levels were measured using both chromogenic and one-stage assays. FVIII activity was consistently 1.5 to 1.7-fold higher with the one-stage assay compared to the chromogenic assay. The one-stage assay utilizes an (b) (4) while the chromogenic assay (b) (4) . This observation demonstrates that ROCTAVIAN-produced hFVIII-SQ has higher activity than normal plasma during early stages of coagulation reaction in the one-stage assay.

- After administration of ROCTAVIAN at the dose of 6E13 vg/kg, FVIII activity increased and reached the peak levels with the median [min, max] time of 26.0 [2.0, 111.0] weeks. The mean (SD) and median [min, max] peak FVIII activity were 84.4 (81.9) IU/dL and 61.3 [4.0, 463.0] IU/dL, respectively.

- There were two subpopulations in the Phase 3 study: rollover population of 112 subjects whose baseline ABR and FVIII usage data were prospectively collected and directly enrolled population of 22 subjects who were enrolled directly without prospective ABR data collection. FVIII activity results were assessed separately for the two subpopulations due to differences in baseline ABR data collection, corticosteroids use, and duration of follow-up. FVIII activity levels after administration of ROCTAVIAN are summarized in Table 4.

**Table 4. Factor VIII Activity Levels (IU/dL) Over Time**

| Timepoint | Rollover Population N = 112 | | Directly Enrolled Population N = 22 | |
|---|---|---|---|---|
| | **CSA** | **OSA** | **CSA** | **OSA** |
| **Month 3** | N = 111 | N = 111 | N = 22 | N = 22 |
| Mean (SD) | 34.9 (40.4) | 54.6 (60.8) | 31.4 (25.7) | 48.3 (36.0) |
| Median (Q1, Q3) | 20.7 (10.3, 40.5) | 31.3 (15.3, 71.7) | 20.9 (12.6, 45.7) | 36.0 (22.4, 63.9) |
| Min, Max | 0, 249.5 | 1.5, 335.8 | 0, 85.8 | 4.5, 126.0 |
| **Month 6** | N = 111 | N = 111 | N = 22 | N = 22 |
| Mean (SD) | 55.4 (57.5) | 84.9 (83.1) | 40.0 (37.9) | 63.0 (57.2) |
| Median (Q1, Q3) | 38.8 (16.8, 76.5) | 62.0 (28.0, 115.2) | 33.2 (14.7, 46.3) | 53.5 (23.7, 78.2) |
| Min, Max | 0, 367.3 | 1.9, 483.9 | 0, 169.4 | 1.8, 261.9 |
| **Month 10** | N = 111 | N = 111 | N = 20 | N = 20 |
| Mean (SD) | 49.4 (49.5) | 73.6 (70.5) | 44.2 (49.6) | 70.2 (70.9) |
| Median (Q1, Q3) | 31.7 (17.1, 64.5) | 51.3 (25.1, 96.2) | 30.9 (14.1, 68.6) | 55.4 (24.8, 101.4) |
| Min, Max | 0, 265.3 | 1.2, 375.6 | 0, 223.6 | 2.4, 313.7 |
| **Month 12** | N = 111 | N = 111 | N = 21 | N = 21 |
| Mean (SD) | 43.6 (45.5) | 64.7 (64.6) | 38.2 (46.3) | 59.7 (67.0) |
| Median (Q1, Q3) | 24.0 (12.5, 63.7) | 40.0 (20.4, 87.5) | 23.9 (11.2, 52.8) | 40.5 (17.4, 82.6) |
| Min, Max | 0, 231.2 | 0, 311.1 | 1.6, 207.4 | 4.4, 294.1 |
| **Month 18** | N = 99 | N = 99 | N = 18 | N = 18 |
| Mean (SD) | 27.7 (32.3) | 40.6 (45.9) | 28.5 (28.9) | 44.5 (43.9) |
| Median (Q1, Q3) | 13.5 (6.9, 36.8) | 22.5 (10.9, 55.30) | 15.3 (10.8, 43.9) | 24.4 (17.7, 60.4) |
| Min, Max | 0, 167.9 | 0, 232.2 | 3.3, 117.0 | 4.2, 173.7 |
| **Month 24** | N = 98 | N = 99 | N = 19 | N = 18 |
| Mean (SD) | 25.0 (35.5) | 38.9 (50.7) | 22.0 (28.7) | 36.0 (40.8) |
| Median (Q1, Q3) | 12.7 (5.1, 26.5) | 22.7 (7.9, 45.7) | 8.9 (5.8, 25.9) | 19.5 (7.9, 37.7) |
| Min, Max | 0, 187.1 | 0, 271.3 | 0, 110.6 | 2.4, 146.7 |
| **Month 36** | N = 96 | N = 97 | N = 15 | N = 15 |
| Mean (SD) | 21.0 (34.0) | 33.8 (47.6) | 20.8 (24.4) | 32.2 (33.1) |
| Median (Q1, Q3) | 10.0 (4.3, 19.8) | 17.7 (7.2, 35.1) | 9.4 (6.6, 31.7) | 20.6 (8.5, 46.7) |
| Min, Max | 0, 217.7 | 0, 291.4 | 0, 74.5 | 1.9, 104.2 |

- The specific activity of ROCTAVIAN -derived hFVIII-SQ was calculated as FVIII (b) (4) . The specific activity of ROCTAVIAN -derived hFVIII-SQ measured by chromogenic assay was comparable to recombinant hFVIII-SQ (ReFacto®).

- A trend of lower factor VIII activity levels was observed in Black subjects within the study population. The mean (SD) peak FVIII activity levels measured by chromogenic assay were 37.2 (27.5) IU/dL and 90.8 (84.5) IU/dL for black subjects and subjects of other races (Asian, white and others). Given the small sample size, the limited number of sites enrolling Black patients relative to the total population, the existence of potential confounding factors, and multiple posthoc analyses, this trend was insufficient to allow meaningful conclusions about the differences in response rates based on race or other factors therein influencing factor VIII expression following ROCTAVIAN infusion.

Drug-Drug Interactions

An in vitro primary human hepatocyte model was used to assess the effects of concomitant administration of isotretinoin, amphetamine, omeprazole, celecoxib, and

selected highly active antiretroviral therapy (HAART) medications with ROCTAVIAN on cytotoxicity and ROCTAVIAN DNA and RNA expression. The results showed that:

- ***Isotretinoin*** suppressed ROCTAVIAN transcription at clinically achievable concentrations. The suppression can be partially reversed after discontinuation of isotretinoin.

- ***Efavirenz*** dose-dependently decreased FVIII transcription without an impact on FVIII DNA or hepatotoxicity after treating human primary hepatocytes for 3 days in-vitro. FVIII RNA expression was not restored after discontinuation of efavirenz.

Immunogenicity

- ***Anti-AAV5 TAb and AAV5 Transduction Inhibition (TI):*** following administration of ROCTAVIAN, all subjects developed anti-AAV5 TAb and reported positive AAV5 TI test results from the first assessment time point at 8-week post dosing and peaked around 36 - 40 weeks post dosing. All subjects had detectable anti-AAV5 TAb and AAV5 TI titers at the study cutoff dates.

- ***FVIII Total Binding Antibody and FVIII Neutralizing Antibody (inhibitors):*** ten subjects in Phase 3 study tested positive for FVIII TAb at one or more time points. Four subjects had a single transient positive Bethesda assay result (>0.6 BU). There were no apparent associations established between FVIII TAb positive results and FVIII activity and any liver enzyme elevations above the normal range.

- ***Cellular Immune Responses against AAV5 capsid:*** Ninety-three percent subjects with available ELISpot testing results showed positive at one or more time points assessed through a maximum of 140 weeks of follow up. No association was observed between capsid specific cellular immune responses and FVIII activity levels (chromogenic assay).

- ***Cellular Immune Responses against hFVIII-SQ:*** Sixty-five percent subjects in Phase 3 study had positive responses following stimulation with FVIII peptide pools. The majority of positive subjects were transiently positive. There was no trend toward higher ALT values nor lower FVIII activity measures at time points where a FVIII-specific cellular response was detected.

## 6. Clinical/Statistical

The clinical reviewer recommendation for approval of ROCTAVIAN for the treatment of adults with severe hemophilia A (congenital factor VIII deficiency with factor VIII activity <1 IU/dL) without pre-existing antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test is based on a single Phase 3 clinical study (Study 270-301) with supportive proof-of-concept clinical evidence from the Phase 1/2 study (Study 270-201).

## a. Clinical Program

Study 270-201 was a first-in-human, Phase 1/2 open-label, dose-escalation study of ROCTAVIAN [adeno-associated vector 5 (AAV5)-based gene therapy that expresses the SQ form of human FVIII (hFVIII)] in patients with severe hemophilia A treated previously either with prophylactic or episodic FVIII. The primary study objectives were to assess the safety and determine the dose of ROCTAVIAN needed to achieve FVIII activity levels > 5 IU/dL at 16 weeks post-infusion. Seven subjects in the study received the intended commercial dose of $6 \times 10^{13}$ vg/kg.

Study 270-301 was a prospective, Phase 3, open-label, single-dose, single-arm, multinational study investigating ROCTAVIAN administered to adult subjects with severe hemophilia A. Of the 134 subjects in the study, 112 subjects completed a lead-in period of at least 6 months during which data on the baseline annualized bleeding rate (ABR), while on prophylaxis with FVIII replacement therapy, were collected prospectively. These 112 subjects received a single dose of ROCTAVIAN and constituted the rollover population evaluated for effectiveness. All study subjects have been followed for at least 3 years after treatment. All subjects were required to be negative for pre-existing antibodies to AAV5 using the ARUP Laboratories AAV5 DetectCDx™ total antibody assay which was developed to be approved contemporaneously with ROCTAVIAN.

Efficacy was based on ABR (all bleeds) during the efficacy evaluation period (EEP) defined as the period between (1) the later of Study Day 33 (Week 5) or the end of FVIII prophylaxis (including a washout period) after ROCTAVIAN treatment and (2) the earlier of: study completion, last visit prior to data cutoff, or withdrawal from the study. The primary efficacy outcome was a test of non-inferiority (NI) for the difference in ABR (all bleeds) in the EEP compared to baseline ABR; the NI margin was 3.5 bleeds per year.

The study demonstrated a change in the mean ABR in the EEP from a mean baseline ABR of 5.4 bleeds per year to a mean of 2.6 bleeds per year. The change from baseline in ABR (95% confidence interval) was -2.8 (-4.3, -1.2) bleeds per year. A total of 13 patients (12%) had used factor VIII replacement products or emicizumab during the efficacy evaluation period for prophylaxis, with a median start time at 2.3 (range: 0.1 to 3.3) years. An ABR of 35 was imputed for the periods when these patients were on prophylaxis during the EEP. The NI analysis met the pre-specified NI margin, indicating the effectiveness of ROCTAVIAN.

Among the 112 patients, 5 (4%) did not respond and 17 patients (15%) lost response to ROCTAVIAN treatment over a median time of 2.3 (range: 1.0 to 3.3) years.

The median (Q1, Q3) FVIII activity levels, as assessed by the chromogenic substrate assay, at months 12, 24, and 36 following the treatment with ROCTAVIAN were 24.0 (12.5, 63.7), 12.7 (5.1, 26.5), and 10.0 (4.3, 19.8) IU/dL respectively.

The basis of FDA's conclusion of effectiveness of ROCTAVIAN comes from a single adequate and well-controlled trial demonstrating the clinically meaningful benefit of ROCTAVIAN on ABR (total bleeds) post-treatment compared to ABR at baseline. The evidence of ROCTAVIAN effectiveness assessed with the clinically meaningful ABR outcome supports the approval of ROCTAVIAN.

**b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance**

Bioresearch Monitoring (BIMO) inspection assignments were issued for two foreign and five domestic clinical investigator study sites participating in the conduct of Protocol 270-301. The inspections did not reveal substantive issues that impact the data submitted in this original Biologics License Application (BLA).

**c. Pediatrics**

This application is exempt from Pediatric Research Equity Act (PREA) because it is intended for a biologic product for which orphan designation has been granted. This product is not indicated in pediatric subjects.

**d. Other Special Populations**

The efficacy of ROCTAVIAN has not been studied in any special populations.

**7. Safety and Pharmacovigilance**

**Safety**

In the ROCTAVIAN development program, the safety population consisted of 134 subjects who received the planned dose of ROCTAVIAN in Study 270-301. All 134 subjects reported at least one treatment emergent adverse event (TEAE). A total of 576 AEs in 123 subjects (92%;123/134) were considered related to ROCTAVIAN; the most observed reactions were modest (Grade 1 or 2) elevations in ALT [alanine aminotransferase]. Most common (≥5%) adverse events related to ROCTAVIAN included nausea (31%), fatigue (16%), infusion-related reactions including anaphylaxis and hypersensitivity reactions (7%), headache (7%), abdominal pain (6%), and vomiting (6%).

Six serious adverse events (SAEs) related to ROCTAVIAN were reported in 5 subjects and included anaphylaxis, hypersensitivity reaction, presyncope, maculopapular rash and ALT elevation > 5-20 ULN. One subject died of (b) (6) that was considered unrelated to ROCTAVIAN or immunosuppressive medications.

Laboratory abnormalities (≥ 20% subjects) include increases in ALT (81%), AST [aspartate aminotransferase (69%)], LDH [lactate dehydrogenase (57%)], CPK [creatine phosphokinase (45%)], and FVIII activity levels (28%) above the upper limit of normal (ULN). No subjects developed an inhibitor to FVIII or thrombosis. One subject was diagnosed with B-cell acute lymphoblastic leukemia (ALL) ~ 3 years after ROCTAVIAN administration. Another subject in another trial of ROCTAVIAN was diagnosed with parotid gland carcinoma ~ 5.5 years following ROCTAVIAN infusion. Both malignancies were assessed as not attributed to ROCTAVIAN based on vector insertion site analysis and whole genome sequencing. No cases of hepatocellular carcinoma (HCC) were reported.

Ninety-seven of 112 (87%) efficacy evaluable subjects received immunosuppressive treatment (IS) with corticosteroids or alternate immunosuppressive medications (AIS) to

mitigate the immune response to AAV5 capsid (as evidenced by increase in ALT) and to preserve transgene expression. Ninety-two (82%) received corticosteroids while 35% received AIS. Median (range) duration of corticosteroid and AIS use was 35 (3.1 to 120) weeks and 26 (6 to 118) weeks respectively. The most common (≥ 10%) AEs due to corticosteroid use included acne (34%), insomnia (27%), mood disorder (20%), cushingoid (20%), rash (18%), weight gain (16%), hypertension (12%), folliculitis (11%), abdominal pain (10%), and vision disorders (10%). Most AEs were Grade 1 or 2; 13 subjects had Grade 3 events that included hypertension, impaired glucose tolerance, infections, bone fracture, gastrointestinal bleeding, worsening of cataracts, acne, and weight gain. Most common AEs from AIS were hypomagnesemia (15%) and diarrhea (10%). There were no Grade 4 or 5 events from the use of immunosuppressive medications.

**Pharmacovigilance**

There is no post-marketing safety data available for ROCTAVIAN as of 1/6/2023. The Applicant will conduct routine pharmacovigilance with adverse event reporting in accordance with 21 CFR 600.80. Ongoing clinical trials, and two voluntary post-marketing studies will be conducted to provide up to 15 years follow-up in evaluating safety and effectiveness of ROCTAVIAN.

- Study 1 is an observational phase 4 study, with a prospective cohort study design that will collect data directly from the subjects and their health care providers during routine clinical practice. It will enroll subjects for 5 years or until 200 subjects have been reached.

- Study 2 is an observational phase 4 study with a retrospective cohort study design, in which data will be collected secondarily from external registries. The sponsor plans to include 720 patients.

The Applicant is planning to offer two online education programs focused on providing patients with information on hemophilia A treatments (through a Shared Decision-Making Tool) and gene therapy (through the Gene Therapy Learning Academy).

The available safety data do not substantiate a need for a Post-marketing Requirement safety study or a Risk Evaluation and Mitigation Strategy (REMS). There is no agreed-upon Post-marketing Commitment safety study for this product.

## 8. Labeling

The proposed proprietary name, ROCTAVIAN, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on, March 6, 2023, and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on March 10, 2023.

APLB reviewed the proposed package and container labels, prescribing information, and patient package insert on June 5, 2023, and found them acceptable from a promotional and comprehension perspective.

## 9. Advisory Committee Meeting

No advisory committee meeting was held because initial review of information submitted in the BLA did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

## 10. Other Relevant Regulatory Issues

ROCTAVIAN has received Orphan Drug, Breakthrough, and RMAT designations. The original BLA submission was reviewed under priority review and the BLA resubmission was reviewed as a Class 2 resubmission.

## 11. Recommendations and Benefit/Risk Assessment

### a. Recommended Regulatory Action

The Applicant has provided substantial evidence of effectiveness based on a single, adequate, and well-controlled clinical trial with supportive evidence from a small initial clinical investigation. The evidence of treatment effect in the single adequate and well-controlled trial is based on persuasive clinically meaningful improvement in ABRs in a sufficient number of subjects using the subjects' own baseline ABRs as the control prior to ROCTAVIAN administration. This Class 2 resubmission has addressed the deficiencies outlined in the Complete Response letter issued on August 18, 2020.

The Applicant has met the statutory requirements for regulatory approval and the review team recommends approval of ROCTAVIAN, an adeno-associated virus vector-based gene therapy, for the treatment of adults with severe hemophilia A (congenital Factor VIII deficiency with factor VIII activity < 1 IU/dL) without pre-existing antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test.

### b. Benefit/Risk Assessment

ROCTAVIAN has demonstrated efficacy by reducing the mean baseline ABR of 5.4 bleeds per year to the mean ABR of 2.6 bleeds per year with a change (95% confidence interval) of -2.8 (-4.3, -1.2) during the efficacy evaluation period. The non-inferiority analysis met the pre-specified NI margin of 3.5 bleeds per year, indicating the effectiveness of ROCTAVIAN in subjects with severe hemophilia A. Although FVIII activity and thus durability of benefit declines over time, 80% of subjects continued to benefit and remained off routine prophylaxis 3 years after ROCTAVIAN administration.

The most common adverse events included ALT elevation, infusion-related reactions, nausea, fatigue, headache, abdominal pain, and vomiting. The majority of subjects required corticosteroids and/or other immunosuppressive medications to mitigate the immune response to capsid and preserve transgene expression. The majority of AEs related to corticosteroid or other immunosuppressive medications use were consistent with the safety profile expected for these medications and included acne, insomnia, mood disorders, cushingoid, rash, weight gain, hypertension, folliculitis, abdominal pain, vision disorders, diarrhea, and hypomagnesemia. Grade 3 infections occurred in 7% of subjects of which 3 were treated with IV antimicrobial therapy; there were no Grade 4 or 5 events related to immunosuppression.

Careful patient selection prior to administration of ROCTAVIAN, recommendations for close monitoring, and AEs related to the use of immunosuppressive medications are described in the label. Long-term safety of ROCTAVIAN (including collection of significant AEs related to immunosuppressive medications) will be evaluated in a prospective long-term voluntary study in patients who receive commercial ROCTAVIAN. There is a theoretical concern for a potential for development of hepatocellular carcinoma, which is described in the label with recommendations for long-term monitoring in subjects with risk factors for hepatocellular carcinoma. Monitoring for other risks, such as FVIII inhibitor development and thrombosis in settings of FVIII activity levels elevated above normal have been adequately addressed in the label. Overall, the safety profile of ROCTAVIAN is acceptable.

Thus, considering the magnitude of the effect on bleeding events and the generally mild risks (including those related to immunosuppression) which can be mitigated by careful patient selection and close monitoring, the overall benefit-risk profile favors approval of ROCTAVIAN in adults with severe hemophilia A (congenital factor VIII deficiency with factor VIII activity < 1IU/dL) without pre-existing antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test.

The companion diagnostic (AAV5 DetectCDx™) for detection of pre-existing total antibodies to AAV5 capsid to help select patients suitable for ROCTAVIAN administration is expected to be approved contemporaneously.

**c. Recommendation for Post-marketing Activities**

Routine pharmacovigilance activities will be conducted as proposed by the applicant in the Pharmacovigilance Plan, with adverse event reporting as required under 21CFR600.80. Ongoing clinical trials, a long-term follow-up extension study of the clinical trials, and two voluntary observational post-marketing sponsor studies (studies 270-601 and 270-801) will provide up to 15 years of safety and effectiveness follow-up data.

The review team has determined that ROCTAVIAN does not require a Post-marketing Requirement safety study or a Risk Evaluation and Mitigation Strategy (REMS). There are also no Post-marketing Commitment safety studies for ROCTAVIAN.