BLA Clinical Review Memorandum

Application Type	BLA Resubmission
STN	125720/69
CBER Received Date	September 29, 2022
PDUFA Goal Date	June 30, 2023
Division / Office	BHB/OTP
Priority Review (Yes/No)	N/A
Reviewer Name(s)	Kavita Natrajan, MD Kavita Natrajan -S Digitally signed by Kavita Natrajan -S Date 2023 06 28 21 33 53 -0400
Review Completion Date / Stamped Date	June 28, 2023
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Applicant	BioMarin Pharmaceutical Inc.
Established Name	Valoctocogene roxaparvovec
(Proposed) Trade Name	ROCTAVIAN
Pharmacologic Class	Gene Therapy
Formulation(s), including Adjuvants, etc.	Preservative-free, light-sensitive solution containing 2 x 10^{13} vector genomes (vg) per mL in vials
Dosage Form(s) and Route(s) of Administration	Single-use intravenous infusion
Dosing Regimen	Single dose of 6 x 10^{13} vector genomes (vg) per kg body weight
Indication(s) and Intended Population(s)	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
Orphan Designated (Yes/No)	Yes

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GLOSSARY

AAV5	adeno-associated virus serotype 5
ABR	annualized bleeding rate
AE	adverse event
AIH	autoimmune hepatitis
AIS	alternate immunosuppressant
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
ARUP	Associated Regional and University Pathologists
AST	aspartate aminotransferase
BLA	Biologics License Application
BLOD	below limit of detection
BMN 270	Valoctocogene roxaparvovec; ROCTAVIAN
BU	Bethesda unit
CFR	Code of Federal Regulations
CDRH	Center for Devices and Radiological Health
CDx	companion diagnostic
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CMV	cytomegalovirus
CPK	creatine phosphokinase
CR	Complete Response
CSA	chromogenic substrate assay
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
EEP	efficacy evaluation period
EHL	extended half-life
FDA	U.S. Food and Drug Administration
FVIII	Congenital factor VIII
GGT	gamma glutamyl transferase
GT	gene therapy
HCC	hepatocellular carcinoma
hFVIII-SQ	B-domain deleted SQ form of human coagulation factor VIII
HTN	hypertension
IAE	infusion-associated event
IND	Investigational New Drug
IRR	infusion-related reaction
IS	immunosuppressant(s)
ITT	intent-to-treat
IV	intravenous
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMF	mycophenolate mofetil
NI	noninferiority
NSAID	nonsteroidal anti-inflammatory drug
OSA	one-stage assay
PREA	Pediatric Research Equity Act

qPCR	quantitative polymerase chain reaction
REMS	Risk Evaluation and Mitigation Strategy
RP	routine prophylaxis
SAE	serious adverse event
SD	standard deviation
SHL	standard half-life
TAb	total antibody
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
USPI	United States Prescribing Information
vg	vector genomes
VWF	von Willebrand factor
WRO	written response only

1. EXECUTIVE SUMMARY

Congenital factor VIII (FVIII) deficiency (hemophilia A) is the most common, inherited, X-linked recessive, congenital coagulation factor deficiency. Deficiency of the essential blood coagulation FVIII results in impaired hemostasis and increased bleeding tendency. The severity of hemophilia A is characterized as either severe, moderate, or mild, and is based on residual FVIII activity of <1 IU/dL, 1 to <5 IU/dL, or 5 to <40 IU/dL, respectively. The clinical bleeding phenotype is based on residual FVIII activity with patients with severe hemophilia having repetitive, spontaneous bleeds in absence of prophylactic hemostatic treatments, while patients with moderate and mild hemophilia have occasional to rare spontaneous bleeding, respectively, and tend to require greater degrees of hemostatic challenge to manifest bleeding compared to those with severe disease. A goal of modern hemophilia management is to prevent spontaneous bleeds by supplying a replacement factor that will maintain higher FVIII activity levels in the range seen with moderate to mild hemophilia. Therapies until 2017 included plasma derived or recombinant FVIII products with standard half-life (SHL) or extended half-life (EHL), given exogenously two to three times a week intravenously (IV). Emicizumab (Hemlibra), a monoclonal bispecific antibody with a novel mechanism of action of bridging factor IX and factor X, thus bypassing the need for FVIII in the clotting cascade, was approved in 2017 for routine prophylaxis (RP). Advantages of emicizumab include a long half-life, thus requiring less frequent administrations, ability to deliver it subcutaneously, thus avoiding the need for repeated IV access, and its usefulness in patients with and without inhibitors to FVIII. The most recent (February 2023) approval for hemophilia treatment is ALTUVIIIO, a recombinant FVIII with a very long half-life that permits weekly dosing.

Valoctocogene roxaparvovec (BMN 270; AAV5-hFVIII-SQ; ROCTAVIAN) is an adeno-associated virus serotype 5 (AAV5)-based gene therapy (GT) 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. Following a single IV administration, ROCTAVIAN preferentially targets liver cells for transduction and results in expression of the hFVIII-SQ protein.

The original Biologics License Application (BLA) submission (125720/0) was received on December 23, 2019. Applicant stated that the data met the requirements for an accelerated approval but sought full approval based on the data submitted and the transformative nature of a one-time therapy for hemophilia. A total of 22 subjects from Study 270-301 were efficacy

evaluable. However, the majority of subjects had a follow-up of <12 months. Seven subjects in Study 270-201, who received the intended commercial dose, with a longer follow-up of at least 36 months could not inform durability of treatment effect of ROCTAVIAN in Study 270-301, given differences in FVIII activity kinetics and corticosteroid use between the two studies. The surrogate endpoint of "responder status," defined as achieving a median FVIII activity level of (b) (4) IU/dL between weeks 23 and 26 following ROCTAVIAN as assessed by the chromogenic substrate assay (CSA), did not predict the clinically meaningful endpoint of annualized bleeding rate (ABR), because of high inter- and intrasubject variability in FVIII activity levels over time, the confounding effect of corticosteroids on FVIII activity levels, small sample size, and short follow-up. Thus, a Complete Response (CR) letter was issued August 18, 2020, with the Applicant being requested to provide data on all 134 planned subjects in Study 270-301, with a minimal follow-up of 2 years and at least a year of follow-up following cessation of immunosuppression in subjects who received such treatment. The primary endpoint was revised to ABR (all bleeds). Additional clinical data were also requested for vector integration, vector shedding in seminal fluid, FVIII assays in the event of exogenous FVIII product administration in subjects who received GT, and the impact of concomitant medications on FVIII activity or on hepatocellular injury. The Applicant was also requested to address several statistical concerns, including confounding from use of one-time RP on treatment effect of ROCTAVIAN, adequacy of good baseline data including adequacy of RP and bleeding phenotype prior to ROCTAVIAN, and impact of a less stringent follow-up schedule on interpretability of FVIII activity levels with inappropriate imputation methods.

The Applicant has submitted data on all 134 subjects in Study 270-301 with at least 2 years of follow-up following ROCTAVIAN in the Class 2 resubmission (data cutoff November 2021). Additional data with a minimum of 3 years of follow up for all subjects (data cutoff November 2022) was submitted in February 2023, for which a major amendment was issued.

The Applicant seeks an indication for "treatment of adults with hemophilia A (congenital factor VIII deficiency) (b) (4) without antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test."

The primary basis to support licensure comes from a single, large, adequately controlled trial, the GENEr8-1 (Study 270-301), with supportive evidence demonstrating product's biologic effect from an earlier Phase 1/2 trial, Study 270-201.

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) (AAV5-hFVIII-SQ/BMN 270)] 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 required 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 x 10^{13} vg/kg. Data from Study 270-301 was not included in the efficacy analysis given uncertainty of product comparability and difference in corticosteroid use that may impact transgene expression.

Study 270-301 is a Phase 3, open-label, single-dose, multicenter, multinational trial of a one-time infusion of ROCTAVIAN administered at a dose of 6×10^{13} vector genomes (vg)/kg to 134 adult subjects with severe hemophilia A. Of the 134 subjects, 112 subjects (termed the rollover population) completed a lead-in period of at least 6 months wherein baseline ABR was prospectively collected prior to ROCTAVIAN administration and were included in the evaluation of efficacy. The remaining 22 subjects had baseline ABR retrospectively collected (termed the

directly enrolled population) and were only included in the analysis of safety. Besides the difference in how baseline ABR data was collected, these two subpopulations also differed in: 1) the use of corticosteroids and/or other immunosuppressants (IS) for alanine aminotransferase (ALT) elevation and preservation of transgene expression; 2) country/region of enrollment; and 3) duration of follow-up. Because of the differences in the protocol for IS, subjects in the rollover population received a longer duration and an increased amount of corticosteroids. Subjects in the directly enrolled population were primarily from the United States (75%) and had a longer follow-up, with 17 of 22 subjects being followed for ≥4 years post infusion. In the rollover population, only a minority of subjects (14%) were from the United States. All except 3 of 134 subjects completed the week 156 visit at time of data cutoff. One subject died of (b) (6) (unrelated to ROCTAVIAN or corticosteroid use) at week 95, while two other subjects were lost to follow-up at weeks 66 and 104. At the time of the 3-year data cutoff, 88 subjects had been off all IS (for any reason) for at least 1 year. All subjects were required to be negative for pre-existing total antibodies to AAV5, as detected by the Associated Regional and University Pathologists (ARUP) Laboratories AAV5 DetectCDx™ (companion diagnostic) that will receive contemporaneous approval with ROCTAVIAN.

The median age of the trial population was 30 years (range of 18 to 70 years). The majority were White (72%) and from countries other than the United States (78%). Asians and Blacks accounted for 14% and 11% of the population, respectively. All except two subjects were HIV-negative. Forty-one and 20 subjects had history of hepatitis C and B, respectively. No subjects on emicizumab prophylaxis were enrolled in the study. Subjects with prior and current FVIII inhibitors, active acute or chronic infection, or history of thrombosis or thrombophilia, hepatic cirrhosis, or advanced hepatic fibrosis were excluded from the study.

Efficacy was based on the ABR (all bleeds; total) during the efficacy evaluation period (EEP) after treatment with ROCTAVIAN compared with the ABR (total) during the lead-in/baseline period in the 112 subjects in the rollover population. The EEP started from Study Day 33 (Week 5) or the end of factor VIII prophylaxis including a washout period after ROCTAVIAN treatment, whichever was later, and ended when a patient completed the study, had the last visit, or withdrew or was lost to follow up from the study, whichever was the earliest. An ABR of 35 was imputed for the periods when 13 subjects were on prophylaxis (includes RP and frequent one-time prophylaxis use) during the EEP. The mean imputed EEP ABR was 2.6 bleeds/year, compared to a mean observed baseline ABR of 5.4 bleeds/year, with a mean difference in ABR of -2.8 (95% confidence interval (CI): -4.3, -1.2) bleeds/year. The noninferiority (NI) analysis met the prespecified NI margin, indicating the effectiveness of ROCTAVIAN. The median (Q1, Q3) FVIII activity levels over time, as measured by the CSA, were 38.8 (16.8, 76.5), 24.0 (12.5, 63.7), 12.7 (5.1, 26.5), and 10.0 (4.3, 19.8) at 6, 12, 24, and 36 months, respectively. Ten of the 112 subjects were identified by the Applicant as having returned to RP as of the 3-year data cutoff. However, per FDA analysis, a total of 22 subjects [20% (including 10 subjects who had returned to RP)] were identified as having not ever having benefitted from ROCTAVIAN (n=5), or for whom benefit was lost (n=17) over a median time of 2.3 (range: 1.0 to 3.3) years as of the 3-year data cutoff. In the directly enrolled population of 22 subjects, 1 subject did not respond (5%) and 6 subjects (27%) lost response to ROCTAVIAN over a median time of 3.6 (range: 1.2 to 4.3) years as of the 3-year data cutoff.

The safety population consists of all 134 subjects in Study 270-301 who received ROCTAVIAN at the proposed dose. Summary level safety data from Studies 270-201 and 270-303 were reviewed but not included in the analysis. The most common nonlaboratory adverse reactions following ROCTAVIAN (incidence ≥5%) were infusion-related reactions (IRRs), including

hypersensitivity reactions and anaphylaxis, nausea, headache, fatigue, vomiting, diarrhea, and abdominal pain. Laboratory adverse events [(AEs; (incidence ≥10%)] include elevations > upper limit of normal (ULN) in ALT, aspartate aminotransferase (AST), creatine phosphokinase (CPK), lactate dehydrogenase, gamma glutamyl transferase (GGT), bilirubin, and FVIII activity level. The majority of subjects (95%;127/134) had ALT ≥1.5 times baseline or > ULN, with 107 subjects (81%; 109/134) with ALT > ULN. The majority of ALT elevations were Grade 1 or 2; 11 subjects (8%) had Grade 3 ALT elevation. Overall, 97 subjects (87%; 97/112) in the rollover population received IS for ALT elevation. Ninety-two (82%; 92/112) subjects received corticosteroids (prednisone or prednisolone), while 39 subjects (35%) received alternate immunosuppressants (AIS) that included tacrolimus and mycophenolate. The median (range) duration of overall IS, corticosteroid, and AIS use was 39.6 (3.4, 131), 35 (3.1, 120), and 26 (6, 118) weeks respectively. Twenty subjects received more than a year of IS.

Five subjects had six serious adverse events (SAEs) attributed to ROCTAVIAN. SAEs included anaphylaxis, Grade 3 ALT elevation, and symptoms of hypersensitivity reaction. Eleven subjects experienced SAEs due to IS use, including infections, diabetes mellitus, hypertension (HTN), rectal hemorrhage, cataracts, bone fractures, and diarrhea. All SAEs resolved. There was one death due to (b) (6), which was unrelated to ROCTAVIAN or IS use. No subjects developed thrombosis or FVIII inhibitor. Two subjects developed malignancies in clinical trials of ROCTAVIAN. One subject developed acute lymphoblastic leukemia (ALL) approximately 2.5 years following ROCTAVIAN, while another subject developed parotid gland acinar carcinoma about 5.5 years following treatment. Both malignancies were assessed as being likely not related to ROCTAVIAN following integration site analysis and whole genome sequencing testing. No subjects have developed hepatocellular carcinoma.

The Applicant has provided substantial evidence of effectiveness and safety based on a single, adequate, and well-controlled clinical trial (Study 270-301) providing evidence of clinical benefit, supported by the initial clinical investigation (Study 270-201) that served as a proof-of-concept trial. Despite the decline in durability over time, a substantial number of subjects with ongoing follow-up (90/112; 80%) continue to benefit 3 years post ROCTAVIAN administration and have remained off RP. Clinical benefit of ROCTAVIAN off corticosteroid therapy has been demonstrated. The study met the primary efficacy endpoint with an overall favorable benefit-risk assessment. The clinical review team recommends approval of ROCTAVIAN for the following indication: “ROCTAVIAN is an adeno-associated virus vector-based gene therapy indicated for the treatment of adults with severe hemophilia A (congenital FVIII deficiency with FVIII activity level of <1 IU/dL) without pre-existing antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test.” The companion diagnostic for detection of pre-existing antibodies to AAV5 capsid is being approved contemporaneously. A Risk Evaluation and Mitigation Strategy (REMS) was not implemented since statutory requirements for REMS were not met. There was extensive IS use in the clinical trial and it is expected that the majority of patients in the post marketing setting will use IS with the expectation that physicians can manage IS as outlined clearly in the label. Other considerations for not requiring a REMS include : 1) most AEs from IS use were Grade 1 or 2 and aligned with AEs seen with the use of IS in other disorders; 2) the risk of IS use is not to a degree that will outweigh the benefit in absence of a REMS; 3) hematologists administering GT are expected to be well-versed in the use, monitoring, and treatment of AEs associated with IS use; and 4) careful patient selection and close monitoring should further mitigate the risks associated with IS use. The indication was restricted to patients with severe hemophilia given the inability to predict who will benefit and for how long, uncertainties on the optimal immunosuppressive strategy, degree of IS use in the population that serves as the basis for efficacy determination, the enrolled trial population (all with severe hemophilia A), and the

recent availability of other options (emicizumab and ALTUVIIIO) that may provide a better benefit-risk profile in patients with moderate hemophilia A as compared to GT. The Applicant has addressed all the clinical deficiencies in the CR letter.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Table 1. Demographic Characteristics, Efficacy Population, Study 270-301

Parameter	Efficacy Population N=112
Sex, n (%)	-
Male	134 (100)
Age (at enrollment in years)	-
Mean (SD)	31.7 (10.3)
Median (min, max)	30 (18, 70)
Race, n (%)	-
White	96 (71.6)
Black	15 (11.2)
Asian	19 (14.2)
Other/not provided	3 (2.2)
Ethnicity, n (%)	-
Non-Hispanic or Latino	127 (94.8)

Source: Adapted from CSR Study 270-301 pp. 162-363
Abbreviations: n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; SD, standard deviation.

Reviewer Comments:

- *All subjects were treated and completed at least the 3-year visit except for one subject who died of* (b) (6) *at week 95 and two subjects who were lost to follow-up at weeks 66 and 104. One-hundred and twenty-three subjects completed at least 156 weeks of follow-up.*

- *Limited numbers of Black, Asian, and Hispanic subjects make it challenging to draw conclusions about the efficacy of ROCTAVIAN in these racial/ethnic groups. Since the predilection for clinical bleeding is primarily dependent on the degree of FVIII deficiency, differences in the efficacy of ROCTAVIAN by race are expected to be minimal. Therefore, it is reasonable to extrapolate the efficacy data from Whites to other ethnic groups. However, exploratory analyses in this trial revealed that Black race was potentially associated with lower FVIII activity (not adjusted for multiplicity) compared to White or Asian race—odds ratio (95% CI) of 0.246 (0.085, 0.712) with a p-value of 0.0097. However, the majority of Black subjects were from a single site in South Africa therefore limiting the reviewers' ability to draw conclusions regarding differences in response to therapy based on race.*

- *As the study included only one subject above the age of 60, there was insufficient data to draw conclusions regarding safety and efficacy in the geriatric population.*

1.2 Patient Experience Data

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☒	Patient-reported outcome	6.1.11.2
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Hemophilia A is the most common, inherited, recessive X-linked congenital bleeding disorder that predominantly affects males and occurs in about 1 in 4,000 to 5,000 live male births. Severity of the disease based on endogenous FVIII activity is well-defined, and is classified as severe, moderate, or mild based on FVIII activity levels of <1%, 1% to <5%, or 5% to <40% of normal FVIII activity. The hallmark of the disease is the propensity to bleed spontaneously, with patients with severe disease having spontaneous bleeds, while those with moderate or mild disorder typically have few to no spontaneous bleeds and require a greater degree of trauma to manifest a bleed. The most common (70% to 80%) site of bleeding is the joint, followed by bleeding into the muscle (10% to 20%). Bleeds at other sites are fortunately rarer; intracranial hemorrhage occurs in <5% of subjects. Per the Centers for Disease Control registry data between 2014 and 2017, 79% of hemophilia A subjects were White,13% were Black, and 5% were Asian, American

Indian/Alaska Native, Native Hawaiian, or Other Pacific Islander (Carcao 2012; Srivastava et al. 2013; Centers for Disease Control and Prevention 2022).

A goal of modern hemophilia management is to prevent spontaneous bleeds by administering exogenous, plasma derived or recombinant FVIII products that will maintain FVIII activity levels to a value of >1% to 5% (i.e., in the range of subjects with the moderate form of the disease.) This approach is known as RP. This treatment option has limitations, including regular IV injections and risk of infection. Periodic infusion resulting in variable FVIII activity may result in breakthrough bleeding episodes. One of the most serious consequences of exogenous FVIII product administration is the development of inhibitor to FVIII—an antibody that essentially neutralizes the activity of exogenous FVIII therapy, which then necessitates the use of bypassing agents like recombinant FVIIa and/or immune tolerance induction for the treatment of hemophilia A. Inhibitor development is more common in hemophilia A as compared to hemophilia B, occurring in about 20% to 30% of patients (Ehrenforth et al. 1992; Kulkarni et al. 2017). The rate of inhibitor formation is also higher in certain race/ethnic groups (e.g., Black Americans and those with Indian, Asian, or Hispanic ancestry) (Gunasekera et al. 2015). The magnitude of the inhibitor response can be quantified through the performance of a functional inhibitor assay from which a Bethesda unit (BU) inhibitor titer can be reported. The definitions are ≥0.6 to 5 BU for a “low responding inhibitor” and ≥5 BU for a “high responding inhibitor.” Emicizumab, a humanized, bispecific monoclonal antibody that bridges factor IXa and factor X simultaneously, and essentially substituting for the scaffold role of FVIIIa in coagulation was approved in 2017 and is used for RP in patients with and without inhibitors. Emicizumab is not effective for treatment of acute bleeding in hemophilia A.

Primary RP (i.e., administration of regular, continuous, exogenous FVIII products or emicizumab in the absence of documented joint disease and started before the second clinically evident large joint bleed and age 3 years) is the standard of care for patients with hemophilia A, at least in the Western world (Srivastava et al. 2013; Oldenburg 2015). While patients on on-demand therapy (i.e., treatment with exogenous FVIII product only during a bleed) may experience 20 to 50 bleeds per year and develop arthropathy early in life, patients on RP typically develop joint disease much more slowly over several decades. The value of the RP in preventing or slowing progression of joint disease was established in the landmark joint outcome study (Aledort et al. 1994; Manco-Johnson et al. 2007).

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Treatment for hemophilia A requires replacement therapy with exogenous plasma-derived or recombinant exogenous FVIII products. Recombinant products are of two kinds: SHL and EHL products. Emicizumab is a humanized, bispecific antibody that directly bridges factor IXa and factor X, bypassing the need for FVIIIa in coagulation.

Table 2 below summarizes products currently approved for RP for hemophilia A.

Table 2. Approved Products for Routine Prophylaxis in Congenital Hemophilia A

Product Name & Type	Half-Life (Hours)	Year Approved
Standard half-life products	-	-
Advate (recombinant)	9-12	2003
Hemofil M (plasma-derived)	15	1966
Kogenate FS (recombinant)	11-15	2000
Koate (plasma-derived)	16	1974
Kovaltry (recombinant)	12-14	2016
Novoeight (recombinant)	8-12	2018
Nuwiq (recombinant)	12-17	2015
Recombinate (recombinant)	15	1992
Xyntha (recombinant)	8-11	2020
Extended half-life products (all recombinant)	-	-
Adynovate (PEGylated)	13-16	2021
Afstyla (single chain)	10-14	2016
Eloctate (Fc fusion)	13-20	2017
Esperoct (glycoPEGylated)	17-22	2019
Jivi (PEGylated)	17-21	2018
ALTUVIIIO (human FVIII-Fc-VWF-XTEN)	48	2023
Monoclonal antibody	-	-
Hemlibra (humanized bispecific antibody)	26.9±9.1 days	2017
Plasma derived FVIII and VWF products	-	-
Humate P	12.2 (range 8.4-17.4)	1999
Alphanate	17.9±9.6	1978

Source: Hoots, WK and AD Shapiro, 2019, Hemophilia A and B: Routine management including prophylaxis, published by UpToDate in Waltham, MA.
Abbreviations: FS, formulated with sucrose; FVIII, Congenital factor VIII; PEG, polyethylene glycol; VWF, von Willebrand factor; XTEN, half-life extension technology.

The majority of products are also approved for the perioperative and control and treatment of bleeding episode indications except for emicizumab, which is only approved for RP but includes patients with inhibitors, and the plasma derived FVIII and VWF products, which are not approved for the perioperative indication. The majority of products are approved for use in children and adults except for JIVI, which is approved for patients 12 years of age and older, and Humate P, which is approved only in adults. In order to maintain a trough FVIII level of >1%, most recombinant and plasma derived FVIII products are dosed intravenously 2 to 3 times a week, depending on the half-life. The latest EHL recombinant product, ALTUVIIIO, has a half-life that is more than twice that of the other long-acting recombinant products and is thus dosed once a week. Emicizumab is initially dosed once a week for 4 weeks, followed by a maintenance dose once a week, biweekly, or once a month. Emicizumab has two advantages in that it is administered subcutaneously and can be used in patients with hemophilia A with inhibitors to FVIII. However, emicizumab cannot be used for treatment for an acute bleed; it is only given for the prevention of bleeds.

There is no approved GT for hemophilia A.

2.3 Safety and Efficacy of Pharmacologically Related Products

Currently, there are no approved gene therapies for patients with hemophilia A.

2.4 Previous Human Experience With the Product (Including Foreign Experience)

ROCTAVIAN received conditional approval by the European Medicines Agency in August 2022. No postmarketing data is available for review given the recent approval.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

February 6, 2017: Type B Pre-IND Meeting

The FDA advised the Applicant to consider ABR as the primary endpoint and to observe both FVIII activity levels and bleeding rates for a period of 52 weeks from the time of infusion. FDA requested a plan to address the discrepancies observed with the two assays for FVIII activity levels. Bleeding rates for patients on prophylactic therapy would be an appropriate control. The Agency requested a statistical analysis plan and agreed with the dose escalation plan. The Agency requested justification for not including a plan to monitor for hepatic malignancies. The Applicant was also asked to consider codevelopment of a companion diagnostic (CDx) assay for detection of AAV-neutralizing antibodies for use in selecting subjects for the primary study of ROCTAVIAN for marketing approval.

June 7, 2018: Type B Breakthrough Therapy Initial Comprehensive Meeting

The FDA advised the Applicant that FVIII activity level could be considered a surrogate endpoint if the issues related to the assay discrepancies could be resolved and target FVIII activity levels that predict for hemostasis could be substantiated. In addition, the Agency noted its concern with the absence of in-study control data and the Applicant's plans to utilize retrospectively collected control data. In addition, the Agency requested that subjects be observed for a period of 26 weeks after steady-state levels of FVIII activity are reached.

November 2018: Type B Meeting

The Agency agreed that the CSA would be an acceptable assay to measure FVIII activity levels for its use as a surrogate endpoint. Although a target FVIII activity level of (b) (4) IU/dL was proposed, the Agency noted that there was insufficient data from Study 270-201 to support a threshold activity that predicts for improvement in bleeding rates. The Agency also noted that given the differences observed with the two assays, plasma-based levels to support a threshold level for ROCTAVIAN to correlate hemostatic outcomes were insufficient. The Agency requested from the Applicant a proposal to include in their planned interim analysis a method to assess a single value in each 4-week interval in their plans to correlate FVIII activity level to bleeding outcomes. The Agency requested that the Applicant not pool data from Studies 270-201 and 270-301 to assess the correlation between FVIII activity level and ABR, given the differences between Studies 270-201 and 270-301 with regard to the data collection for baseline bleeding rates.

February 12, 2019: Type B Meeting

The Applicant provided a proposal to submit a BLA with an abbreviated follow-up than what was discussed with the Agency in February 2017. In this revised plan, the Applicant proposed to provide data for 13 of 20 subjects, with follow-up of 26 to 49 weeks following study drug administration to also include data from a minimum of 6 responder subjects who would be followed for 26 weeks after reaching a level of (b) (4) IU/dL. The Applicant also proposed to provide data from Study 270-201 to support the limited durability data that was anticipated from Study 270-301. The

Agency noted that the limited data from six responder subjects with durability data for 26 weeks following stable levels may impact the robustness of the data and encouraged the Applicant to provide a more robust sample of subjects with durability data. The Applicant informed FDA that the recording of bleeding events and treatment factor usage, based on electronic diary and infusion log, would not have data related to success of the treatment outcome for subjects on prophylactic treatment phase prior to study entry. In addition, the hospital-based treatment of bleeding would not be captured. FDA noted that these limitations would be review issues. FDA also noted that the definition of the responder status remained unclear for those subjects who had fluctuating levels of FVIII activity that fell below (b) (4) IU/dL during the 26-week observation period. The Applicant justified that subjects in Study 270-201 who achieved a responder status did not experience a decline in factor activity level but agreed that such an issue would represent a review issue for Study 270-301.

July 2019: Type B Pre-BLA Meeting

An agreement was reached to include a supplemental listing in the BLA submission for the eighth subject who met the responder definition that includes 3 weeks of follow-up data following the data cutoff date of April 30, 2019. The timing, format, and content of the safety update report at 120 days following the BLA submission was found to be acceptable by the Agency. The Applicant confirmed that they were planning to submit a CDx assay for review by the Center for Devices and Radiological Health (CDRH), developed through ARUP laboratories. The Agency reiterated that although the short-term clinical data did not detect tumor formation, tumorigenicity remains a safety concern with ROCTAVIAN and additional recommendations regarding long-term follow-up would be forthcoming pending review of the BLA.

April 2020: Midcycle Review of Original (125720/0) Submission

No meeting minutes were generated.

June 2020: Late-Cycle Meeting of Original BLA Submission

Substantive review issues across multiple disciplines were identified. The clinical issues included differences between Studies 270-201 and 270-301 in terms of response, durability of response, FVIII levels, and use of systemic corticosteroids. The issue of substantial intra- and inter-variability in FVIII levels in both studies was also raised. Issues stemming from limited safety data, given the short follow-up and risk of vector integration, and potential for long-term risk of malignancy were also raised.

October 2020: Type A Meeting Following Issuance of Complete Response

Durability of ABR and FVIII expression with a follow-up of at least 2 years was requested by the Agency. The Agency also requested that the Applicant address the issue of vector integration and risk of malignancy. The Agency did not agree to proposed statistical modeling by the Applicant to address lack of durability of treatment effect in Study 270-301. The Agency recommended that the Applicant review the comments in the CR letter, revise the protocol and statistical analysis plan accordingly, and submit it to the IND as an amendment for Agency review.

May 2021: Type C CMC Written Response Only (WRO)

Please refer to the chemistry, manufacturing, and controls (CMC) memo for details. The Agency agreed to the following changes in the resubmission: introduction of a new residual DNA detection method, a proposed updated module 3, and a proposed structure and format of the CMC package.

November 2021: Type C WRO

The meeting pertained to the content and format for the Class 2 resubmission. The Agency agreed to the following: the 6-month review clock as is designated for a Type 2 submission; an updated draft label, Pharmacovigilance Plan, and CR letter response document; a proposed structure and format for module 4, contents of module 5 including updated clinical study reports, integrated summary of safety, but not integrated summary of efficacy; and plan not to submit a 120-day safety update. The Agency did not agree to accept all additional non-CR letter module 3 updates.

May 2022: Pre-BLA (Resubmission) Type C WRO

The Agency noted that the proposed data package may be reasonable, although adequacy of data to address CR letter deficiencies will be determined upon review. The Agency reiterated that ABR (all bleeds) was the acceptable primary efficacy endpoint. The Agency did not agree to regularly scheduled teleconferences during review. The Agency tentatively agreed that the nonclinical evaluation of product for vector integration in nonhuman primates and proposed liver biopsies may be sufficient, and additional studies may not be needed prior to approval, the EEP for ABR to week 5 or beyond (day 33) to last visit, or 3 days after the end of RP to last visit, whichever is later. The Agency recommended a sensitivity analysis where all exogenous FVIII use would be counted as a bleeding event. Several additional comments were made regarding IS use, actual FVIII levels > ULN, occurrence of thromboembolic events, detailed narratives, detailed information on the parotid carcinoma in a subject in Study 270-201, separate dataset for baseline data, and confirmation of inspection around month 3 of the review cycle.

September 2022: BLA Resubmission Class 2

BLA with a 2-year data cutoff for Study 270-301 was submitted.

February 2023 Major Amendment

Additional data based on a 3-year data cutoff for Study 270-301 was submitted. A major amendment was issued, delaying the review clock by 3 months with the current action due date of June 30, 2023.

2.6 Other Relevant Background Information

The original BLA submission (125720/0) was received on December 23, 2019. Applicant had stated that the submission met statutory requirements for AA but requested a full approval based on the totality of data submitted and the transformative nature of gene therapy. Data obtained in an interim analysis on 22 subjects in Study 270-301 and 15 subjects in Study 270-201 with severe hemophilia A were submitted. Only 7 subjects in Study 270-201 received the proposed dose of 6×10^{13} vg/kg. The surrogate endpoint was "responder status," defined as achieving a median FVIII activity level of (b) (4) IU/dL between weeks 23 and 26 following ROCTAVIAN, as assessed by the CSA that would predict for clinically meaningful impact on ABR. Ten additional subjects in Study

270-301 were included for assessment of safety. However, a CR letter was issued August 18, 2020. The key clinical issues that resulted in a CR being issued are highlighted below.

1) Lack of sufficient evidence of durability of ROCTAVIAN. The majority of subjects in Study 270-301 had been followed for <12 months. Subjects in Study 270-201, who had longer follow-up, were therefore expected to provide data on the durability of benefit. However, there was difficulty in extrapolating results from Study 270-201 to Study 270-301 given different kinetics of FVIII activity between the 2 studies (subjects in Study 270-301 had lower peak FVIII activity, and slope of decline was faster [3/22 subjects with FVIII activity of 0 by year 1]). The reasons for the difference were not clear but were hypothesized to be perhaps due to different manufacturing processes and use of a different corticosteroid regimen. Lack of durability precluded an adequate benefit-risk assessment, and the Applicant was requested to provide data with at least 2 years of follow-up for Study 270-301.

2) Confounding from corticosteroid use. Since corticosteroids are used to dampen the immune response to AAV5 capsid and thus preserve transgene expression, interpretation of FVIII activity in the context of ongoing corticosteroid use is difficult. Thus, the Applicant was requested to address the confounding of corticosteroid use on FVIII activity.

3) High inter- and intrasubject variability of FVIII limited the usefulness of the surrogate endpoint of “responder status” based on FVIII activity to predict for the clinical benefit endpoint of ABR. Thus, the Applicant was requested to change the primary efficacy endpoint to ABR and revise the statistical analysis plan accordingly.

Other clinical deficiencies identified, and for which more data was requested, include data on vector integration, vector shedding in seminal fluid, FVIII assays in the event of exogenous FVIII product in subjects who received GT, and the impact of concomitant medications on FVIII activity or hepatocellular injury. Statistical deficiencies included confounding from use of one-time RP on treatment effect of ROCTAVIAN, adequacy of good baseline data, including adequacy of RP and bleeding phenotype prior to ROCTAVIAN, and impact of a less stringent follow-up schedule on interpretability of FVIII activity levels with inappropriate imputation methods. Additionally, there were deficiencies identified by the CMC and Clinical Pharmacology disciplines.

The Applicant has submitted data in the resubmission to address all of the identified deficiencies in the CR letter.

Reviewer Comments:

- *The Applicant has addressed the clinical issues that led to the CR.*
- *Specifically, data has been submitted for all 134 subjects in Study 270-301 with at least 2 years of follow-up. Sixty-four of 97 subjects in the rollover population who received IS were off IS at the time of the 2-year data submission to address the issue of durability of response off IS. All but one subject who received IS for ALT elevation were off IS at the time of the 3-year data cutoff.*
- *The primary efficacy endpoint was changed to ABR (all bleeds) with change in the statistical analysis plan as requested.*

- *A liver sub study was initiated to provide data on vector integration; integration data in liver biopsies in five subjects* has been submitted. Additional data on vector shedding in seminal fluid was submitted.

- *Data on exogenous FVIII use during surgeries with associated hemostatic response and increase in FVIII activity was collected, as was medication interactions (including in vitro studies) that demonstrate the impact of certain medications on liver health and FVIII. Some of this information is in the United States Prescribing Information (USPI).*

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The BLA was submitted electronically and formatted as an electronic Common Technical Document according to FDA guidance for electronic submission. The submission consisted of the five modules in the Common Technical Document structure. The modules were adequately organized and integrated to allow the conduct of a complete clinical review.

3.2 Compliance With Good Clinical Practices and Submission Integrity

The Applicant noted that the study complied with good clinical practices. There were no clinical study conduct or data integrity issues that impacted the clinical review of this submission.

Bioresearch Monitoring inspections were issued for four domestic and two foreign sites (South Africa and Brazil) that participated in Study 270-301. The inspections did not reveal any substantive issues that impact the data submitted in this original BLA.

Reviewer Comments:

- *Clinical sites in South Africa and Brazil were chosen for inspection since they enrolled a significant number of subjects in Study 270-301 and were noted to have higher IS use compared to other sites.*

3.3 Financial Disclosures

Covered clinical study (name and/or number): Study 270-301, Study 270-201
Was a list of clinical investigators provided? ☒ Yes ☐ No (Request list from applicant)
Total number of investigators identified: 239
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0 Is an attachment provided with details of the disclosable financial interests/arrangements? ☒ Yes ☐ No (Request details from applicant) Is a description of the steps taken to minimize potential bias provided? ☒ Yes ☐ No (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 39 Is an attachment provided with the reason? ☒ Yes ☐ No (Request explanation from applicant)

The two investigators with significant payments of other sorts:

1) Dr. John Pasi (Site 1727 for Study 270-301): a total payment of (b) (4), (b) (6) was made to Dr. Pasi between April 2016 and December 2020, mainly for his role in the Steering Group for ROCTAVIAN but also including: the European Medicines Agency meeting in London; World Federation of Hemophilia, American Society of Hematology, and International Society on Thrombosis and Haemostasis Steering Group service; the advisory group on the pediatric program in London; review of FDA papers, protocol amendments, and investor teleconferences and presentations; and the phenylketonuria investigation meeting, including preparation, presentations, participation, and support. Only three subjects from this site were enrolled in the rollover population (primary efficacy analysis population) in Study 270-301.

2) Dr. Savita Rangarajan (Site 1745 for Study 270-301): a total payment of (b) (4), (b) (6) was made to Hampshire Hospital National Health Service Foundation Trust between July 2015 and February 2018 to run the following study that was based on recruitment accomplished: "A seroprevalence study of the presence of Adenovirus-Associated Virus Vector-serotypes AAV2, AAV5 and AAV8 neutralizing activity and antibodies in Patients with Hemophilia A." Only one subject from this site was in the rollover population (primary efficacy analysis population) enrolled in Study 270-301.

BioMarin acted with due diligence to obtain updated financial information on 39 investigators at the time of resubmission but could not do so because these individuals had left the study site.

Reviewer Comments:

- *The review of the financial disclosures did not identify issues that could unfavorably impact the clinical review of this submission.*

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Please refer to the CMC clinical review memo for details. For manufacturing processes (b) (4) used during Study 270-301, the CMC team determined that there were no appreciable differences and that the product obtained from these manufacturing processes are comparable. There were differences in the attributes between process (b) (4) (Study 270-201) and processes (b) (4) used in Study 270-301, per the CMC team.

Reviewer Comments:

- *Because of the differences in attributes between products obtained by the manufacturing processes used for Study 270-201 and Study 270-301, a decision was made not to use Study 270-201 data for efficacy determination.*

4.2 Assay Validation

AAV5 Total Antibody Assay

The eligibility criteria for Study 270-301 included subjects who are negative to pre-existing antibodies to AAV5, because pre-existing antibodies may decrease the efficiency of transduction of the AAV5-based GT. To ensure that the eligibility criteria of the study were met, the Applicant developed a CDx test in partnership with ARUP Laboratories to select subjects who had the "Not Detected" result by the CDx assay. False negatives of the AAV5 antibody assay could be expected to have reduced efficacy of the GT. The analytical performance of the assay has been reviewed by CDRH to ensure the assay is safe and effective for use as a CDx to the AAV5-based GT. The reviews of these assays have been conducted in parallel and in a mutually consultative manner with the clinical team in the Office of Therapeutic Products (OTP) throughout the product development and during the BLA review.

The AAV5 DetectCDx™ is a CDx device intended for use with ROCTAVIAN, a GT indicated for patients with hemophilia A that is a recombinant, replication incompetent AAV5 vector containing a DNA genome. The AAV5 DetectCDx™ uses a bridging immunoassay and electrochemiluminescence reaction to detect antibodies to AAV5 in human sodium citrated (3.2%) plasma specimens. The AAV5 DetectCDx™ uses a combination of concurrently conducted screening and confirmatory steps to detect antibodies to the AAV5 capsid. A positive result in the screening step is confirmed in the confirmatory step prior to providing a test result of "Detected" to indicate the presence of anti-AAV5 antibodies. A "Not Detected" test result indicates that anti-AAV5 antibodies were not detected in the screening step or that the confirmatory step did not confirm the presence of anti-AAV5 antibodies. The AAV5 DetectCDx™ is performed only at ARUP Laboratories, a single Clinical Laboratory Improvement Amendments- and College of American Pathologists-certified laboratory site located in Salt Lake City, Utah.

During the review of the Premarket Approval application for the CDx, the CDRH review team has found that high levels of certain endogenous substances at certain concentrations, including hemoglobin, triglycerides, and rheumatoid factor, have the potential to affect the qualitative output of the assay. Cholesterol was not tested as a potential endogenous interferent to the assay, and its effect on the assay is unknown. A number of exogenous substances at certain concentrations (medications used by subjects, e.g., emicizumab, recombinant and plasma derived FVIII, certain nonsteroidal anti-inflammatory drugs (NSAIDS), oxycodone, atorvastatin, omeprazole etc.) were

tested for assay interference but none was found. Celecoxib was not tested and thus its effect on the assay is unknown. The CDRH review team did not find any apparent correlation between no-/low-responders to the GT and assay readout for the limited number of subjects included in the Premarket Approval/BLA submissions.

FVIII Activity Assays

Please refer to the CMC (Office of Plasma Protein Therapeutics) review memo on this topic for details.

Following ROCTAVIAN infusion, 1.6-fold higher OS than CS FVIII activity was consistently observed in human plasma samples, which was unexpected because the commercial recombinant B-domain deleted FVIII therapies demonstrate an opposite OS/CS ratio, including the ratio of (b) (4) for the recombinant product Xyntha/ReFacto, which is based on the (b) (4) as ROCTAVIAN.

The biochemical root causes for this discrepancy have been investigated. A (b) (4) ROCTAVIAN transgene produced FVIII-SQ compared to native FVIII. Hence, the chromogenic activity of ROCTAVIAN was considered a more conservative and reliable clinical measure for FVIII activity and was selected as the assay to assess the secondary endpoint of FVIII activity to evaluate efficacy of ROCTAVIAN.

In the analysis of central laboratory measure, unimputed FVIII activity data by both assays in the primary efficacy population in Study 270-301 at several timepoints (i.e., weeks 4, 12, 24, 52, and 104) and at data cutoff, the ratio of FVIII activity measured by the one-stage assay (OSA) to that measured by CSA had a range of ratios—1 to 3.5. Ratios are not consistent across the same subject at the different timepoints in several instances.

Reviewer Comments:

- *Based on root cause analysis for the differing OS to CS ratios between FVIII derived from recombinant products and ROCTAVIAN-derived FVIII activity, transgene FVIII-SQ has been demonstrated to have unique activity characteristics that distinguish it from the FVIII-SQ concentrate product Xyntha/ReFacto and samples of patients with moderate or mild hemophilia. Therefore, the association between FVIII activity in blood and the risk of bleeding (i.e., prophylactic efficacy) for ROCTAVIAN subjects may not be the same as for moderate and mild hemophilia or patients treated with replacement therapies including those based on the FVIII-SQ sequence in the published literature. Because the OS assay may overestimate FVIII activity in ROCTAVIAN subjects, the proposal to use the lower value reported by the CSA for primary analyses of clinical study results appears reasonable.*

- *An information request was sent to Applicant to request the range of ratios observed both by central and local laboratories and to provide a root cause analysis for the variability (e.g., data entry errors, assay variability, subject factors) The Applicant acknowledged that the variability in the OSA/CSA ratio is caused primarily by validated analytical variability of CS and OS assays. Individual FVIII assay variability can be "compounded" when calculating the ratio of the two assays.*

- *Per the Applicant, "The ratio serves as a guideline for conversion if only one assay is available and there is a desire to compare previous values using the other assay and has no impact to the FVIII analysis and interpretation of these results." We accepted the Applicant's explanation of method variability as the root cause of variability in the OS/CS ratios reported by the central laboratory in clinical studies. However, in actual practice the ratios may be different than the 1.5 to 1.6 reported in the trial due to difference in reagents used by local laboratories. Healthcare providers are encouraged to use the same time of OSA or CSA reagents to monitor subjects over time. This information has been conveyed in section 5.4 in the label.*

4.3 Nonclinical Pharmacology/Toxicology

Please refer to the Pharmacology/Toxicology reviewer memo for details.

The following summary is based on a high-level summary provided by the Pharmacology/Toxicology reviewer.

IV administration of ROCTAVIAN at dose levels up to 1.77×10^{14} vg/kg in adult male hemophilia A mice resulted in dose-dependent increases in plasma hFVIII-SQ protein levels, plasma hFVIII activity, vector transduction in the liver, and hFVIII RNA expression. In GLP single-dose toxicology studies conducted in adult male mice, with study durations up to 6 months, IV administration of ROCTAVIAN at dose levels of 6.53×10^{13} vg/kg and higher resulted in dose-dependent adverse histopathologic findings in the heart, lung, epididymis, and thymus. ROCTAVIAN-related mortality, adverse clinical observations, and changes in gross pathology were observed at dose levels of 6.53×10^{13} vg/kg and higher and were associated with adverse cardiac findings. Development of high anti-AAV5 capsid antibody titers and variable levels of anti-hFVIII-SQ antibodies were observed through 6 months. In a non-GLP toxicology study in adult male (b) (4) monkeys that evaluated the safety of ROCTAVIAN through 3 months, IV administration of up to 5.44×10^{13} vg/kg resulted in a dose-dependent prolongation of activated partial thromboplastin time. 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 (TAb) titers through 3 months. Vector DNA biodistribution in mice showed highest concentration 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. A mouse germline transmission study did not detect any ROCTAVIAN vector DNA in the liver of F1-generation mice. The vector integration data in nonhuman primates and toxicology data obtained in mice and nonhuman primates (e.g., BMN 270-16-045 and BMN 270-16-046) indicate a mostly episomal form of vector DNA, low level and broad distribution of integration events, no evidence of ROCTAVIAN-related clonal expansion, preferential vector integration site(s), or tumor formation.

During the review of BLA 125720/0, the clinical reviewer had concerns regarding lymphoma found in two animals in the treatment group. However, these two mice had ROCTAVIAN doses 2,500x and 300x-fold lower than the recommended clinical dose and were immunocompromised (b) (4) background]). Mice in three higher dose cohorts did not have findings of lymphoma. The Applicant, however, attributed the findings of lymphomas on the susceptibility of in-bred mouse strains based on a literature reference stating that the incidence of spontaneous lymphomas in the wild-type immunocompetent (b) (4) strain ranges between 20% and 45%. Given the presence of confounding factors such as mouse immune status/genetic strain and the

lack of dose-effect, it is uncertain if the lung lymphomas in the two mice were related to ROCTAVIAN. Across the 20 nonclinical studies (mouse and nonhuman primates) submitted by the Applicant, there were 2 additional instances of tumor findings: 1 lymphoma in a control wild-type mouse and 1 lung adenoma in a wild-type mouse administered with 2×10^{14} vg/kg of ROCTAVIAN. No tumors or lymphomas were noted in the other 18 nonclinical studies.

4.4 Clinical Pharmacology

Please refer to the Clinical Pharmacology reviewer memo for details.

The clinical pharmacology section of this BLA is supported by two clinical studies: a Phase 1/2, dose-escalation study (Study 270-201) evaluating the safety, tolerability, and efficacy of ROCTAVIAN in patients with severe hemophilia A, and one Phase 3 study (Study 270-301) evaluating the efficacy and safety of ROCTAVIAN in patients with hemophilia A with residual FVIII ≤1 IU/dL receiving prophylactic FVIII infusions.

Clinical pharmacology assessments of ROCTAVIAN include ROCTAVIAN vector DNA biodistribution and viral shedding, ROCTAVIAN transgene expression (FVIII activity levels, ROCTAVIAN-derived hFVIII-SQ protein levels), and immunogenicity (humoral and cellular) monitoring.

4.4.1 Mechanism of Action

ROCTAVIAN is an AAV5-based GT vector causing the expression of the B-domain deleted SQ form of a recombinant hFVIII-SQ under the control of a liver-specific promoter. After IV infusion of ROCTAVIAN, the genetically engineered DNA vector sequence is expected to be delivered into liver cells to achieve stable, durable expression of active FVIII in the plasma. The expressed hFVIII-SQ replaces the missing coagulation FVIII needed for effective hemostasis.

4.4.2 Human Pharmacodynamics

Following ROCTAVIAN infusion, vector DNA is processed in vivo to form largely full-length, episomal transgenes that increase hFVIII-SQ. Liver biopsy samples from five subjects and parotid tumor tissue from one subject also showed integration into human DNA. The pharmacodynamic effect of ROCTAVIAN was assessed by measurement of circulating FVIII activity. Administration of ROCTAVIAN resulted in a dose-dependent increase in plasma FVIII activity and hFVIII-SQ protein levels, with doses ranging from 6×10^{12} vg/kg to 6×10^{13} vg/kg. Please refer to Section 6.1.11.2 (efficacy evaluation) for discussion of FVIII activity in Study 270-301.

Considerable high inter-subject variability was observed in FVIII activity and hFVIII-SQ protein levels. ROCTAVIAN transgene expression does not appear to be associated with age, weight, body mass index, baseline ABR, baseline annualized FVIII usage, history of hepatitis B, history of hepatitis C, country, individual mean and time matched VWF level, baseline ALT, or baseline CPK, per the review of BLA 125720/0.

Substantial differences between Study 270-301 and Study 270-201 were observed in ROCTAVIAN-produced FVIII activity and hFVIII-SQ protein levels. In Study 270-301, ROCTAVIAN-derived hFVIII-SQ (FVIII activity and hFVIII-SQ protein) achieved peak levels around 10 weeks earlier than the peak time observed in Study 270-201. FVIII activity and hFVIII-SQ protein levels in Study 270-301 were also substantially lower than those in Study 270-201. The median peak FVIII activity levels measured using the CSA were 49.3 IU/dL (range: 4.0 to

229.0 IU/dL) and 56.3 IU/dL (range: 4.0 to 112.0 IU/dL) for the intent-to-treat (ITT) and modified ITT (mITT) subject groups, respectively. Additional differences, such as different usage of corticosteroids, were also noted. The reason for the difference in activity levels in the two studies is unclear; however, changes in the manufacturing process and corticosteroid use in Study 270-301 were different from those in Study 270-201, which may have been a contributing factor.

Reviewer Comments:

- *Lower FVIII activity was noted in Black subjects in Study 270-301 (see Section 6.1.11.5), but the sample size is too small to draw definitive conclusions.*
- *Review of FVIII activity in the primary efficacy population (N=112) in Study 270-301 demonstrates that there is no steady-state FVIII activity, and most subjects showed a sharp decline from the peak. With continued follow-up, FVIII activity continues to decline for reasons that are not entirely clear.*

4.4.3 Human Pharmacokinetics

Following administration of ROCTAVIAN, vector DNA was detected in blood and all matrices evaluated (saliva, semen, stool, and urine). Vector DNA determination was made using a quantitative polymerase chain reaction (qPCR) assay that is sensitive to transgene DNA, including fragments of degraded DNA. The qPCR assay does not indicate whether DNA is present in the vector capsid, cell, or fluid phase of the matrix (e.g., seminal fluid, or if the intact vector is present.) Plasma and semen matrices were also evaluated for encapsidated (potentially infectious) vector DNA using an immunoprecipitation qPCR assay. The peak concentration of ROCTAVIAN vector DNA was observed between 1 and 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 during continued follow-up. The peak levels and duration of detection of ROCTAVIAN vector DNA increased in a dose-dependent manner within the doses ranging from 6×10^{12} vg/kg to 6×10^{13} vg/kg. Encapsidated DNA was observed in plasma up to 10 weeks following ROCTAVIAN administration.

In the 140 evaluable subjects from Studies 270-201 and 270-301, all subjects achieved the first of 3 consecutive measurements below the lower limit of quantification (LLOQ) for vector DNA in semen by 36 weeks, and 139 (99%) subjects achieved 3 consecutive measurements that were below limit of detection (BLOD) or negative by the time of the data cut. In the 138 evaluable subjects from Studies 270-201 and 270-301, the maximum time to the first of three consecutive measurements BLOD for encapsidated vector DNA in semen was 12 weeks.

In both studies, all subjects achieved 3 consecutive measurements below the LLOQ (5 vg/5 mL) 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 cut. 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 achieved 3 consecutive measurements BLOD or negative in urine and saliva, and 92 (65%) subjects achieved 3 consecutive measurements BLOD or negative in stool by the time of the data cut.

4.4.4 Immunogenicity Assessment

Please refer to the clinical pharmacology review for detailed discussion.

The immunogenicity assessment was conducted by measuring AAV5 TAb, AAV5 transduction inhibition, FVIII TAb, FVIII neutralizing antibodies (inhibitors), and cellular immune responses.

All subjects were required to be negative for inhibitors to FVIII (<0.6 BU) using the Nijmegen-modified Bethesda assay following a lifetime minimum exposure of 150 days to FVIII products.

All subjects seroconverted to anti-AAV5 antibody positive within 8 weeks of ROCTAVIAN administration, with peak antibody response occurring by 36 weeks. The interferon-gamma ELISpot assay was used to determine the cellular response to AAV5 capsid and FVIII transgene product. Cellular immune responses against AAV5 capsid were detected starting week 2 and reverted to negative in the majority of subjects by week 52 following ROCTAVIAN. FVIII-specific cellular responses were detected, often sporadically, at a single timepoint and reverted to being negative in most subjects.

No association could be established between anti-AAV5 capsid and anti-FVIII cellular immune responses and ALT elevation or FVIII activity.

4.5 Statistical

Please refer to the statistical reviewer memo for details. The primary objective of the Phase 3 study (270-301) during resubmission was to demonstrate the NI of ROCTAVIAN following treatment, as compared to a 6-month lead-in period of RP with exogenous FVIII product administration. The primary efficacy analysis was a NI comparison between the ABR (all bleeds) during the EEP, defined as the earlier of week 5 (day 33) post-infusion or discontinuation of RP with appropriate washout depending on type of RP (3 days for SHL products and 5 days for EHL products), and the earlier of either the last visit prior to data cutoff, withdrawal from study, or completion of study. The change from baseline post-therapy was the difference in ABR post-GT to ABR at baseline with a NI margin of 3.5 using the CI approach. If the upper bound of the 95% CI for NI is <3.5, then the null hypothesis would be rejected and ABR (all bleeds) following GT would be declared noninferior to RP. The Applicant proposed then to test for superiority of GT over that of RP once NI was established using the same CI. Sensitivity analyses included ABR (all bleeds) in subjects off IS for at least 12 months (n=64), counting exogenous FVIII use post-GT as a bleed and in alternatively defined EEPs. A sensitivity analysis was also performed in subjects who resumed RP with either emicizumab or exogenous FVIII therapy by imputing the change value from baseline as zero.

4.6 Pharmacovigilance

Please refer to the Office of Biostatistics and Epidemiology review memo for further details.

The concerns that will be further evaluated in the post marketing setting include the identified risks of hepatotoxicity and infusion reactions including hypersensitivity reactions, potential concerns for development of FVIII inhibitors, thromboembolic events, germline transmission, development of malignancies due to vector integration, and horizontal transmission. In addition, an attempt will be made to collect currently missing information on use of ROCTAVIAN in females, long-term effects, and use in patients with liver impairment.

The general risk minimization plan proposed by the Applicant is transparent communication of risks of therapy through information in the package insert, and voluntarily provided patient information, and educational material (Health Care Professionals Guide, Patient Wallet Card).

The Global Pharmacovigilance Plan includes a follow-up study (270-401) of 15 years that will follow all subjects who participated in any clinical trial of ROCTAVIAN. The Applicant has also proposed two additional post marketing studies, both with a duration of 15 years: 1) Study 270-801 to analyze aggregate data collected within hemophilia registries, and 2) Study 270-601, a patient cohort study that will prospectively enroll commercially dosed patients around the time of infusion.

Additional measures to support safe and appropriate use proposed by the Applicant voluntarily include focused training of hemophilia treatment centers with patient selection and mitigation measures tor safe and effective use, dry runs to judge the readiness of hemophilia treatment centers for GT, initiatives to enable shared decision making (shared decision-making tool, hemophilia GT academy), and ongoing transparent communication to inform about emerging safety risks (e.g., malignancy).

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The clinical efficacy review focused on 112 subjects in the rollover population in the Phase 3 Study-270-301 that was submitted in module 5. Safety data and FVIII activity data of all 134 subjects in Study 270-301 (112 subjects in rollover population and 22 subjects from the directly enrolled population) was included in the label.Safety data from other studies of ROCTAVIAN [Study 270-201 (N=15), Study 270-303 (N=1), Study 270-302 (N=1)], and Study 270-303 [N=19]), were reviewed; pertinent information was included in the memo.

Reviewer Comments:

- *The safety tables of AE related to ROCTAVIA include all 134 subjects in Study 270-301. Corticosteroid use impacts efficacy and safety. Given differences in corticosteroid use between the rollover population and directly enrolled population in Study 270-301, AEs related to corticosteroid use for the rollover population is included in the label since this is the efficacy evaluable population and instructions for corticosteroid use in the label align with use in this population. Safety data from other studies of ROCTAVIAN were not included in the label since number of subjects in Study 270-301 is adequate to inform safety and differences in product and/or corticosteroid use limit interpretability of data from other studies.*

- *The clinical reviewer has reviewed the clinical efficacy and safety portion of this resubmission. There was no subject matter expert or board-certified hematology supervisor that provided input or advice on how to conduct or focus on the aspects of the review. Division supervision was provided on information/data presented to them for discussion.*

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The following materials from the submission were reviewed:

Module	Information
1.3.4	Financial Certification and Disclosure
1.6.3	Meetings
1.11.4	Complete Response Letter response June 24, 2022
1.14	Labeling
1.16.1	PVP
2.5	Clinical Overview
2.7.3	Summary of Clinical Efficacy
2.7.4	Summary of Clinical Safety
2.7.6	Synopses of Individual Studies
5.3.5.1	CSR for Study 270-301, Clinical Pharmacology Report, Subject Narratives
16.1	Appendices to include study information, datasets and CRFs
5.3.5.3	Integrated Summary of Safety
5.3.5.4	Other Study reports to include details on parotid carcinoma

In addition, the clinical and statistical reviewer memos from BLA 125720/0 were reviewed along with literature references on hemophilia A, RP in hemophilia A, emicizumab therapy, and GT for hemophilia.

5.3 Table of Studies/Clinical Trials

Table 3. Studies/Clinical Trials Reviewed for This BLA

Study #	Study Design	Study Objective	Dosing Regimen	Duration (Subject Participation)	Subjects Enrolled*	Status	Last Patient Completion Date (Actual or Projected)	Report Data Included in BLA
270-201	Phase 1/2, Open-Label, Dose-Escalation	To assess the safety, tolerability, and efficacy of a ROCTAVIAN single IV infusion in patients with severe HA (FVIII ≤1 IU/dL)	Single dose at 1 of 4 doses: 6×10^{12} vg/kg (n=1) 2×10^{13} vg/kg (n=1) 6×10^{13} vg/kg (n=7) 4×10^{13} vg/kg (n=16)	Approx. 7 years	15	Ongoing (enrollment completed)	March 2024	Interim full CSR with safety and efficacy from 15 subjects *MA Data cutoff: March 29, 2021*
270-203	Phase 1/2, Safety, Tolerability, and Efficacy Study	To evaluate the safety, tolerability, and efficacy of ROCTAVIAN in patients with severe HA and pre-existing antibodies against AAV5 vector capsid at various levels of AAV5 antibody titers	Single dose at 6×10^{13} vg/kg	Approx. 5 years	1 enrolled; Approx. 10 planned	Ongoing (enrolling)	June 2027	Interim abbreviated CSR with safety and efficacy from 1 subject *MA Data Cutoff: May 31, 2021*
270-205	Phase 1/2, Safety, Tolerability, and Efficacy Study in HA Patients with Active or Prior Inhibitors	To assess whether ROCTAVIAN can safely alter the clinical phenotype of HA patients with FVIII activity ≤1 IU/dL at the time of detected inhibitors, who have developed FVIII neutralizing antibodies (inhibitors) during HA treatment that are persistent (active) or have resolved (prior)	Single dose at 6×10^{13} vg/kg	Approx. 5 years	0 enrolled; Approx. 20-40 planned	Initiated (enrolling)	June 2027	None

Study #	Study Design	Study Objective	Dosing Regimen	Duration (Subject Participation)	Subjects Enrolled*	Status	Last Patient Completion Date (Actual or Projected)	Report Data Included in BLA
Phase 3 Studies	-	-	-	-	-	-	-	-
270-301	Phase 3, Open-Label, Single Arm	To evaluate the efficacy and safety of ROCTAVIAN at a dose of 6×10^{13} vg/kg in HA patients with baseline FVIII activity levels ≤1 IU/dL receiving prophylactic FVIII infusions	Single dose at 6×10^{13} vg/kg	2-year analysis: 104 weeks Long-term follow-up: Approx. 5 years	134	Ongoing (enrollment completed)	November 2024	Interim full CSR with efficacy and safety from 134 subjects *MA Data Cutoff: November 15, 2021*
270-302	Phase 3, Open-Label, Single Arm	To evaluate the efficacy and safety of ROCTAVIAN at a dose of 4×10^{13} vg/kg in HA patients with baseline FVIII activity levels ≤1 IU/dL receiving prophylactic FVIII infusions	Single dose at 4×10^{13} vg/kg	Final analysis: 52 weeks Long-term follow-up: Approx. 5 years	1; 40 originally planned	Ongoing (enrollment discontinued)	May 2023	Interim abbreviated CSR with safety and efficacy from 1 subject *MA Data Cutoff: May 31, 2021*
270-303	Phase 3b, Open-Label, Single-Arm	To evaluate the efficacy and safety of ROCTAVIAN with prophylactic CS in HA patients	Single dose at 6×10^{13} vg/kg	Approx. 5 years	19 enrolled; Approx. 20 planned	Ongoing (enrolling)	September 2026	Interim abbreviated CSR with safety from 19 subjects *MA Data Cutoff: December 20, 2021*

Study #	Study Design	Study Objective	Dosing Regimen	Duration (Subject Participation)	Subjects Enrolled*	Status	Last Patient Completion Date (Actual or Projected)	Report Data Included in BLA
Phase 4 Studies	-	-	-	-	-	-	-	-
270-401	Phase 4, Noninterventional	To evaluate the long-term effects of ROCTAVIAN in patients with HA previously treated in a BioMarin clinical trial	None	Approx. 10 years	175-300 planned	Planned	TBD	None

Source: Table 2.7.3.1.2.1 in Summary of Clinical Efficacy
Abbreviations: AAV5, adeno-associated virus serotype 5; BLA, Biologics License Application; CS, corticosteroids; CSR, clinical study report; FVIII, Congenital factor VIII; HA, hemophilia A; N, number of subjects in the specified group, or the total sample.

Efficacy Considerations for This BLA Application Review

The efficacy review focused on the study results from the Phase 3 Study 270-301 in 112 adult subjects with severe hemophilia A (FVIII activity ≤1 IU/dL) who had prospectively collected baseline ABR data on RP for at least 6 months prior to receiving ROCTAVIAN (rollover population).

Safety Data Considerations for This BLA Application Review

The safety database comprised 134 subjects from Study 270-301. However, IS use for ALT elevation was evaluated only in the 112 subjects in the efficacy evaluable population (also termed the rollover population) given the differences in IS between the directly enrolled and rollover population. Summary level safety data from other studies of ROCTAVIAN (270-201, 270-303) were reviewed but not included in the labeling or clinical reviewer analysis except under certain circumstances (e.g., occurrence of malignancy in Study 270-201).

5.4 Consultations

An internal consultation with a CMC reviewer with expertise in AAV integration was obtained to review the two malignancies (parotid carcinoma and B-cell ALL) reported after ROCTAVIAN administration in terms of appropriateness of methodology used to ascertain the role of the AAV vector in the malignancy. CMC reviewer input was also sought to independently evaluate integration studies on the five liver biopsy samples from subjects who received ROCTAVIAN as part of the liver biopsy sub study.

5.4.1 Advisory Committee Meeting

An advisory committee meeting was not held. An advisory committee meeting was initially considered, given the CR to the original submission. However, upon preliminary review of the efficacy data, it was felt that efficacy as claimed would hold up, and that safety concerns, especially pertaining to the issue of prolonged IS use, were within the scope of the practice of hematology and could be addressed through labeling.

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study 270-301

270-301: Pivotal Phase 3 study; open-label, single-arm with dose of 6×10^{13} vg/kg

6.1.1 Objectives (Primary, Secondary, etc.)

The **primary objective** was to assess the impact of ROCTAVIAN compared to FVIII prophylaxis on the number of bleeding episodes, irrespective of exogenous FVIII replacement treatment in the EEP [from week 5 post-ROCTAVIAN infusion (Study day 33) or the end of FVIII prophylaxis plus the washout period (3 days for products of SHL or plasma-derived and 5 days for products of EHL), whichever is later, until a subject completes the study, reaches last visit by the data cutoff for the 2-year analysis, or withdraws from the study, whichever is the earliest (hereafter referred to as "Post FVIII Prophylaxis to Last Visit")].

Secondary objectives included the following:

- To assess the impact of ROCTAVIAN (compared to FVIII prophylaxis) on the number of bleeding episodes requiring exogenous FVIII treatment in the EEP (i.e., treated bleeds in the EEP, as defined in the primary objective)
- To assess the efficacy of ROCTAVIAN (compared to no treatment) defined as FVIII activity, as measured by the CSA at Week 104 following IV infusion of ROCTAVIAN
- To assess the impact of ROCTAVIAN (compared to FVIII prophylaxis) on the usage of exogenous FVIII replacement therapy in the EEP (as defined in the primary objective)
- To assess the impact of ROCTAVIAN (compared to FVIII prophylaxis) on health-related quality of life (as assessed by the Haemo-QoL-A Total Score and Physical Functioning, Consequences of Bleeding, and Role Functioning domain scores) at Week 104 following IV infusion of ROCTAVIAN

The **tertiary efficacy objective** of the study was to assess the impact of ROCTAVIAN (compared to FVIII prophylaxis) on additional patient-reported outcomes (as assessed by the EQ-5D 5-L; Work Productivity and Activity Impairment plus Classroom Impairment Questions: Hemophilia Specific; and Patient Reported Outcomes, Burdens, and Experiences questionnaire) at Week 104 following IV infusion of ROCTAVIAN.

The **safety objectives** of the study were:

- To evaluate the safety of ROCTAVIAN during the first 52 weeks following IV infusion
- To assess the long-term safety of ROCTAVIAN

The **exploratory objectives of the liver biopsy** were:

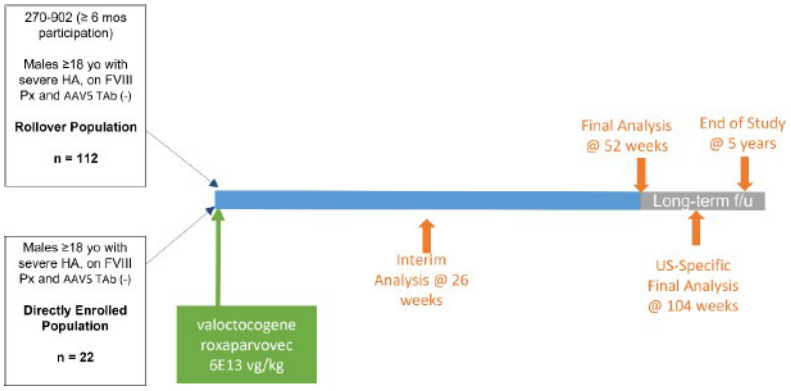
- To examine the histopathology of the liver following ROCTAVIAN therapy, including assessing for possible safety findings (e.g., fibrosis, fatty liver disease, lymphocytic invasion)
- To quantify FVIII DNA, RNA, and protein expression within hepatocytes
- To determine which forms of recombinant AAV vector DNA are present at the time of biopsy
- To determine the transduction pattern of ROCTAVIAN in humans (i.e., peri-portal hepatocytes, central vein hepatocytes)

6.1.2 Design Overview

Study 270-301 was a single-arm, open-label, multinational trial that enrolled a total of 134 subjects from 48 sites worldwide. Of the 134 subjects (ITT population), 112 subjects participated in Study 270-902, a noninterventional study wherein ABR on routine FVIII prophylaxis was prospectively collected for at least 6 months prior to subjects "rolling over" to Study 270-301 to receive ROCTAVIAN. These 112 subjects constituted the "rollover population," the primary efficacy evaluable population for this study. The remaining 22 of the 134 subjects had 12-month ABR data on routine FVIII prophylaxis collected retrospectively and are termed as the "directly enrolled population." Two of the 22 directly enrolled subjects were HIV-positive and were excluded from the mITT (N=132). The study is ongoing, but enrollment is complete.

All subjects (112 after the lead-in phase of at least 6 months on Study 270-902) received a single, one-time dose of ROCTAVIAN at a dose of 6×10^{13} vg/kg. All subjects were required to be followed for at least 5 years following the infusion in Study 270-301. Subjects were then to be followed in the long-term follow-up Study 270-401 for an additional 10 years (total of 15 years follow-up from infusion). The investigational plan included an interim analysis at 26 weeks, a final analysis at 52 weeks, and an FDA-requested analysis at 104 weeks.

Figure 1. Design, Study 270-301



Source: CSR Study 270-301; pp. 77
Abbreviations: AAV5, adeno-associated virus serotype 5; f/u, follow-up; FVIII, Congenital factor VIII; HA, hemophilia A; Px, prescription; n, number of subjects in the specified group, or the total sample; TAb, total ant body.

Reviewer Comments:

- *FDA requested that subjects who received IS need to be followed for at least a year after coming off IS.*

- *FDA requested analysis at 104 weeks due to the fact that short follow-up and lack of establishing durability of benefit were one of the main concerns leading to CR of the original submission.*

6.1.3 Population

Key Inclusion Criteria

1) Males ≥18 years of age with hemophilia A and residual FVIII levels of ≤1 IU/dl as evidenced by the medical history
2) Must have been on prophylactic FVIII replacement therapy for at least 12 months prior to study entry with availability of high quality, well-documented history of bleeding episodes and FVIII usage during this time
3) Treated/exposed to FVIII concentrates or cryoprecipitates for a minimum of 150 exposure days
4) No prior history of a FVIII inhibitor
5) Willing to abstain from alcohol consumption for at least 52 weeks following study product infusion
6) Agree to effective contraception for at least 12 weeks and thereafter for a time period until three consecutive semen samples are negative for viral vector DNA below the limit of detection

Key Exclusion Criteria

1) Pre-existing antibodies to AAV5 capsid
2) Active infection or immunosuppressive disorder, including HIV
3) Significant liver dysfunction with the following laboratory abnormalities: AST/ALT/GGT/Bilirubin/alkaline phosphatase >1.25 X ULN or international normalized ratio ≥1.4
4) Prior liver biopsy showing fibrosis of 3 or 4 as per the Batts-Ludwig or METAVIR score (or equivalent if another scale is used)
5) Liver cirrhosis by ultrasound
6) Platelet count <100K, Creatinine ≥1.5 mg/dL
7) Chronic or active hepatitis B; active hepatitis C
8) History of arterial or venous thromboembolism or acquired or inherited thrombophilia, including conditions with increased thrombosis risk (e.g., atrial fibrillation)

Reviewer Comments:

- *Initially, HIV was not an exclusion criterion. However, one subject with HIV in another trial developed significant transaminitis, and thus subjects with HIV were subsequently excluded (after protocol amendment 3) from Study 270-301. The cause of transaminitis in that subject was ultimately deemed to be due to efavirenz and, subsequently, HIV subjects are again being allowed to enroll on trials of ROCTAVIAN. However, except for 2 subjects (N=134) in Study 270-301, all subjects were HIV-negative. No subject in the efficacy*

evaluation population in Study 270-301 (N=112) had HIV. There is therefore limited data on safety and efficacy of ROCTAVIAN in HIV subjects, including the risk of prolonged IS use in such subjects. This information has been incorporated in section 8.6 of the USPI

- *The definition of severe hemophilia based on baseline FVIII activity level as stated in the inclusion criteria is not consistent with the WHF definition of severe hemophilia and straddles the lower end of the range of baseline FVIII activity for moderate hemophilia. Furthermore, there was no requirement to document the actual baseline FVIII activity from historical records; investigators had to check off an eligibility list that contained the criterion of FVIII activity level of ≤ 1%. Review of the narratives revealed that no moderate hemophilia subjects with FVIII activity of 1% had been enrolled in the trial. Lack of enrollment of moderate hemophilia patients in the trial was one of the reasons of restricting the indication to severe hemophilia A subjects only.*

- *Subjects with prior history and active inhibitors to FVIII were excluded from the trial. Thus, there is limited information of the safety and efficacy of ROCTAVIAN in such subjects. This information has been conveyed in section 8.7 of the USPI. Subjects with active inhibitors to FVIII are excluded from receiving ROCTAVIAN (section 2 of USPI). However, active inhibitors were not listed as a contraindication since the Applicant is conducting trials of ROCTAVIAN in hemophilia A patients with inhibitors. Patients with a prior history of FVIII inhibitors are not precluded from receiving ROCTAVIAN in the commercial setting since an individual subject's history of FVIII inhibitors e.g., remote history of low-titer inhibitor, may not pose a safety or efficacy concern following ROCTAVIAN treatment. Thus, the decision to administer ROCTAVIAN or not in these subjects has been left up to the prescriber's discretion*

6.1.4 Study Treatments or Agents Mandated by the Protocol

Each subject received a single, one-time IV infusion of ROCTAVIAN. The recommended dose is 6×10^{13} vg/kg and the total dose is thus dependent on body weight. The drug product is supplied with a concentration of 2×10^{13} vg/mL.

Reviewer Comments:

- *Nominal titer dosing was used during Study 270-301.*

- *Fifteen subjects (13.4%) in the rollover population and 7 subjects (31.8%) in the directly enrolled population received between 90% and 95% of the planned dose (i.e., received between 5.5 and 5.6 × 10^{13} vg/kg) due to variability in drug concentration across the lots of ROCTAVIAN used in this study.*

6.1.5 Directions for Use

ROCTAVIAN is to be administered IV via a peripheral catheter or butterfly needle flushed with saline. Drug product will be kept at room temperature prior to administration. An electric pump with an in-line, low-protein binding 0.22 micron filter will be used. The initial rate of infusion will be 1 mL/min, which can be increased every 30 minutes by 1 mL/min to a maximum of 4 mL/min. The drug product is considered stable at room temperature for (b) (4) hours following completion of product thaw. Vital signs need to be monitored every 15 minutes during the infusion and appropriate resuscitation equipment must be present in the event of a hypersensitivity reaction. Subject should be observed for 8 hours following completion of infusion. In the event that subject

has an acute illness on day of infusion, the infusion must be postponed to another day and screening procedures must be repeated as needed.

6.1.6 Sites and Centers

Study 270-301 was conducted in 13 countries around the world. Only 16 subjects in the efficacy evaluable population of 112 subjects were enrolled in the United States.

6.1.7 Surveillance/Monitoring

The schedule of events at screening and infusion (day 1) is depicted in Table 4 below.

Table 4. Schedule of Events, Screening and Infusion, Study 270-301

Assessment	Prior to BMN 270 Infusion			BMN 270 Infusion Visit (Day 1)[k]
	Screening[*] (Day -28 to Day -1)	Smart Rescreening[i] (Day -28 to Day -1)	Baseline (Day -7 to Day -1)[h]	
Informed consent	X			
Demographics (age, sex, race, ethnicity)	X			
Medical History	X			
Physical Examination[a]	X		X	X
Height and Weight	X			
Vital Signs	X	X	X	X
Assessment of Adverse Events and Concomitant Medications	X	X	X	X
Documentation of bleeding episodes and FVIII usage for previous 12 months (by either subject or clinical information)	X	X	X	
Distribution of subject diaries and training in their use[l]	X			
Electrocardiogram	X			
Liver Ultrasound	X			
hFVIII Assays[b]	X	X[j]	X	
AAV5 TAb Assays[c]	X	X	X	X
AAV5 TI Assay			X	
Screen for Hepatitis B, Hepatitis C, HIV[d]	X			
Blood chemistry, hematology, and coagulation tests[e]	X	X	X	
Fasting lipid panel (blood triglycerides, total cholesterol, HDL cholesterol, and LDL cholesterol)				X
Urine Tests[e]	X	X	X	
Liver Tests[e]	X	X	X	
PBMC collection (for baseline determination of AAV5 and FVIII specific cellular immunity)			X	
Von Willebrand Factor Antigen (VWF:Ag)			X	
TGA Assay[g]			X	
PCR of vector DNA in blood, saliva, urine, semen, and stools			X	X
Biomarker testing[f]	X			
Exploratory biomarker assessments[g]			X	
Haemo-QOL-A assessment			X	
EQ-5D-5L			X	
HAL			X	
WPAI+CIQ:HS			X	
PROBE			X	
BMN 270 Infusion				X
Hypersensitivity blood assessments[m]				X[m]

Source: Clinical protocol Study 270-301 version 7
Abbreviations: AAV5, adeno-associated virus serotype 5; FVIII, Congenital factor VIII; Haemo-QOL-A, Haemophilia-Specific Quality of Life Questionnaire for Adults; HAL, Haemophilia Activities List; HDL, high-density lipoprotein; hFVIII, human coagulation factor VIII; LDL, low-density lipoprotein; PBMC, peripheral blood mononuclear cells; PCR, polymerase chain reaction; PROBE, Patient Reported Outcomes, Burdens, and Experiences; TAb, total ant body; TGA, thrombin generation assay; TI, transduction inhibition; WPAI+CIQ:HS, Work Productivity and Activity Impairment Questionnaire + Classroom Impairment Questions: Hemophilia Specific.

Post-infusion follow-up is shown in Table 5 below.

Table 5. Schedule of Events, Weeks 1 to 16, Study 270-301

Table 9.1.2: Schedule of Events – Post-Infusion Follow-Up (Week 1-16)

	Follow-Up After BMN 270 Infusion – Weeks*																
	Week 1																
Assessment	D4	D8	2	3	4	5[g]	6	7[g]	8	9[g]	10	11[g]	12	13[g]	14	15[g]	16
Study Day*	4	8	15	22	29	36	43	50	57	64	71	78	85	92	99	106	113
Physical examination[a]		X	X	X	X	X[g]	X	X[g]	X	X[g]	X	X[g]	X	X[g]	X	X[g]	X
Weight[a]					X				X				X				X
Assessment of Adverse Events and Concomitant Medications (including review of subject diary for bleeding and FVIII use)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs		X	X	X	X	X[g]	X	X[g]	X	X[g]	X	X[g]	X	X[g]	X	X[g]	X
Blood chemistry, hematology, and coagulation tests[b]			X		X						X						X
Urine Tests[b]													X				
Liver Tests[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FVIII assays[c]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FVIII antibody titer					X				X				X				X
PCR of vector DNA in blood, saliva, urine, semen, and stools[d]	X	X	X	X	X		X		X				X				X
Exploratory biomarker assessments[e]							X						X				X
Haemo-QOL-A assessment					X								X				
EQ-5D-5L					X								X				
HAL					X								X				
WPAI+CIQ:HS					X								X				
PROBE					X								X				
AAV5 TAb Assay									X								X
AAV5 TI Assay									X								X
Testing for reactivation of hepatitis B and hepatitis C																	X[f]
PBMC collection (for determination of AAV5 and FVIII specific immunity)			X		X		X		X		X		X		X		X
VWF:Ag													X				

Source: Clinical protocol Study 270-301 version 7
Abbreviations: AAV5, adeno-associated virus serotype 5; BMN 270, Valoctocogene roxaparvovec (ROCTAVIAN); FVIII, Congenital factor VIII; Haemo-QOL-A, Haemophilia-Specific Quality of Life Questionnaire for Adults; HAL, Haemophilia Activities List; PBMC, peripheral blood mononuclear cells; PCR, polymerase chain reaction; PROBE, Patient Reported Outcomes, Burdens, and Experiences; Tab, total antibody; TI, transduction inh bition; WPAI+CIQ:HS, Work Productivity and Activity Impairment Questionnaire + Classroom Impairment Questions: Hemophilia Specific; VWF, von Willebrand factor.

Reviewer Comments:

- *The frequency of monitoring for liver enzyme elevation and FVIII activity was every week for 36 weeks, every 2 weeks until week 52, and every 4 weeks in year 2. During years 3 to 5, monitoring was every 6 weeks or longer.*

- *Close follow-up is essential in the first year for initiation or alteration in IS in order to preserve transgene expression, mitigate hepatotoxicity, and monitor and manage AEs from IS. The monitoring in the USPI is aligned to reflect the need for close monitoring in year 1—weekly for at least 26 weeks, and every 1 to 2 weeks between weeks 27 and 52.*

An independent Data Monitoring Committee was convened for Study 270-301 and responsibilities included: ongoing review of safety and efficacy for individual study subjects, recommendation on whether to enroll subjects at a dose lower than 6 x 10^{13} vg/kg based on overall benefit-risk

analysis, review of safety and efficacy data for comparability of drug manufacturing lots within Study 270-301 and between Studies 270-201 and 270-301, and any other recommendations based on evaluation of trial data.

6.1.8 Endpoints and Criteria for Study Success

The primary efficacy endpoint was ABR for all bleeds. Efficacy measurements included recording of bleeding episodes, associated treatment (or not), and FVIII activity levels by both the CSA and OSA methods.

Reviewer Comments:

- *Initially, the proportion of subjects achieving FVIII activity as measured by the CSA and meeting criterion of "responder status" was the basis of the primary efficacy analysis. A subject was considered to be a responder if FVIII activity by the CSA between weeks 23 and 26 was* (b) (4) *IU/dL. However, during the review of the original submission, it was realized that data to demonstrate a correlation between FVIII activity levels of* (b) (4) *IU/dL as predictive of clinical benefit (ABR) was insufficient and hampered by a limited sample size, short follow-up, concomitant immunosuppressive therapy, declining FVIII activity levels, and intra- and inter-subject variability. For these reasons, the primary endpoint was changed to the clinical benefit endpoint of ABR for all bleeds.*

- *The primary endpoint of ABR (all bleeds) is disease specific, appropriate, and clinically relevant. This study was designed to compare each subject's ABR post-treatment with his own baseline ABR while undergoing adequate RP. The endpoint of ABR requires demonstration of durability in the consideration of effectiveness. The intrasubject comparison as a control is appropriate.*

- *ABR all bleeds, as opposed to only treated bleeds, was chosen as the primary efficacy endpoint for the following reasons:*

  - *The effect of GT should impact all bleeds and not just treated bleeds. In fact, if untreated bleeds are usually not treated because of being less severe in nature, GT would be expected to impact these bleeds more than more severe bleeds that are treated.*

  - *There could be reasons besides the severity of bleed that may result in nontreatment of a bleed (e.g., lack of access to FVIII product in a timely fashion). Since the trial was conducted in many regions of the world, it was possible that such factors like differences in standard of care, access to FVIII concentrate, etc., could impact if bleeds were treated or not. If there arose many instances wherein bleeds that would normally be treated were not treated due to regional differences, this could pose a challenge in the interpretation of results.*

6.1.9 Statistical Considerations & Statistical Analysis Plan

Please refer to the Statistical Review memo for further details. Please also see 6.1.11.1 for details.

6.1.10 Study Population and Disposition

Subjects were adult males with severe hemophilia A.

6.1.10.1 Populations Enrolled/Analyzed

ITT Population (N=134)—all subjects dosed in Study 270-301

mITT Population (N=132)—all HIV-negative subjects dosed in Study 270-301

Rollover Population (N=112)—all subjects dosed in Study 270-301 who previously participated in Study 270-902 (all subjects were HIV-negative)

Directly Enrolled Population (N=22)—all subjects dosed in Study 270-301 who did not previously participate in Study 270-902

Directly Enrolled HIV-Negative Population (N=20)—all HIV-negative subjects dosed in Study 270-301 who did not previously participate in Study 270-902

Subjects in the rollover population (N=112) were analyzed for efficacy and safety. The directly enrolled population (N=22) was analyzed only for safety.

6.1.10.1.1 Demographics

Per Table 6, the majority of the population was White and outside of the United States. Since there could be important differences in the RP received depending on the country/region of participation, which in turn could impact the efficacy evaluation, characteristics of the RP received are described here (see Section 6.1.10.1.2 below). Differences in IS could impact safety and efficacy and hence details of IS by country/region of participation are also provided (see Section 6.1.11.3 below).

Table 6. Demographic Characteristics, by Country of Participation, Efficacy Evaluable Population (N=112)

Characteristic	U.S. (N=16)	Non-U.S. Total (N=96)	Australia (N=13)	Belgium (N=5)	Brazil (N=18)	Germany (N=3)	Spain (N=6)	France (N=3)	UK (N=15)	Israel (N=5)	Italy (N=1)	South Korea (N=1)	Taiwan (N=10)	South Africa (N=16)	Total Rollover Population (N=112)
Age (years)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Mean (SD)	29.2 (6.0)	32.3 (11.2)	32.4 (11.3)	47.2 (10.1)	28.4 (6.8)	33.0 (9.5)	28.8 (5.7)	35.0 (3.0)	32.7 (11.1)	26.2 (5.5)	70.0 (NA)	58.0 (NA)	37.2 (14.9)	29.2 (6.0)	31.8 (10.6)
Median	29.5	30.0	29.0	50.0	27.0	32.0	29.5	35.0	32.0	26.0	70.0	58.0	37.0	25.0	30.0
Range	20, 38	19, 70	19, 53	33, 57	19, 41	24, 43	22, 34	32, 38	20, 56	19, 33	70, 70	58, 58	21, 58	20, 43	19, 70
Race, n (%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Asian	1 (6.3)	16 (16.7)	1 (7.7)	0	0	1 (33.3)	0	0	3 (20.0)	0	0	1 (100)	10 (100)	0	17 (15.2)
Black or African American	1 (6.3)	13 (13.5)	0	0	2 (11.1)	0	0	0	1 (6.7)	0	0	0	0	10 (62.5)	14 (12.5)
Native Hawaiian or Pacific Islander	1 (6.3)	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.9)
White	13 (81.3)	65 (67.7)	11 (84.6)	5 (100)	16 (88.9)	2 (66.7)	6 (100)	2 (66.7)	11 (73.3)	5 (100)	1 (100)	0	0	6 (37.5)	78 (69.6)
Not provided	0	2 (2.1)	1 (7.7)	0	0	0	0	1 (33.3)	0	0	0	0	0	0	2 (1.8)
Ethnicity, n (%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hispanic or Latino	1 (6.3)	4 (4.2)	1 (7.7)	0	1 (5.6)	0	2 (33.3)	0	0	0	0	0	0	0	5 (4.5)
Not Hispanic or Latino	15 (93.8)	92 (95.8)	12 (92.3)	5 (100)	17 (94.4)	3 (100)	4 (66.7)	3 (100)	15 (100)	5 (100)	1 (100)	1 (100)	10 (100)	16 (100)	107 (95.5)
Prior chronic infection, n (%)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hepatitis B	1 (6.3)	16 (16.7)	2 (15.4)	0	1 (5.6)	2 (66.7)	0	0	1 (6.7)	4 (80.0)	1 (100)	0	3 (30.0)	2 (12.5)	17 (15.2)
Hepatitis C	6 (37.5)	27 (28.1)	6 (46.2)	3 (60.0)	3 (16.7)	1 (33.3)	0	1 (33.3)	4 (26.7)	1 (20.0)	1 (100)	1 (100)	6 (60.0)	0	33 (29.5)
HIV	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Source: Applicant response to IR dated 11.03.2022
Abbreviations: IR, information request; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; SD, standard deviation.

Reviewer Comments:

- *Most (n=10) of the Black subjects in the trial were enrolled in a single site in South Africa. They may not be representative of the Black population with hemophilia in the United States.*

- *The incidence of hepatitis B was lower in the U.S. population compared to in other regions (e.g., southeast Asia).*

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

All subjects in the rollover population had severe hemophilia A and were on RP for at least 12 months prior to study entry. The mean ABR was 5.36 (6.93), while the median ABR was 3.28 with a range of 0 to 34.6. About one-third of subjects had 0 bleeds/year (n=34; 30.4%), while 31 (27.7%), 30 (26.8%), and 17 (15.2%) had >0 to 4, >4 to 10, and >10 bleeds per year, respectively. The baseline mean ABR (standard deviation [SD]) for treated bleeds was 4.83 (6.47), while the median was 2.80 with a range of 0 to 33.1. Seventeen and 33 subjects had history of hepatitis B and hepatitis C, respectively. The majority (82 [73%]) had 0 target joints at study entry, while 13 (11.6%), 9 (8%), 6 (5.4%), and 2 (1.8%) subjects had 1, 2, 3, and >3 target joints, respectively. Genotyping data revealed that 49 (43.8%) subjects had the intron 22 inversion, while 60 subjects (53.6%) had non-intron 22 inversions. Genotyping data was missing in three subjects.

Baseline ABR and infusion data by country is shown in Table 7 below.

Table 7. Baseline ABR, Target Joints, and FVIII Usage by Country, Study 270-301

		Non-US													Total Rollover (N=112)
	US (N=16)	Non-US Total (N=96)	Australia (N=13)	Belgium (N=5)	Brazil (N=18)	Germany (N=3)	Spain (N=6)	France (N=3)	UK (N=15)	Israel (N=5)	Italy (N=1)	South Korea (N=1)	Taiwan (N=10)	South Africa (N=16)	
Number of target joints at baseline, n(%)															
0	10 (62.5)	72 (75.0)	10 (76.9)	5 (100)	18 (100)	2 (66.7)	2 (33.3)	1 (33.3)	11 (73.3)	3 (60.0)	1 (100.0)	0	4 (40.0)	15 (93.8)	82 (73.2)
1	3 (18.8)	10 (10.4)	1 (7.7)	0	0	0	0	1 (33.3)	2 (13.3)	1 (20.0)	0	0	4 (40.0)	1 (6.3)	13 (11.6)
2	0	9 (9.4)	1 (7.7)	0	0	0	4 (66.7)	1 (33.3)	1 (6.7)	1 (20.0)	0	1 (100.0)	0	0	9 (8.0)
3	2 (12.5)	4 (4.2)	1 (7.7)	0	0	1 (33.3)	0	0	0	0	0	0	2 (20.0)	0	6 (5.4)
≥ 3	1 (6.3)	1 (1.0)	0	0	0	0	0	0	1 (6.7)	0	0	0	0	0	2 (1.8)
Baseline AFU, IU/kg/year (6-months baseline)															
Mean (SD)	5441.34 (2404.44)	3714.48 (1496.99)	3815.95 (835.65)	3884.30 (1493.71)	3339.36 (1279.48)	2906.92 (2184.16)	5133.64 (1734.27)	4163.54 (1338.17)	3845.04 (1430.61)	5775.08 (3103.41)	3229.45 (NA)	4897.90 (NA)	3419.04 (739.63)	2910.66 (1023.27)	3961.17 (1751.47)
Median	4827.70	3661.38	4042.68	4331.47	3170.54	2025.23	4941.68	3617.88	3753.78	4778.69	3229.45	4897.90	3634.49	2647.01	3754.42
Range	1760.0, 10181.9	1296.4, 11251.1	1469.1, 4935.8	1361.6, 5196.6	1715.3, 6483.7	1301.4, 5394.1	2546.9, 7867.0	3184.4, 5688.3	1296.4, 6433.2	3541.7, 11251.1	3229.5, 3229.5	4897.9, 4897.9	1961.0, 4557.1	1576.7, 5167.7	1269.4, 11251.1
Baseline AFR, infusions/year (6-months baseline)															
Mean (SD)	128.80 (36.18)	137.04 (54.24)	128.02 (40.66)	118.53 (53.63)	168.20 (61.24)	153.25 (101.71)	168.64 (103.82)	105.59 (12.49)	140.86 (43.88)	156.50 (39.65)	120.30 (NA)	197.07 (NA)	95.00 (27.03)	120.04 (27.51)	135.87 (51.99)
Median	134.75	125.09	105.94	121.75	156.54	105.06	143.62	108.42	138.08	147.90	120.30	197.07	100.14	109.62	128.56
Range	52.7, 183.3	39.5, 363.8	67.3, 193.0	39.5, 181.9	87.7, 363.8	84.6, 270.1	71.6, 361.9	91.9, 116.4	52.2, 187.5	117.4, 222.2	120.3, 120.3	197.1, 197.1	52.5, 139.2	87.1, 192.2	39.5, 363.8
Baseline ABR (all bleeds) (6-months baseline)															
Mean (SD)	5.72 (8.68)	5.30 (6.65)	3.32 (3.06)	4.70 (4.27)	1.90 (3.05)	8.28 (9.49)	5.44 (9.30)	5.67 (8.07)	4.91 (3.70)	10.75 (6.68)	4.36 (NA)	1.70 (NA)	9.57 (10.53)	6.50 (8.51)	5.36 (6.93)
Median	3.53	3.17	2.73	3.38	0.00	3.16	1.55	2.11	4.37	11.93	4.36	1.70	6.73	3.60	3.28
Range	0.0, 34.6	0.0, 32.7	0.0, 8.2	1.5, 11.9	0.0, 9.7	2.4, 19.2	0.0, 24.0	0.0, 14.9	0.0, 10.4	2.2, 19.2	4.4, 4.4	1.7, 1.7	0.0, 32.7	0.0, 30.5	0.0, 34.6
Baseline ABR (treated bleeds) (6-months baseline)															
Mean (SD)	5.54 (8.31)	4.71 (6.16)	2.86 (2.35)	4.70 (4.27)	1.90 (3.05)	4.43 (2.84)	4.88 (8.64)	5.32 (8.32)	4.33 (3.91)	9.98 (6.01)	1.74 (NA)	1.70 (NA)	8.32 (10.11)	6.09 (8.13)	4.83 (6.47)
Median	3.53	2.58	2.73	3.38	0.00	3.16	0.90	1.05	3.78	11.57	1.74	1.70	5.44	3.10	2.80
Range	0.0, 33.1	0.0, 30.8	0.0, 6.9	1.5, 11.9	0.0, 9.7	2.4, 7.7	0.0, 22.0	0.0, 14.9	0.0, 10.4	2.2, 17.9	1.7, 1.7	1.7, 1.7	0.0, 30.8	0.0, 30.5	0.0, 33.1

Source: Applicant response to IR dated 11.03.2022
Abbreviations: ABR, annualized bleeding rate; AFR, annualized FVIII infusion rate; AFU, annualized FVIII usage; FVIII, Congenital factor VIII; IR, information request; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; SD, standard deviation.

Reviewer Comments:

- *The baseline ABR in the U.S. population is comparable to that of the entire non-U.S. population taken together. Some countries (e.g., Israel) had a high mean baseline ABR, but the number of subjects is small, thereby limiting interpretation of these findings.*

- *The number of target joints in the U.S. population was lower compared to the non-U.S. population, but differences among the non-U.S. countries could account for this with perhaps a few outliers driving the difference. Difference in target joints does not appear to correlate with FVIII usage (e.g., subjects in Brazil had lower FVIII usage as measured by IU/kg/year compared to U.S. subjects and yet there were no target joints in any subject) thus indicating adequate prophylaxis in these subjects.*

In the RP lead-in period prior to GT (N=112), majority of subjects received SHL RP (includes plasma-derived products). Majority of patients received intermediate intensity RP followed by high-intensity RP in about a third of subjects. Only a handful of subjects received low-intensity RP. The intensity and type of product used for RP by country is given below.

Table 8. Type and Intensity of Routine Prophylaxis by Country

	US (N=16)	Non-US													Total Rollover (N=112)
		Non-US Total (N=96)	Australia (N=13)	Belgium (N=5)	Brazil (N=18)	Germany (N=3)	Spain (N=6)	France (N=3)	UK (N=15)	Israel (N=5)	Italy (N=1)	South Korea (N=1)	Taiwan (N=10)	South Africa (N=16)	
Baseline period prophylaxis regimen															
Subjects on only SHL prophylaxis during baseline period, n(%)	12 (75.0)	72 (75.0)	7 (53.8)	4 (80.0)	17 (94.4)	2 (66.7)	4 (66.7)	0	10 (66.7)	5 (100)	0	1 (100)	6 (60.0)	16 (100)	84 (75.0)
Subjects on only EHL prophylaxis during baseline period, n(%)	4 (25.0)	19 (19.8)	5 (38.5)	1 (20.0)	1 (5.6)	0	2 (33.3)	2 (66.7)	5 (33.3)	0	1 (100)	0	2 (20.0)	0	23 (20.5)
Subjects on mixed SHL/EHL during baseline period, n(%)	0	5 (5.2)	1 (7.7)	0	0	1 (33.3)	0	1 (33.3)	0	0	0	0	2 (20.0)	0	5 (4.5)
Intensity of FVIII prophylaxis at baseline															
Number of subjects with evaluable prescribed FVIII prophylaxis data at baseline (%)[e]	11 (68.8)	84 (87.5)	12 (92.3)	4 (80.0)	16 (88.9)	3 (100)	4 (66.7)	3 (100)	14 (93.3)	2 (40.0)	1 (100)	1 (100)	9 (90.0)	15 (93.8)	95 (84.8)
Subjects with high intensity FVIII prophylaxis during baseline period[a,d]	8 (72.7)	26 (31.0)	4 (33.3)	3 (75.0)	5 (31.3)	1 (33.3)	3 (75.0)	1 (33.3)	5 (35.7)	1 (50.0)	0	0	2 (22.2)	1 (6.7)	34 (35.8)
Subjects with intermediate intensity FVIII prophylaxis during baseline period[b,d]	3 (27.3)	55 (65.5)	7 (58.3)	1 (25.0)	11 (68.8)	1 (33.3)	1 (25.0)	2 (66.7)	8 (57.1)	1 (50.05)	1 (100)	1 (100)	7 (77.8)	14 (93.3)	58 (61.1)
Subjects with low intensity FVIII prophylaxis during baseline period[c,d]	0	3 (3.6)	1 (8.3)	0	0	1 (33.3)	0	0	1 (7.1)	0	0	0	0	0	3 (3.2)

Source: Applicant response to IR dated 11.03.2022
a. High-intensity prophylaxis defined by WFH guidelines of >4,000 IU/kg/year SHL products.
b. Intermediate intensity prophylaxis defined by WFH guidelines of 1,500-4,000 IU/kg/year.
Abbreviations: EHL, extended half-life; FVIII, Congenital factor VIII; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; SHL, standard half-life; WFH, World Federation of Hemophilia.

Reviewer Comments:

- *The type of FVIII products used, SHL versus EHL, was similar in the U.S. versus non-U.S. population.*

- *Study 270-301 was initiated in December 2017 and emicizumab was approved by the FDA in October 2018. Thus, emicizumab was not available at start of the pivotal study and was unlikely widely used when majority of subjects were dosed with ROCTAVIAN especially in non-US countries. Hence, the effectiveness of ROCTAVIAN has not been compared to emicizumab as no subject in Study 270-301 was on emicizumab RP. Currently, emicizumab is in widely used for RP and thus prescribers will have to weigh lack of comparative effectiveness between ROCTAVIAN and emicizumab prior to GT administration in subjects on emicizumab RP. We decided to leave the suitability of GT for an individual patient on emicizumab RP up to the prescriber rather than have a stepwise approach to therapy e.g., restricting ROCTAVIAN use to subjects who have inadequate control of bleeding on emicizumab.*

- *The intensity of prophylaxis was higher in U.S. subjects, but subjects in countries with less intense RP regimens still had joint outcomes similar or better than those of U.S. subjects. Thus, it appears that the differences in intensity of RP did not have meaningful impact on efficacy outcomes.*

The major medical issues reported at study entry pertained to joint issues, followed by history of hepatitis B or C. Of 112 subjects, 67 reported hemophilic arthropathy/arthropathy at baseline while 31 and 12 subjects reported history of hepatitis C and B, respectively. Surgical history mainly encompassed those performed on joints and included synoviorthesis (n=13), arthrodesis (n=9), knee arthroplasty (n=9), and synovectomy (n=8). Depression and anxiety were reported in 10 and 11 subjects, respectively. One subject had prior history of coronary artery disease, and two subjects had prior history of jugular vein thrombosis that did not meet exclusionary trial criteria.

Reviewer Comments:

- *The medical and surgical history of subjects at study entry was as expected in this subject population.*

6.1.10.1.3 Subject Disposition

Figure 2 below summarizes subject disposition in Study 270-301.

Figure 2. Disposition of Subjects, Study 270-301

Source: CSR for Study 270-301; pp. 153
Abbreviations: N, number of subjects in the specified group, or the total sample.

For the 37 subjects who were screen failures (includes N=14 in the directly enrolled population and N=23 in the rollover population), the reasons for being a screen failure were as follows: antibodies to AAV5 capsid (n=26), significant liver dysfunction with abnormal laboratory results (n=7), failure to be on prophylactic FVIII replacement therapy for at least 12 months prior to study entry (n=1), investigator/Applicant opinion that subject would be unable to fully comply with study requirements (n=1), and unwillingness to provide informed consent (n=1).

For the 10 subjects (5 each in the directly enrolled and rollover populations), the reasons for being enrolled but not dosed included withdrawal from study prior to dosing (n=5), withdrawal due to abnormal liver function tests at baseline assessment (n=4), and HIV infection (n=1; at this time protocol had been amended to exclude subjects with HIV).

Follow-up for subjects is shown in Table 9 below.

Table 9. Follow-Up, Study 270-301

Category	Directly Enrolled, HIV- (N=20)	Directly Enrolled (N=22)	Study 270-902 Rollover (N=112)	mITT (N=132)	ITT (N=134)
Subjects treated, n (%)[a]	20 (100.0)	22 (100.0)	112 (100.0)	132 (100.0)	134 (100.0)
Continuing in study	19 (95.0)	21 (95.5)	110 (98.2)	129 (97.7)	131 (97.8)
Completed Week 156	19 (95.0)	21 (95.5)	102 (91.1)	121 (91.7)	123 (91.8)
Discontinued from study	1 (5.0)	1 (4.5)	2 (1.8)	3 (2.3)	3 (2.2)

Source: Table 14.1.1.1., 3-Year Update for Study 270-301; pp. 169
Abbreviations: ITT, intent-to-treat; mITT, modified intent-to-treat; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample.

As of the 3-year data cutoff in November 2022, 131 of 134 subjects had completed their week 156 study visit prior to data cutoff with 123 subjects completing at least 156 weeks of follow up. One subject in the rollover population died of (b) (6) at week 95, 2 subjects (one each in the directly enrolled and rollover populations) were lost to follow up at weeks 66 and 104 respectively.

6.1.11 Efficacy Analyses

The primary efficacy endpoint was ABR (all bleeds) in the EEP, which began at the earlier of either week 5 (day 33) or discontinuation of RP (with an appropriate washout period depending on type of product used) and continued to the earlier of the last visit prior to data cutoff, withdrawal from study, or study completion.

6.1.11.1 Analyses of Primary Endpoint(s)

The mean ABR for all bleeding episodes was reduced following ROCTAVIAN infusion in comparison to the mean baseline ABR on RP period prior to GT. The mean ABR during RP was 5.4 bleeds/year, compared to the mean ABR post-ROCTAVIAN in the EEP of 2.6 bleeds/year. The mean difference in ABR was -2.8 (95% CI: -4.3, -1.2) bleeds/year. The difference in the ABR meets the prespecified NI margin of 3.5. In the rollover population, a total of 5 patients (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 (min, max) ABR at baseline and in the EEP are 3.3 (0, 34.6) and 0.3 (0, 35.0) respectively.

Reviewer Comments:

- *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. The range of bleeds experienced by hemophilia subjects on on-demand treatment varies widely (Manco-Johnson et al. 2013; Trakymiene and Carlsson 2014; Tiede et al. 2016; Miesbach et al. 2020). The ABR of 35 was considered a plausible scenario (lower end of the range) for subjects with severe hemophilia on on-demand therapy. The imputation was proposed by the statistical reviewer, is reasonable, and agreed upon by the Applicant.*

- *ROCTAVIAN shows a decrease in ABR from baseline to the post-treatment period. However, a positive effect will be seen in subjects with a high baseline ABR unless the subject is a non-responder to treatment at the outset. High baseline ABRs may be due to inadequate RP or poor compliance to RP. Eleven subjects were deemed to have inadequate RP (see Section 6.1.11.3). The vast majority (104 of 112) of subjects had good to fair adherence to RP per accepted definitions of adherence in the published literature. There was no meaningful change in the benefit seen with sensitivity analysis excluding subjects with inadequate RP.*

- *One-time treatment with ROCTAVIAN appears to provide a multi-year benefit and freedom from use of RP despite waning durability of response over time. Eighty percent of subjects were still benefitting from ROCTAVIAN at the 3-year data cutoff analysis. Although it is expected that durability of response will continue to decrease with time, the slope of decline in benefit and the percentage of subjects who will return to RP eventually is unknown at this time.*

- *Identification of subjects who never responded or lost response to ROCTAVIAN treatment was determined by reviewing FVIII or emicizumab use for treatment of bleed or as on-time RP, type of bleed- spontaneous versus traumatic, and course of FVIII activity levels. There were subjects who should have returned to RP based on the pattern and type of bleeding*

but had not done so for reasons that are not clear. Even in subjects stated to have returned to RP by the Applicant, review of the bleeding events data revealed that RP should have been instituted at an earlier timepoint than that stated. Thus, return to RP alone does not indicate failure of treatment and detailed review of bleeding events, medication use, and FVIII activity helps determining lack of response or loss of response to treatment.

- *Two subjects who had lost response to ROCTAVIAN treatment and had resumed RP had an ABR > baseline even after resuming RP with FVIII product and/or emicizumab. Initially Applicant reported that one of these subjects had a FVIII inhibitor that was confounded by emicizumab used. Emicizumab can cause a false negative and not a false positive inhibitor titer. However, upon further clarification, this report of inhibitor test positivity was deemed to be in error. Review of data did not raise any concern for increase in bleeding caused by drug product. As such, there is no biologic plausibility of ROCTAVIAN resulting in an increased bleeding phenotype, but this concern was investigated given that it was raised during review of the original BLA submission.*

- *Applicant's claim of superiority of ROCTAVIAN treatment over FVIII RP was not granted for a number of reasons including single-arm nature of the trial with inherent bias, different FVIII products used at baseline (i.e., comparator not uniform), inadequate RP at baseline in some subjects, and impact of missing data.*

ABR (all bleeds) was evaluated by subtype of bleeds to include spontaneous bleeds and joint bleeds. The observed spontaneous bleed count as a proportion of total bleeds at baseline and during the EEP was 42% and 41% respectively, while the observed joint bleed counts as a proportion of total bleeds at baseline and during the EEP were 57% and 45% respectively.

ABR for treated bleeds (NI margin of 3.5) decreased from a mean of 4.83 at baseline to 0.83 following ROCTAVIAN, with a change of -4.00 (95% CI: -5.24, -2.76) that translates into an 83% reduction in the mean. Median ABR for treated bleeds was 2.80 at baseline and was 0 following GT. Of the 44 subjects who had treated bleeds during the EEP, the majority (34/44) had EEP ABR ≤ baseline ABR; 5 of the remaining 10 subjects had an increase of < 1 bleed/year. Mean (SD) for treated spontaneous bleeds at baseline and in the EEP were 1.96 (3.45) and 0.38 (1.19) respectively while mean (SD) for treated joint bleeds was 2.80 (4.26) and 0.46 (1.37) at baseline and during EEP respectively.

A total of 464 bleeding events in 80 subjects were reported during the EEP (3-year data cutoff), including 277 treated bleeds (60%), 157 untreated bleeds (34%), and 30 bleeds associated with a surgery or procedure (6.5%). Forty percent of bleeding events were spontaneous while 60% were traumatic. Joint bleeds accounted for 43.5% of all bleeds including 9% in target joints while the remainder of bleeding events occurred at other locations.

For data provided as of the 2-year cutoff, the majority of treated bleeds were mild or moderate in severity, the vast majority of bleeds were treated at home, and the mean (SD) number of treatment days for a bleeding event was 1.3 (0.7). Sixteen subjects had target joint involvement as defined by ≥3 spontaneous bleeds in the same joint over a contiguous 6-month period. All 21 target joints in these 16 subjects were considered resolved during the EEP, with resolution defined (by the International Society on Thrombosis and Haemostasis criterion) as ≤2 spontaneous bleeds in the same joint over a 12-month period.

One-Time Routine Prophylaxis Use Post-Gene Therapy

There were 14 subjects who used exogenous FVIII therapy as a one-time RP in the EEP as of the 2-year data cutoff (this number excludes those who used exogenous FVIII for treatment of bleeds). Of these 14 subjects, 12 had few one-time RP use (n=7 with one-time use, n=4 with use 2 times, and n=1 with use 3 times). Seven subjects did not have a reason listed for use, and for the remaining five subjects, reasons for use included prophylaxis prior to physical activity likely to cause bleeding, vaccination, pharmacokinetics assessment, and liver biopsy. The subject who reported one-time RP use for pharmacokinetics assessment had already resumed RP. Two of 14 subjects had 37 and 23 instances of use of one-time RP, with both subjects having physical activity cited as the reason for such use. A subject with 37 instances of one-time RP took a long time coming off RP following GT, and all FVIII activity values beyond week 68 were contaminated by exogenous FVIII administration. Baseline ABR was 19.2, which decreased to 4.4 following ROCTAVIAN. The subject (SUBJID (b) (6) with 23 instances of one-time RP use was stated to have resumed RP at week 56. Of the 23 instances of reported one-time RP use, only 4 were recorded prior to resumption of RP at week 56.

Reviewer Comment

- *One-time RP use makes it difficult to isolate the treatment effect of ROCTAVIAN. While it is acknowledged that subjects responding to ROCTAVIAN treatment may need to boost FVIII activity levels above that achieved with ROCTVIAN through use of exogenous products depending on degree of anticipated hemostatic challenge e.g., vigorous physical exercise, multiple one-time RP use confounds interpretability of true effect of ROCTAVIAN in prevention of bleeding and may indicate loss of response to treatment.*

- *Both subjects described above (with 23 and 37 instances of one-time RP) were deemed to be non-responders to ROCTAVIAN treatment.*

Subjects With ABR in EEP > Baseline ABR

There were 20 subjects at the 2-year data cutoff who had an EEP ABR > baseline ABR (see Table 10 below). Of these 20 subjects, 3 subjects (SUBJID (b) (6) did not have EEP ABR > baseline ABR at the 3-year data cutoff and had not lost response to treatment. Fourteen new subjects were identified as having EEP ABR > baseline ABR between year 2 and year 3 data analysis for a total of 31 subjects with EEP ABR > baseline ABR at the 3-year data cutoff.

Table 10. Subjects With EEP ABR > Baseline ABR, Study 270-301 at 2-Year Data Cutoff

SUBJID	Baseline ABR (All Bleeds)	EEP ABR (All Bleeds)	EEP ABR (Treated Bleeds)	CS Y/N	Alternate IS Y/N	FVIII Activity (IU/dL) by CSA at Week 104
(b) (6)	0	0.4	0	Y	N	28.5
	0	0.5	0	Y	N	12.8
	0	0.5	0	Y	N	9.7
	0	0.5	0	Y	N	57.1
	0	0.5	0	Y	N	<1.5
	0	0.5	0	N	N	32.4
	0	0.5	0	Y	N	3
	0	1	0.5	Y	N	3.7
	0	1	0	Y	Y	2.1
	0	1	0.5	Y	N	26.2*
	0	1	0.5	Y	N	7.5
	0	1.4	0.5	Y	Y	4.4
	0	3	0	Y	Y	8
	0	5.8	5.8	Y	Y	11.8
	1.1	2.2	2.2	Y	N	10.4
	1.2	1.3	0.9	Y	Y	14.8
	1.3	1.5	0	Y	N	9.2
	4.4	6.4	3.9	Y	N	5.5**
	2.1	10.1	9.6	Y	N	1.9
	4.9	17.3	17.3	N	N	1.6

Source: FDA analysis
* FVIII activity at week 100.
** Factor activity prior to resuming RP on day 905.
Abbreviations: ABR, annualized bleeding rate; CS, corticosteroid; CSA, chromogenic substrate assay; EEP, efficacy evaluation period; FVIII, Congenital factor VIII; IS, immunosuppressant; RP, routine prophylaxis.

Reviewer Comments:

- *At the 2-year data cutoff, the majority of subjects (11/14) with 0 bleeds at baseline had minimal increase (≤1) in ABR in the EEP; all had zero treated bleeds. Even in the 3 subjects with baseline ABR of 0 who had an EEP ABR of >1, there were no treated bleeds. Of the 6 subjects with baseline ABR >0, 3 subjects had minimal increase in ABR in the EEP. Only 3 subjects (SUBJIDs (b) (6)) had a significant increase in EEP ABR, especially SUBJIDs (b) (6) . Of these 3 subjects, one subject (b) (6) resumed RP on day 705 despite having a FVIII activity of 5.5 IU/dL (CSA) given his active lifestyle, one subject (b) (6) was deemed to have never responded to ROCTAVIAN (never received IS and had negligible FVIII activity throughout) while SUBJID (b) (6) had lost response by the time of the 3-year data cutoff with FVIII activity < 5 IU/dL at most timepoints. An additional 2 subjects had lost response to ROCTAVIAN treatment at the time of the 3-year data cutoff.*

- *Two of the 14 new subjects identified at the 3-year data cutoff as having EEP ABR > baseline ABR had lost response to ROCTAVIAN treatment.*

6.1.11.2 Analyses of Secondary Endpoints

FVIII Activity

Please also see Clinical Pharmacology review memo for analyses of FVIII activity.

FVIII activity was measured by both the CSA and the OSA. The secondary endpoint of FVIII activity at week 104 following ROCTAVIAN infusion was based on the CSA, the more conservative of the two assays. FVIII activity levels at every timepoint for the analysis had to be "uncontaminated" (i.e., not taken within 72 hours of a SHL FVIII product or within 5 days of an EHL product). FVIII activity levels were grouped and analyzed in 4-week interval blocks (e.g., week 52 FVIII activity level includes values from weeks 49 to 52). Please see Table 11 below with updated FVIII activity as of month 36 following ROCTAVIAN administration.

Table 11. FVIII Activity Levels (IU/dL) Over Time

Timepoint	Rollover Population CSA	Rollover Population OSA	Directly Enrolled Population CSA	Directly Enrolled Population 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)
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	1.50, 335.75	0, 85.8	4.5, 126
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, 115.2)	33.2 (14.7, 46.3)	53.5 (23.7, 78.2)
Min, max	0, 367.3	1.89, 483.9	0, 169.4	1.8, 261.9
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)
Median (Q1, Q3)	24.0 (12.5, 63.7)	40.0 (21.4, 87.5)	23.9 (11.2, 52.8)	40.5 (17.4, 82.6)
Min, max	0.00, 231.15	0, 311.1	1.6, 207.4	4.4, 294.1
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

Source: Clinical Pharmacology FDA analysis of ADF8B dataset
Based on the median factor VIII activity level measures taken during Weeks 23 to 26 for Month 6, during Weeks 49 to 52 for Month 12, a 4-week window around Week 104 for Month 24, and a 6-week window around Week 156 for Month 36.
Abbreviations: CSA, chromogenic substrate assay; N, number of subjects in the specified group, or the total sample; OSA, one-stage assay; SD, standard deviation.

Reviewer Comments:

- *FVIII activity continued to decline beyond 12 months. The reasons for such decline are unclear.*
- *The slope of decline appears to be less between months 24 and 36 as compared to between months 12 and 24.*

Peak FVIII activity mean (SD) and median (range) by the CSA were 88.5 (86.2) and 61.8 (4.5 to 462.6), respectively. Mean (SD) and median (range) days post-infusion that peak FVIII activity occurred, as measured by the CSA, were 220 (124) and 185.5 (59 to 777), respectively. Sixty-six subjects (of 112 total and of 98 subjects who received IS) were on corticosteroids at the time of documentation of peak FVIII activity by CSA; 23 subjects were on AIS at this time. Fifteen of 23 subjects on AIS were also on corticosteroids at the time of documentation of peak FVIII activity.

Eighteen subjects had peak FVIII activity after cessation of corticosteroid use, with time of occurrence ranging from 6 to 214 days.

Peak FVIII activity mean (SD) and median (range), as measured by the OSA, were 128 (108) and 93 (6.4 to 500), respectively. Mean (SD) and median (range) days post-infusion that peak FVIII activity occurred, as measured by the OSA, were 214 (129) and 183 (51 to 777), respectively.

Reviewer Comments:

- *There was wide variation in the peak FVIII activity achieved as measured by the CSA and the day such activity peaked.*
- *In some subjects, peak FVIII activity or levels close to peak activity occurred over several days/weeks. The analyses above, however, represent only a single day of the peak activity.*
- *FVIII activity declined significantly from the peak in most subjects.*
- *There was lack of congruence of the day/time period in peak FVIII activity as measured by the two assays in some subjects. Some of these instances could be explained by assay variability but, in some instances, peak FVIII activity as measured by the two assays occurred several days/weeks apart.*

The number of subjects at weeks 52, 104, and 156 for a particular range of FVIII activity at these timepoints are shown below.

Table 12. Number of Subjects Achieving Factor VIII Activity Thresholds at Weeks 52, 104, and 156 (N=112), Study 270-301

Rollover Population (N = 112)			
Factor VIII Activity Threshold Achieved by Assay	**Year 1** N = 111 n (%)	**Year 2** N = 98 n (%)	**Year 3** N = 96 n (%)
CSA			
> 150 IU/dL	6 (5%)	2 (2%)	2 (2%)
40 - ≤ 150 IU/dL	37 (33%)	14 (14%)	9 (9%)
15 - < 40 IU/dL	37 (33%)	27 (28%)	23 (24%)
5 - < 15 IU/dL	18 (16%)	33 (34%)	35 (36%)
3 - < 5 IU/dL	3 (3%)	10 (10%)	8 (8%)
< 3 IU/dL	10 (9%)	12 (12%)	19 (20%)

Source: FDA Clinical Pharmacology Analysis of ADF8B 3-year dataset
Percentages rounded up or down to nearest integer.
Abbreviations: BLOQ, below limit of quantification; CSA, chromogenic substrate assay; FVIII, Congenital factor VIII; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample.

Reviewer Comments:

- *Not all subjects with FVIII < 5 IU/dL at week 156 had returned to RP of were deemed as having lost response to ROCTAVIAN. Subject/investigator discretion in the return to RP, and FVIII levels in the moderate range (>1% to 5%) could that confers benefit in this subject population could explain why not all subjects returned to RP.*

- *About a quarter of subjects had FVIII activity ≥15% at 3-years, which is considered the minimal level in the mild hemophilia range that provides good benefit in terms of prevention, at least for spontaneous joint bleeds (den Uijl et al. 2011) .*

Bleeding Episodes Within Different Ranges of FVIII Activity (Chromogenic Assay)

A snapshot of episodes of bleeding within different ranges of FVIII activity as measured using the CSA at the 2-year data cutoff are provided below. This table includes bleeds in 10 subjects prior to the start of the EEP and the 65 subjects who bled during the EEP in the study. Overall, there were 311 bleeds in 75 subjects.

Table 13. FVIII Activity Range by CSA and Bleeds at 2-Year Analysis, Study 270-301 (N=311 Bleeds)

FVIII Activity Range IU/dL	Number of Bleeding Episodes	Severity Mild/Moderate/ Severe/Unknown	Type of Bleed Traumatic/Spontaneous	Treated Y/N
<3	119	78/16/0/25	54/65	94/25
3 - <5	40	29/5/0/6	18/22	34/6
5 - <40	119	47/11/1/60	72/47	59/60
>40	33	1/1/0/31	28/5	2/31

Source: FDA analysis of BLDISF8 dataset in Applicant response to IR dated 10.21.2022
Abbreviations: CSA, chromogenic substrate assay; FVIII, Congenital factor VIII; IR, information request; N, number of subjects in the specified group, or the total sample.

Reviewer Comments:

- *The correlation of FVIII activity range to bleeds does NOT reflect time that the subject spent within a given FVIII activity range. It is just a snapshot of bleeds, with the corresponding FVIII activity obtained at a timepoint closest to the bleeding event.*

- *A significant number of bleeds occurred during FVIII activity between 5 and 40 IU/dL. However, the proportion of traumatic bleeds in the 5 to 40 IU/dL category was more, while the number of spontaneous bleeds at FVIII activity <3 IU/dl was more consistent with the increased risk of spontaneous bleeds with decreasing FVIII activity in hemophilia.*

- *Thirty-three bleeds occurred at normal FVIII activity levels. However, the majority of these were traumatic and practically none were treated. Since report of a bleed is subjective, it is possible that some of these events were not true bleeds but symptoms, such as pain from arthropathy, that subjects may have considered to be bleeds.*

- *Factors other than FVIII levels can influence bleeds (e.g., prior target joints, genes regulating inflammatory response, activity level of the subject, etc.) Thus, correlation between FVIII activity levels and bleeds may be challenging.*

- *The true hemostatic efficacy of a given FVIII activity level obtained by transgene expression may not be what we typically have used for recombinant or plasma-derived products. Assay variability between the CSA and OSA, and variability in performance of these individual assays, also makes correlation of FVIII activity to risk of bleeding/bleeding phenotype post-GT challenging. However, in general, subjects with higher FVIII activity levels did better, and subjects who resumed RP were usually had FVIII activity <5.*

FVIII Activity Range by CSA and Bleeds by Timing of Bleeds Post-infusion

Overall, 30 bleeds in 24 subjects occurred prior to the start of EEP, 22 bleeds in 16 subjects occurred in the EEP prior to the start of IS, 116 bleeds in 40 subjects occurred during IS, and 143 bleeds in 36 subjects occurred off IS. A subject may have had bleeds during one or more periods. Ten subjects had bleeds only prior to the start of the EEP. The following table depicts the FVIII activity range and the timing of bleeds post-infusion (i.e., prior to the start of EEP, in the EEP but prior to the start of IS, during IS, and off IS).

Table 14. Timing of Bleeds in Relation to FVIII Activity Ranges at 2-Year Analysis, Study 270-301

Timing of Bleeds (Number of bleeds) Total N=311 bleeds	**No. of Bleeds Within <3 IU/dL FVIII Activity Range by CSA**	**No. of Bleeds Within 3- <5 IU/dL FVIII Activity Range by CSA**	**No. of Bleeds Within 5-40 IU/dL FVIII Activity Range by CSA**	**No. of Bleeds Within >40 IU/dL FVIII Activity Range by CSA**
Prior to Start of EEP (n=30)	18	3	6	3
EEP Prior to Start of IS (n=22)	7	6	9	0
During EEP on IS (n=116)	25	11	62	18
During EEP off IS (n=143)	69	29	42	12

Source: FDA analysis of BLDSISF8 dataset in Applicant response to IR dated 10.21.2022
Abbreviations: CSA, chromogenic substrate assay; EEP, efficacy evaluation period; FVIII, Congenital factor VIII; IR, information request; IS, immunosuppressant; N, number of subjects in the specified group, or the total sample.

Exogenous FVIII Use

There was substantial reduction in exogenous FVIII use as subjects came off RP and used FVIII only for treatment of bleeds if needed. Please see Table 15 below for reductions in exogenous FVIII utilization.

Table **15**. Exogenous FVIII Utilization for Rollover Population, Study 270-301

	Baseline	**Post-Baseline**				
		Incremental (Year 2 Data Cutoff to Year 3 Data Cutoff)		**EEP***		
Cohort	**AFU (IU/kg/yr)**	**FVIII Utilization (IU/kg)**	**AFU (IU/kg/yr)**	**FVIII Utilization (IU/kg)**	**AFU (IU/kg/yr)**	**Change from Baseline (IU/kg/yr)**
Rollover Population (N=112)						
Mean (SD)	3961.17 (1751.47)	236.46 (585.94)	241.12 (598.42)	373.94 (942.19)	124.91 (316.35)	-3836.26 (1776.78)
Median	3754.42	0.00	0.00	33.20	10.86	-3651.81
Min, Max	1296.4, 11251.1	0.0, 3189.8	0.0, 3218.5	0.0, 6405.9	0.0, 2045.2	-11251.1, -937.9

Source: Adapted from Table 2.3.3.1 (pp. 60) in 3-Year Efficacy Update for Study 270-301
Abbreviations: AFU: Annualized FVIII Utilization; EEP, efficacy evaluation period; FVIII, Congenital factor VIII; N, number of subjects in the specified group, or the total sample; SD, standard deviation.

6.1.11.3 Subpopulation Analyses

Subjects With Positive TAb Test to AAV5 Capsid

All subjects in Study 270-301 had to be negative for antibody to AAV5 capsid at screening using a TAb test that is being evaluated as a CDx. In the rollover population, three subjects were negative at screening but were positive on day 1 (day of infusion)- considered borderline to low level of antibodies by CDRH reviewer. These three subjects received ROCTAVIAN since the results of the antibody test on day 1 were not available prior to dosing. Brief narratives of these three subjects are given below.

SUBJID (b) (6)

25-year-old male with no concomitant medications or illnesses reported at study entry had an ABR of 0 for all and treated bleeds at baseline. Subject tested AAV5 TAb-negative at screening (b) (6) but had an antibody titer of 91 on day 1 (b) (6) He was treated with corticosteroids for transaminitis. He had FVIII activity of 3.7 IU/dL by CSA at week 104. He had an ABR of 1 (all bleeds) and 0.5 (treated bleeds) in the EEP. He had two spontaneous bleeds on days 39 and 52 when FVIII activity was <3.0; both bleeds were treated, but one was treated outside the window for what is considered a treated bleed. He was adjudicated as having lost response to ROCTAVIAN treatment based on the analysis of the data at the 3-year cutoff.

SUBJID (b) (6)

58-year-old male with history of hepatitis C; good adherence to RP at baseline; numerous medical conditions including diabetes mellitus, dyslipidemia, HTN, joint surgeries, and osteopenia; two target joints; and concomitant medications of a statin, telmisartan, metformin, bifendate, and *Silybum marianum* at study entry. He had an ABR of 1.7 (all bleeds and treated bleeds). He was AAV5 TAb-negative at screening (b) (6) but tested AAV5 TAb-positive (antibody titer <20) on day 1 (b) (6) He received AIS for transaminitis. He had continued ALT elevations, which were then not treated. Had FVIII activity < 5 IU/dL by CSA at week 104.

SUBJID (b) (6)

30-year-old black male with severe hemophilia A and no other medical conditions or concomitant medication use with baseline ABR of 0 bleeds at study entry who had a Ab titer of 56 on day 1. He received corticosteroids and AIS for transaminitis. FVIII activity by CSA was 5.4 IU/dL at week 104 and 8.2 IU/dL at last visit prior to 2-year data cutoff.

Reviewer Comment

- *Given that only 3 subjects had borderline /low levels of total Abs to AAV5, this information was not placed in the label since no conclusions can be drawn on the impact of these antibodies on the treatment effect of GT in these 3 subjects.*

Subjects With HIV

There were no subjects with HIV in the rollover population (efficacy evaluable population) in Study 270-301. Only 2 subjects in the directly enrolled population of 22 subjects had HIV, and a brief description of these 2 subjects is given below.

SUBJID (b) (6)

52-year-old White male with history of hepatitis B, hepatitis C (2014 to 2017), and HIV since 1988, with extensive medical and surgical history: adrenal insufficiency, depression, insomnia, sleep apnea, generalized osteoarthritis, peripheral neuropathy, HTN, osteoporosis, bilateral hip replacement, and left knee replacement. He received ROCTAVIAN on (b) (6) . His medications at study entry included COX-2 inhibitor, sertraline, lisinopril, montelukast, Eviplera (rilpivirine, emtricitabine, and tenofovir), and other medications taken as needed (tranexamic acid, cyclobenzaprine, hydroxyzine, loperamide, zolpidem, hydrocodone, inhaled salbutamol, and orphenadrine). His ABR prior to study entry was 2.8 for all bleeds and treated bleeds. No target joints were reported at baseline.

At the 2-Year data cutoff, the subject had not received any IS, and week 104 FVIII activity by CSA was 5.8 IU/dL. Post-treatment ABR was 2.2 for all bleeds and 1.9 for treated bleeds. He had a total of 7 bleeding events in the EEP (2-year data cutoff) of which 6 were treated. Two of 7 bleeds were spontaneous: a day 853 hip bleed and a day 1043 left ankle bleed. No one-time RP use was reported. He returned to emicizumab RP at week 194; FVIII activity by CSA prior to return to RP was 4.6 IU/dL.

SUBJID (b) (6)

49-year-old male with HIV since 1984, hepatitis B (unknown dates), hepatitis C (1994 to 2013), ventriculo-peritoneal shunt, hydrocephalus, arthropathy, osteoarthritis, osteonecrosis, jugular vein thrombosis, porphyria, dyslipidemia, gastroesophageal reflux disease, arthrodesis, and right hip replacement received ROCTAVIAN on (b) (6) . Concomitant medications at study entry included omeprazole, darunavir, dolutegravir, and ritonavir. Screening liver ultrasound showed multiple hepatic angiomas. No target joints were reported at baseline. ABR at baseline was 5.8 for all bleeds and treated bleeds.

He received corticosteroids for transaminitis for a total of 27 weeks. Post-therapy ABR was more than baseline ABR at 16.1 for all bleeds during EEP starting day 143, and ABR of 12.8 for treated bleeds. The majority of bleeding events post-GT were spontaneous, especially starting day 441. He received one-time RP on 51 occasions; no reasons were given. By week 104, his FVIII activity was < 3 IU/dL (CSA); he resumed RP at week 174 with emicizumab. FVIII activity prior to resumption of RP was 1.9 IU/dL.

Reviewer Comments:

- *Data on safety and efficacy in HIV subjects is limited, and this fact has been reflected in the USPI in section 8.6. Both HIV+ subjects in the ITT population have resumed RP. One subject received IS while the other did not; no significant AEs related to IS observed in the one subject who did receive IS.*

- *SUBJID* (b) (6) *should have returned to RP at least starting day 441 and, as such, his excessive one-time RP use starting around the same time frame confounds efficacy determination from GT. His low FVIII activity during this time frame and the multiple bleeds also support the determination that he should have resumed RP.*

U.S. vs. Non-U.S. Regions of the World

Given that the majority of the efficacy evaluable subjects in Study 270-301 were not enrolled in the United States, an analysis of baseline characteristics, efficacy data, and IS use between U.S. versus non-U.S. subjects was done. Table 16 below shows the efficacy data for the primary efficacy endpoint of all bleeds.

Table 16. ABR (All Bleeds) in Subjects Enrolled in the U.S. vs. Non-U.S. Countries

	US (N=16)	Non-US (N=96)	Total Rollover Population (N=112)
Baseline ABR (All Bleeds), no/year			
Mean (SD)	5.7 (8.7)	5.3 (6.7)	5.4 (6.9)
Median	3.5	3.2	3.3
Q1, Q3	0.0, 8.3	0.0, 7.8	0.0, 7.9
Range	0, 35	0, 33	0, 35
Post-Baseline EEP ABR (All Bleeds), no/year			
Mean (SD)	1.6 (2.4)	1.2 (2.6)	1.2 (2.5)
Median	0.4	0.5	0.5
Q1, Q3	0.0, 1.7	0.0, 1.0	0.0, 1.2
Range	0, 8	0, 17	0, 17
Change from Baseline to Post-Baseline EEP ABR (All Bleeds)			
Mean (SD)	-4.2 (8.5)	-4.1 (6.7)	-4.1 (6.9)
Median	-2.6	-2.1	-2.2
Q1, Q3	-5.7, 0.0	-6.4, 0.0	-6.4, 0.0
Range	-33, 6	-32, 12	-33, 12
Percent reduction from baseline in mean ABR (%)	72.9	77.8	77.0

Source: Modified from Table 7 of Applicant response to IR sent 11.03.2022
Abbreviations: ABR, annualized bleeding rate; EEP, efficacy evaluation period; IR, information request; N, number of subjects in the specified group, or the total sample; SD, standard deviation.

Reviewer Comments:

- *As shown above, ABR (all bleeds) was similar between the U.S. and non-U.S. population.*
- *Although there was some variation by country (e.g., reduction in all bleeds in Israel was >95%) the small number of subjects per country make any comparisons unmeaningful since a single subject or a small number of subjects likely skewed the data.*

Analysis by Adequacy of Routine Prophylaxis

The primary efficacy endpoint is based on intrasubject comparison of ABR (all bleeds) on RP versus ABR (all bleeds) following GT. Therefore, inadequate RP could make results post-GT appear more favorable, and hence a sensitivity analysis for subjects with inadequate RP was performed.

There were 11 subjects in the efficacy evaluation population (N=112) who were deemed to have fair or poor RP (n=4) or for whom this information was missing (n=7). The primary efficacy analysis excluding these subjects is shown in Table 17 below. This analysis also included the impact of

such subjects in the group of 64 subjects that had discontinued IS for >1 year at time of data cutoff and during the different periods of IS use.

Table 17. Sensitivity Analysis Excluding Subjects With Inadequate RP, Study 270-301

	270-301 Rollover Population (N=112)						270-301 Rollover Population Off IS ≥ 1 Year (N=64)					
	Total Population (N=112)			Excluding subjects with inadequate routine prophylaxis (N=101)			Total Population (N=64)			Excluding subjects with inadequate routine prophylaxis (N=59)		
	Period on IS	Period off IS	Total EEP	Period on IS	Period off IS	Total EEP	Period on IS	Period off IS	Total EEP	Period on IS	Period off IS	Total EEP
Baseline Summary of ABR for All Bleeds (bleeds/year)												
Mean (SD)	5.36 (6.93)			5.29 (7.02)			5.98 (6.61)			5.88 (6.56)		
Median	3.28			3.18			3.95			3.87		
Min, Max	0.0, 34.6			0.0, 34.6			0.0, 30.5			0.0, 30.5		
Subjects with zero bleeds, n (%)	34 (30.4)			31 (30.7)			17 (26.6)			15 (25.4)		
Post FVIII Prophylaxis Period Summary of ABR for All Bleeds (bleeds/year)												
n	98	111	112	89	100	101	64	64	64	59	59	59
Mean (SD)	1.25 (2.30)	1.06 (2.98)	1.23 (2.54)	1.35 (2.39)	0.96 (2.64)	1.13 (2.09)	1.35 (2.49)	0.94 (2.89)	1.19 (2.18)	1.47 (2.56)	0.94 (2.97)	1.20 (2.21)
Median	0.00	0.00	0.49	0.00	0.00	0.49	0.00	0.00	0.49	0.00	0.00	0.49
Min, Max	0.0, 12.7	0.0, 20.6	0.0, 17.3	0.0, 12.7	0.0, 20.6	0.0, 13.3	0.0, 12.7	0.0, 20.6	0.0, 13.3	0.0, 12.7	0.0, 20.6	0.0, 13.3
Subjects with zero bleeds, n (%)	58 (51.8)	75 (67.0)	47 (42.0)	50 (49.5)	66 (65.3)	40 (39.6)	40 (62.5)	43 (67.2)	26 (40.6)	35 (59.3)	39 (66.1)	23 (39.0)

Source: Applicant response to IR dated 11.15.2022; adapted from Table 1 of the response
Abbreviations: ABR, annualized bleeding rate; EEP, efficacy evaluation period; FVIII, Congenital factor VIII; IR, information request; IS, immunosuppressant; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; RP, routine prophylaxis; SD, standard deviation.

Reviewer Comments:

- *There was no meaningful change in the conclusions on analysis of the primary endpoint when subjects with inadequate RP were excluded.*

Analysis by Immunosuppression Use and Duration Off Immunosuppressive Therapy

Of the 112 subjects in the rollover population (efficacy evaluable population), 14 subjects never received any IS, 64 subjects were off IS for a year or longer, and 33 subjects were off IS for <1 year at the time of the 2-year data cutoff. One subject was still on IS at the time of data cutoff. A sensitivity analysis for the primary efficacy endpoint was done on these three subpopulations of subjects and is depicted in Table 18 below. Also shown is the FVIII activity by the CSA at week 104 in Table 19 below.

Table 18. Sensitivity Analysis by IS Use and Time Off IS Therapy, Study 270-301

	270-301 Rollover Population (N=112)*							
	Subjects Who Never Received IS (N=14)		Subjects Off IS ≥ 1 Year (N=64)			Subjects Off IS <1 Year (N=33)		
	Period on IS	Period off IS/ Total EEP	Period on IS	Period off IS	Total EEP	Period on IS	Period off IS	Total EEP
Baseline Summary of ABR for All Bleeds (bleeds/year)								
Mean (SD)	7.70 (11.41)		5.98 (6.61)			3.18 (4.43)		
Median	3.73		3.95			1.40		
Min, Max	0.0, 34.6		0.0, 30.5			0.0, 18.5		
Subjects with zero bleeds, n (%)	4 (28.6)		17 (26.6)			13 (39.4)		
Post FVIII Prophylaxis Period Summary of ABR for All Bleeds (bleeds/year)								
Mean (SD)	NA	1.67 (4.56)	1.35 (2.49)	0.94 (2.89)	1.19 (2.18)	1.06 (1.95)	1.05 (2.33)	1.15 (2.12)
Median	NA	0.00	0.00	0.00	0.49	0.00	0.00	0.49
Min, Max	NA	0.0, 17.3	0.0, 12.7	0.0, 20.6	0.0, 13.3	0.0, 8.6	0.0, 9.7	0.0, 10.1
Subjects with zero bleeds, n (%)	NA	8 (57.1)	40 (62.5)	43 (67.2)	26 (40.6)	18 (54.5)	24 (72.7)	13 (39.4)

Source: Modified from Table 5 of Applicant response to IR dated 11.15.2022
Abbreviations: ABR, annualized bleeding rate; EEP, efficacy evaluation period; FVIII, Congenital factor VIII; IR, information request; IS, immunosuppressant; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; SD, standard deviation.

Table 19. FVIII Activity by CSA in Different IS Subgroups, Study 270-301

	270-301 Rollover Population (N=112)*		
	Subjects Who Never Received IS (N=14)	Subjects Off IS ≥ 1 Year (N=64)	Subjects Off IS <1 Year (N=33)
Week 104 Median FVIII Activity Level (IU/dL)			
Mean (SD)	32.07 (46.76)	22.38 (28.64)	21.27 (37.84)
Median	20.15	11.00	11.20
Q1, Q3	5.10, 32.40	4.90, 26.10	4.80, 20.60
Min, Max	0.0, 185.9	0.0, 144.4	0.0, 187.1
Week 104 Median FVIII Activity Level Within Ranges (IU/dL), n (%) within ranges			
< 5 IU/dL	**3 (21.4)**	**16 (25.0)**	**9 (27.3)**

Source: Modified from Table 7 of Applicant response to IR dated 11.15.2022
Abbreviations: CSA, chromogenic substrate assay; FVIII, Congenital factor VIII; IR, information request; IS, immunosuppressant; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; SD, standard deviation.

Reviewer Comments:

- *Mean ABR for subjects who never received IS seems higher at baseline and post-GT, but small numbers preclude any meaningful conclusions. In general, the ABR across all three populations is not meaningfully different following GT, and statistically significant reduction in ABR was seen across all groups.*
- *The ABR (mean 1.19 with SD of 2.18 and median of 0.49) in the 64 subjects off IS for a year or longer establishes the durability of benefit of ROCTAVIAN following immunosuppressive therapy.*
- *The mean and median FVIII activity at week 104 seems to be higher in subjects who never received IS compared to those off IS for <1 year or off IS for a year or longer, but the difference may be due to small sample size. There have been no predictors of FVIII activity response identified to date.*
- *At the 3-year data cutoff, 88 of 112 subjects had been off IS (administered for any reason) for at least a year. Of the 12 subjects who used IS between years 2 and 3, 7 used IS for < 3 days for reasons other than ALT elevation. Of the remaining 5 subjects who used IS between the year 2 and year 3 data cutoff for a longer duration of time, 4 subjects had reasons other than ALT elevation- muscle injury, Crohn's disease, joint pain, autoimmune disease, and treatment of B-cell leukemia. One subject who was on IS at time of 2-year data cutoff discontinued all IS prior to 3-year data cutoff but had not yet completed a year off all IS. No subject initiated IS for ALT elevation between years 2 and 3. Thus, practically all subjects were off IS for ALT elevation for > 1 year at the time of the 3-year data cutoff.*

Analysis Based on Start Day of EEP

In the rollover population (N=112), the start of the EEP was day 33 (week 5) post-ROCTAVIAN infusion, or the end of FVIII prophylaxis plus the washout period (depending on the type of product used for RP—SHL versus EHL), whichever was later. Eighty-nine of 112 subjects had the start of

the EEP on or before Day-33, while 23 subjects had the EEP start after day 33 with a range of 34-60 days. For one subject who is stated to have discontinued RP on day 117 (start of EEP day 120), start of EEP was imputed as day 33 since this subject was considered to have never responded to ROCTAVIAN. In order to assess if there was an impact on the primary efficacy endpoint based on the 24 subjects whose EEP started later than day 33, a sensitivity analysis was done and is depicted in Table 20 below. Nine, 3, and 1 of 24 subjects who discontinued RP after day 33 did so on day 34, day 35, and day 36, respectively. Eleven of 24 subjects had the EEP start on day 38 or later, and a brief description of these subjects is provided in Table 21 below.

Table 20. ABR Sensitivity Analysis Based on EEP Start Day: 2-Year Analysis, Study 270-301

	Rollover Population (N=112)	
	EEP started after Day 33 (N=24)	**EEP started on or before Day 33 (N=88)**
Baseline ABR for All Bleeds (no/yr)		
Mean (SD)	5.50 (5.89)	5.32 (7.22)
Median	4.25	3.01
Min, Max	0.0, 19.2	0.0, 34.6
EEP ABR for All Bleeds (no/yr)		
Mean (SD)	1.56 (3.68)	1.14 (2.15)
Median	0.0	0.49
Min, Max	0.0, 17.3	0.0, 13.3
Subjects with Zero All bleeds, n (%)	13 (54.2)	34 (38.6)
Change from Baseline in ABR for All Bleeds (no/yr)		
Mean (SD)	-3.94 (6.81)	-4.18 (6.99)
Median	-2.67	-2.06
Min, Max	-18.5, 12.4	-32.7, 8.0
Percent Reduction from Baseline in Mean ABR for All Bleeds (%)	71.7	78.6
Mean Change from Baseline in ABR for All Bleeds p-value (t-test)	0.0095	< 0.0001
95% CI for Mean Change from Baseline in ABR for All Bleeds (no/yr)	-6.82, -1.06	-5.66, -2.70

Source: Table 14 of Applicant response to IR dated 11.15.2022
Abbreviations: ABR, annualized bleeding rate; CI, confidence interval; EEP, efficacy evaluation period; IR, information request; n (%), number of subjects with the specified characteristic; N, number of subjects in the specified group, or the total sample; SD, standard deviation.

Table 21. Subjects With EEP Start Day of ≥38 Days in Study 270-301; 2-Year Data

SUBJID	EEP Start Day	Baseline ABR (all bleeds)	EEP ABR (all bleeds)	Week 104 FVIII activity by CSA	Comments
(b) (6)	38	13	0	1.9	Had FVIII < LLQ till ADY 176 (week 26)
	39	7.7	0	11.9	Peak FVIII by CSA 120.5; FVIII by OSA > ULN weeks 13-27
	39	0	0	5.4	-
	39	0	0	5	-
	40	18.5	0	9.4	-
	41	3.2	0.4	<1.5	At week 104, FVIII by OSA also <1 IU/dL (starting week 88 ADY 623); FVIII 0 by CSA starting ADY 293 (week 44)
	43	9.9	1	<1.5	Day 85-141 and then starting day 323 (week 48) FVIII by CSA < LLQ; FVIII by OSA < LLQ since day 351
	46	0	0	5.5	-
	56	5	2.4	2.8	Five bleeds in EEP, of which 2 were spontaneous and 3 were treated
	60	4.9	17.3	1.6	Had FVIII by CSA < LLQ throughout; bleeds starting day 75; 34 bleeds in EEP of which 17 were spontaneous. FVIII activity by OSA also in the <5 range throughout. Was considered a non-responder to treatment
	120	19.2	4.4	All values beyond week 68 were confounded by exogenous FVIII use	Treated bleeds at baseline 7.7/year. Had 37 instances of one-time RP use. Was considered a non-responder to treatment.

FDA analysis of data provided in Applicant response to IR dated 11.15.2022
Abbreviations: ABR, annualized bleeding rate; ADY, analysis day; CSA, chromogenic substrate assay; EEP, efficacy evaluation period; FVIII, Congenital factor VIII; IR, information request; LLQ, lower limit of quantification; OSA, one-stage assay; RP, routine prophylaxis; ULN, upper limit of normal.

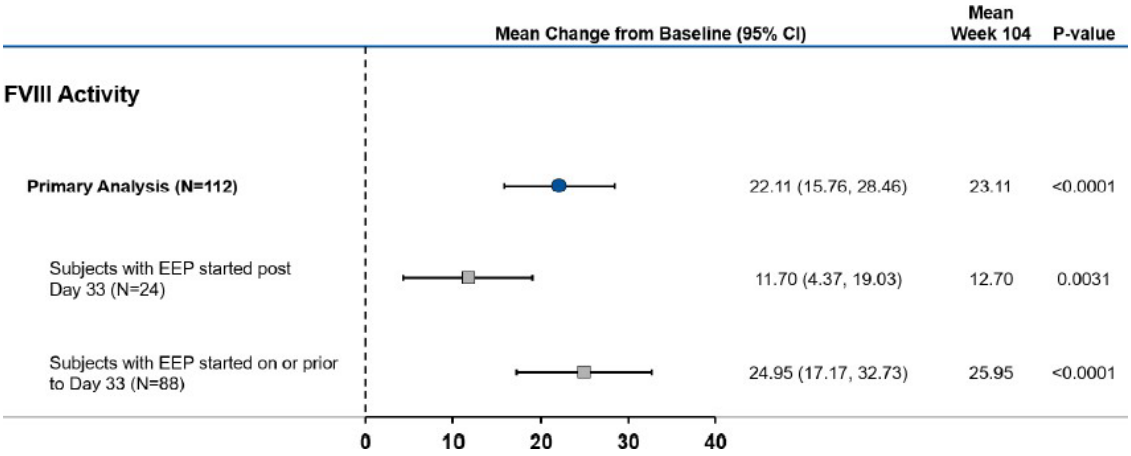
The secondary endpoint of FVIII activity was analyzed by start of EEP and is shown in Table 22 below.

Table 22. FVIII Activity by Chromogenic Assay by Start of EEP: 2-Year Analysis, Study 270-301

	Rollover Population (N=112)	
	EEP started after Day 33 (N=24)	EEP started on or before Day 33 (N=88)
Week 104 Median FVIII Activity Level (IU/dL)		
Mean (SD)	12.70 (17.36)	25.95 (36.72)
Median	5.45	13.60
Min, Max	0.0, 79.8	0.0, 187.1

Source: Modified from Table 16 of Applicant response to IR dated 11.15.2022
Abbreviations: EEP, efficacy evaluation period; FVIII, Congenital factor VIII; IR, information request; N, number of subjects in the specified group, or the total sample; SD, standard deviation.

Figure 3. Forest Plot of FVIII Activity by Chromogenic Assay Based on EEP Start Day



Source: Figure 4 of Applicant response to IR dated 11.15.2022; based on 2-Year Analysis
Abbreviations: CI, confidence interval; FVIII, Congenital factor VIII; EEP, efficacy evaluation period; IR, information request; N, number of subjects in the specified group, or the total sample.

Reviewer Comments:

- *Failure to come off RP in a timely manner following GT could signal primary non-response to treatment.*
- *Two subjects—*(b) (6) *—should have been on RP even if they were not put on it by their physicians or chose not to, given that ABR in EEP was significantly greater than baseline ABR, and given the low FVIII activity plus several instances of one-time RP use for SUBJID* (b) (6) *(these two subjects were handled as non-responders in the primary efficacy analysis*

6.1.11.4 Dropouts and/or Discontinuations

One subject in the rollover population (N=112) died of (b) (6) at week 95 while another subject was lost to follow up at week 104. Please see the safety section for details of subject who died.

6.1.11.5 Exploratory and Post Hoc Analyses

The Applicant did post hoc and exploratory analysis of FVIII activity against multiple variables (e.g., age at enrollment, weight, race, FVIII genotype, VWF level, concomitant medication use, history of hepatitis B or C, time to first ALT elevation with varying thresholds, number of ALT elevations, cumulative corticosteroid dose, etc.) Of these, only two associations were statistically significant ($p < 0.05$; not adjusted for multiplicity): the Black race was associated with lower FVIII activity compared to the White race, while the intron 22 inversion genotype was associated with higher FVIII activity compared to non-intron 22 inversion genotypes.

Table 23. FVIII Activity by Race and FVIII Genotype: Exploratory Analyses

Predictor	Odds Ratio Estimate for Higher FVIII Activity	95% CI of Odds Ratio	P-value
Race (vs White)			
Asian	1.834	0.739, 4.548	0.1907
Black or African-American	0.246	0.085, 0.712	0.0097
Other	0.078	0.007, 0.870	0.0381
Genotype			
Intron 22 inversion	2.645	1.362, 5.138	0.0041
Missing	1.455	0.226, 9.345	0.6929

Source: Table 11.4.1.5.2 (pp. 229) CSR for Study 270-301; Analysis of data at 2-Year data cutoff
Abbreviations: CI, confidence interval; FVIII, Congenital factor VIII.

6.1.12 Safety Analyses

6.1.12.1 Methods

The key materials used for the safety review include the clinical protocol for Study 270-301, resubmission of the BLA, the Applicant's response to information requests, draft labeling for ROCTAVIAN, published literature, and prior regulatory history.

Please see Section 6.1.7 for details on the schedule of safety monitoring for Study 270-301.

The clinical review of safety was primarily based on analysis of a total of 134 subjects in the pivotal Study 270-301 (i.e., 112 subjects in the rollover population [efficacy evaluable population] and 22 subjects in the directly enrolled population). Safety data from 7 subjects dosed in Study 270-201 (data cutoff March 29, 2021) and 19 subjects in Study 270-303 (data cutoff December 20, 2021) with prophylactic corticosteroid use, all of whom who received the proposed commercial dose of ROCTAVIAN, were also reviewed but were not included in the label (except for event of special interest like malignancy) for the following reasons: 1) drug product in Study 270-201 was thought to be possibly different than the one used in Study 270-301; the CMC reviewer did not definitively comment on whether the drug product used in Study 270-201 was comparable to the one used in the pivotal study; 2) the number of subjects in the pivotal study is adequate to inform safety of the drug product; and 3) Study 270-303 has very limited follow-up. In this section, safety in the 134 subjects in Study 270-301 (data cutoff November 15, 2022) will be described. Safety data at the 3-Year data cutoff was reviewed and included as appropriate.

Per protocol, an AE was defined as any untoward medical occurrence in subjects, temporally associated with the use of study intervention whether or not considered related to the study intervention. The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 was used to grade AEs. AEs that did not have a corresponding CTCAE term were assessed according to general guidelines for grading used in CTCAE version 4.03. SAEs were assessed using the standard definition (i.e., AEs that are life-threatening; require hospitalization; result in death, persistent significant disability, or congenital anomaly/birth defect in the child/fetus of the subject exposed to the study product; or is an important medical event or reaction that, based on medical judgement, may jeopardize the subject's daily living or result in one of the aforementioned outcomes.) Events of Special Interest included ALT > ULN or ≥1.5 x baseline value, events meeting criteria for Hy's law (ALT or AST ≥3 x ULN plus total bilirubin ≥3 x ULN), thromboembolic event, systemic hypersensitivity, anaphylactic or anaphylactoid

reactions, inhibitors to FVIII, and malignancy except non-melanoma skin cancer. AEs were collected and reported after infusion of ROCTAVIAN up to a period of 5 years; prior to ROCTAVIAN infusion and after signing informed consent, only SAEs were collected and reported.

Reviewer Comments:

- *The IS regimen used in the 2 populations in Study 270-301 and in Studies 270-201 and 270-303 are very different and thus, only AEs related to IS in the rollover population (N=112) in Study 270-301 are detailed.*
- *All studies were reviewed, and any AEs determined to be important were included in the safety assessment (e.g., malignancy, systemic hypersensitivity, etc.)*

6.1.12.2 Overview of Adverse Events

All 134 subjects in the ITT population reported at least one treatment-emergent adverse event (TEAE) as of the 3-year data cutoff, of which 92% (123/134) were assessed as related to ROCTAVIAN by the investigator. Six of 63 SAEs in 5 subjects were considered related to ROCTAVIAN (see Section 6.1.12.4 below). Four subjects in the ITT population had an AE that resulted in interruption of ROCTAVIAN infusion, but all subsequently completed the infusion. Fifty subjects (37%) had TEAEs ≥ Grade 3 with 6 TEAEs of Grade 4 severity in 4 subjects in the rollover population. One death in the study was considered unrelated to ROCTAVIAN or IS. TEAEs ≥10% in Study 270-301 are shown in Table 24 below.

Table 24. Incidence of Adverse Events by Preferred Term, Occurring in at Least 10% of all Treated Subjects, Study 270-301

Preferred Term, n (%)	Directly Enrolled (N=22)	Rollover (N=112)	ITT (N=134)
Subjects with any AE	22 (100)	112 (100)	134 (100)
ALT increased	19 (86.4)	102 (91.1)	121 (90.3)
Arthralgia	14 (63.6)	46 (41.1)	60 (44.8)
Headache	12 (54.5)	46 (41.1)	58 (43.3)
Nausea	12 (54.5)	40 (35.7)	52 (38.8)
AST increased	14 (63.6)	35 (31.3)	49 (36.6)
Fatigue	10 (45.5)	31 (27.7)	41 (30.6)
Acne	2 (9.1)	34 (30.4)	36 (26.9)
Upper respiratory tract infection	8 (36.4)	28 (25.0)	36 (26.9)
COVID-19	3 (13.6)	31 (27.7)	34 (25.4)
Pyrexia	4 (18.2)	30 (26.8)	34 (25.4)
Nasopharyngitis	8 (36.4)	22 (19.6)	30 (22.4)
Back pain	8 (36.4)	21 (18.8)	29 (21.6)
Diarrhea	5 (22.7)	24 (21.4)	29 (21.6)
Insomnia	3 (13.6)	24 (21.4)	27 (20.1)
Oropharyngeal pain	6 (27.3)	20 (17.9)	26 (19.4)
Cough	7 (31.8)	18 (16.1)	25 (18.7)
Vomiting	5 (22.7)	20 (17.9)	25 (18.7)

Preferred Term, n (%)	Directly Enrolled (N=22)	Rollover (N=112)	ITT (N=134)
Weight increased	5 (22.7)	17 (15.2)	22 (16.4)
Hypertension	2 (9.1)	16 (14.3)	18 (13.4)
Myalgia	3 (13.6)	15 (13.4)	18 (13.4)
Pain in extremity	4 (18.2)	14 (12.5)	18 (13.4)
Blood CPK increased	3 (13.6)	14 (12.5)	17 (12.7)
Cushingoid	1 (4.5)	15 (13.4)	16 (11.9)
Muscle strain	4 (18.2)	12 (10.7)	16 (11.9)
Rhinitis	3 (13.6)	11 (9.8)	14 (10.4)

Source: Table 2.4.2.1 from 3-Year Efficacy Update Report.
AEs with onset or worsening after the investigational product were included. AEs were coded using MedDRA version 20.1
Percentages were calculated using the total number of subjects (N) in each analysis population as the denominator. Subjects with more than one of the same PT were counted only once for that PT.
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, Coronavirus Disease 2019; CPK, creatine phosphokinase; ITT, intent-to-treat; n (%), number of subjects with the specified characteristic; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term.

Adverse events by severity are listed in Table 25 below.

Table 25. Incidence of Treatment Emergent Adverse Events by Grade, Study 270-301

AE Grade	Directly Enrolled N=22 Incidence (%)	Rollover N=112 Incidence (%)	ITT N=134 Incidence (%)
Any TEAE	22 (100)	112 (100)	134 (100)
Grade 1	22 (100)	112 (100)	134 (100)
Grade 2	20 (91)	103 (92)	123 (92)
Grade 3	9 (41)	39 (35)	48 (36)
Grade 4	0	4 (3.6)	4 (3.0)
Grade 5	0	1	1 (0.7)

Source: adapted from Table 2.4.2.2. 3-Year Update Report
Abbreviations: ITT, intent-to-treat; N, number of subjects in the specified group, or the total sample; TEAE, treatment emergent adverse event.

Forty-eight subjects (36%) experienced a total of 85 Grade 3 AEs, including those related to IS use. Grade 3 events related to ROCTAVIAN included increased ALT, increased AST, hypersensitivity reaction, and anaphylaxis. Grade 3 events related to IS use included acne, weight gain, diabetes mellitus, HTN, infections, gastrointestinal hemorrhage, bone fractures, cataracts, and hypophosphatemia. All except three (anxiety, weight gain, synovitis) Grade 3 events had resolved. Grade 4 events occurred in four subjects and included depression, coronary artery disease, B-cell ALL, and joint swelling; none were considered related to ROCTAVIAN or IS use. All except two (B-cell ALL, joint swelling/arthralgia) Grade 4 events had resolved as of the 3-year data cutoff.

Table 26 below depicts the incidence of TEAEs considered related to ROCTAVIAN.

Table 26. Adverse Reactions Observed in at Least 2% of Subjects Treated With ROCTAVIAN, Study 270-301 (N=134)

System Organ Class (SOC) Preferred Term	Any Grade (%)	Grade 3 or Higher (%)
Gastrointestinal disorders		
Nausea	42 (31)	0 (0)
Abdominal pain	8 (6)	0 (0)
Vomiting	8 (6)	0 (0)
Diarrhea	6 (4.5)	0

System Organ Class (SOC) Preferred Term	Any Grade (%)	Grade 3 or Higher (%)
General disorders and administrative site conditions		
Fatigue	21 (16)	0 (0)
Infusion-related reactions*	9 (6.7)	2 (1.5)
Nervous system disorders		
Headache	9 (7)	0 (0)
Dizziness	3 (2.2)	0 (0)

Source: FDA analysis of ADAE dataset
* Not a SOC; includes symptoms from more than one SOC; in the USPI percentages rounded to nearest integer
Abbreviation: ADAE, Adverse Event Analysis.

In Study 270-301, the two subpopulations—rollover and directly enrolled—had different definitions of what constituted as hepatotoxicity due to immune response to AAV5 capsid. Thus, the ALT trigger to initiate and taper corticosteroids was different, with the result that subjects in the rollover population had much higher and prolonged use of corticosteroids compared to the directly enrolled population (see Section 6.1.12.5 on hepatoxicity below). AIS was used only in the rollover population. Since the efficacy, and most of the safety, of ROCTAVIAN is based on the 112 subjects in the rollover population, the AEs related to corticosteroid and AIS use in the rollover population are described below. Infections are described in a separate table.

Table 27. Adverse Events Occurring in at Least 5% of the Rollover Population With Corticosteroid Use, Study 270-301

Preferred Term or FDA Group Term	All Grade AE n (%) N=92	Grade 3 n (%) N=92
Acne	31 (34)	1 (1.1)
Insomnia	25 (27)	0 (0)
Mood disorder*	18 (20)	0 (0)
Cushingoid*	18 (20)	0 (0)
Rash*	17 (18.5)	0 (0)
Weight increased	15 (16)	1 (1.1)
Hypertension*	11 (12)	3 (3.3)
Abdominal pain*	9 (9.8)	0 (0)
Vision disorders*	9 (9.8)	1 (1.1)
Anxiety*	7 (7.6)	0 (0)
Fatigue*	6 (6.5)	0 (0)
Bone fracture*	5 (5.4)	1 (1.1)
Gastroesophageal reflux disease*	5 (5.4)	0 (0)
Glucose tolerance impaired*	5 (5.4)	1 (1.1)
Increased appetite	5 (5.4)	0 (0)
Skin striae	5 (5.4)	0 (0)

Source: FDA analysis of ADAE dataset
* Indicates FDA Group term—see Appendix A.
Abbreviations: ADAE, Adverse Event Analysis; AE, adverse event; N, number of subjects in the specified group, or the total sample; N (%), number of subjects with the specified characteristic.

Reviewer Comment

- *In the USPI (section 6.1), AE secondary to corticosteroid use percentages rounded to nearest integer*

Adverse events due to corticosteroid use in the rollover population (less than 5%) included myalgia, nausea, tremor, hyperhidrosis (n=4 each; 4.3%); muscular weakness, osteoporosis,

tachycardia (n=3 each; 3.3%); edema, headache, iron deficiency, muscle spasm, palpitations, and vomiting (n=2 each; 2.2%). Other AEs related to corticosteroid use, that occurred in a single subject but are important, included adrenal insufficiency, secondary hypogonadism, osteopenia, steatohepatitis, rectal hemorrhage (due to upper gastrointestinal bleed), and psychiatric/neurologic symptoms of aggression and disturbance in attention.

Forty-one of 92 subjects (45%) on corticosteroids had a total of 68 infections while on corticosteroid therapy. The five Grade 3 events included influenza B, infection of undetermined origin, periungual infection, gastroenteritis, and community-acquired pneumonia with hypoxia. Bacterial infections included folliculitis, syphilis, conjunctivitis, and periungual infection. Fungal infections included oral thrush, tinea, and fungal infection of the feet. Viral infections included herpes zoster, influenza A and B, coronavirus disease 2019, and unspecified viral illness. Pathogen-unspecified infections included infections of the skin and upper respiratory tract most commonly. Two subjects had urinary tract infections, while a single case each of pneumonia, gastroenteritis, conjunctivitis, nail infection, infection of undetermined origin, and dental infection were reported. One subject had a Grade 3 fungal infection within a month of stopping corticosteroids and tacrolimus that was treated with oral antifungal therapy. Infections that occurred while subjects were on corticosteroid therapy are depicted in Table 28 below.

Table 28. Infections in Subjects on Corticosteroids in the Rollover Population, Study 270-301

Infection Type	All Grade n (%) N=92	Grade 3 or Higher n (%) N=92
Pathogen unspecified	28 (30)	3 (3.2)
Bacterial	12 (13)	1 (1)
Fungal	8 (8.7)	0 (0)
Viral	7 (7.6)	1 (1)

Source: FDA analysis of ADAE dataset
Abbreviations: ADAE, Adverse Event Analysis; N, number of subjects in the specified group, or the total sample; N (%), number of subjects with the specified characteristic.

An overview of laboratory abnormalities in the ITT population are shown in Table 29 below.

Table 29. All Grade Laboratory Abnormalities, Study 270-301

Laboratory Abnormalities	Number of Patients (%) N=134
ALT increases > ULN	109 (81%)
AST increases > ULN	92 (69%)
LDH increases > ULN	77 (57%)
CPK increases > ULN	60 (45%)
Factor VIII activity levels > ULN[a]	39 (29%)
GGT increases > ULN	24 (18%)
Bilirubin increases > ULN	18 (13%)

Source: Applicant analysis of ADLB dataset
a. Patients with one or more instances of factor VIII activity levels > 170 IU/dL (ULN of the CSA) or > 150 IU/dL (ULN of the OSA).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; CSA, chromogenic substrate assay; GGT, gamma glutamyl transferase; LDH, lactate dehydrogenase; N, number of subjects in the specified group, or the total sample; OSA, one-stage assay; ULN, upper limit of normal.

Twelve (9%), 9 (7%), and 1 (1%) of the subjects experienced Grade 3 ALT, AST, and GGT elevations, respectively, while 7 (5%) subjects and 5 (4%) subjects experienced Grade 3 and Grade 4 CPK increases, respectively.

Thirty-nine subjects in the rollover population were treated with AIS that included tacrolimus, MMF, and corticosteroids other than prednisone or prednisolone. Adverse events from AIS use are shown in Table 30 below.

Table 30. Adverse Events Related to Alternate Immunosuppression, Study 270-301

Adverse Event	All Grade AE n (%) N=39	Grade 3 AE n (%) N=39
Hypomagnesaemia	6 (15)	0 (0)
Diarrhea	4 (10)	0 (0)
Abdominal pain*	3 (7.7)	0 (0)
Gastroesophageal reflux disease*	2 (5)	0 (0)
Hypophosphatemia	2 (5)	1 (2.6)

Source: FDA analysis of ADAE dataset
* Indicates FDA Group term; see Appendix A.
Abbreviations: AE, adverse event; ADAE, Adverse Event Analysis; N, number of subjects in the specified group, or the total sample; N (%), number of subjects with the specified characteristic.

Other AEs from AIS use that are less than 5% but clinically meaningful include HTN, increased creatinine, proteinuria, anemia, headache, dizziness, muscle spasms, disturbance in attention, tremor, hyperkalemia, hypokalemia, and alopecia. One subject had Grade 3 CMV pneumonia.

Reviewer Comments:

- *Most adverse events from corticosteroid and AIS use were Grade 1 and 2. No Grade 4 or 5 events were observed. Grade 3 infections (requiring IV antimicrobial therapy) were rare (n=3).*

- *Applicant analysis had 7 Grade 3 infections; these included the 5 infections in Table 28, one fungal skin infection that occurred shortly after cessation of IS, and subject with CMV pneumonia attributed to AIS. The clinical reviewer has confirmed the Applicant's analysis.*

6.1.12.3 Deaths

One subject died of (b) (6) during the study. At study entry (b) (6) was considered mild and well-controlled on medication. Starting day 214 after ROCTAVIAN, he developed (b) (6) (Grade 4) and Grade 3 (b) (6) and was hospitalized. (b) (6) were reported at this time. There were several hospitalizations with fluctuation in the grade of symptoms, including hospitalization on day 347 wherein (b) (6) episodes were reported. Subsequently, on day 391, improvement of symptoms was noted, including assessment at a visit 9 months following the last hospitalization. However, he died by (b) (6) on day 669; no autopsy was performed. This subject did not receive any IS during the trial.

Reviewer Comments:

- *The clinical reviewer agrees with the Applicant's adjudication of death being unrelated to ROCTAVIAN or IS (none given).*

- *There were no additional deaths reported at the time of the 3-year data cutoff submission.*

6.1.12.4 Nonfatal Serious Adverse Events

A total of 63 SAEs in 32 subjects were reported at the time of the 3-year data cutoff. Only 6 of the 47 SAEs were considered related to ROCTAVIAN by the Applicant. The 6 SAEs in 5 subjects considered related to the SAE included ALT elevation (n=2), anaphylactic reaction (n=1), presyncope and maculopapular rash (n=1), and hypersensitivity (n=1). Three of these 6 SAEs were Grade 3—ALT elevation (n=2) and anaphylactic reaction (n=1). Seven SAEs in 4 subjects were considered related to IS use by the Applicant—6 related to corticosteroid use and 1 related to AIS use. These 7 SAEs included diabetes related to steroids (n=2), HTN (n=1), rectal hemorrhage (n=1), pneumonia (n=1), and a positive influenza A test in the subject with an SAE of pneumonia. One subject had cytomegalovirus (CMV) pneumonia attributed to AIS. All SAEs related to IS/AIS use by the Applicant were Grade 3. All SAEs resolved. The SAE of (b) (6) (unrelated to ROCTAVIAN or IS use) resulted in death. These SAEs are summarized by System Organ Class in the table below.

Table 31. Nonfatal Severe Adverse Events by System Organ Class, Study 270-301

SOC	Number of SAEs	SAEs (AEDECOD Terms)
Injury, poisoning and procedural complications	8	Postprocedural hemorrhage, periprosthetic fracture, acetabulum fracture, lower limb fracture, hand fracture, skin laceration, traumatic hematoma
Infections and infestations	8	Influenza A, CMV pneumonia, infection, pneumonia, gastroenteritis (n=2), URTI, diverticulitis*
Gastrointestinal disorders	5	Rectal hemorrhage (n=2), hemoperitoneum, diarrhea (n=2)
Eye disorders		Cataract (n=2), macular hole, retinal detachment
Psychiatric disorders	4	Depression (n=2), major depression, (b) (6)
General disorders and administration site conditions	3	Pain, noncardiac chest pain, peripheral swelling
Immune system disorders	3	Anaphylactic reaction (n=2), hypersensitivity reaction
Investigations	3	ALT increased (n=2), influenza A virus test positive
Metabolism and nutrition disorders	2	Diabetes mellitus, steroid diabetes
Cardiac disorders	1	Coronary artery disease
Musculoskeletal and connective tissue disorders	1	Arthropathy
Nervous system disorders	1	Presyncope
Renal and urinary disorders	1	Nephrolithiasis
Respiratory, thoracic, and mediastinal disorders	1	Apnea
Skin and subcutaneous tissue disorders	1	Rash maculo-papular
Vascular disorders	1	Hypertension

Source: FDA analysis of ADAE dataset; * actual AEDECOD term used was diverticulum
Abbreviations: ADAE, Adverse Event Analysis; ALT, alanine aminotransferase; CMV, cytomegalovirus; SAE, serious adverse event; SOC, system organ class; URTI, upper respiratory infection.

The clinical reviewer identified additional SAEs (than the Applicant) which were attributed to IS/occurred in the context of ongoing IS use, and underlying immunosuppression may have contributed to the event. These include the following SAEs (see table below):

Table 32. Serious Adverse Events Related to Immunosuppression, Rollover Population, Study 270-301

SUBJID	SAE	Grade	Additional Comments
(b) (6)	Influenza	3	On CS + MMF during the event
	Cataract	3	On prolonged CS including during the SAE
	Acetabulum fracture	3	Was on prednisone and budesonide with overlap between day 135 and day 190. Although fracture was preceded by mechanical fall; steroids could have contributed; no information on evaluation for osteoporosis
	Infection	3	On CS and then on tacrolimus
	Lower limb fracture	3	On CS and tacrolimus with overlap of these agents between days 337 and 514. Although fracture attributed to vigorous physical activity, steroids could have contributed; no information on evaluation for osteoporosis
	Diarrhea	3	Was on CS + tacrolimus during SAE
	Diverticulitis	3	On prednisone, budesonide, and MMF

Source: FDA analysis of ADAE dataset
Abbreviations: CS, corticosteroids; MMF, mycophenolate mofetil; SAE, serious adverse event.

Brief narratives of the six SAEs in five subjects considered related to the study product are given below.

SUBJID (b) (6) (ALT Elevation)

43-year-old HIV-negative White male with severe hemophilia A and past history of hepatitis B, hepatitis C, and epilepsy. The subject had a baseline ALT of 28 U/L that rose during week 5 to 230 (Grade 3), for which prednisone was started. However, ALT rose to 448 U/L during week 6, prompting a change to 3 pulse doses of methylprednisolone, which resulted in a decrease in ALT. The subject was subsequently restarted on prednisolone with declining ALT but still above baseline, and therefore budesonide was added. ALT returned to normal week 21 and prednisone was discontinued week 27, while budesonide was discontinued only at week 44.

SUBJID (b) (6) (ALT Elevation)

34-year-old male with severe hemophilia A and past history of hepatitis C with a baseline ALT of 52 U/L. Reported a rising ALT above baseline starting week 6, with prednisone started at week 7. Although the subject responded to prednisone, ALT started to rise during taper, and thus prednisone dose was adjusted. Subject was started on MMF week 19 for failure of steroids to bring ALT back down to baseline. Subject's ALT began to rise again at week 29 despite being on a stable low dose of prednisone at 5 mg and MMF at a dose of 500 mg bid. He also received methylprednisolone x 3 doses during week 35. He subsequently discontinued steroids but resumed corticosteroids following another ALT elevation; continued on MMF. Grade 3 ALT elevation of 255 on day 239 that resolved on day 253 was the SAE.

SUBJID (b) (6) (Anaphylactic Reaction)

36-year-old Asian male with history of hemophilia arthropathy, Gilbert's syndrome, and drug hypersensitivity to an unknown FVIII product received ROCTAVIAN infusion starting at 1 mL/min that was titrated up to 2 mL/min about an hour after the start of the infusion. About 20 minutes after the increased rate of infusion, he developed a generalized urticarial rash on his abdomen, arms, and right knee, and also reported puffy/watery eyes, numbness, and itchiness. Infusion was held and he was given antihistamine (chlorphenamine 10 mg IV) and hydrocortisone 100 mg IV,

following which the rash began to subside and the infusion was restarted at 1 mL/min. One hour after restarting the infusion he had a worsening rash now covering both arms, lower abdomen, both knees, and left thigh. Hence, infusion was stopped, and a second dose of hydrocortisone 100 mg IV was given. Sinus tachycardia was noted. Infusion was restarted at 1 mL/min and a complete dose of ROCTAVIAN was administered. Subject was hospitalized post-infusion. He remained tachycardic, had several episodes of rigors, became hypotensive (blood pressure 85/55 mmHg), and had 3 episodes of diarrhea. He received paracetamol, IV fluids, and antibiotics. On day 2, he had severe diaphoresis and nausea which subsequently resolved; rash subsided. He had fever and BP was better. He subsequently was discharged from hospital on day 5. Mild decrease in Hb, platelet count and mild increase in ALT, bilirubin, creatinine, and lactate dehydrogenase were noted; serum tryptase levels were within normal range; complement level and components were normal.

SUBJID (b) (6) (Hypersensitivity Reaction)

23-year-old male who started ROCTAVIAN infusion at 4 mL/min. The subject had acute onset of sneezing, runny nose, watery eyes, coughing, and symptoms in the back of throat ~25 minutes after start of infusion (Grade 2 hypersensitivity reaction); no change in breathing was noted and vital signs were reported to be normal. Infusion was stopped and methylprednisolone, diphenhydramine, famotidine, and subcutaneous epinephrine were administered, after which the subject felt better and infusion was resumed at 2 mL/min, with diphenhydramine premedication, and completed. Subject was hospitalized for observation. Subject was noted to have Grade 2 nasopharyngitis and bilateral hand swelling on day 2, with hand swelling resolving on day 3 and nasopharyngitis resolved on day 21. Both events were considered related by the investigator; day 2 symptoms treated with NSAID, decongestant, and intranasal steroid.

SUBJID (b) (6) (Presyncope, Maculo-Papular Rash)

33-year-old male who started ROCTAVIAN infusion at 4 mL/min. Twenty minutes after start of infusion he developed Grade 2 maculopapular rash; no respiratory symptoms and vital signs were reported to be normal. Infusion interrupted and chlorphenamine and hydrocortisone were given. Infusion was restarted about 2 hours later at 3 mL/min, following which rash reappeared (about 30 minutes after restarting infusion). Thereafter, infusion was increased to 4 mL/min and completed. Subsequently, subject got out of bed and had a Grade 2 presyncopal event and thereafter hit his head and had a Grade 1 injury. Subject was hospitalized for observation and given prednisolone. Was discharged home on day 2; rash resolved on day 153.

A brief description of selected (based on clinical reviewer judgement) SAEs related to corticosteroid or AIS use is given below.

SUBJID (b) (6) (CMV Pneumonia)

54-year-old Asian male with no history of HIV and history of hepatitis B and C in the past who received corticosteroids (days 139 to 197) and tacrolimus (days 148 to 204) for 8.4 and 8.1 weeks, respectively, for ALT elevation. He had Grade 3 dyspnea on day 205 and was noted to be tachypneic and hypoxic. He was diagnosed with Grade 3 CMV pneumonia (bronchoscopy positive for CMV) and was treated with ganciclovir with subsequent improvement of his symptoms. CMV pneumonia was considered resolved on day 224.

SUBJID (b) (6) (Pneumonia, Influenza A)

28-year-old White male with no history of hepatitis or HIV who received corticosteroid for a total of 29.3 weeks and tacrolimus for 43.6 weeks for ALT elevation. Corticosteroid and tacrolimus use overlapped between days 125 and 284. Total duration of IS use was between days 80 and 429. Complications of corticosteroid therapy included weight gain (Grade 1), chorioretinopathy (Grade 1), acne, insomnia, irritability, and steatohepatitis. Following a liver biopsy on day 244, he developed shortness of breath, right flank pain, dizziness, and sweating. He presented the following day to the emergency department, wherein a computed tomography (CT) scan showed a Grade 1 perihepatic hematoma and atelectasis. He was noted to be hypoxic (day 245) and was diagnosed with Grade 3 pneumonia; a test for Influenza A was positive. Pneumonia was considered resolved on day 249.

SUBJID (b) (6) (Influenza B)

20-year-old male with no history of HIV or hepatitis who received the following IS for ALT elevation: corticosteroids for 52.1 weeks, budesonide for 4 weeks (considered AIS even though steroid since it is prednisone), MMF for 28 weeks, and tacrolimus for 23.3 weeks. The subject had significant overlap in use of these agents—corticosteroid and budesonide days 101 to 128; corticosteroid and MMF days 121 to 207 and then 215 to 316; and corticosteroid, MMF, and tacrolimus days 246 to 316. He was hospitalized with Grade 3 influenza B infection on day 176, which was considered resolved on day 182. He was on corticosteroids and MMF during this time.

SUBJID (b) (6) (Acetabulum Fracture)

43-year-old White male with no history of HIV and history of hepatitis B and hepatitis C who received 21 weeks of corticosteroids (prednisone), 7 days of methylprednisolone (considered AIS), and 25 weeks of budesonide (also considered AIS since it is not prednisone) for ALT elevation. He had a Grade 3 acetabular fracture after a mechanical fall on day 112 (slipped on a stone walk). He was treated conservatively with good resolution of pain and good mobility. The event had resolved at the time of the 2-year data cutoff. Although the Applicant considered this event as not related to corticosteroids/AIS (in this instance AIS was a corticosteroid also), given history of fall prior to fracture, we cannot rule out the role of corticosteroids in predisposition to fracture, given that he had been on corticosteroids since day 38 and there are no assessments for bone health reported.

SUBJID (b) (6) (Lower Limb Fracture)

33-year-old Black male with no history of HIV or hepatitis who received 69.7 weeks of corticosteroids and 25.4 weeks of tacrolimus for elevated ALT. He had a Grade 3 tibia/fibula stress fracture secondary to exercise (had reported vigorous activity a month prior to the event), diagnosed on day 253. The fracture was casted/splinted and considered resolved on day 365; he had a repeat fracture on day 484 and had the cast placed again. The investigator reported the subject doing well at time of data cutoff. The subject was on corticosteroids days 39 to 526 and tacrolimus days 337 to 514. No assessment of bone health was reported. Although vigorous activity can cause stress fracture, the prolonged use of corticosteroids prior to this event does not rule out the contribution of corticosteroid impact on bone health prior to this event. Hence, the clinical reviewer has adjudicated this event as possibly being related at least in part due to corticosteroids.

SUBJID (b) (6) (Diverticulitis, Rectal Hemorrhage)

34-year-old Black male with no history of HIV or hepatitis who received corticosteroids for a total of 58.7 weeks, AIS (budesonide) for 55.7 weeks, MMF for 34.4 weeks, and tacrolimus for 20 weeks. He received corticosteroids, budesonide, and MMF between days 58 and 298, while all four agents were used days 219 to 298. He had rectal hemorrhage due to diverticulitis days 167 to 170. He was on prednisone 7.5 mg/day, budesonide 18 mg/day, and MMF 1500 mg twice per day at the time of this event. FVIII activity by CSA prior to hemorrhage was 22.2 IU/dL. A total of two doses of Eloctate (exogenous FVIII) was given on days 167 and 171. Diverticulitis resolved on day 191.

6.1.12.5 Adverse Events of Special Interest

Infusion Related and Hypersensitivity Reactions

The Applicant identified infusion-related and hypersensitivity reactions using three separate strategies during or within 48 hours of ROCTAVIAN infusion as follows:

1) Infusion-associated events, defined as AEs occurring during the above timeframe
2) Systemic hypersensitivity using the Standard MedDRA Query of hypersensitivity-narrow scope
3) Anaphylactic or anaphylactoid using the Standard MedDRA Query anaphylactic reaction-algorithmic. Here, a number of criteria need to be fulfilled in order to increase specificity. These include either a term from Category A, a term from Category B (upper airway/respiratory), a term from Category C (angioedema, urticaria, pruritis, flush), a term from Category D (cardiovascular/hypotension), or a term from Category B or C

Examples of how AEs were categorized as they relate to ROCTAVIAN infusion are shown below.

Table 33. Examples of Analysis of AEs Associated With ROCTAVIAN Infusion

Events occurred within 48 hours of infusion	IAEs	IRRs	Hypersensitivity events	Algorithmic Anaphylactic reaction
Definition	Events during or within 48 hours of infusion	Events during or within 6 hours of infusion	Events during or within 48 hours of infusion Mapping to MedDRA Hypersensitivity narrow SMQ	Events during or within 48 hours of infusion Mapping to MedDRA Algorithmic Anaphylactic reaction SMQ
Example 1 (Subject A)				
Diarrhea	**Yes**	No	No	No
Example 2 (Subject B)				
Presyncope*	**Yes**	**Yes**	No	No
Example 3 (Subject C)				
Urticaria *	**Yes**	**Yes**	**Yes**	No
Example 4 (Subject D)				
Rash*	**Yes**	**Yes**	**Yes**	**Yes**
Hypotension*	**Yes**	**Yes**	**Yes**	

Source: Applicant response to IR dated 02.02.2023
* Event occurred during or within 6 hours after infusion.
Abbreviations: AE, adverse event; IAE, infusion-associated event; IRR, infusion-related reaction; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, Standard MedDRA Query.

Reviewer Comments:

- *Gastrointestinal symptoms were not included in the analysis of anaphylaxis. Review of AEs did not identify additional cases of hypersensitivity reaction or anaphylaxis.*
- *There is no standardized definition of infusion-related AEs (i.e., infusion reactions). The terminology used here is therefore protocol specific.*

The infusion-associated event (IAE) definition was the broadest umbrella intended to capture the anaphylaxis, anaphylactoid reaction, cytokine mediated adverse drug reactions, hypersensitivity reactions, and other AEs associated with infusion (e.g., nausea, headache, fatigue, etc.) during and within 48 hours of ROCTAVIAN infusion.

Fifty subjects (50/134) had 88 IAEs. Fifty-five of the 88 IAEs (62.5%; 55/88) were adjudicated by the investigator as being related to ROCTAVIAN.

Reviewer Comments:

- *The clinical reviewer adjudicated another 16 IAEs as being related to ROCTAVIAN, for a total of 71 of 88 IAEs in 41 subjects as being related to ROCTAVIAN.*
- *All of these additional IAEs that were considered related to the product were Grade 1/2 in severity and included headache, nausea, vomiting, diarrhea, dizziness, and fatigue.*

- *These events were considered related to the product based on the fact that these events had an onset similar to those adjudicated as related by investigators in instances of these AEs in other subjects.*

Of the 71 IAEs considered related to ROCTAVIAN, 49, 20, and 2 events were Grade 1, 2, and 3, respectively. Grade 3 events included anaphylactic reaction and hypersensitivity (one subject each), and a brief narrative of these events is given above (see Section 6.1.12.4 narratives on SUBJID (b) (6) and SUBJID (b) (6)). The most common IAEs (all Grade 1 or 2; incidence >2%) related to ROCTAVIAN included nausea (27%, 19/71), fatigue (15.5%, 11/71), headache (11%, 8/71), diarrhea (5.6%, 4/71), dizziness (4.2%, 3/71), vomiting (4.2%, 3/71), abdominal pain (4.2%, 3/71), lethargy (2.8%, 2/71), and infusion-related reaction (2.8%, 2/71). Other IAEs included chills, cough, decreased appetite, dysgeusia, dyspepsia, head injury (related to presyncope), nasopharyngitis, peripheral edema, presyncope, proteinuria, pruritis, rash, and throat irritation. The median time to onset of IAEs (n=71 events) that were considered related to ROCTAVIAN was 2 days (range of 1 to 3 days). The median duration of IAEs was 4 days (range of 1 to 153 days); mean duration (SD) was 12.8 days (22.4). Intervention was required in only 30 of 88 IAEs (34%; 30/88) and included NSAIDS, corticosteroids, antihistamines, and topical agents for rash.

Infusion was interrupted between 10 minutes and 2.25 hours for 4 IAEs in 4 subjects—maculopapular rash, hypersensitivity, anaphylactic reaction, and infusion site extravasation. All subjects resumed and completed the infusion. Six subjects had interruptions in infusion for reasons other than AEs (e.g., infusion pump not working properly). Since some of the IAEs, including hypersensitivity, were seen when infusion was started at 4 mL/min, the protocol was modified to start the infusion at 1 mL/min and escalate to a maximum of 4 mL/min as tolerated.

Reviewer Comments:

- *IAEs considered related to ROCTAVIAN (n=71 events) will be included in the analysis for the AE table in the label under AEDECOD terms or the FDA Group term where applicable*.

A subset of IAEs were termed IRRs and included AEs that occurred during or within 6 hours of ROCTAVIAN infusion. IRRs were considered most likely to be related to ROCTAVIAN and are included in the draft label by the Applicant as adverse drug reactions.

Twelve subjects had a total of 17 AEs collected under the umbrella of IRRs. Of these 17 AEs, 13 AEs in 9 subjects are considered related to ROCTAVIAN. AEs (AEDECOD term) included anaphylactic reaction, hypersensitivity, rash, pruritis, headache, cough, dizziness, dysgeusia, nausea, presyncope, throat irritation, and IRR. Of the IRRs related to ROCTAVIAN, the majority were Grade 1/2 (n=5 Grade 1; n=6 Grade 2), while 2 IRRs were Grade 3. Grade 3 events in two subjects included anaphylactic reaction and hypersensitivity, which are described in Section 6.1.12.4 above under subject narratives of SAEs (USUBJIDs (b) (6) . The narrative on the subject (SUBJID (b) (6)) with Grade 2 events of presyncope and rash has also been described in the section on SAEs. One Grade 3 event of HTN that was not considered related resolved without any intervention. All IRRs resolved.

Reviewer Comments:

- *The clinical reviewer agrees with the Applicant's analysis of relatedness of IRRs to ROCTAVIAN*.

- *All subjects with hypersensitivity reactions and anaphylaxis are included in IRRs.*
- *For anaphylactic reaction in SUBJID* (b) (6) *, infusion should not have resumed since this could have proved to be fatal. A statement conveying that subjects with suspected anaphylaxis should not have their infusion discontinued has been placed in the label.*

Hypersensitivity reactions constituted a subset of IRRs. Six subjects were identified as having hypersensitivity reactions that included anaphylaxis. Three of these subjects (SUBJIDs (b) (6))have been described in Section 6.1.12.4 on SAEs. A brief narrative of the remaining three subjects is given below.

SUBJID (b) (6)

23-year-old male who developed hives, urticaria, and a maculopapular rash on the bilateral lower extremities, forearms, face, and abdomen 5 hours post-ROCTAVIAN infusion. Symptoms resolved 2 hours later after diphenhydramine.

SUBJID (b) (6)

25-year-old male who developed symptoms of right eye redness, ocular pruritis, periocular maculopapular rash, and infusion site redness 15 minutes after completing ROCTAVIAN infusion. Symptoms resolved 30 minutes after receiving IV diphenhydramine.

SUBJID (b) (6)

27-year-old male developed Grade 2 rash and cough 80 minutes after start of infusion (rate was 1 mL/min at time of symptoms). Symptoms resolved 1 hour after treatment with diphenhydramine. Infusion was escalated to a rate of 3 mL/min and completed.

Reviewer Comments:

- *One subject (SUBJID* (b) (6) *) with facial swelling starting on day 1 (AE from day-651) was deemed not to have had hypersensitivity reaction. Applicant attributed this to corticosteroid use, but review of data revealed that subject was not on corticosteroids till day 58. Typically, hypersensitivity does not last for such a long time (651 days). Therefore, in absence of additional information, clinical reviewer deemed this event as not being related to ROCTAVIAN or corticosteroids.*

Anaphylaxis

A single subject had anaphylaxis following ROCTAVIAN (see Section 6.1.12.4 for narrative). This subject was deemed not to have anaphylaxis since infusion was not stopped or slowed down in response to symptoms of cough and rash (both Grade 1) and infusion was completed as scheduled.

Hepatotoxicity

Administration of a liver-directed AAV GT can result in immune response to the capsid of the AAV-vector, which can result in liver enzyme (ALT, AST) elevation (transaminitis). Transaminitis impacts both safety (hepatotoxicity) and efficacy since loss of transduced hepatocytes may result in decreased FVIII activity levels. Liver enzyme elevation not only > ULN but above baseline but

still within the normal range can signal transaminitis. ALT elevation was used to define transaminitis after ROCTAVIAN administration.

The definition of hepatotoxicity based on ALT elevation, and thus the trigger for initiation of corticosteroids, was different in the directly enrolled and rollover populations in Study 270-301. The ALT level at which taper of corticosteroids, or other IS, was allowed also differed in the two subpopulations. In the directly enrolled population, corticosteroids were initiated for ALT ≥ 1.5 x ULN; later the protocol was amended, wherein corticosteroids were initiated for ALT > ULN and 2 x subject's baseline ALT. Corticosteroids were tapered for a declining ALT, especially when ALT < ULN. In the rollover population, corticosteroids were initiated for ALT ≥ 1.5 x baseline or ALT > ULN and tapered only when ALT reached baseline. The ALT trigger for corticosteroid use was also defined as an Event of Special Interest in the Study 270-301 protocol.

Overall, 127 of 134 subjects (95%) had 667 events of ALT elevation, as defined by ≥ 1.5 x baseline or ALT > ULN. Of these 127 subjects, 107 (95.5%; 107/112) and 20 (91%; 20/22) subjects in the rollover and directly enrolled populations had 127 and 540 events of ALT elevation, respectively. Three-hundred and five and 76 events of ALT > ULN occurred in 89 (79.5%) and 20 (91%) subjects in the rollover and directly enrolled populations, respectively. Most events of ALT elevation were Grade 1 or Grade 2; eleven subjects (8%) had Grade 3 elevations (two subjects in the directly enrolled population and nine subjects in the rollover population). All Grade 3 elevations resolved. At the 3-year data cutoff, 23 of 667 3.4%) and 18 of 540 (3.3%) ALT elevations in the ITT and rollover population respectively were ongoing. Nine and 8 ALT elevations in the ITT and rollover population respectively were > ULN; all episodes were Grade 1 except for Grade 2 elevation in one subject with autoimmune hepatitis (AIH). No subject was receiving IS for ALT elevations at year 3 data cutoff except for subject with AIH. See Table 34 below for timeframe of occurrence of ALT elevations.

Table 34. Timeframe of Occurrence of ALT ≥ 1.5 x Baseline or > ULN, Study 270-301

Time from Infusion to Onset of Episode of ALT Elevation	Directly Enrolled Population N=127 Episodes (%)	Rollover Population N=540 Episodes (%)	ITT N=667 Episodes (%)
≤26 weeks	46 (36)	228 (42)	(41)
>26 - ≤52 weeks	37 (29)	144 (27)	(27)
>52 - ≤78 weeks	10 (7.9)	59 (11)	69 (10)
>78 - ≤104 weeks	8 (6.3)	44 (8.1)	52 (7.8)
>104 - ≤156 weeks	12 (9.4)	54 (10)	66 (9.9)
>156 weeks	14 (11)	11 (2)	25 (3.7)

Source: Applicant response to IR dated 05.26.2023
Percentages may have been rounded to nearest integer.
Abbreviations: ALT, alanine aminotransferase; IR, information request; ITT, intent-to-treat; N, number of subjects in the specified group, or the total sample; ULN, upper limit of normal.

The median time to the first ALT elevation (as defined by ALT ≥ 1.5 x baseline or ALT > ULN) in the rollover population was 7.1 weeks (range of 0.4 to 159.1 weeks) with a median duration (range) of 3.9 weeks (0.1 to 134.9 weeks). Twenty-nine percent of ALT elevations were associated with a decline (defined as decline in FVIII activity ≥ 30%) in FVIII activity.

Overall, 97 of 112 subjects (87%) in the rollover population received IS with corticosteroids or AIS for ALT elevation. Ninety-two (82%; 92/112) and 39 (35%; 39/112) subjects received corticosteroids and AIS, respectively. Five subjects received only AIS. Corticosteroids included prednisone or prednisolone; AIS included corticosteroids other than prednisone or prednisolone (budesonide [n=6], methylprednisolone ([n=7]), tacrolimus (n=24), and MMF (n=13). Nine

subjects received more than one AIS. In the subjects for whom data is available, reasons for AIS use were failure of corticosteroids to return ALT to < ULN or baseline (N=26), site preference (n=4 for methylprednisolone), intolerance to corticosteroids (n=2), contraindication to corticosteroids (n=1), and other reasons (ALT not improving, steroid intolerance [n=1]). Median duration of IS use in 97 subjects was 39.6 weeks (range 3.4 to 131.3 weeks) with a mean (SD) of 39 (20) weeks. Median duration of corticosteroid use in 92 subjects was 34.9 (rounded to 35 weeks in label) weeks with a range of 3.1 to 120 weeks and a mean (SD) of 36.65 (19.93) weeks. Median duration of AIS use in 39 subjects was 25.9 (rounded to 26 weeks in label) weeks with range of 6 to 118 weeks.

Reviewer Comments:

- *The lower ALT threshold for corticosteroid use, and the more conservative taper when ALT reached baseline in the rollover population, was subsequent to an interim analysis based on the subjects in the directly enrolled population. Thus, the goal was to improve transgene expression with more intense immunosuppression. This resulted in a longer duration and increased amount of corticosteroid use in the rollover population compared to the directly enrolled population.*

- *The Applicant stated that despite the increase in IS in the rollover population, there was no increase in FVIII activity compared to the directly enrolled population, and hence proposed a less intense IS regimen in the label. While we agreed that more IS did not result in an increase in FVIII activity in the rollover population, we did not agree that in absence of such an approach the FVIII activity may not have been lower, thus impacting the ABR adversely. Hence, the IS regimen used for the rollover population (efficacy evaluable population) was placed in section 2 in the USPI.*

- *Based on graphs depicting FVIII activity, ALT elevation, and immunosuppression, it appears that at least in some instances, decisions regarding IS use were based on FVIII activity rather than ALT levels. However, such complexity of decision making was not captured. Version 6 of the protocol also had FVIII activity parameter incorporated in the decision making for use of corticosteroids. In response to an IR, the Applicant stated that in most instances, investigators adhered to the protocol while making decisions regarding IS use, and that ALT levels rather than FVIII activity served as the basis of change in immunosuppression. Hence, in the USPI, ALT levels serve as the trigger for initiation and basis for taper of corticosteroids.*

- *There is sparse data on the benefit of corticosteroid use beyond 52 weeks since the majority of elevations after 52 weeks were not treated with IS. It is difficult to distinguish between the natural decline in FVIII activity associated with ROCTAVIAN administration and that induced perhaps by a delayed immune response. However, in some subjects, ALT elevation beyond 52 weeks was associated with a clear-cut and steep decline in FVIII activity.*

- *There was some variability noted in ALT levels measured in central versus local laboratories such that it impacted decisions on IS. Hence the recommendation placed in label to use the same laboratory for ALT levels, if feasible.*

- *Some subjects had AST elevation along with ALT elevation, but no subject initiated corticosteroids or AIS for an AST elevation alone.*

- *Despite more extensive IS use in the rollover population, AEs related to corticosteroid or AIS use, including infections, were generally Grade 1 or 2 and in keeping with the side effect profile of these agents' use in other disorders.*

Autoimmune hepatitis (AIH) was reported in a single subject in Study 270-301. A brief description of the AE is given below.

SUBJID (b) (6)

36-year-old Asian male with history of hemophilia, fatty liver disease (since 2008), and screening ALT of 47 IU/L (>ULN) was diagnosed with AIH at week 134 following ROCTAVIAN. Between weeks 71 and 128, his ALTs remained > ULN and ranged from 56 to 159 IU/L. He had a positive antinuclear antibody test (1:80) and elevated immunoglobulin G (16.7 g/L) but was negative for anti-smooth muscle and liver kidney microsome type 1 antibodies. He was originally diagnosed with metabolic syndrome (weight gain, hypercholesterolemia, and impaired glucose tolerance) at week 100, was advised on weight loss, and started on metformin. But after consultation with a hepatologist, diagnosis of Grade 2 AIH was made at week 134 and he was started on budesonide. The liver biopsy done (while on steroids) showed features of steatohepatitis, but AIH could not be ruled out. His ALT decreased in response to budesonide and increased with steroid tapering. At week 190, he was switched to azathioprine for treatment of AIH, with a decrease (but not normalization) in ALT levels.

Reviewer Comments:

- *Information on AIH was placed in Clinical Trials section 6.1 of the USPI. Given confounding due to the presence of steatohepatitis, occurrence in a single subject, and difficulty in AIH diagnosis, it was decided not to place this information in section 5 of the USPI.*

Medications can impact transgene expression directly or indirectly via impact on corticosteroids or other IS used to preserve transgene expression. Isotretinoin was shown to decrease FVIII activity in a single subject without causing ALT elevation; FVIII activity was partially restored upon cessation of medication, The impact of isotretinoin on decrease in FVIII transcription was also demonstrated in an in vitro study. One subject with HIV had Grade 3 hepatotoxicity that was subsequently attributed to efavirenz. An in vitro study in hepatocytes showed decreased FVIII transcription with the addition of efavirenz, with no restoration of FVIII activity upon cessation of drug.

Reviewer Comments:

- *The impact of isotretinoin and efavirenz on FVIII activity and the importance of avoidance of these medications in subjects who receive ROCTAVIAN has been detailed in section 7 of the USPI. Information on the importance of monitoring concomitant medication use is also placed in section 5.2 of the USPI.*

- *Since excessive alcohol consumption can cause hepatotoxicity and result in loss of transduced hepatocytes and decreased FVII activity, information on the importance of alcohol abstinence for at least a year and restraint subsequently has been incorporated in the USPI in sections 5.2 and 17. The Applicant had advocated for only 6 months of abstinence from alcohol, but given that alcohol-induced hepatotoxicity may impact product efficacy at any timepoint following administration, we decided to adhere to what was in the*

study protocol. The maximum number of ALT elevations associated with immune-mediated response to AAV5 capsid occurs in the first year following ROCTAVIAN, and thus it is important to minimize other factors that could cause ALT elevation, thus confounding assessment of transaminitis that may require treatment with IS. This recommendation is also consistent with the recommendation in the EMA label.

Elevated FVIII Activity and Thromboembolic Events

Thirty-eight subjects (28%; 28/134) had FVIII activity > ULN by OSA (>150 IU/dL). Sixteen of these 38 subjects had FVIII activity > ULN both on CSA (>170 IU/dL) and OSA. Fifteen subjects (15/134; 11%) had FVIII activity >250 IU/dl on the CSA while 2 subjects had FVIII levels above the assay limits of quantification(b) (4) IU/dl for CSA and (b) (4) IU/dl for OSA). The median (range) of FVIII activity > ULN by OSA and CSA were 11.8 (0.7 to 97.7) and 13.5 (0.7 to 62.9) weeks respectively. At the 2-year data cutoff, only 2 and 4 subjects had FVIII activity > ULN by CSA and OSA respectively. One subject (b) (6) had noncardiac chest pain on day 139 along with FVIII activity > ULN; a brief narrative is provided below. No subject had a documented thromboembolic event in setting of elevated FVIII activity > ULN by either assay.

SUBJID (b) (6)

53-year-old white male with history of hepatitis C, HTN, hemophilia arthropathy, and first degree atrioventricular block who had elevated FVIII levels following ROCTAVIAN. He received corticosteroids for ALT elevation days 103 to 233. FVIII activity was > ULN by OSA starting on day 92 till 2-year data cutoff while the FVIII activity by CSA was > ULN staring day 120 till data cutoff. Peak FVIII activity by CSA and OSA was 268.8 IU/dL and 373.1 IU/dL respectively. He had Grade 2, atypical, noncardiac chest pain starting day 138 wherein FVIII activity was > ULN by both assays. Between days 148 and 163, FVIII activity was above the limits of testing—>(b) (4) IU/dL for CSA and (b) (4) IU/dL for OSA. Subject attributed chest pain to gym; troponin was negative, but d-dimer was elevated positive at 2.4 mg/dL. On day 139, lower extremity Doppler was negative for deep venous thrombosis; electrocardiogram showed first degree atrioventricular block (had history of the same). On day 141 his chest pain radiated to the jaw, and he had calf pain and therefore was seen in the emergency department. Cardiac enzymes, CT angiography, and bilateral lower extremity ultrasound were normal (i.e., no evidence of thrombosis). However, troponin was subsequently positive at 54 ng/L and d-dimer rose to 4.6 mg/L. An exercise stress test on day 142 was terminated early due to HTN; no electrocardiogram changes suggestive of ischemia and subject had no symptoms. He was placed on Aspirin and Enoxaparin (60 mg twice per day) despite chest pain not being considered a symptom of a thromboembolic event. Chest pain resolved on day 143. Coronary angiography on day 145 showed 25% to 50% stenosis of left circumflex artery (Class 2 coronary artery disease); his dose of enoxaparin was reduced but he was continued on Aspirin and enoxaparin out of an abundance of caution given FVIII activity > ULN.

Reviewer Comments:

- *The clinical reviewer agrees with the investigator assessment of atypical chest pain being nonindicative of a thromboembolic event. The subject was placed on prophylactic antithrombotic/anticoagulant therapy out of caution given risk factors (e.g., HTN.) D-dimer is nonspecific (can be elevated with exercise) and, in absence of documented thrombosis, is difficult to interpret. An isolated elevation in troponin level is also difficult to interpret.*

The subject would typically not have been subjected to an exercise stress test if probability of having acute coronary event was high. Angiography did not reveal acute thrombosis.

Malignancy

ROCTAVIAN is a liver directed AAV GT but can integrate into the DNA of any cell. AAV vector-based therapy is generally considered low risk for integration compared to lentiviral based therapies. Two malignancies have occurred in clinical trials of ROCTAVIAN, and a brief description of both cases is given below. Both malignancies have been deemed to be unlikely related to ROCTAVIAN.

Parotid Gland Cancer

47-year-old male received ROCTAVIAN at a dose of 6×10^{13} vg/kg in Study 270-201 and presented approximately 5.5 years later with complaint of a right neck lump that had been present for about 1 year. His past history was significant for treated (with interferon) hepatitis C and Grade 1 ALT elevation following ROCTAVIAN that was treated with 14 weeks of corticosteroid therapy. He was a nonsmoker with moderate alcohol consumption and no family history of cancer. Vector shedding in the saliva reported the first and third of three consecutive negative samples at weeks 32 and 40 following ROCTAVIAN. He had a fine needle aspiration of the neck mass performed that showed Grade 2 acinic cell carcinoma. He subsequently underwent a right parotidectomy and neck dissection that revealed a low grade, acinic cell carcinoma with a maximum diameter of 18 mm with no extra parenchymal extension and no lymph node metastasis. Vector integration studies using target enrichment sequencing concluded that the observed events were not linked to tumorigenesis. Whole genome sequencing and a Centogene deep-sequencing diagnostic assay (focused on 149 genes in solid tumors) did not provide conclusive findings.

Reviewer Comments:

- *An internal consultation (from CMC with expertise in integration site analysis and AAV biology) was obtained to ensure that the Applicant's conclusions on the parotid tumor not being related to vector could be accepted, especially in light of the assessed sample for vector integration containing only 2% tumor cells and reported sensitivity of tests employed to assess role of vector in tumorigenesis. The conclusion of the consult reviewer is that the Applicant's assessment is acceptable (i.e., the tumor is unlikely to be related to the vector). No additional testing was recommended by the consultant reviewer.*

B-Cell Acute Lymphoblastic Leukemia

24-year-old Hispanic male received ROCTAVIAN at a dose of 6×10^{13} vg/kg (August 2019) in Study 270-301 and presented approximately 2 years later (October 2021) with vague back pain, intermittent fevers, night sweats, unintended weight loss, and elevated inflammatory markers over the course of several months. He was evaluated for the same with a full body CT scan, laboratory tests, review of blood smear, X-rays, magnetic resonance imaging, etc., all of which were unrevealing. In August of 2022, he presented to the emergency department with back pain and underwent a bone marrow biopsy that revealed a diagnosis of acute B-cell ALL (Grade 4). The complete blood count at this time showed anemia (hemoglobin 7.1 g/dl), leukopenia (white blood cell count 2.0K), and thrombocytopenia (platelet count 142K), with an elevated erythrocyte sedimentation rate of 92 mm/hour and C-reactive protein of 13 mg/dL. The bone marrow was hypercellular with sheets of leukemic blasts. Fluorescence in situ hybridization analysis was

positive for CRLF2 translocation, likely IGH/CRLF2 fusion. Droplet digital PCR for vector sequences in the bone marrow showed <0.003 copies/cell. Next-generation sequencing detected an IKZF1 deletion along with other IKZF1 and JAK2 (Arg683Gly) variants. The subject was started on multiagent chemotherapy.

Reviewer Comments:

- *The clinical reviewer agrees with the Applicant assessment of B-cell ALL being unlikely related to vector. An internal consultation was also sought to assess the role of the vector in this malignancy, and conclusions of the consult were the same (i.e., malignancy unlikely to be related to the vector).*
- *The genetic alterations described above—fusion of IGH/CRLF2, IKZF1 and JAK2—have been well described in the literature with B-cell ALL.*
- *The clinical reviewer had incorporated information on both malignancies in Section 5.5 of the label as in another label in same product class, but this was later removed based on Division and APLB input.*
- *Although both malignancies were assessed as likely not related to ROCTAVIAN, vector integration into DNA of human liver cells and parotid gland tissue including tumor tissue has been demonstrated. Thus, concern for vector related malignancy persists and thus long-term monitoring for safety is important.*

Factor VIII Inhibitors

No subject developed a persistent FVIII inhibitor. Four subjects had detection of inhibitors on the Bethesda assay at one timepoint but subsequently tested negative. One of the four subjects had a titer of 1.4 at screening but was subsequently negative. The other 3 subjects had titers of 4.0, 1.2, and 0.7 BUs at weeks 96, 76, and 96 respectively but tested negative at all subsequent timepoints.

6.1.12.6 Clinical Test Results

Please see section on overview of AEs for laboratory abnormalities in Study 270-301

6.1.12.7 Dropouts and/or Discontinuations

Of the 134 subjects in the ITT population, 1 subject died of (b) (6) at week 95, and 2 subjects were lost to follow up at weeks 66 and 104. The remaining 131 subjects are continuing to be followed on the study.

6.1.13 Study Summary and Conclusions

Overall, ROCTAVIAN demonstrated efficacy with reduction in ABR during the EEP compared to baseline, and increase in FVIII activity. Efficacy was based on ABR in the EEP compared with that in the baseline/lead-in period. The mean EEP ABR was 2.6 bleeds/year, compared to a mean baseline ABR of 5.4 bleeds/year. The mean difference in ABR was -2.8 (95% CI: -4.3, -1.2) bleeds/year. The NI analysis met the pre-specified NI margin, indicating the effectiveness of ROCTAVIAN. The median FVIII activity levels over time, as measured by the CSA, were 39.0, 24.0, 13, and 10.0 IU/dL (numbers rounded to nearest integer) at 6, 12, 24, and 36 months,

respectively. Twenty-two subjects were deemed to have either no response or having lost response at the 3-year data cutoff. There was significant reduction in exogenous FVIII utilization in the EEP compared to baseline. Although there is decline in FVIII activity and loss of effectiveness over time, a significant number of subjects (80%) continue to derive benefit from ROCTAVIAN treatment and have remained off RP at the 3-year data cutoff. Durability of response off IS has been shown. The AEs related to ROCTAVIAN were generally mild and included infusion-related reactions, ALT elevations and a "viral syndrome" with systemic symptoms such as nausea, vomiting, abdominal pain, diarrhea, fatigue and headache. The median duration of CS use for ALT elevation and to preserve transgene expression was 35 weeks; AIS was used in 35% of subjects. Despite extensive IS use, the AEs from corticosteroids and/or AIS use was in keeping with the AE profile of these medications in other disorders. Most AEs were Grade 1 or 2; no subject had Grade 4 or 5 AEs related to IS. The safety profile is acceptable and favors a positive benefit to risk profile. Careful patient selection and close monitoring of subjects post- treatment is paramount in maximizing benefit and minimizing AEs for this one-time GT.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

ROCTAVIAN is not intended for use in women. Clinical studies evaluating ROCTAVIAN required the use of contraception for at least 12 weeks post administration. Subjects were allowed to stop contraception after 12 weeks only if 3 consecutive semen samples demonstrated viral DNA below the limit of detection.

As of the 2-year data cutoff, five pregnancies in partners of men who received ROCTAVIAN were reported. No clinical sequelae were reported in four of five pregnancies; one subject declined consent to provide additional information. An additional three pregnancies were reported at the time of the 3-year data cutoff.

9.1.2 Use During Lactation

ROCTAVIAN is not intended for use in women. There is no information regarding the presence of ROCTAVIAN in human milk, the effects on the breastfed infant, or the effects on milk production.

9.1.3 Pediatric Use and PREA Considerations

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

9.1.4 Immunocompromised Patients

See Section 6.1.11.3 on discussion of 2 subjects with HIV infection enrolled in Study 270-301of ROCTAVIAN. A third subject with HIV positivity was enrolled in another trial of ROCTAVIAN and had hepatotoxicity attributed to efavirenz that was part of his HIV treatment; hepatotoxicity resolved with efavirenz discontinuation. Enrollment of subjects with HIV infection required subjects to have an undetectable viral load and a CD4 count of >500/mm^3. Subjects with other

immunosuppressive disorders or on immunosuppressive medications were excluded from clinical trials of ROCTAVIAN.

Reviewer Comment

- *Use of ROCTAVIAN in subjects with HIV was debated especially given the extensive IS required in most subjects, and the paucity of data in such subjects in Study 270-301. However, given IS use in HIV positive subjects who safely undergo organ transplantation, it was decided not to exclude HIV positive subjects from receiving ROCTAVIAN. The limited data on such subjects has been conveyed in the highlights (Use in Specific Populations) and section 8.6 of the label. Active acute or uncontrolled chronic infections are listed as contraindications to ROCTAVIAN treatment and thus would bar patients with acute or chronic, uncontrolled HIV infection from receiving treatment.*

9.1.5 Geriatric Use

A single subject ≥65 years of age was treated with ROCTAVIAN in clinical studies. Clinical studies of ROCTAVIAN did not include sufficient numbers of subjects ≥65 years of age to determine whether the efficacy or safety differs compared to younger subjects.

10. CONCLUSIONS

ROCTAVIAN has demonstrated efficacy with reduction in ABRs, and the primary efficacy endpoint in Study 270-301 was met. The mean ABR in the EEP, as of the 3-year data cutoff, was 2.6 bleeds/year with a compared with a mean ABR of 5.4 during the lead-in period with a mean difference in ABR was -2.8 (95% CI: -4.3, -1.2) bleeds/year. Durability of effect does decline over time. However, the majority (80%) of subjects remained off RP at the time of the 3-year data cutoff. A CDx for detection of total antibodies to AAV5 is set to receive premarket approval simultaneously; the test will aid in selection of subjects for ROCTAVIAN treatment.

The most common AEs included elevations in ALT as defined in the protocol, infusion reactions, nausea, fatigue, headache, diarrhea, and abdominal pain. The majority of subjects in clinical trials received corticosteroids for ALT elevation in an attempt to preserve transgene expression and to reduce hepatotoxicity. The side effects of corticosteroid therapy, especially with prolonged use at high doses, are of concern. The most common (≥ 10%) side effects of corticosteroids included acne, rash, weight gain, cushingoid, HTN, insomnia, folliculitis, abdominal pain, vision disorders, and mood disorders. Grade 3 infections occurred in 7 subjects of whom 3 required IV antimicrobial therapy. There were 14 SAEs from corticosteroids or other IS use and included infections, cataract, diabetes, HTN, bone fractures, diarrhea, diverticulitis, and gastrointestinal hemorrhage. Clinical trial data on AEs associated with corticosteroid use are described in section 6.1 of the label. Monitoring for corticosteroid side effects is in the highlights and section 5.2 of the label, and criteria for selection of patients for ROCTAVIAN includes assessment for suitability of IS in section 2 of the USPI. The Applicant has conveyed the need for, and risks of prolonged IS in the HCP guide and patient information (voluntary endeavors by the Applicant); careful patient selection has been emphasized in the USPI and HCP guide. There is a potential for hepatocellular carcinoma (HCC), which is adequately described in the USPI and will be evaluated in the 15-year long-term extension study. The safety profile is acceptable.

Thus, considering the magnitude of the effect on bleeding events, the ability of the majority of subjects to remain off RP with follow-up of at least 3-years, and the fact that the risks especially

related to corticosteroid use are consistent with use in other nonmalignant conditions, the overall benefit-risk profile favors approval of ROCTAVIAN in patients with severe hemophilia A.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

See Table 35 below.

Table 35. Risk-Benefit Considerations and Recommendations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Hemophilia A is a hereditary bleeding disorder characterized by recurrent bleeding which, if left untreated, leads to chronic arthropathy, muscular atrophy, and deformities. • Treatment of bleeds may delay these complications but does not prevent them. • Primary prophylaxis with regular FVIII injections or emicizumab initiated at an early age is the standard of care. • FVIII replacement products require frequent lifelong infusions. Emicizumab is given subcutaneously but still requires lifelong, regular therapy; it cannot be given for treatment of bleeds. The psychosocial impact of this commitment can also be debilitating.	• Hemophilia A is a hereditary, life-threatening disease. • Hemophilia A can have a debilitating impact on physical and psychosocial well-being.
Unmet Medical Need	• Available treatment options requiring lifelong infusions/injections include: - Plasma-derived and recombinant VIII products are approved for treatment and prophylaxis of hemophilia A - Emicizumab, a monoclonal antibody given subcutaneously	• There is an unmet need for the lifelong requirement for FVIII replacement infusions or other therapy in patients with hemophilia A for the prevention of bleeding.
Clinical Benefit	• One trial informed the safety and effectiveness of ROCTAVIAN. • The main efficacy outcome was a noninferiority test of ABR (all bleeds) during the efficacy evaluation period (EEP) after ROCTAVIAN treatment compared with ABR during the pretreatment lead-in period. • The mean ABR (all bleeds) during the EEP with ROCTAVIAN treatment was 2.6 bleeds/year compared to a mean ABR of 5.4 bleeds/year during the lead-in period with a mean difference in ABR was -2.8 (95% CI: -4.3, -1.2) bleeds/year • Durability of benefit: FVIII activity declines over time, and an increasing number of subjects return back to routine prophylaxis with time.	• The evidence of clinical benefit of ABR was demonstrated by reduction of bleeds in the efficacy evaluable period post-treatment. • ABR (all bleeds) represents an appropriate clinical benefit endpoint for subjects with hemophilia A. • Despite waning durability with time, the majority of subjects were still off routine prophylaxis at 3 years post-treatment, which represents clinical benefit.
Risk	• The most common adverse reactions with ROCTAVIAN (incidence ≥5%) were infusion reactions, ALT elevation, nausea, headache, fatigue, diarrhea, vomiting, and abdominal pain. • The majority of subjects (92 of 112) required corticosteroids for ALT elevation; 40 of 92 subjects used alternate immunosuppressants. • Long-term risk of hepatocellular carcinoma (HCC) and other malignancy exists • Risks of thrombosis with FVIII levels > ULN and inhibitors to FVIII exist, but none were reported in trial.	• ROCTAVIAN has an acceptable safety profile, and the risks are addressed in the package insert, including long-term monitoring for HCC. • The risks associated with corticosteroid or other immunosuppressant use are as those for their use in other disorders.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• The most substantial risks of treatment are hepatotoxicity, infusion reactions, and the potential for HCC and other malignancies. Risks of immunosuppression to mitigate hepatotoxicity and preserve FVIII activity exist. • Risk management plans include the warnings and precautions, and common adverse events listed in the prescribing information.	• The risks can be mitigated through routine medical management, adequate information on monitoring and management in the USPI, and voluntary measures by the Applicant for including a Guide for HCPs, the Patient Card, and shared decision making. • The data do not support the need for a risk evaluation and mitigation strategy.

Abbreviations: ABR, annualized bleeding rate; ALT, alanine aminotransferase; CI, confidence interval; FVIII, Congenital factor VIII; HCP, health care professional; ULN, upper limit of normal; USPI, United States Prescribing Information.

11.2 Risk-Benefit Summary and Assessment

ROCTAVIAN has demonstrated efficacy with reduction in ABRs during the EEP compared to baseline ABRs and increased FVIII expression. The mean ABR during the EEP was 2.6bleeds/year compared to a mean ABR of 5.4 during the baseline lead-in period on RP with FVIII products. The mean difference in ABR was -2.8 (95% CI: -4.3, -1.2) bleeds/year. The NI analysis met the pre-specified NI margin, indicating the effectiveness of ROCTAVIAN. The median FVIII activity levels (rounded to nearest integer) as assessed by the CSA were 39, 24, 13, and 10 IU/dL at 6, 12, 24, and 36 months respectively. Despite waning FVIII levels and increasing numbers of subjects returning to RP time, inability to predict who will benefit from ROCTAVIAN and for how long, and the optimal IS regimen, the majority of subjects treated with ROCTAVIAN remained off RP and derived clinical benefit from ROCTAVIAN at the 3-year data cutoff post-treatment.

The most commonly reported AEs included ALT elevation, infusion reactions, fatigue, nausea, headaches, vomiting, diarrhea, and abdominal pain. There is concern for AEs related to corticosteroid or other IS use since a majority of subjects received IS in clinical trials and are expected to do so post approval to mitigate hepatotoxicity and preserve transgene expression. Evaluation for suitability for IS prior to ROCTAVIAN treatment has been emphasized in the label and patient information. Monitoring for AEs related to corticosteroid use has been included in section 5.2 of the label, and clinical trial experience with corticosteroids and other IS has been included in section 6.1 of the USPI. There is a potential for HCC, which is adequately described in the USPI brochure. Patients with a high risk of HCC will be monitored with liver ultrasound and alpha fetoprotein testing at regular intervals for 5 years, and patients are encouraged to enter a long-term (15-year) follow-up study to monitor safety and efficacy. The possibility of risk of other malignancies has also been conveyed in the USPI. Emphasis has also been placed in the USPI on the need for close monitoring and follow-up for safety and efficacy, especially for the first year following ROCTAVIAN treatment. Applicant has conveyed information on need for and risks of IS in the voluntarily provided HCP Guide and Patient Information brochure. The safety profile is acceptable.

The benefit-risk profile of ROCTAVIAN is favorable in adults with severe hemophilia A.

11.3 Discussion of Regulatory Options

The available data support regular approval for the indication of ROCTAVIAN in patients with congenital severe hemophilia A (FVIII activity <1 IU/dL).

In the original submission of this BLA in 2020, FVIII activity levels between weeks 23 and 26 following ROCTAVIAN had been proposed as the surrogate endpoint for the clinical benefit endpoint of ABR. However, due to the difficulties of accepting FVIII activity as a surrogate endpoint as outlined in Section 2.6, the primary efficacy endpoint was changed to ABR (all bleeds). Bleeding in patients with hemophilia is a contemporaneous event that is associated with a given FVIII activity level. In general, the lower the FVIII activity, the higher the risk and rate of observed bleeding events. Thus, there is really no need for a surrogate endpoint since the clinical event of bleeding and the FVIII activity level are not sequential in their occurrence. Thus, approval is based on the clinically meaningful endpoint of ABR (all bleeds). Given the risks of IS, uncertainty of long-term risks, characteristics of the trial population (only subjects with severe hemophilia included), availability of newer treatment options for hemophilia A that reduce the burden of IV administration (e.g., emicizumab and ALTUVIIIO), difficulty in the ability to predict upfront as to

who will benefit and for how long, uncertainties regarding the optimal immunosuppressive regimen in GT for hemophilia A in general, and the small number of patients with moderate hemophilia that are expected to be eligible for this therapy, the indication is restricted to patients with severe hemophilia A.

In AAV vector-based gene therapies, pre-existing neutralizing anti-AAV antibodies may impede transgene expression at desired therapeutic levels. In the clinical studies with ROCTAVIAN, a TAb assay to detect pre-existing antibodies to AAV5 was used to select patients for ROCTAVIAN treatment. Only patients with a result of "not detected" on this assay were eligible to receive ROCTAVIAN. This assay (AAV5 DetectCDx™ total antibody assay by ARUP Laboratories) is being approved as a CDx by CDRH contemporaneously to aid in appropriate selection of patients for ROCTAVIAN treatment.

11.4 Recommendations on Regulatory Actions

In consideration of granting priority review and regular approval to ROCTAVIAN in adults with severe hemophilia A, the clinical reviewer considered the magnitude of benefit observed in the ABR post-treatment with a one-time administration of the product.

The Applicant has provided substantial evidence of effectiveness based on a single adequate and well-controlled clinical trial, with supportive evidence from the initial clinical investigation and preclinical studies. The evidence of treatment effect in the single adequate and well-controlled trial is based on a clinically meaningful and statistically significant benefit in ABRs in a sufficient number of subjects, utilizing the subjects' own ABRs collected prospectively for at least 6 months prior to ROCTAVIAN administration as the control, which is appropriate. The risks of therapy, including the risks from IS use that will be required in the majority of patients, are within the scope of management of routine clinical practice and have been adequately addressed in the USPI.

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

Based on the available data, the clinical reviewer recommends regular approval of ROCTAVIAN.

11.5 Labeling Review and Recommendations

The draft label has been modified to reflect the efficacy and safety data presented in this memo.

The major changes to the draft label pertaining to safety include the following:

1) The corticosteroid regimen used in the rollover population of 112 subjects that informed efficacy and safety was placed in section 2.3 for reasons outlined in Section 6.1.12.5. AEs related to corticosteroids and AIS use were incorporated in section 6.1; monitoring for and management of AEs related to corticosteroid use was placed in highlights and section 5.2.
2) Monitoring recommendations for ALT elevation were changed for much closer monitoring than proposed by the Applicant
3) Monitoring for HCC in subjects at high risk for HCC was added

The major changes to the draft label pertaining to efficacy include the following:

1) Removal of data on FVIII usage since this is not the primary or key secondary endpoint
2) Removal of p-values for ABR, as the FDA does not agree with the superiority claim by the Applicant
3) Addition of language on durability of efficacy with inclusion of subjects, not only those who went back on RP but also those for whom ROCTAVIAN was considered never to have worked or stopped working irrespective of return to RP
4) Revision of the ABR table to include imputation for those subjects who used prophylaxis
5) Data on FVIII activity levels moved to section on clinical pharmacology

The section on Use in Special Populations was expanded to highlight the lack of adequate data to inform both safety and efficacy in patients with HIV, current or prior history of inhibitors to FVIII, and hepatic and renal impairment.

11.6 Recommendations on Postmarketing Actions

No postmarketing requirement or postmarketing commitment studies are requested at this time. Routine pharmacovigilance will be done postmarketing. The safety concerns pertaining to the use of IS to manage hepatotoxicity and preserve transgene expression was raised to the Applicant by the pharmacovigilance review team. The Applicant has proposed a risk management plan that includes information in the USPI pertaining to safety, including suitability for ROCTAVIAN based on assessment of suitability for IS under patient selection criteria; a Patient Information that discusses the risks and importance of monitoring; and a Guide for Health Care Professionals that emphasizes the short-term and long-term risks, uncertainties surrounding the use of ROCTAVIAN, the importance of shared decision making prior to treatment, and subsequently, the importance of close monitoring and follow-up. The Patient Information and Healthcare Professional Guide are voluntary documents submitted by the Applicant. Additional voluntary measures proposed by the Applicant include focused training of hemophilia treatment centers to ensure appropriate patient selection and mitigation measures to ensure safe and appropriate use, with assessment of site readiness with dry runs and, a Shared Decision-Making Tool for hemophilia treatment that is being developed by the World Federation of Hemophilia in collaboration with relevant stakeholders, international experts including the National Hemophilia Foundation in the U.S., and an independent medical education organization (COR2ED). The goal of having this tool is to enable patients to make a truly informed decision on hemophilia treatment. Education on GT is also being offered through the Gene Therapy Learning academy to enable patients and families to understand the risks versus benefits of GT.

Subjects with hemophilia in clinical trials will be followed in a long-term extension study, Study 270-401, for a total of 15 years. Two additional studies—270-601 and 270-801—have been proposed to collect data up to 15 years in the postmarketing setting. Study 270-601will prospectively enroll patients who receive commercial product, while Study 270-801 will analyze aggregate data collected within hemophilia registries on subjects who receive GT.

Reviewer Comments:

- *The need for a REMS was discussed given the extent of IS use, but it was not recommended given that corticosteroid use, as will be used for subjects receiving ROCTAVIAN, falls within the scope of routine clinical practice, and healthcare providers are well versed in the monitoring for, and management of, AEs related to corticosteroid or*

other IS use. A REMS would not address the concern for adverse events due to noncompliance with appropriate follow-up. Statutory requirements for REMS were not met. Collection of Grade 3 and higher AEs related to IS use will be added to the two postmarketing, long-term follow-up studies (270-601 and 270-801).

- *The clinical reviewer finds the above proposed measures adequate to inform the safety of ROCTAVIAN.*

APPENDIX A. FDA GROUP TERMS

FDA Group terms and corresponding and Preferred Terms used in this review

FDA Group Term	Preferred Terms
Abdominal pain	Abdominal pain, abdominal discomfort, abdominal distension, abdominal tenderness, abdominal pain upper, abdominal pain lower, epigastric discomfort
Anaemia (anemia)	Anaemia, iron deficiency anaemia
Anxiety	Anxiety, feeling jittery, nervousness, restlessness, agitation, feeling rushed, post-traumatic stress disorder
Bone fracture	Acetabulum fracture, lower limb fracture, tibia fracture, stress fracture
Cushingoid	Cushingoid, fat tissue increased, face oedema, swelling face
Edema (oedema)	Oedema, oedema peripheral, peripheral swelling
Fatigue	Fatigue, lethargy, malaise, sluggishness
Gastroesophageal reflux disease (GERD)	GERD, dyspepsia
Glucose tolerance impaired	Glucose tolerance impaired, glycosylated hemoglobin increased, hyperglycaemia (hyperglycemia), diabetes mellitus, steroid diabetes
Hypertension	Hypertension, blood pressure increased, blood pressure diastolic increased
Increased appetite	Increased appetite, hunger
Insomnia	Insomnia, sleep disorder
Mood disorders	Depression, depressed mood, mood altered, mood swings, irritability, anger, substance-induced psychotic disorder
Rash	Rash, rash maculo-papular, rash pustular, dermatitis acneiform, papulopustular rosacea, urticaria
Tachycardia	Tachycardia, heart rate increased, sinus tachycardia
Tremor	Tremor, intention tremor
Vision disorders	Photopsia, glaucoma, vision blurred, cataract, chorioretinopathy