

Application Type	BLA Resubmission after Previous Complete Response Letter
STN	125720/0/69
CBER Received Date	Resubmission after Previous Complete Response Letter: September 29, 2022 Major Amendment: February 15, 2023
PDUFA Goal Date	June 30, 2023
Division / Office	DCEH/OCE/OTP
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Priority Review	Yes
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Review Completion Date / Stamped Date	Original Version: June 30, 2023 Revised Version: February 15, 2024
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Applicant	Biomarin Pharmaceutical Inc.
Established Name	valoctocogene roxaparvovec-rvox
(Proposed) Trade Name	ROCTAVIAN
Pharmacologic Class	Adeno-associated virus vector-based gene therapy
Dosage Form(s) and Route(s) of Administration	Solution for intravenous infusion containing 2×10^{13} vg valoctocogene roxaparvovec-rvox per mL, in vials containing an extractable volume of not less than 8 mL (16×10^{13} vg)
Dosing Regimen	Single dose at a recommended dose of 6×10^{13} vector genomes (vg) per kilogram of body weight
Indication(s) and Intended Population(s)	ROCTAVIAN is an adeno-associated virus vector-based gene therapy indicated for the treatment of adults with severe hemophilia A (congenital factor VIII deficiency with factor VIII activity < 1 IU/dL) without pre-existing antibodies to adeno associated virus serotype 5 detected by an FDA-approved test.

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GLOSSARY

AAV5	Adeno-associated virus serotype 5
ABR	Annualized Bleeding Rate
AE	Adverse Event
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CI	Confidence interval
CMC	Chemistry, Manufacturing, and Controls
COVID-19	Coronavirus disease 2019
CSR	Clinical Study Report
DCO	Data Cut-off Date
DNA	Deoxyribonucleic Acid
eCTD	electronic Common Technical Document
e-diary	Electronic diary
EEP	(ABR) efficacy evaluation period
EU	European Union
FDA	Food and Drug Administration
FVIII	Factor VIII
FU	Follow-up
gc	Genome copies
HA	Hemophilia A
IA	Interim Analysis
IND	Investigational New Drug
IU	International Unit
IV	Intravenous
mITT	Modified Intent-to-Treat
NAb	Neutralizing Antibodies
NI	Non-inferiority
kg	Kilogram
RP	Routine Prophylaxis

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
UK	United Kingdom
USA	United States of America
vg	Vector genomes
vg/kg	Vector genomes per kilogram

1. Executive Summary

ROCTAVIAN is an investigational one-time single-dose gene therapy for the treatment of adults with severe hemophilia A (HA). ROCTAVIAN consists of adeno-associated virus serotype 5 (AAV5) capsids containing a transgene encoding the B-domain deleted SQ form of the human coagulation factor VIII under the control of a liver-specific promoter.

The Applicant submitted an original Biologics License Application (BLA) for both accelerated approval and traditional approval of ROCTAVIAN to the Food and Drug Administration (FDA) in December 2019, and FDA issued a complete response decision in August 2020. The deficiencies included inability to establish that FVIII:C levels at Weeks 23-26 could be a surrogate endpoint reasonably likely to predict annualized bleeding rate (ABR), limited sample size and follow-up (FU) duration, and inability to extrapolate results from another ROCTAVIAN study with a longer FU due to different clinical activities observed between that study and the main study on the to-be-commercialized version of ROCTAVIAN.

This class 2 BLA submission is intended to provide a complete response to the complete response letter issued for the original BLA submission. The submission includes data on 170 subjects with severe HA who were treated with ROCTAVIAN at one of four dose levels (6E12, 2E13, 4E13, or 6E13 vg/kg) in one of five ongoing clinical trials. The maximum follow-up was 5.5 years post-treatment. The efficacy database consists of the 134 subjects treated in Study 301, and the safety database includes the 170 subjects treated in the five ongoing trials.

Study 301 is an ongoing phase 3, single-arm, multi-regional trial investigating the safety and efficacy of a single dose of 6E13 vg/kg of ROCTAVIAN in adult male HA subjects with residual FVIII levels ≤ 1 IU/dL, without detectable pre-existing antibodies to the AAV5 capsid, and without a documented history of a detectable FVIII inhibitor. Subjects must have been on prophylactic FVIII replacement therapy for at least 12 months prior to study entry. After intravenous infusion of ROCTAVIAN, subjects may continue exogenous prophylactic FVIII replacement therapy for 4 weeks, a time when ROCTAVIAN was expected to manifest its effect. Subjects would then remain in Study

301 for 5 years, and then be transferred to a long-term follow-up study for a total FU of 15 years post treatment. Study follow-up visits are weekly through Week 36, then biweekly through Week 52, then every 4 weeks in Year 2, and every 6 weeks in Years 3-5. Subjects deemed to experience treatment failure would follow an abbreviated visit schedule after Week 52 by attending visits every 12 weeks and end-of-year visits during Years 2-5. The data cut-off date was set so that all treated subjects in Study 301 had at least 3 years of FU post treatment.

Study 301 consisted of two cohorts: the Directly Enrolled (DE) cohort (N=22, with 2 HIV-positive subjects) and the Rollover (RO) cohort (N=112, no HIV-positive subjects). There are two differences between the two cohorts. First, they differ in how baseline data were collected: RO subjects had completed approximately 6 months of participation in a non-interventional study where bleed episodes and FVIII product use data were prospectively collected to serve as baseline prior to their entry into Study 301, whereas baseline data for the DE subjects were retrospectively collected. The second difference is in the immunosuppression (IS) regimen, which is extended in the RO cohort. The RO cohort is the primary efficacy analysis set and the DE cohort is supportive with about one more year of FU than the RO cohort.

The primary objective was to demonstrate non-inferiority (NI) in ABR after ROCTAVIAN treatment during the efficacy evaluation period (EEP) compared to ABR with FVIII prophylaxis during baseline, in the RO cohort. All bleeding episodes, regardless of treatment, were counted towards ABR. 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. The primary efficacy analysis was an NI comparison between the EEP ABR and baseline ABR in the RO cohort, with an NI margin of 3.5 bleeds/year on the mean difference between the ABRs.

Secondary efficacy objectives included assessment of other endpoints, e.g., FVIII:C level and usage of exogenous FVIII replacement therapy, at various timepoints, and further descriptive characterization of bleeding episodes.

The primary efficacy analysis yielded an estimate of the mean ABR difference (EEP - Baseline) of -2.8 bleeds/year with a 95% confidence interval of (-4.3, -2.1) bleeds/year, therefore meeting the NI success criterion which required the upper bound of the CI to be less than 3.5, indicating the effectiveness of ROCTAVIAN. The mean (standard deviation [SD]) of Baseline ABR was 5.4 (6.9) bleeds/year, and was 2.6 (6.2) bleeds/year for EEP ABR. The total EEP for all RO subjects was 342.8 person-years. A total of 13 subjects used factor VIII products or emicizumab for prophylaxis during the EEP for a total of 14.4 person-years, with a median start time at 2.2 (range: 0.1 to 3.3) years. For the primary analysis, an ABR of 35 bleeds/year was imputed for these 14.4 person-years when subjects were on prophylaxis during EEP.

Most RO subjects (92/112, 82.1%) who received ROCTAVIAN in Study 301 also received corticosteroids to suppress the immune system for the gene therapy to be effective and safe, with a median duration of 8.0 (range: 0.7 to 27.2) months. For the DE cohort, 14/22 (63.6%) subjects also received corticosteroids for the same purpose, with a median duration of 5.1 (range: 1.8 to 18.1) months.

In the RO cohort, 5 subjects (4.5%) did not respond to ROCTAVIAN treatment and 17 subjects (15.2%) lost response to ROCTAVIAN treatment over a median time of 2.3 (range: 1.0 to 3.3) years. In the DE cohort, 1 subject (4.5%) did not respond and 6 subjects (27.3%) lost response over a median time of 3.6 (range: 1.2 to 4.3) years.

FDA Office of Plasma Protein Therapeutics reviewers has concluded that transgene FVIII protein (circulating in plasma of ROCTAVIAN treated subjects) is different from the endogenous human FVIII protein (in normal pooled plasma which is used as a reference standard in clinical FVIII activity assays), and is also different from those of XYNTHA/REFACTO concentrate (FVIII exogenous replacement products). As such, transgenic FVIII:C levels may not be mapped to severity of HA using criteria developed based on endogenous human FVIII protein, i.e., a transgenic FVIII:C level between 1 and 5 IU/dL does not mean the subject's phenotype was converted to moderate HA.

Different assays and different agents yield different readings of FVIII:C from the plasma sample after ROCTAVIAN treatment. In this review, I used the FVIII:C levels measured by the chromogenic substrate assay at a central lab. For most RO subjects, FVIII:C experienced substantial decline over time. The 50%ile was 38.5 IU/dL at Week 26 visit, 24.0 at Week 52, 11.6 at Week 104, and 8.2 IU/dL at Week 156 visit. A total of 22 subjects (20%) had 0.0 of FVIII:C reported or imputed for the Week 156 visit.

Regarding safety, among 170 subjects treated with ROCTAVIAN, there was one death (b) (6). One subject was diagnosed with acinic cell carcinoma of the tail of the parotid gland. Another subject was diagnosed with B-cell type acute leukemia. The Applicant assessed these events as unrelated to ROCTAVIAN.

In summary, the efficacy results of Study 301 provided sufficient statistical evidence to support the non-inferiority of ROCTAVIAN treatment to factor VIII prophylaxis in terms of ABR during the efficacy evaluation period starting around Day 33 with a median follow up of 3.1 (range: 1.8 to 3.8) years after ROCTAVIAN treatment. The majority of patients who received ROCTAVIAN also received corticosteroids to suppress the immune system for the gene therapy to be effective and safe. Treatment response to ROCTAVIAN may decrease over time.

2. Clinical and Regulatory Background

The investigational product under consideration, ROCTAVIAN (valoctocogene roxaparvovec-rvox), is a single-dose adeno-associated virus serotype 5 (AAV5) vector-based gene therapy. The vector is replication-incompetent and consists of an AAV5

capsid containing a transgene encoding the B-domain deleted SQ form of the human coagulation factor VIII (hFVIII-SQ) under the control of a liver-specific promoter. It is intended that a single intravenous (IV) infusion of ROCTAVIAN will achieve prolonged endogenous expression of active human FVIII protein in the plasma, synthesized from vector-transduced liver tissue, that will functionally replace the missing coagulation factor VIII needed for effective hemostasis in hemophilia A patients. ROCTAVIAN was also known as BMN270 or AAV5-hFVIII-SQ during clinical development. The proposed dose is 6E13 vector genomes per kilogram of body weight (vg/kg).

The proposed indication is “*ROCTAVIAN is an adeno-associated virus vector-based gene therapy indicated for the treatment of adults with severe hemophilia A (congenital factor VIII deficiency)* (b) (4) *without antibodies to adeno associated virus serotype 5 detected by an FDA-approved test and without a history of factor VIII inhibitors.*”

2.1 Disease or Health-Related Condition(s) Studied

Hemophilia A (HA) is an X-linked recessive bleeding disorder caused by mutations in the F8 gene, which codes for the factor VIII (FVIII) protein, an essential cofactor in the coagulation cascade. The mutations lead to expression of inadequate quantities of FVIII or a biologically dysfunctional FVIII, resulting in a defective coagulation process. The prevalence of hemophilia A is commonly reported as 1 in 5,000 in the male population. However, these estimates are affected by access to diagnosis, registry and treatment.

FVIII activity (FVIII:C) level, with a normal range of 50 to 150 international unit (IU)/dL, is used to classify HA into categories of severe HA (FVIII:C < 1%), moderate HA (FVIII:C 1% to < 5%), or mild HA (FVIII:C 5% to < 40%). In the absence of treatment, patients with mild HA are expected to bleed excessively only after surgery, tooth extractions or major injuries, while those with severe HA are expected to bleed spontaneously or after slight, otherwise insignificant trauma. Patients with moderate HA are expected to experience occasional spontaneous bleeding, and prolonged bleeding with minor trauma or surgery. The hallmark clinical characteristic of untreated severe FVIII deficiency is bleeding (spontaneous or after trauma) into major joints such as ankles, knees, and elbows, eventually leading to painful and disabling hemophilic arthropathy. Intracranial bleeds and bleeds into internal organs may be life-threatening. Bleeding risk may vary widely among patients with severe HA, as well as in moderate HA.

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

For decades, the standard of care for HA without inhibitors (neutralizing allo-antibodies that inhibit FVIII activity) has been systemic protein replacement therapy with IV infusion of plasma-derived or recombinant FVIII factors. Types of usage and related Food and Drug Administration (FDA) licensed indications include:

- Episodic (on-demand) treatment where replacement factor is given at the time of bleeding
- Continuous (regular) routine prophylaxis where factor is given to prevent bleeding for at least 45 of 52 weeks (85%) of a year
- Intermittent (periodic) prophylaxis or peri-operative management where factor is given to prevent bleeding for short periods of time such as during and after surgery.

While safe and effective, factor replacement therapies have the following challenges that prevent them from achieving elimination of breakthrough bleeding events and progressive joint deterioration in all patients.

- The most serious complication is the formation of inhibitors that preclude the hemostatic effect of factor replacement in 30% of severe HA patients and 5% to 10% of non-severe HA patients. Inhibitors are associated with increased morbidity and mortality, with only limited additional treatment options until recently (e.g., bypassing agents, immune tolerance induction, and recently emicizumab).
- Frequent IV infusions impose heavy treatment burden and may lead to poor adherence and inadequate routine prophylaxis, which then result in a seesaw pattern in FVIII availability and low trough levels between infusions.

In the last decade, chemical modification or bioengineering of FVIII have given rise to approved extended half-life recombinant (EHL-rFVIII) factor replacement therapies, reducing infusion frequency from about every two days to about every four days and maintaining higher trough levels for more effective bleeding prevention. A regimen may be individually adjusted to less or more frequent dosing based on bleeding risks.

During the same time, there has been an explosion in the development of nonfactor therapies, i.e., new therapeutic products based on new mechanisms other than the replacement of the deficient FVIII. Some approaches enhance coagulation by inhibiting physiological anticoagulants in the natural anticoagulant pathways to rebalance hemostasis. Examples include Fitusiran, an investigational RNA interference therapeutic targeting antithrombin and Concizumab, a humanized anti-tissue factor pathway inhibitor monoclonal antibody. These therapies are intended to treat patients with hemophilia A or B, with or without inhibitors, and are administered subcutaneously at a weekly or lower frequency.

The most recent advance in nonfactor therapy for hemophilia A is the approval of HEMLIBRA® (emicizumab-kxwh), “indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors.” HEMLIBRA is an engineered humanized bispecific monoclonal

antibody that binds to and bridges both activated coagulation factor IX (FIX) and coagulation factor X (FX), thereby mimicking or substituting the function of activated FVIII. It was initially approved in November 2017 for HA patients with inhibitors; the indication was later expanded in October 2018 to include patients without inhibitors. It is subcutaneously injected at a weekly to once every four weeks frequency. HEMLIBRA has been used more widely in the past few years in developed countries.

While these nonfactor therapies have the advantages of a subcutaneous mode of administration, long half-life, and no expectation to induce inhibitors to FVIII or be inhibited by existing FVIII inhibitors, they do have other safety concerns, e.g., thrombotic events. In addition, HA patients on emicizumab routine prophylaxis still need factor replacement to treat bleeds or prevent surgery bleeds.

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

On August 24, 2022, European Commission granted conditional marketing authorization (CMA) to Roctavian for use in the European Union *for the treatment of severe haemophilia A (congenital factor VIII deficiency) in adult patients without a history of factor VIII inhibitors and without detectable antibodies to adeno associated virus serotype 5 (AAV5)*. CMA are valid for one year and can be renewed annually. The marketing authorization application was re-submitted to the European Medicines Agency on June 25, 2021, including ≥ 1 year follow-up from the 134 participants in the main study, Study 301, after its withdrawal on November 4, 2020.

Information on the benefit and post-authorization conditions are excerpted, in italicized form, from the <https://www.ema.europa.eu/en/medicines/human/EPAR/roctavian-0#overview-section> website:

What benefits of Roctavian have been shown in studies?

A main study involving 134 adult male patients with severe haemophilia A found that Roctavian was effective at increasing the level of factor VIII activity and that this increase was sustained for at least 2 years. 104 weeks after receiving a single dose of the medicine, 75.4% of the patients had an average factor VIII activity level of at least 5 international units per decilitre (IU/dL), which is a measure of mild haemophilia. In addition, the yearly number of bleeding episodes decreased by 85.5% and the need for additional factor VIII replacement treatment dropped by 97.5%.

What information is still awaited for Roctavian?

Since Roctavian has been given conditional authorisation, the company that markets Roctavian will provide additional data from ongoing studies on the long-term safety and effectiveness of the medicine in patients with severe haemophilia A and will carry out a study on when to best start corticosteroid treatment in these patients to avoid liver problems. The company will also

provide data from a registry of patients treated with Roctavian to study its long-term safety and effectiveness.

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

Under review is a Biologics License Application (BLA) Class 2 resubmission providing a complete response to the Food and Drug Administration (FDA) complete response letter (CRL) issued for the original BLA submission.

Reviewer Comment #1

The clinical development, including the applicant's discussions and negotiations with FDA, has been complex as more knowledge about this first-in-class product emerged and the protocol and statistical analysis plan (SAP) were revised accordingly. I will focus only on the critical questions and (final) negotiation outcomes in this review memo, often synthesizing information from multiple rounds of interactions and extensive documentations. I will not cover non-essential elements, e.g., episodes of treated bleeds and quality of life endpoints, to maintain focus. I have also changed some terms used and consolidated the exposition of analyses and results for ease of comprehension without changing the substance. For example, there were five efficacy analysis sets defined in Study 301, the main study, that included various combinations of two cohorts and whether the two HIV-positive subjects were included. I instead focus exposition on the two clearly defined cohorts with mnemonic terms and include additional discussions of the two HIV-positive subjects when needed. I have also abbreviated the study identifiers from 270-xxx to xxx. For example, I will refer to Study 270-301 as Study 301.

Designations granted by the FDA

- Orphan Drug Designation (#15-5109) for treatment of Hemophilia A. February 29, 2016.
- Breakthrough Therapy Designation for treatment of Hemophilia A. October 24, 2017.
- Regenerative Medicine Advanced Therapy Designation. March 4, 2021.

Milestones and important interactions

- Pre-IND Meeting. February 16, 2017. Minutes dated March 17, 2017.
- The original submission under IND 17659, including the protocol for Study 301, the main study. September 1, 2017.
- The original BLA submission for BLA 125720/0/0. December 23, 2019.

- CRL letter issued by the FDA for the original BLA. August 18, 2020.

Prior to submitting the original BLA, the applicant intended to apply for accelerated approval based on results on FVIII activity at Weeks 23-26 post-treatment, as a surrogate endpoint for the clinical endpoint of annualized bleeding rate (ABR). However, the applicant requested consideration for both the accelerated approval and traditional approval pathways in the BLA, citing “*a significant reduction in bleeds following infusion.*”

The main study supporting the BLA was Study 301, which included two cohorts: Directly Enrolled (DE) cohort and Rollover (RO) cohort. The RO cohort was to enroll 110 subjects who had been on prophylactic FVIII replacement therapy and whose baseline data had been collected prospectively in a non-interventional study (NIS, Study 902), and the primary efficacy endpoint was annualized bleeding rate (ABR) 52 weeks post-treatment. The original BLA, however, included only efficacy data from an interim analysis (IA) of the DE cohort. The DE cohort treated 22 subjects whose baseline data was collected retrospectively, and the primary efficacy endpoint was proportion of FVIII activity responders – subjects whose median FVIII activity level during Weeks 23-26 post treatment was ^{(b) (4)} IU/dL – to serve as a surrogate endpoint for ABR. The primary analysis was a test against the null hypothesis that this proportion was less than or equal to 10%. This analysis was intended to support accelerated approval in conjunction with evidence from Study 301 data that FVIII responder status was reasonably likely to predict ABR.

The original BLA also included data from Study 201, a non-IND (Investigational New Drug), first-in-human (FIH), dose escalation study conducted in the United Kingdom (UK). Subjects were treated at four dose levels, including seven subjects treated with the same dose as the one used in Study 301. These seven subjects had follow-up (FU) data for around 3 years and were to be considered for extrapolation of effect durability to Study 301 subjects, given the limited FU in Study 301 subjects and that durability was an important component of benefit-risk assessment.

- Key meetings and communications in the period from the issuance of the CRL to the resubmission.
 - Type A meeting. October 5, 2020. Meeting minutes dated October 29, 2020.
 - Pre-BLA meeting. Written Responses Only (WRO). May 16, 2022.
- FDA granted one-year extension requested by the applicant to file the Class 2 resubmission on August 18, 2021, and then again on August 23, 2022.
- BLA Class 2 resubmission to BLA 125720/0/69. September 29, 2022

- The data package had a data cut-off date (DCO) of November 15, 2021, which was based on having followed up all treated subjects in Study 301 for at least two years post-treatment.
- BLA major amendment with updated 3-year data to BLA 125720/0/90. February 15, 2023
 - The updated data package had an updated DCO of November 15, 2022, which was based on having followed up all treated subjects in Study 301 for at least three years post-treatment.
 - This major amendment extended the goal date by an additional three months to June 30, 2023.

Study 301 protocol and statistical analysis (SAP): Most recent versions as of the resubmission and major amendment dates

- Study 301 protocol. Amendment 7 (US). July 15, 2021
- Study 301 statistical analysis plan for two-year analysis (2-year analysis SAP). Version 2.0. December 13, 2021
- Study 301 statistical analysis plan for long-term follow-up analysis (Long-term follow-up analysis SAP). Version 1.0. December 12, 2022

Reviewer Comment #2

Below, to the end of Section 2.5, I summarize issues and considerations identified during the review of the original BLA and/or communicated with the Applicant. These considerations will direct the review of this BLA resubmission. For easier reading, I have not italicized the text below due to its length.

Alignment of clinical context, trial clinical questions and objectives, corresponding endpoints and analyses for durability

HA patients have multiple effective treatment options, and decades of experience have shown a good safety profile with conventional factor replacement therapies. All these therapies require chronic repeat administrations. ROCATIAN will likely be a one-time-only therapy, because immune reactions to the AAV capsid would lead to the formation of neutralizing antibodies that prevent effective repeat of vector delivery, at least with the same AAV serotype. Therefore, the relevant clinical question is how long patients will continue to respond to the one-time ROCATIAN treatment. Potential safety issues in this novel class of therapies, given the high bar on safety profile set by the current factor therapy, may also necessitate comparatively longer-term follow-up and adequate sample size in the registration trials. This consideration on durability led to two agreements between the Applicant and the FDA: (1) The data package for the BLA resubmission would include at least two years of FU for all treated subjects, which subsequently

included at least three years of FU for all subjects. (2) The primary efficacy analysis would include all data up to the last visit prior to the DCO, not just data of set duration for all subjects (e.g., 18 months). In addition, durability will be evaluated by exploratory descriptive analyses. All Study 301 subjects had been treated by the time the original BLA was submitted in December 2019. The 112 Rollover cohort subjects in the proposed labeling population were treated from January 8, 2019 to November 15, 2019.

Primary efficacy endpoint: ABR

In the CR letter, FDA recommended using ABR as the primary efficacy endpoint and the Applicant agreed. All bleeding episodes, regardless of treatment, were counted towards ABR.

Confounding of treatment effect in the ABR endpoint: Use of exogenous FVIII replacement products after ROCTAVIAN treatment

Reasons reported for exogenous FVIII use after ROCTAVIAN treatment include “Treatment for bleed,” “Surgery/procedure,” “Usual Factor VIII prophylaxis,” and “One-time Factor VIII prophylaxis” (OTP). At the time of the original BLA, the Applicant indicated that no reason was collected for OTP. They subsequently collected OTP reasons per FDA request and reported in subject narratives when the information was available. They reported that the most common reasons for OTP was anticipation of physical activity, and four OTP were used for an upcoming procedure such as a tattoo or endoscopy. Frequent OTP use (e.g., weekly for a period in some subjects) will confound the treatment effect of ROCTAVIAN in ABR. The FDA is also concerned that some OTP uses might have been for subclinical bleeds, bleeds occurring without symptoms and which usually cannot be detected by standard physical and ultrasound examinations, and as a result bleeds might have been undercounted.

FVIII activity and assays

FVIII activity (FVIII:C) level, another efficacy outcome, complements the clinical endpoint ABR. ABR is subjective to an extent and is subject to influence of multiple non-treatment factors. FVIII:C is objective, with considerable knowledge about it from years of use and research on exogenous replacement factor products. Severity of HA is characterized in reference to innate FVIII:C. Practitioners adjust replacement product regimens in HA patients to achieve certain FVIII:C levels, including in preparation for surgeries.

At the time, FDA was concerned with the observation of an unexpected assay discrepancy and its implication on the hemostasis effect of transgenic FVIII:C level. Broadly, there are two types of FVIII:C assays: one-stage clotting assays (OSA, clotting) and chromogenic substrate assays (CSA). In plasma of HA patients treated with the recombinant B-domain deleted product XYNTHA/REFACTO, which (b) (4) DNA with ROCTAVIAN, OSA vs CSA have consistently shown a ratio of ~0.7, while this ratio is, unexpectedly, 1.7 and 1.5 in ROCTAVIAN Study 201 and Study 301,

respectively. FDA had requested additional investigations to understand the root cause of this discrepancy between transgenic and recombinant FVIII:C assay results.

FDA had concluded, based on these investigations, that (excerpted from FDA assay review memo with light editing):

- The discrepancy in the ratio of FVIII:C measured by the two assays is not a laboratory error but an indication of **differences between the transgene FVIII protein** (circulating in plasma of ROCTAVIAN treated patients) **and that of the endogenous human FVIII protein** (in normal pooled plasma which is used as a reference standard in clinical FVIII activity assays).
- Similarly, the disagreement between the ratios in ROCTAVIAN patient plasma with those in XYNTHA (also known as REFACTO) supplemented plasma **is likely caused by the different biochemical properties** of the transgene FVIII molecules produced in the liver of ROCTAVIAN patients and those of the XYNTHA/REFACTO concentrate.
- The discrepancies in the FVIII:C assay (both OSA vs. CSA and central reagent vs local reagent) **are caused by the unique features of FVIII molecules expressed in the livers of patients after ROCTAVIAN gene therapy**. Thus, the assay discrepancies cannot be resolved through changing the assay type (OSA or CSA), reagents/brands, or FVIII assay calibrators.
- It is currently unknown as to which of the FVIII forms, either the infused replacement proteins or those expressed by transgene via gene therapy, are more efficient in producing hemostasis in patients (i.e., the relative potency of these proteins is not known). Therefore, it is not possible to recommend which of the FVIII:C assays, OSA or CSA, is more suitable for the use in clinics.

In addition to the above discrepancy, FVIII:C levels measured with OSA was about 1.5 times of that with CSA. The OSA to CSA ratio depends on assay reagents and can range from 1.3 to 2.0. Therefore, the same type of OSA or CSA reagents should be used to monitor FVIII:C levels over time. There are also additional variabilities inherent to hemostasis measurements.

Based on the above observations and conclusions, I have adopted the following considerations for FVIII:C level in reviewing Study 301, which I also applied in the review of the original BLA. These considerations had also been communicated with the Applicant.

- In this review I will use the central lab CSA measurement of FVIII:C level.
- I recognize that there is no single definitive FVIII:C level, but rather a range of numerical readings from different combinations of assay and reagent. There are sometimes comments in the line of “although CSA gives a negligible FVIII:C value, OSA is not negligible so there can be some activity remaining.” However,

despite differences in these numerical readings, the same subject would have just a single hemostasis ability at any one given time.

- We would not map any numerical value of transgenic FVIII:C onto severity of HA (defined by endogenous human FVIII protein) or FVIII:C from replacement products. Rather we would view transgenic FVIII:C in a qualitative way, i.e., in general a higher FVIII:C value might lead to better hemostasis than a lower FVIII:C value using the same assay and reagent, especially when the difference between the two values is large. We should focus on examining the time course of FVIII:C, in combination with bleed pattern and use of replacement product/emicizumab over time, to identify when a subject might have lost response to ROCTAVIAN.
- There are additional factors that complicate interpretation of numerical readings of transgenic FVIII:C level. The lower limit of quantification was 2%. I will sometimes use terms like negligible to refer to levels reported as 0.0 or very low (< 2%) in the submitted data.

Use of immunosuppression (IS), including corticosteroids (CS) or alternative immunosuppressive therapy (AIS)

The majority of Study 301 subjects received reactive IS to control elevations in transaminases and to prevent loss of transgene expression after ROCTAVIAN treatment. On the other hand, in Study 201, subjects received either prophylactic CS (i.e., prior to ALT elevation) or reactive CS (i.e., in response to ALT elevations). Furthermore, the IS use also differed between the DE cohort and the RO cohort in Study 301, with more extended regimen for the latter. Because extending the period of CS in the RO cohort compared to the DE cohort had led to increase in AEs/SAEs, the applicant had proposed to recommend a limited CS regimen different from the one used in the RO cohort, which form the primary basis for efficacy evaluation, in the draft package insert. To support this proposal, the applicant had provided various statistical analyses claimed to show that use of different CS regimens would not have affected the treatment effect (TE) observed in the RO cohort. FDA disagreed with this assessment and had communicated to the Applicant in multiple interactions that it was impossible to assess whether different IS regimens would result in similar TE; there is no data on what the TE would have been in the hypothetical scenario that the RO cohort subjects did not receive the IS regimen they actually had in the trial. While this “no effect on TE” claim cannot be evaluated and the actual IS regimen use was an integral component of the treatment regimen leading to the observed TE, I defer the recommendation on IS regimen to use to the clinical reviewer. The applicant continues to explore the optimal IS regimen. The clinical utility of a prophylactic CS regimen is being explored in Study 303, another ongoing study, and the Applicant plans to conduct an analysis once all subjects (n=20) have been enrolled and completed 52 weeks of FU.

Prior to the BLA resubmission, FDA had communicated to the Applicant that the data package should have a cutoff when all subjects had been off any IS regimen used to control elevations in transaminases and to prevent loss of transgene expression for at least one year. During the pre-BLA meeting prior to the resubmission, Applicant communicated that not all subjects could achieve this off-IS goal by the 2-year DCO. FDA determined that the data package nonetheless included adequate data for the resubmission.

Emicizumab: Impact in the hemophilia A treatment landscape, clinical development programs and benefit-risk assessment in investigational products

Since its first approval by FDA in 2017, emicizumab has started to dominate the HA treatment landscape. It has also impacted the ROCTAVIAN clinical development program: (1) Of the 17 Study 301 subjects who the Applicant reported as resuming routine prophylaxis (RP) after ROCTAVIAN treatment, 8 had switched from using FVIII replacement products to using emicizumab; (2) With chronic use of emicizumab in HA patients, inhibitor titers decrease over time and patients with positive inhibitor tests in the past may now demonstrate a negative inhibitor result (<0.6 BU) if they have not been exposed to FVIII for a long time. The applicant had broadened the eligibility criteria in Study 205, where ROCTAVIAN is planned to be used to treat HA patients with FVIII inhibitors, as a result.

Superiority: Statistical testing and claims

The Applicant planned to test for superiority in ABR of ROCTAVIAN treatment compared to routine prophylaxis (RP). I had determined that superiority testing would be uninterpretable in this context based on review of the original ROCTAVIAN BLA and study results in other gene therapies for hemophilia A and hemophilia B (the review teams agreed), and had communicated this position to the Applicant prior to the BLA resubmission. The reasons for un-interpretability of superiority statistical testing includes the following.

- In general, during the baseline period, a substantial proportion of subjects did not receive an adequate RP regimen or did not comply with the prescribed RP regimen, and as a result the baseline comparator was not well-characterized standard of care (SOC) RP regimens, and therefore could not support a meaningful assessment on superiority. In the original ROCTAVIAN BLA, 8 of the 22 subjects had received FVIII replacement products at an annual rate of 49 to 97 infusions/year during the baseline period, far lower than the 100 to 150 infusions/year expected of SOC RP regimens, even for EHL products. On a side note, 6 of those 8 subjects had an ABR of < 1 bleeds/year and one had an ABR of 2.8, indicating that those subjects might not need SOC RP to control bleeding. The 8th subject had an ABR of 104.6 bleeds/year. I will discuss this later.
- The majority of Study 301 subjects had used immunosuppression (IS), in particular corticosteroids (CS), for an extended time (median 8.9 months in the

RO cohort), which confounded the effect of ROCTAVIAN. It is unethical to withhold IS use during the study, and IS use is an integral component of the ROCTAVIAN treatment regimen of HA patients. It is impossible to assess the efficacy of ROCTAVIAN alone, in the absence of the concomitant use of IS. Therefore, any comparison of ROCTAVIAN effect with RP should consider the additional risks associated with prolonged use of IS.

- As observed in the original BLA and will be made clear in the review of the resubmission below, the efficacy of ROCTAVIAN declines over time, unlike RP which could presumably be used indefinitely. It is unclear what duration (e.g., 3 or 5 years after ROCTAVIAN treatment) should be used for the superiority testing.

On a related note, the European Medicines Agency (EMA) in their June 23, 2022 Assessment Report on ROCTAVIAN for HA patients made a similar decision with a statement that *“the applicant is requested to remove claims of statistical significance / superiority from the SmPC (Summary of Product Characteristic)”*. The reason for EMA was that type 1 error rate was not formally controlled in this open-label trial due to frequent substantive changes to the protocol and SAP, including revisions after DCO, as well as multiple interim analyses. While the frequent modification is true, I consider the inability to precisely control the type 1 error rate of much less importance than the scientific reasons cited above. I had asked the Applicant to use a significance level of 0.05 in the RO cohort instead of the 0.0498 they once proposed to account for IA previously performed in the DE cohort. As we will see in the memo, it is more important to characterize several important aspects of the treatment effect using appropriate descriptive statistics answering relevant questions than aiming for precise type 1 error control that will not change the answer qualitatively.

Role of Study 201

In the initial proposed labeling, in addition to efficacy results from Study 301, the Applicant stated that the 7 subjects treated at the proposed dose of 6E13 vg/kg of ROCTAVIAN in Study 201 continued to show a clinically meaningful response to treatment after 5 years of FU. These statements may misrepresent the efficacy of the to-be-commercialized version of ROCTAVIAN. The FDA CRL letter, dated August 18, 2020, stated that *“..., because the clinical activity of the product is substantially different in the two studies, the results of Study 270-201 are not a reliable indicator of the clinical activity of the Study 270-301 product, which you propose for commercial use.”* Furthermore, Study 201, started as a non-IND FIH exploratory dose-escalation study, was not an adequate and well-controlled study. The review team has decided Study 201 cannot contribute to any efficacy claims in the package insert and will not be reviewed for efficacy.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

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

None notable.

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

5.1 Review Strategy

As of the data cut-off date (DCO) of the Class 2 resubmission, there are 5 ongoing treatment studies with a total of 170 treated subjects: Study 301 (n=134, main study), Study 201 (n=15, dose-escalation study), Study 302 (n=1, 4E13 vg/kg dose), Study 303 (n=19, use prophylactic CS instead of reactive CS as used in Study 301), Study 203 (n=1, AAV5-positive subjects). Study 902, a non-interventional study (NIS), prospectively collected baseline data for Study 301 subjects prior to their entry into Study 301. Study 901, another NIS, collected information on seroprevalence of antibodies and neutralizing factors against AAV serotypes in HA patients. Both non-interventional studies were completed. Study 401, a long-term extension study, is being planned to follow up all subjects receiving ROCTAVIAN in one of the treatment studies for a total of 15 years post-infusion. In addition, the Applicant has proposed two post-marketing studies (both with an expected duration of approximately 15 years), one analyzing the aggregate data collected within the established hemophilia registries (Study 801) and one patient cohort study prospectively enrolling commercially dosed patients around the time of their initial infusion (Study 601). For additional information on the studies, see Figure 1 and Table 1 under Section 5.3.

The efficacy database consists of Study 301 (n=134).

The safety database consists of the 170 subjects treated in the 5 ongoing treatment studies.

Both the initial Class 2 resubmission with the 2-year DCO of November 15, 2021 and the updated information with the 3-year DCO of November 15, 2022 will be reviewed.

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

The basis of this statistical review includes documents in IND 17659, the Class 2 BLA resubmission in BLA 125720/0/69 with a 2-year DCO of November 15, 2021, the updated submission in BLA 125720/0/90 with a 3-year DCO of November 15, 2022, Application Orientation Meeting (AOM) slides, information requests (IRs) from the

FDA, and IR responses from the Applicant. Documents reviewed are listed below. Documents are BLA documents submitted to BLA 125720/0/69, unless noted otherwise.

- Protocols and SAPs for Study 301 under IND 17659
- Meeting minutes under IND 17659
- Module 1.14 Labeling
- Module 1.2 Reviewer’s Guide
- Module 1.11.4 Applicant’s point-by-point response to FDA CRL and pre-BLA WRO
- Module 2.5 Clinical Overview
- Module 2.7.3 Summary of Clinical Efficacy
- Module 2.7.4 Summary of Clinical Safety
- Module 2.7.6 Synopses of Individual Studies
- Module 5.2 Tabular Listing of all Clinical Studies
- Module 5.3.5.1 Study 301 Clinical Study Report (CSR) and supporting documents and datasets
- Updated documents and datasets in BLA 125720/0/90

5.3 Table of Studies/Clinical Trials

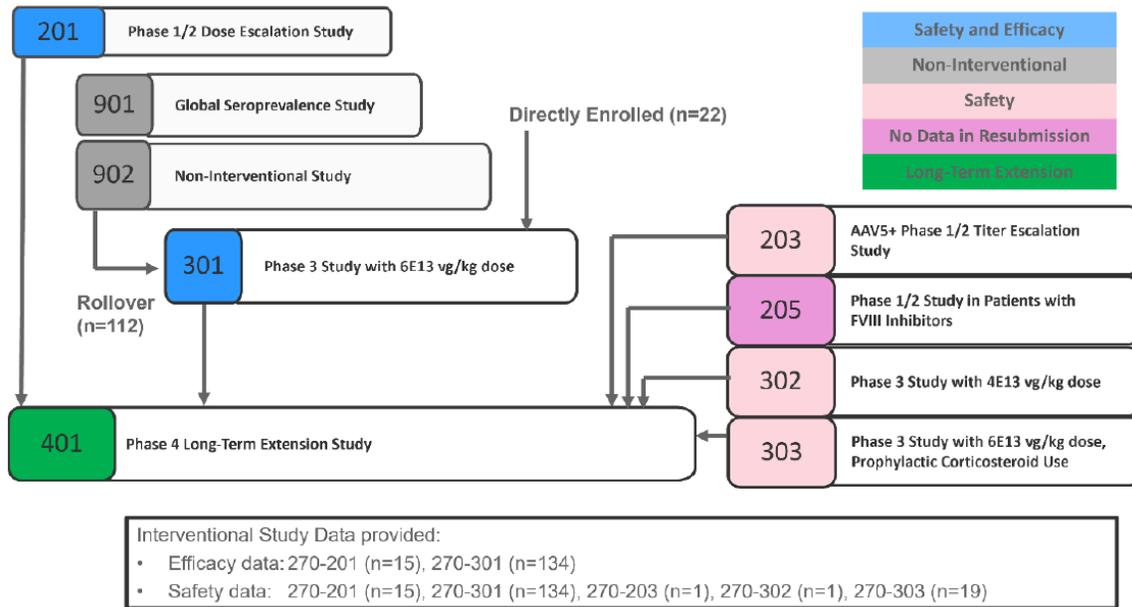
The ROCTAVIAN clinical development program consists of six interventional studies and two non-interventional studies (NISs) (Figure 1 and Table 1). This Class 2 resubmission includes results from 5 ongoing interventional studies (Studies 201, 203, 301, 302, and 303) and 2 completed NISs (Studies 901 and 902). One additional interventional study (Study 205) in patient with FVIII inhibitor has not yet enrolled any subject. In addition, a long-term extension study (Study 401) is being planned to follow up subjects who complete participation in one of the treatment studies further for a combined total of 15 years post-infusion.

This class 2 resubmission includes data on 170 subjects with severe HA who were treated with ROCTAVIAN at one of four dose levels (6E12, 2E13, 4E13, or 6E13 vg/kg) in one of the five ongoing clinical studies. The maximum FU was 5.5 years post-treatment. An additional 5 subjects had been treated since the various cutoff dates for these 5 studies, including 2 subjects in Study 203 and 3 subjects in Study 303, based on the most recent IND annual report in July 2022.

HIV subjects and Study 302. Study 302 was planned to treat 40 subjects at the 4E13 vg/kg dose. The sponsor decided to discontinue this study after only one subject was treated, based on results from the 6E13 vg/kg dose studies (Studies 301 and 201). This

treated subject was HIV-positive. Because of adverse events (AEs) observed on this subject, all ROCTAVIAN study protocols were amended to add certain HAART drugs as prohibited medications. In addition, all studies stopped further enrollment of HIV-positive subjects. By this time, two other HIV-positive subjects had been treated in Study 301.

Figure 1. ROCTAVIAN clinical development program



Source: BLA 125720/0/69, Module 2.5, Clinical Overview, p.9, Figure 2.5.1.2.1.

Table 1. Summary of ROCTAVIAN clinical studies

Study ID	Study description*	Number of subjects	Study and CSR status
301	<p>Main study</p> <p>Phase 3 5-year follow-up (FU) efficacy and safety study of the 6E13 vg/kg dose in severe hemophilia A (HA) patients who were receiving prophylactic FVIII infusions and without a history of FVIII inhibitors and negative for AAV5 antibodies</p> <p>Two cohorts:</p> <p>Directly enrolled (DE) subjects (n=22) without prospectively collected baseline data</p> <p>Rollover (RO) subjects (n=112) with prospectively collected baseline data from Study 902</p>	<p>134 treated</p> <p>Enrollment completed</p>	<p>Ongoing</p> <p>Full CSR with safety and efficacy with 2-year DCO, at least 2 years of follow-up (FU) for all subjects</p> <p>Updated report with 3-year DCO, at least 3 years of FU for all subjects</p>
302	<p>Phase 3 5-year FU efficacy and safety study of the 4E13 vg/kg dose in severe HA patients who were receiving prophylactic FVIII infusions</p>	<p>1 HIV-positive severe HA subject treated</p> <p>40 planned</p> <p>Enrollment discontinued</p>	<p>Ongoing</p> <p>Abbreviated CSR with safety and efficacy</p>
303	<p>Phase 3 5-year FU efficacy and safety of the 6E13 vg/kg dose in severe HA patients with use of prophylactic corticosteroids</p>	<p>19 treated</p> <p>20 planned</p> <p>(22 treated as of 2022 IND annual report)</p>	<p>Ongoing</p> <p>Interim abbreviated CSR with safety</p>
201	<p>Phase 1/2 5-year FU dose-finding study</p> <p>Non-IND first-in-human trial conducted in the United Kingdom</p> <p>Dose in vg/kg (number subjects): 6E12 (n=1), 2E13 (n=1), 4E13 (n=6), 6E13 (n=7)</p>	<p>15 treated</p> <p>Enrollment completed</p>	<p>Ongoing</p> <p>Full CSR with safety and efficacy</p>
203	<p>Phase 1/2 5-year FU efficacy and safety study of the 6E13 vg/kg dose in severe HA patients</p>	<p>1 treated</p> <p>10 planned</p>	<p>Ongoing</p> <p>Abbreviated</p>

	with positive total anti-capsid antibody to AAV5	(3 treated as of 2022 IND annual report)	CSR with safety and efficacy
205	Phase 1/2 5-year FU efficacy and safety study of the 6E13 vg/kg dose in severe HA patients with active or prior inhibitors	20 planned, 10 each for two cohorts with antibody titers ≤ 500 or > 500	Planned
401	Phase 4 long-term extension study in subjects with severe HA who received ROCTAVIAN in a prior Biomarin clinical trial for a combined FU of 15 years post-infusion in the treatment study and Study 401		Planned
901	NIS evaluating seroprevalence of antibodies and neutralizing factors against AAV serotypes in HA patients previously treated with FVIII concentrates with up to 6 months of longitudinal sample collection	546 HA patients with residual FVIII ≤ 2 IU/dL	Completed Final report
902	NIS prospectively following and collecting bleeding episodes and other baseline data in severe HA patients in routine clinical practice for up to 52 weeks	294 severe HA patients	Completed Final report

* All studies are single-arm studies treating severe HA patients with a single dose of 6E13 kg/vg of ROCTAVIAN, unless stated otherwise. The table is current as of the DCO of November 15, 2021. Different studies may have different cutoff dates that were earlier than the 2-year DCO. I have included the updated information on number of treated subjects from the most recent IND annual report submitted to FDA on July 2022, if that differs from what is in the BLA.

NIS: Non-interventional study. CSR: Clinical study report.

Source: Adapted from - BLA 125720/0/69, Module 5.2, Table 5.2, including information from IND annual report submitted on July 2022.

5.4 Consultations

None notable.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

The efficacy database consists of Study 270-301, referred to as Study 301 in this memo.

6.1 Trial #1: Study 270-301

Study 301 is titled “*A Phase 3 Open-Label, Single-Arm Study to Evaluate the Efficacy and Safety of BMN 270, an Adeno-Associated Virus Vector–Mediated Gene Transfer of Human Factor VIII in Hemophilia A Patients with Residual FVIII Levels ≤ 1 IU/dL Receiving Prophylactic FVIII Infusions*”.

Reviewer Comment #3

The protocol and SAP had gone through several rounds of substantial and substantive revisions, some after the FDA’s Complete Response decision on the original BLA, or even after the data cut-off. Some of these revisions were made to incorporate the evolving understanding of this first-in-class product (e.g., FVIII:C was not a suitable surrogate endpoint for ABR), and requests from FDA and other non-US regulatory agencies which sometimes may differ, e.g., with regard to FU expected before submission of marketing applications. The most recent versions of the protocol and SAP were not in complete alignment, partially resulting from agreements from several rounds of negotiations between the Applicant and the FDA being reflected only in the SAP. The most recent version of the SAP did not reflect FDA’s recommendation on the primary efficacy endpoint (ABR_{all}) and included $ABR_{treated}$ instead. The protocol and SAP include a substantial amount of information due to this history that are not relevant to the final evaluation of efficacy of ROCTAVIAN based on Study 301. Furthermore, there are also difference in some elements between the clinical study report (CSR) and the SAP. To maintain focus, I will include only design elements and analyses relevant to the choice of the information to include in the labeling in this Section. Description of some design elements, e.g. study objective, will be rephrased to facilitate easier comprehension. In the rest of this memo, ABR means ABR_{all} , unless explicitly noted otherwise.

6.1.1 Objectives (Primary, Secondary, etc)

The primary objective was to demonstrate non-inferiority (NI) in ABR after ROCTAVIAN treatment during the efficacy evaluation period (EEP) compared to ABR with FVIII prophylaxis during baseline.

Secondary efficacy objectives included assessment of other endpoints, e.g., FVIII:C level and usage of exogenous FVIII replacement therapy, at various timepoints, and further descriptive characterization of bleeding episodes.

6.1.2 Design Overview

Study 301 is an ongoing phase 3, single-arm, multi-regional study investigating the safety and efficacy of a single dose of 6E13 vg/kg of ROCTAVIAN in male adult HA subjects with residual FVIII levels ≤ 1 IU/dL, without detectable pre-existing antibodies to the AAV5 capsid, and without a documented history of a detectable FVIII inhibitor. Subjects must have been on prophylactic FVIII replacement therapy for at least 12 months prior to study entry.

After intravenous infusion of ROCTAVIAN, subjects may continue exogenous prophylactic FVIII replacement therapy for 4 weeks, a time when ROCTAVIAN was expected to manifest its effect. Subjects would then remain in Study 301 for 5 years post treatment, and then be transferred to a long-term follow-up study for a total FU of 15 years post treatment.

The data cutoff (DCO) date was November 15, 2022, when all subjects had FU of at least 3 years post treatment.

Study 301 consisted of two cohorts: the Directly Enrolled (DE) cohort (n=22, with 2 HIV-positive subjects) and the Rollover cohort (n=112, no HIV-positive subjects). There are two differences between the two cohorts. First, they differ in how baseline data were collected: RO subjects had completed approximately 6 months of participation in a non-interventional study where bleed episodes and FVIII product use data were prospectively collected to serve as baseline prior to their entry into Study 301, whereas baseline data for the DE subjects were retrospectively collected. The second difference is in the immunosuppression (IS) regimen, which is extended in the RO cohort. The RO cohort is the primary efficacy analysis set and the DE cohort is supportive.

6.1.3 Population

Major inclusion criteria were:

1. Males \geq 18 years of age with HA and residual FVIII activity levels \leq 1 IU/dL as evidenced by medical history
2. Must have been on prophylactic FVIII replacement therapy for at least 12 months prior to study entry
3. High-quality, well-documented historical data concerning bleeding episodes and FVIII usage over the previous 12 months must be available
4. Treated/exposed to FVIII concentrates or cryoprecipitate for a minimum of 150 exposure days (EDs)
5. No previous documented history of a detectable FVIII inhibitor.

Major exclusion criteria were:

1. Detectable pre-existing antibodies to the AAV5 capsid
2. Any evidence of active infection or any immunosuppressive disorder, including HIV infection
3. Significant liver dysfunction
4. History of arterial or venous thromboembolic events

5. Major surgery planned in the 52-week period following the ROCTAVIAN infusion.

HIV-positive subjects were excluded starting from protocol amendment 3 (August 24, 2018), after an HIV-positive subject in Study 302 developed markedly elevated transaminase levels after receiving 4E13 vg/kg of ROCTAVIAN, which led to subsequent exclusion of HIV-positive subjects from all ROCTAVIAN trials.

6.1.4 Study Treatments or Agents Mandated by the Protocol

A single dose of 6E13 vg/kg of ROCTAVIAN was infused intravenously.

6.1.6 Sites and Centers

The DE cohort (n=22) came from 14 sites in 2 countries: the United States of America (USA) (14/22, 63.6%) and the Great Britain (GBR) (8/22, 36.4%).

The RO cohort (n=112) came from 42 sites in 13 countries or regions (Table 2), with 8 overlapping sites with the DE cohort. All sites treated 1 to 5 subjects, except for the single site at South Africa which treated 16 subjects, and one of the five sites at Brazil which treated 15 subjects.

All subjects were in post-treatment FU when the COVID-19 pandemic was declared, which led to complete or partial closure of 44 sites in 12 countries. The Applicant modified study conduct to continue the study during the pandemic. The Applicant reported that *the number of missed visits was greatly mitigated by the use of mobile nursing. Only 13 subjects in the two cohorts combined (9.7%) missed at least 1 study visit due to the pandemic, and no subject missed more than 6 visits.*

Table 2. Distribution of subjects by country or region in the Rollover cohort (n=112)

Country or Region	Code	Number of Subjects	Percent of Subjects	Number of Sites
Brazil	BRA	18	16.1%	5
South Africa	ZAF	16	14.3%	1
United States of America	USA	16	14.3%	8
Great Britain	GBR	15	13.4%	8
Australia	AUS	13	11.6%	5
Taiwan	TWN	10	8.9%	5

Spain	ESP	6	5.4%	2
Belgium	BEL	5	4.5%	1
Israel	ISR	5	4.5%	1
France	FRA	3	2.7%	2
Germany	DEU	3	2.7%	2
Italy	ITA	1	0.9%	1
South Korea	KOR	1	0.9%	1

6.1.7 Surveillance/Monitoring

After intravenous infusion of ROCTAVIAN, subjects might continue prophylaxis with exogenous FVIII replacement therapy for 4 weeks, a time by which ROCTAVIAN was expected to manifest its effect. Subjects would then remain in Study 301 for 5 years post treatment, and then be transferred to a long-term follow-up study for a total FU of 15 years post treatment. Assessment of AEs and concomitant medications (including review of subject diary for bleeding and FVIII use), as well as FVIII:C assays, will occur according to the following schedule: weekly through Week 36, then biweekly through Week 52, then every 4 weeks in Year 2, and every 6 weeks in Years 3-5. Subjects deemed to experience treatment failure would follow an abbreviated visit schedule after Week 52 by attending visits every 12 weeks and end-of-year visits during Years 2-5. The data cutoff date was November 15, 2022, when all subjects had FU of at least 3 years post treatment.

6.1.8 Endpoints and Criteria for Study Success

The primary endpoint was a non-inferiority (NI) comparison in ABR of ROCTAVIAN treatment during the efficacy evaluation period (EEP) compared to ABR with FVIII prophylaxis during baseline. The EEP started from Study Day 33 (Week 5) after ROCTAVIAN treatment, or the end of post-ROCTAVIAN FVIII prophylaxis (including the washout period of 3 days for standard half-life (SHL) or plasma-derived products and 5 days for extended half-life (EHL) products, respectively), whichever was later. The EEP ended when a subject completed the study, reached last visit by the data cut-off for the 3-year analysis, or withdrew or lost to FU from the study, whichever was the earliest.

Secondary efficacy objectives included assessment of other endpoints, e.g., FVIII:C level and usage of exogenous FVIII replacement therapy, at various timepoints, and further descriptive characterization of bleeding episodes.

The trial would be considered a success if the upper bound of the 95% confidence interval (CI) on the mean difference of ABR is below the non-inferiority margin of 3.5 bleeds/year.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Non-inferiority margin

The NI margin was 3.5 bleeds/year in mean difference between ABR during EEP and baseline ABR. The SAP stated that mean ABRs of prophylactic treatment products had a range of approximately 3 to 6 bleeds/year, mean ABRs of episodic treatments had a range of approximately 30 to 60, and proposed an NI margin of 3.5 to preserve 90% of the efficacy of prophylactic over episodic treatments. The rationale was provided for ABR_{treated}, FDA nonetheless found the proposed NI margin also acceptable for ABR_{all}.

Sample size

The sample size of 130 subjects (134 actual) in the DE and RO cohorts combined was planned to provide sufficient data to assess both safety and efficacy of ROCTAVIAN, based on both clinical and statistical considerations.

The sample size of 110 subjects (112 actual) in the RO cohort, the analysis set for the primary efficacy endpoint ABR, was planned to achieve a 95% statistical power to reject the NI null hypothesis with an NI margin of 3.5. Specifically, it was assumed that the mean baseline and EEP ABRs were 3.5 and 1 bleeds/years, respectively, and the ABR had a negative binomial distribution with a dispersion parameter of 2.2. The ABR standard deviations (SDs), as a result, were 7.8 and 1.8, respectively. The mean (SD) of the change from baseline to EEP ABR was -2.5 (8) bleeds/year, assuming a correlation of zero between the ABRs in the two periods. Under this assumption, a sample size of 110 will have at least 95% power to demonstrate that the mean change in ABRs is less than 3.5, the NI margin, using a one-sample t-test with a 2-sided significance level of 0.05. The SAP also stated that this sample size will have approximately 90% power to demonstrate superiority.

Analysis populations/sets

Reviewer Comment #4

The SAP defines five analysis populations using intention-to-treat or modified intention-to-treat terms that are various combinations of the DE and RO cohorts, including or excluding the two HIV-positive DE subjects. I find it unnecessary to introduce these additional terms for the analysis sets. Specifically, the RO cohort will be the analysis set for the NI comparison of the primary efficacy endpoint ABR. The DE cohort will not be included for the ABR NI analysis because its retrospectively collected baseline data was

deemed unreliable, and it differs from the RO cohort in the extent of immunosuppression (IS) use. Both cohorts will be used for additional descriptive efficacy analyses and safety analyses. The two HIV-positive DE subjects will be mentioned when it is needed to highlight their results in some analyses.

Primary analysis for the primary efficacy endpoint in the RO cohort: NI comparison of ABR

For the primary analysis, the baseline period is approximately 6 months for each subject in the non-interventional Study 902 where baseline data were prospectively collected. The EEP after ROCTAVIAN treatment was as defined above. All bleed episodes, except those due to surgeries/procedures, are counted, regardless of whether the bleed was treated.

The primary analysis is a 95% confidence interval (CI) constructed for the mean difference between EEP ABR and baseline ABR, assuming a one-sample t-distribution with the variance estimated from the data. If the upper bound of the 95% CI is less than 3.5 bleeds/year, NI has been achieved and ROCTAVIAN will be deemed effective.

Reviewer Comment #5

Due to the length of this reviewer comment, I will not italicize it. This reviewer comment ends at the beginning of Section 6.1.10.

Primary analysis with imputation of hypothetical ABR for subjects on prophylaxis during EEP

During EEP, exogenous FVIII replacement products or emicizumab were used by some subjects, with one of four possible indications for use recorded: *Treatment for bleed, Surgery/procedure, Usual Factor VIII prophylaxis (UF8P), One-time Factor VIII prophylaxis (OTP)*.

Prophylactic use of UF8P and OTP during EEP confounds the ROCTAVIAN treatment effect in ABR. To mitigate this confounding, I will impute an ABR of 35 bleeds/year for EEP periods that were confounded by this prophylactic use. This imputation falls in the lower end of the range of mean ABR of 30 to 60 bleeds/year for similar patients receiving episodic factor treatments, as stated in the SAP.

The SAP defines restart of FVIII prophylaxis after ROCTAVIAN treatment as the first UF8P administered at least once a week for ≥ 4 consecutive weeks. These subjects were identified by the Applicant as resuming routine prophylaxis (RP). It is unknown what decides whether a replacement product use will be recorded as UF8P or OTP. Some subjects used OTP at a weekly frequency during the latter part of their EEP. Some OTPs had no documented reasons.

The FDA had communicated with the Applicant, after seeing some OTP use in the review of the limited data in the original BLA, that the confounding effect of OTP should be addressed. One concern was that some OTP might have been used to treat subclinical bleeds and therefore disregarding them would result in undercounting bleed episodes. The SAP added a sensitivity analysis counting each OTP and UF8P use as a bleed episode. Imputing an ABR of 35 bleeds/year for the period confounded by OTP or UF8P use, regardless of whether the use meets the SAP definition of resuming RP, is a considerably more favorable approach to ROCTAVIAN than the proposed sensitivity analysis and may also be more reasonable.

In what follows, the primary analysis on ABR in the RO cohort will use this imputation, unless explicitly noted otherwise.

Additional statistical considerations regarding efficacy evaluation

1. Immunosuppression (IS) use. The majority of Study 301 subjects used corticosteroids (CS) and other IS medicines to manage ALT elevations and potential loss of transgene expression. IS use also confounds the treatment effect of ROCTAVIAN. However, due to the extent of its use, I view IS use as an integral component of the ROCTAVIAN treatment regimen and will not attempt to isolate the treatment effect of ROCTAVIAN in the absence of such IS use. I will describe the extent of IS use in the results section.
2. FVIII:C. I will summarize the FVIII:C data to highlight the time course, instead of testing whether the mean FVIII:C was greater than zero at some time points, as proposed in the SAP.
3. Treatment failure over time. In the proposed labeling, the Applicant reported the proportion of subjects resuming RP per the SAP definition as a way to assess the durability of the ROCTAVIAN effect. This approach does not capture all the treatment failure, which more closely reflects durability, as there are subjects who did not resume RP despite increased bleeding and negligible FVIII:C and there are subjects who used OTP in a prophylactic manner. During labeling negotiation, I proposed to use the combination of three variables (bleed episodes, FVIII:C, and prophylactic use of products) to identify treatment failures and their start times.
4. Superiority claim. The SAP planned statistical testing for superiority of ROCTAVIAN over RP. I have summarized why superiority testing is uninterpretable in Section 2.5. I will discuss this in more detail in the analysis section below.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

By the DCO of November 15, 2022 for the 3-year analysis, 112 RO subjects and 22 DE subjects had been treated and followed up for at least 3 years.

6.1.10.1.1 Demographics

Table 3 summarizes the demographics of the 134 treated subjects in Study 301. All subjects were male; 48.5% of subjects overall (48.2% of the RO cohort and 50.0% of the DE cohort) were between the ages of 18 and 30 years. The mean (SD) age at enrollment was 31.7 (10.3) years; the oldest subject was 70 years old.

Table 3. Demographics of Study 301 subjects.

	DE cohort (n=22)	RO cohort (n=112)
Age at enrollment: Summary statistics (years)		
Mean (SD)	30.9 (8.7)	31.8 (10.6)
Median	29.5	30.0
Minimum, Maximum	18, 52	19, 70
Age at enrollment: n (%)		
18 to < 30 years	11 (50.0)	54 (48.2)
30 to < 50 years	10 (45.5)	46 (41.1)
≥ 50 years	1 (4.5)	12 (10.7)
Race: n (%)		
Asian	2 (9.1)	17 (15.2)
Black or African American	1 (4.5)	14 (12.5)
Native Hawaiian or other Pacific Islander	0 (0.0)	1 (0.9)
White	18 (81.8)	78 (69.6)
Not provided due to patient privacy	1 (4.5)	2 (1.8)

Source: Adapted from - BLA 125720/0/69, Study 301 CSR, p.162, Table 11.2.1.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

All 134 treated subjects in Study 301 were receiving prophylactic FVIII and negative for FVIII inhibitors at the time of study entry. Table 4 summarizes the baseline ABR and FVIII replacement product use for the two cohorts. Table 5 summarizes the medical history. The Applicant concluded that “Overall, apart from the underlying hemophilia A, the 270-301 subject population was relatively healthy, with few reported concomitant conditions aside from procedures and sequelae related to the underlying hemophilia (arthropathies, osteoarthritis) or resolved hepatitis C infection.” No subjects enrolled in Study 301 had a history of or risk factors for thromboembolic disease; one subject had a history of coronary artery disease, and two subjects had a history of previous jugular vein thrombosis.

Table 4. Baseline^a characteristics of Study 301 subjects

	DE cohort (n=22)	RO cohort (n=112)
Baseline ABR: Summary statistics (bleeds/year)		
Mean (SD)	9.1 (22.6)	5.4 (6.9)
Median	1.4	3.3
Minimum, Maximum	0.0, 104.6	0.0, 34.6
Baseline ABR: n (%)		
0 bleeds/year	7 (31.8)	34 (30.4)
> 0 to 4	9 (40.9)	31 (27.7)
> 4 to 10	1 (4.5)	30 (26.8)
> 10	5 (22.7)	17 (15.2)
Baseline annualized number of FVIII infusions: Summary statistics (infusions /year)		
Mean (SD)	146 (79)	136 (52)
Median	120	129
Minimum, Maximum	49, 359	40, 364
History of previous diseases: n (%)		
Hepatitis B	3 (13.6)	17 (15.2)
Hepatitis C	8 (36.4)	33 (29.5)

HIV	2 (9.1)	0
Number of target joints: n (%)		
0	15 (68.2)	82 (73.2)
1	4 (18.2)	13 (11.6)
2	0	9 (8.0)
3	2 (9.1)	6 (5.4)
> 3	1 (4.5)	2 (1.8)

^a Baseline FVIII usage and ABR data were calculated using different baseline periods and sources for the DE and RO cohorts. Subjects in the DE cohort each has 12 months of retrospective historical data for baseline. Subjects in the RO cohort each has a baseline period of around 6 months in the NIS 902 (Day 1) up to the ROCTAVIAN infusion in Study 301.

Source: Adapted from - BLA 125720/0/69, Study 301 CSR, p.165, Table 11.2.2.

Table 5. Medical history reported by $\geq 5\%$ of Study 301 subjects by preferred term

System Organ Classification	DE cohort (n=22)	RO cohort (n=112)
Subjects with at least 1 Reported Medical History Event: n (%)	21 (95.5)	103 (92.0)
Haemophilic arthropathy	11 (50.0)	46 (41.1)
Hepatitis C	8 (36.4)	31 (27.7)
Arthropathy	2 (9.1)	21 (18.8)
Hepatitis B	2 (9.1)	12 (10.7)
Synoviorthesis	1 (4.5)	13 (11.6)
Anxiety	2 (9.1)	11 (9.8)
Depression	3 (13.6)	10 (8.9)
Arthrodesis	3 (13.6)	9 (8.0)
Arthralgia	2 (9.1)	8 (7.1)
Knee arthroplasty	1 (4.5)	9 (8.0)

Seasonal allergy	4 (18.2)	7 (6.3)
Synovectomy	2 (9.1)	8 (7.1)
Central venous catheterization	2 (9.1)	7 (6.3)
Rhinitis allergic	0	8 (7.1)
Appendectomy	0	7 (6.3)
Circumcision	0	7 (6.3)
Headache	3 (13.6)	4 (3.6)

Source: Adapted from - BLA 125720/0/69, Study 301 CSR, p.169, Table 11.2.2.1.

Baseline FVIII replacement therapies

Table 6 summarizes FVIII replacement therapies of Study 301 subjects prior to their entering Study 301.

As a rough way to evaluate the adequacy of FVIII prophylaxis at baseline, in the review of the original BLA, I used annualized infusion days rate (AIR) of < 100 infusion days per year as a yardstick, recognizing that a comprehensive evaluation is outside of the purview of the statistical memo and deferring that to the clinical reviewers. I communicated my concerns about the implication of potential inadequacy of FVIII prophylaxis at baseline for some subjects on the efficacy inference for ROCTAVIAN in the CRL. The Applicant responded to this issue in the resubmission, but the information included contained errors. They corrected these errors in response to my IR in BLA 125720/0/114 submitted on June 20, 2023, and also included information on AIR, which would be easier to gauge the frequency of FVIII product use than the metrics they initially included in the response to the CRL. These results are excerpted below, with light editing for clarity and length.

For the RO cohort at baseline (N=112), 84 subjects received only standard half-life (SHL) products, 22 subjects received only extended half-life (EHL) products, and 6 subjects received a combination of EHL/SHL products for any purpose. Plasma-derived products were considered as SHL products in this analysis.

- Among the 84 subjects who were on SHL products only, 11 (13%) had a baseline AIR of less than 100 (range: 39 to 98) days/year. The median baseline ABR for the 11 subjects was 4.9 (range: 0 to 21.3) bleeds/year.
- Among the 22 subjects who were on EHL products only, 7 (32%) had a baseline AIR of less than 100 (range: 69 to 91) days/year. The median baseline ABR for the 7 subjects was 0.0 (range: 0 to 14.9) bleeds/year.

- Among the 6 subjects who were on a combination of SHL/EHL products, 1 (17%) had a baseline AIR of less than 100 days/year. That subject had an AIR of 51 days/year and a baseline ABR of 3.4 bleeds/year.

For the DE cohort at baseline (N=22), 13 subjects received only SHL products, 7 subjects received only EHL products, and 2 subjects received a combination of EHL/SHL products for any purpose.

- Among the 13 subjects who were on SHL products only, 3 (23%) had a baseline AIR of less than 100 days/year. The baseline AIR and baseline ABR for the 3 subjects were 80, 93, and 97 days/year and 2.8, 0, and 104.6 bleeds/year, respectively.
- Among the 7 subjects who were on EHL products only, 4 (57%) had a baseline AIR of less than 100 days/year. The baseline AIR and baseline ABR for the 4 subjects were 83, 89, 98, and 99 days/year and 0.9, 0, 1.8 and 0.9 bleeds/year, respectively.
- Among the 2 subjects who were on a combination of SHL/EHL products, 1 (50%) had a baseline AIR of less than 100 days/year. That subject had a baseline AIR of 49 days/year and a baseline ABR of 0 bleeds/year.

Reviewer Comment #6

This subsection on “Baseline FVIII replacement therapies” is excerpted from the 2-year CSR (pp.169-171) with light editing for clarity and conciseness. I have the following observations.

- *The baseline FVIII replacement therapies are a mixture of several products of varying efficacy, probably at least partially due to regional difference in clinical practice.*
- *For routine prophylaxis (RP) with EHL products, the infusion frequency is about every 4 days, which gives an annual infusion rate of about 90 infusions/year with equally spaced infusions. For SHL products, that frequency needs to be doubled to about 180 infusions/years. The baseline FVIII infusion frequencies in Study 301 RO subjects reported in the text appears to include not only infusions for prophylaxis, but also infusions for treatment of bleed and for surgery/procedure. It is also unknown whether those infusions are evenly spaced out. Nonetheless, there are subjects who received infusions below expected RP infusions frequencies. Some of these subjects with infrequent infusions had low baseline ABR, which may indicate that these subjects have genuine low bleeding risk, and it would be difficult to know whether a low ABR after ROCTAVIAN treatment was due to ROCTAVIAN treatment effect or due to the subject’s genuine low bleeding risk. Some of these subjects with infrequent infusions had high baseline ABR, indicating that these subjects might not had received an adequate RP regimen.*

Taken together, the observations that the baseline RP regimen was a mixture of multiple products and that some subjects might not have received adequate RP precludes a meaningful comparison of ROCTAVIAN comparison with RP with a purpose to show superiority.

Note that the purpose of this comment is to draw a qualitative conclusion about interpretability of superiority testing. For a comprehensive review about baseline RP regimens in Study 301, please refer to the clinical review memo.

Table 6. Prior^a FVIII replacement therapies of Study 301 subjects

Preferred Drug Name	DE cohort (n=22)	RO cohort (n=112)
Standard Half-Life: n (%)	14 (63.6)	69 (61.6)
Octocog Alfa	8 (36.4)	47 (42.0)
Moroctocog Alfa	5 (22.7)	15 (13.4)
Turoctocog Alfa	1 (4.5)	4 (3.6)
FVIII, Recombinant	0	2 (1.8)
Simoctocog Alfa	1 (4.5)	1 (0.9)
Lonoctocog Alfa	0	1 (0.9)
Extended Half-Life: n (%)	9 (40.9)	28 (25.0)
Efmoroctocog Alfa	8 (36.4)	22 (19.6)
Rurioctocog Alfa Pegol	1 (4.5)	5 (4.5)
Damoctocog Alfa Pegol	0	1 (0.9)
Plasma-Derived: n (%)	1 (4.5)	23 (20.5)
FVIII (antihemophilic factor)	1 (4.5)	21 (18.8)
Wilate	0	2 (1.8)
FVIII (antihemophilic factor); von Willebrand factor	0	1 (0.9)
Unknown investigational drug: n (%)	1 (4.5)	0

^a For DE cohort, prior therapies include medications taken within 30 days prior to screening and within 1 year prior to screening. For RO cohort, prior therapies include those from Day 1 in the NIS 902 to prior to ROCTAVIAN treatment.

Source: Adapted from - BLA 125720/0/69, Study 301 CSR, p.170, Table 11.2.2.2.

Concomitant medication after ROCTAVIAN treatment (2-year data cut-off)

All treated subjects in Study 301 reported concomitant medication use after ROCTAVIAN treatment. Table 7 summarizes concomitant medications received by $\geq 10\%$ of Study 301 subjects. Table 8 summarizes concomitant medications by hepatotoxic categories. These two tables are adapted from the 2-year CSR, as no similar summaries were given in the 3-year safety and efficacy updated report.

Table 7. Concomitant medications received by $\geq 10\%$ of Study 301 subjects, from ROCTAVIAN infusion to the 2-year data cut-off

Preferred Drug Name	DE cohort (n=22)	RO cohort (n=112)
Glucocorticoids: n (%)	20 (90.9)	97 (86.6)
Prednisone	9 (40.9)	59 (52.7)
Prednisolone	8 (36.4)	35 (31.3)
Proton Pump Inhibitors: n (%)	7 (31.8)	69 (61.6)
Omeprazole	3 (13.6)	45 (40.2)
Anilides: n (%)	16 (72.7)	54 (48.2)
Acetaminophen	15 (68.2)	47 (42.0)
Propionic Acid Derivatives: n (%)	10 (45.5)	27 (24.1)
Ibuprofen	9 (40.9)	24 (21.4)
Coxibs: n (%)	7 (31.8)	27 (24.1)
Celecoxib	6 (27.3)	19 (17.0)
Amides: n (%)	6 (27.3)	20 (17.9)
Lidocaine	5 (22.7)	13 (11.6)
Other Systemic Antihistamines: n (%)	5 (22.7)	20 (17.9)
Loratadine	3 (13.6)	11 (9.8)
Calcineurin Inhibitors: n (%)	0	24 (21.4)

Tacrolimus	0	24 (21.4)
Combinations of Penicillins, including Beta-Lactamase Inhibitors: n (%)	2 (9.1)	18 (16.1)
Amoxicillin/Clavulanic Acid	1 (4.5)	14 (12.5)
Pyrazolones: n (%)	0	17 (15.2)
Metamizole sodium	0	16 (14.3)

Source: Adapted from - BLA 125720/0/69, Study 301 CSR, p.173, Table 11.2.2.4.

Table 8. Concomitant medications by hepatotoxic categories in Study 301 subjects, from ROCTAVIAN infusion to the 2-year data cut-off

	DE cohort (n=22)	RO cohort (n=112)
Category A	22 (100)	110 (98.2)
Prednisone	9 (40.9)	59 (52.7)
Acetaminophen	15 (68.2)	47 (42.0)
Prednisolone	8 (36.4)	35 (31.3)
Ibuprofen	9 (40.9)	25 (22.3)
Category B	16 (72.7)	81 (72.3)
Omeprazole	3 (13.6)	45 (40.2)
Celecoxib	6 (27.3)	19 (17.0)
Category C	18 (81.8)	91 (81.3)
Tozinameran	8 (36.4)	38 (33.9)
Tacrolimus	0	24 (21.4)
Category D	8 (36.4)	44 (39.3)
Mycophenolate mofetil	0	13 (11.6)
Ondansetron	2 (9.1)	9 (8.0)
Category E	20 (90.9)	83 (74.1)

Lidocaine	5 (22.7)	15 (13.4)
Fentanyl	3 (13.6)	13 (11.6)
Loratadine	3 (13.6)	11 (9.8)
Uncategorized (includes FVIII replacement therapy)	22 (100)	112 (100)

Source: Adapted from - BLA 125720/0/69, Study 301 CSR, p.174, Table 11.2.2.5.

Immunosuppression (IS) medication after ROCTAVIAN treatment (3-year data cut-off)

Most Study 301 subjects, 77.3% of DE cohort and 82.1% of RO cohort, had used corticosteroids (CS) after ROCTAVIAN treatment (Table 9). A similar proportion of subjects had used CS to manage ALT elevations and potential loss of transgene expression (Table 10). Subjects received alternative immunosuppressants (AIS) other than prednisone or prednisolone, due to inability to tolerate corticosteroids or ineffectiveness of corticosteroids (Table 11).

Reviewer Comment #7

This subsection on “IS medication after ROCTAVIAN treatment” summarizes the IS use, including CS and AIS, to manage ALT elevations and potential loss of transgene expression as well as for other purposes. The three tables have given the same message:

- *The RO cohort received more extensive IS regimen than the DE cohort, with a median 9.3 months of use vs. 4.5 months.*
- *The prolonged use of IS in both cohorts not only make it impossible to isolate the treatment effect due solely to ROCTAVIAN, but also introduce additional risks to the combined ROCAVIAN+IS regimen. Any comparison between the effect of ROCTAVIAN and RP with FVIII replacement or emicizumab should consider not only the efficacy of this combined regimen, but also the attendant risks. This is another reason it is impossible to interpret a superiority comparison of ROCTAVIAN alone compared to RP.*

Table 9. Summary of corticosteroids use for all purposes in Study 301 subjects, from ROCTAVIAN infusion to the 3-year data cut-off

	DE cohort (n=22)	RO cohort (n=112)
Subjects with use of corticosteroids: n (%)	17 (77.3)	92 (82.1)
Time from ROCTAVIAN infusion to first use: weeks		
Mean (SD)	9.5 (4.8)	11.0 (10.4)

Median	8.1	7.9
Minimum, Maximum	0, 20	0, 66
Time from ROCTAVIAN infusion to first CS course: n (%)^a		
≤ 13 Weeks	13 (59.1)	75 (67.0)
> 13 to 26 Weeks	4 (18.2)	10 (8.9)
> 26 to 39 Weeks	0	3 (2.7)
> 39 to 52 Weeks	0	3 (2.7)
> 52 to 78 Weeks	0	1 (0.9)
Number of courses per subject		
Mean (SD)	2.5 (1.2)	3.1 (2.5)
Median	2.0	3.0
Minimum, Maximum	1, 5	1, 20
Total duration of courses per subject: days^b		
Mean (SD)	163 (121)	258 (139)
Median	146	246
Minimum, Maximum	1, 551	22, 841
Total dose per subject: mg		
Mean (SD)	4229 (2489)	9407 (6676)
Median	3685	6950
Minimum, Maximum	40, 10748	960, 31760

The start date of a CS course was defined as the time of initiating the 1st dose of CS or when a dose increase was made, and the end date was defined as the time when CS use was discontinued or a dose increase was made (i.e., any dose increase during CS treatment would be treated as the start of a new course).

^a Based on the total number of subjects in this population.

^b Based on the total number of CS courses with non-missing start and end dates.

Source: Adapted from - BLA 125720/0.90, Study 301 3-year safety and efficacy update report, p.83, Table 2.4.3.1.2.

Table 10. Summary of corticosteroid use for ALT elevation in Study 301 subjects, from ROCTAVIAN infusion to the 3-year data cut-off

	DE cohort (n=22)	RO cohort (n=112)
Subjects with at least 1 event of ALT elevation: n (%)	19 (86.4)	102 (91.1)
Subjects with ALT elevation and use of CS: n (%)	14 (63.6)	92 (82.1)
Time from ROCTAVIAN infusion to first use: weeks		
Mean (SD)	9.9 (4.2)	11.0 (10.4)
Median	8.2	7.9
Minimum, Maximum	4, 20	1, 66
Time from ROCTAVIAN infusion to first CS course: n (%)^a		
≤ 13 Weeks	11 (50.0)	75 (67.0)
> 13 to 26 Weeks	3 (13.6)	10 (8.9)
> 26 to 39 Weeks	0	3 (2.7)
> 39 to 52 Weeks	0	3 (2.7)
> 52 to 78 Weeks	0	1 (0.9)
Number of courses per subject		
Mean (SD)	2.6 (1.2)	3.0 (2.2)
Median	2.0	3.0
Minimum, Maximum	1, 5	1, 20
Total duration of courses per subject: days^b		

Mean (SD)	179 (123)	255 (137)
Median	156	244
Minimum, Maximum	58, 551	22, 841
Total dose per subject: mg		
Mean (SD)	4659 (2439)	9377 (6681)
Median	4218	6950
Minimum, Maximum	2100, 10748	960, 31760

^a Based on the total number of CS courses with non-missing start and end dates.
Source: Adapted from - BLA 125720/0.90, Study 301 3-year safety and efficacy update report, p.84, Table 2.4.3.1.3.

Table 11. Summary of Immunosuppression use for all purposes in Study 301 subjects, from ROCTAVIAN infusion to the 3-year data cut-off

	DE cohort (n=22)	RO cohort (n=112)
Subjects with use of immunosuppression: n (%)	19 (86)	100 (89)
Time from ROCTAVIAN infusion to first IS use: Months		
Mean (SD)	4.8 (8.6)	3.1 (4.5)
Median	1.9	1.9
Minimum, Maximum	0.0, 35.7	0.0, 31.0
1 st Quartile, 3 rd Quartile	1.6, 3.4	1.4, 2.4
Time from ROCTAVIAN infusion to last IS use: Months		
Mean (SD)	15.3 (12.6)	15.3 (8.7)
Median	8.7	13.0
Minimum, Maximum	0.0, 42.1	2.0, 41.0
1 st Quartile, 3 rd Quartile	6.9, 23.1	10.0, 17.0

Duration of IS use from first to last use: Months		
Mean (SD)	10.5 (11.5)	12.2 (8.8)
Median	6.6	10.2
Minimum, Maximum	0.0, 38.5	0.0, 37.5
1 st Quartile, 3 rd Quartile	2.8, 14.2	7.1, 14.3
Duration of IS use excluding overlapping and no-use days: Months		
Mean (SD)	4.8 (4.1)	8.9 (4.8)
Median	4.5	9.3
Minimum, Maximum	0.0, 18.1	0.0, 30.2
1 st Quartile, 3 rd Quartile	2.3, 6.5	5.5, 11.5

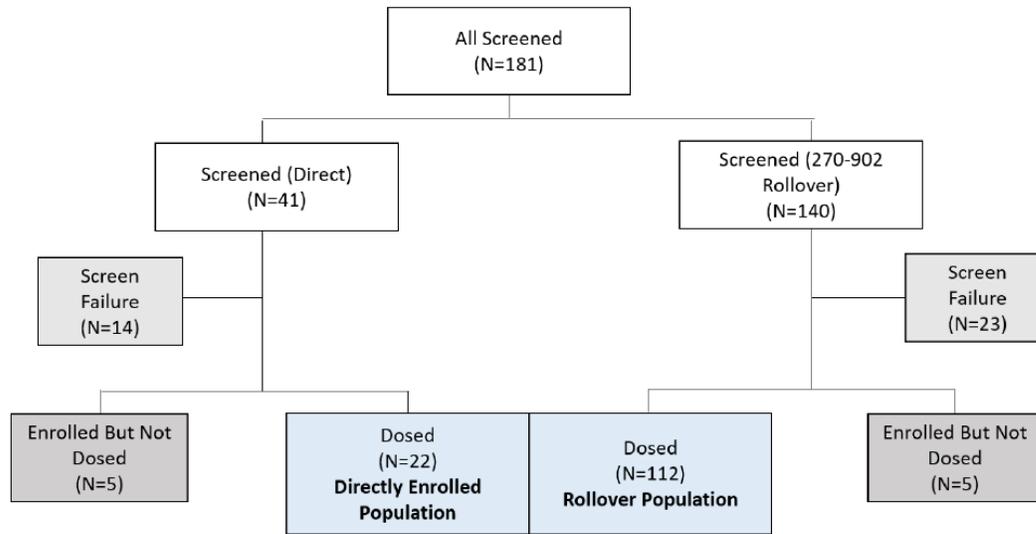
6.1.10.1.3 Subject Disposition

A total of 181 potential subjects were screened for Study 301 (Figure 2). Among the 37 patients who failed screening, the most common reasons were detectable pre-existing AAV5 antibodies (26 patients), liver dysfunction (7 patients), and unlikely to be able to follow the requirements of the study judged by the Investigator and/or Sponsor (2 patients). In addition, one subject did not meet the eligibility criterion of having at least 12 months of prophylactic FVIII replacement therapy prior to study entry and another subject was unwilling/unable to provide informed consent. Of the 144 enrolled subjects, 134 (93.1%) were treated with a dose of 6E13 vg/kg ROCTAVIAN. Ten subjects enrolled but were not dosed, 5 each for the potential DE and RO cohort pools, respectively. Of these 10 subjects, 5 withdrew from the study prior to treatment, 4 had to withdraw due to abnormal liver function tests at the Baseline assessment, and 1 subject withdrew because he was HIV-positive and the protocol had been amended to exclude further enrollment of HIV-positive subjects.

As of the DCO for the 3-year analysis, all subjects remained in the study except for three subjects who discontinued early:

- Subject (b) (6) . DE cohort. Lost to follow up on Day 463 (1.3 years).
- Subject (b) (6) . RO cohort. Lost to follow up on Day 730 (2.0 years).
- Subject (b) (6) . RO cohort. Died (b) (6) on Day 668 (1.8 years).

Figure 2. Study 301 subject disposition



Source: BLA Resubmission 125720/0/69, Study 301 CSR, p.153, Figure 10.1.1.

6.1.11 Efficacy Analyses

In this “Efficacy Analyses” Section, I will focus on the three efficacy-related variables, after ROCTAVIAN treatment: ABR, consumption of FVIII replacement product or emicizumab (CF8E), and FVIII:C.

For ABR, the primary efficacy endpoint, I will focus on the primary NI comparison, taking into account confounding from CF8E reported as “Usual Factor VIII prophylaxis” (UF8P) or “One-time Factor VIII prophylaxis” (OTP) during EEP. I will then examine potential loss of treatment effect over time, i.e., the durability issue in the CRL. For this, I will analyze the three variables together over time to identify treatment failure and its relationship to the timing of “returning to routine prophylaxis” (RTP) reported by the Applicant.

CF8E will not be summarized otherwise. While the Applicant would like to report a reduction, compared to baseline, as support for ROCTAVIAN efficacy, this summary may not add new information or can potentially be misleading. Firstly, it is logical to not use CF8E during EEP when baseline CF8E is the treatment regimen ROCTAVIAN (alone) is to be compared with. Secondly, there are different indications for CF8E during EEP: CF8E for “Treatment for bleed” would have already been captured in ABR, CF8E for “Surgery/procedure” is irrelevant, CF8E for UF8P and OTP confounds ABR and often happened later in the time course. Lumping these four types of CF8E together can be misleading.

FVIII:C time course at the individual level will be summarized in the *6.1.11.2 Analyses of Secondary Endpoints* subsection.

The primary efficacy analysis set is the RO cohort (n=112). The DE cohort (n=22) used an IS regimen different from the RO cohort, and baseline data were collected

retrospectively instead of prospectively. For these two reasons, the two cohorts will not be pooled in any analysis. However, the DE cohort had around one more year of FU than the RO cohort (median FU of 4.3 vs. 3.1 years), and the DE data will be summarized side-by-side with the RO data to assess treatment effect persistence when appropriate, e.g., treatment failure.

6.1.11.1 Analyses of Primary Endpoint(s)

ABR primary analysis in the RO cohort: NI comparison between EEP and baseline

Table 12 summarizes the ABR and bleeding events during baseline and the post-ROCTAVIAN EEP. Because 13 subjects had used factor VIII replacement products or emicizumab during the EEP for prophylaxis, those prophylaxis period during the EEP, for a total of 14.4 person-years, was imputed with an ABR of 35. This results in a mean EEP ABR of 2.6 bleeds/year, compared with a mean baseline ABR of 5.4 bleeds/year. A paired t-test yields an estimate of the mean difference between the EEP and baseline ABR of -2.8 bleeds/year with a 95% confidence interval of (-4.3, -1.2) bleeds/year. The upper bound of the 95% confidence interval is less than the NI margin of 3.5, and therefore the t-test meets the NI comparison success criterion, indicating the effectiveness of ROCTAVIAN. Superiority test was not performed due to its un-interpretability summarized previously. More detail about the 13 subjects receiving prophylaxis during EEP is provided below.

I have performed a sensitivity analysis by imputing different hypothetical ABRs for the periods during EEP when the 13 subjects were on prophylaxis. When the imputed ABR is at least 61 bleeds/year, the upper bound of the 95% CI of the mean difference between the EEP ABR and Baseline ABR would be > 0 and no longer meeting superiority in a statistical sense. When the imputed ABR is at least 125 bleeds/year, the upper bound of the 95% CI of the mean difference between the EEP ABR and Baseline ABR would be > 3.5 and no longer meeting NI in a statistical sense.

Table 12. Summary of ABR and bleeding events in the Rollover cohort (N=112)

ABR and Bleeding Events	Baseline	Post-ROCTAVIAN EEP ¹
Total bleed counts	424	877 ²
Median (range) follow-up duration in years	0.6 (0.5, 1.3)	3.0 (1.7, 3.7)
Follow-up duration in person-years	78.3	342.8
Mean (SD) ABR in bleeds/year	5.4 (6.9)	2.6 (6.2) ²

Median (min, max) ABR in bleeds/year	3.3 (0.0, 34.6)	0.3 (0.0, 35.0) ²
Observed spontaneous bleed count (Proportion of total bleeds) ³	176 (42%)	179 (41%)
Observed joint bleed count (Proportion of total bleeds) ³	240 (57%)	195 (45%)

Min: Minimum; Max: Maximum; SD: Standard Deviation

¹ EEP started on Day 33 for 89 subjects, and from Day 34 to Day 60 for the remaining 23 subjects. EEP ended at 1.8 and 2.0 years for two subjects, respectively, and from 3.0 to 3.8 years for the remaining 110 subjects.

² A total of 13 subjects (11.7%) 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 EEP duration when these subjects were on prophylaxis. The total number of bleeds during EEP without the imputation was 433.

³ For spontaneous and joint bleed counts, no imputation was done for the 13 subjects who had used prophylaxis during their EEPs.

EEP confounded by prophylactic UF8P and OTP use

Table 13 lists the 13 RO subjects and the time when they started using UF8P or OTP that confounded the ROCTAVIAN treatment effect, with the difference between FDA’s adjudication and the Applicant’s report of “Return to prophylaxis” (RTP) noted.

The Applicant defined RTP as:

Restart of prophylactic treatment means restart of FVIII or start emicizumab prophylaxis. Restart of FVIII prophylaxis is defined as the first usual FVIII prophylaxis administered at least once a week for ≥ 4 consecutive weeks. Start of emicizumab prophylaxis is defined as the first emicizumab injection among 2 or more emicizumab injections administered within 31 days.

Table 13 shows that FDA’s analysis identified 3 subjects that the Applicant did not report as meeting their definition of RTP. Of the 10 RTP subjects identified by both the FDA and the Applicant, FDA adjudicated a much earlier confounding start time than the Applicant did, e.g., from Day 812 to Day 33 in Subject (b) (6). The difference in adjudication is often due to the frequency of OTP. For example, Subject (b) (6) started his EEP on Day 120, much later than Day 33, the general day most subjects were off RP after ROCTAVIAN treatment. He had 14 bleeds during EEP from Day 120 to Day 1141 (2.8 years) and used FVIII product on 139 days: 32 times for treatment of bleed, 24 times for UF8P, and 83 times for OTP, and the use for RP and for OTP were interlaced. It is unknown what is the difference between the reasons for OTP and RP. If some OTP were used for treatment of subclinical bleeds, then bleeds would have been undercounted.

Of the 112 RO subjects, 18 used OTP at least once. Except for 6 subjects, all the others used OTP at most 4 times. These 6 subjects used OTP 83, 31, 23, 14, 10, and 10 times, respectively. Of the 22 DE subjects, 9 used OTP at least once. Except for 4 subjects, all the other DE subjects used OTP at most 5 times. These 4 subjects used OTP 52, 27, 20, and 8 times, respectively.

The Applicant agreed with FDA’s adjudication on the confounding periods, except for subject (b) (6). This subject had no bleeding since taking the last UF8P on Day 22, with peak FVIII:C of 80.4 IU/dL on Day 99, until having the first traumatic bleed on Day 930 following a FVIII: C of 6.6 IU/dL on Day 904. From then until the last FU on Day 1261, this subject experienced 7 traumatic bleeds, used “Treatment for bleed” 11 times and OTP 10 times, with unconfounded FVIII:C between 3.4 and 6.4 IU/dL.

I did not perform the confounding analysis for the DE cohort, as NI analysis on ABR was to be performed for the RO cohort only.

Eight subjects started using emicizumab for prophylaxis during their EEPs, 4 subjects in each of the two cohort. The RO subjects had used emicizumab 4, 4, 18, and 32 times, respectively. The DE subjects had used emicizumab 12, 15, 38, and 44 times, respectively.

Table 13. Study Day when Rollover subjects started receiving FVIII replacement or emicizumab during EEP that confounded ROCTAVIAN effect

#	Subject ID	FDA’s Analysis	Applicant’s Analysis, based on 3-year ADSL
1	(b) (6)	33*	423
2	(b) (6)	33*	812
3	(b) (6)	456	456
4	(b) (6)	698*	705
5	(b) (6)	741	741
6	(b) (6)	825*	888
7	(b) (6)	874	874
8	(b) (6)	942*	994
9	(b) (6)	984	984
10	(b) (6)	1222	1222

11	(b) (6)	802**	-
12	(b) (6)	986**	-
13	(b) (6)	1098**	-

*: FDA’s analysis resulted in a start time different from the Applicant’s.

** : Additional subjects that the FDA identified.

Decrease of treatment effect over time

The Applicant reported that, across both the RO and DE cohorts, 5 subjects returned to routine prophylaxis with exogenous FVIII and/or emicizumab (RTP) by the 2-year DCO, and a total of 17 subjects RTP by the 3-year DCO (10 RO and 7 DE subjects). The Applicant proposed to include the number of subjects RTP in the labeling to provide information on durability, i.e., persistence of treatment effect over time.

When I examined the three variables, bleed episode, CF8E, and FVIII:C, together over time for each subject, I realized that we should assess persistence of treatment effect over time based on the tri-variate analysis over time. In particular, the following two types of patterns indicate loss of response to ROCTAVIAN in subjects who was not reported as RTP.

- Some subjects had CF8E in a prophylaxis manner, sometimes with increased bleeding and always with concomitant substantial decrease in FVII:C. OTP was used with or without UF8P, which might had led to these subjects not reported as meeting the Applicant’s definition of RTP.
- Some subjects had increased bleeding frequency concomitant with substantial decrease in FVIII:C, sometimes suddenly and dramatically, as time progressed but did not have CF8E. These latter subjects lost response to ROCTAVIAN but also genuinely did not RTP (unlike the first set of subjects).

I requested the Applicant to perform their own tri-variate analysis to identify subjects who lost response and when they lost response by providing a specific table to fill in, together with two examples, one for a subject who lost response and one for a subject who did not lose response despite being identified as RTP (more on this later).

The Applicant conducted a multi-disciplinary review and identified 20 subjects who lost response, including one who did not respond from the beginning. This result was mostly consistent with my independent assessment, except that I identified 5 of these 20 subjects, instead of 1, as being non-responder from the beginning, and two additional subjects who lost response. The Applicant agreed with my identification of the 5 non-responders, but dispute the two additional subjects.

- One of these two subjects was Subject (b) (6) , described under the subsection “EEP confounded by prophylactic UF8P and OTP use”.

- The other subject was Subject (b) (6) in the RO cohort. This subject had no bleeds since taking the last UF8P on Day 23, with peak FVIII:C of 188.4 IU/dL on Day 191, until having the first spontaneous bleed on Day 420 (FVIII: C 43.4 IU/dL). FVIII:C decreased to < 10 by Day 539. Altogether until the last FU on Day 1127, this subject had 14 bleeds including traumatic and spontaneous bleeds, used two doses of CF8E for treatment of bleed and two doses for surgery/procedure. I adjudicated that response lost starting on Day 986, based on increase frequency of spontaneous bleeds and low FVIII:C (either confounded or between 2-3 IU/dL).

Based on discussion with colleagues in several disciplines, I concluded that my adjudication on these two subjects was reasonable.

As mentioned above, I provided an example of when a subject who was reported by the Applicant to be RTP might not had lost response. Subject (b) (6) was in the DE cohort. His peak FVIII: C was 96.5 IU/dL on Day 197. Between Day 1297 and Day 1424 (128 days), he used 2 doses of CF8E for treatment of a traumatic bleed (the only bleed during the entire EEP) and 15 doses of UF8E and OTP. He did not take any CF8E between Day 1425 until the last FU on Day 1594 (170 days), had no bleeds, and had four unconfounded FVIII:C from 8.4 to 12.2 IU/dL during that period. The Applicant confirmed that there was no missing data for this subject and that RTP was transient, and agreed with my conclusion that this subject might still benefit from ROCTAVIAN through the last day of FU.

Table 14 summarizes the information on proportion of subject who did not respond to ROCTAVIAN and start time when subjects lost response to ROCTAVIAN. In addition to the results summarized above for the RO cohort, the DE cohort had one subject (4.5%) who did not respond to ROCTAVIAN and another 6 subjects (27.3%) who lost response over a median time of 3.6 (range: 1.2 to 4.3) years. The Applicant and I agreed on the adjudication of the DE subjects.

In my assessment of response, I have taken an approach that only concludes non-response when the level of uncertainty is quite low, which might have led to missing some non-response that is not yet quite evident. Nonetheless, for the RO cohort, this result indicates that the remaining 80.3% (90/122) subjects either continue to benefit from ROCTAVIAN or not yet show definite sign that they lost response.

Table 14. Summary of Study 301 subjects who did not respond or lost response to ROCTAVIAN

	RO cohort (n=112)	DE cohort (n=22)
Subjects who did not respond to ROCTAVIAN: n (%)	5 (4.5%)	1 (4.5%)
Subjects who lost response to ROCTAVIAN: n (%)	17 (15.2%)	6 (27.3%)

When subjects lost response: Years		
Median	2.3	3.6
Minimum, Maximum	1.0, 3.3	1.2, 4.3
1 st quartile, 3 rd quartile	1.7, 2.7	1.8, 4.0
Subjects who resumed RP per the Applicant: n (%)	10 (8.9%)	7 (31.8%)
When subjects first resumed RP per Applicant: Years		
Median	2.3	3.5
Minimum, Maximum	1.2, 3.3	1.1, 4.4
1 st quartile, 3 rd quartile	2.0, 2.6	3.3, 3.7

Reviewer Comment #8

In this Section, I have summarized the analyses and results on decrease of treatment effect over time and the confounding effect of CF8E (consumption of FVIII replacement product or emicizumab) during the EEP.

- *HA has existing effective prophylactic treatments with good understanding of their benefit-risk profiles, as well as the burdensome nature of repeat administrations. Gene therapies like ROCTAVIAN hold a promise for persistent effect over time with a different risk profile. It is imperative to assess durability and robustness of the treatment effect for benefit-risk evaluation of these investigational products. This effort would only be possible with an adequate sample size and duration of follow-up, e.g., Study 301. With these data in Study 301, we have also been able to characterize the extent of IS received to achieve this effectiveness (Tables 8 to 11), another essential piece of information for benefit-risk evaluation and patients.*
- *Study 301 captured and reported information on RTP (return to routine prophylaxis), as defined in the SAP. At first glance, RTP information should have captured all the information for loss of treatment response and for confounding. However, this is not the case.*
 - *The tri-variate analysis identified 22 (19.6%) RO subjects who did not respond or lost response to ROCTAVIAN, more than double the number of RTP subjects (10 subjects, 8.9%).*
 - *Some subjects did not resume RP or use more CF8E after losing response, or did not do so until much later. For example, there were 5*

subjects who did not respond to ROCTAVIAN and I record the time they lost response as Day 33, the EEP start time per protocol. The Applicant first reported, after my information request, that these subjects lost response on Days 33, 60, 125, 173, 423, respectively, though then agreed with my conclusion when I shared my analysis. Among these 5 subjects, one did not use CF8E in a prophylactic manner throughout the entire FU. The remaining 4 subjects started CF8E in a prophylactic manner on Days 33, 33, 741, and 825, respectively. These start times are also the times when confounding period started.

In conclusion, RTP information may under-estimate the extent of treatment failure and the extent of treatment confounding. Tri-variate analysis should be performed for each subject to capture these two types of information.

Subjects with increased bleeding after ROCTAVIAN treatment

The CRL letter raised a concern about increased bleeding after ROCTAVIAN treatment observed in some subjects in the review of the original BLA. I requested the Applicant to identify such subjects. The Applicant examined all 134 subjects in Study 301 and concluded that except for two subjects (Table 15), increased bleeding, if observed, was effectively controlled by RTP. In response to FDA's follow-up questions (from other disciplines) regarding these two subjects, the Applicant responded with the following (BLA 125720/0.115, Response document, p.1).

BioMarin acknowledges the increase in ABR observed for these subjects and investigated these subjects accordingly and confirms no FVIII inhibitors, no abnormal laboratory values suggestive of liver synthetic dysfunction or new coagulopathies. We spoke with the study PIs for both subjects who confirmed the adequacy of the prophylaxis regimens and stated that the bleeding observed post resumption of prophylaxis is not outside of expectations given the bleeding they had prior to return to prophylaxis. Both of these subjects reported multiple bleeding events prior to the resumption of prophylaxis. Bleeds are associated with inflammation, and the recovery from this can sometimes be extended, as patients are at risk for further bleeding in an inflamed joint. BioMarin expects that over time and with continued prophylaxis, these patients will experience less bleeding as inflammation resolves. This is particularly the case for (b) (6), who had only resumed prophylaxis for 3.5 months prior to the data cutoff.

This information is included for documentation purpose.

Table 15. Study 301 subjects with increased bleeding after ROCTAVIAN treatment that was not effectively controlled by RP

Subject ID	Baseline FU (Months)	Baseline ABR	EEP: Before RTP FU (Months)	EEP: Before RTP ABR	EEP: From RTP to DCO FU (Months)	EEP: From RTP to DCO Bleed counts	EEP: From RTP to DCO ABR
(b) (6)	12.4	5.8	39.5	16.4	10.1	17	20.2
(b) (6)	6.4	0	31.5	15.6	3.5	5	17.1

¹ Subject (b) (6) . DE cohort. HIV-positive. Had a total of 71 bleeds during EEP, used 82 FVIII doses for treating bleeds, 59 for surgery/procedure, 52 for OTP, and 44 doses of emicizumab.

² Subject (b) (6) RO cohort. Had a total of 46 bleeds during EEP, used 21 FVIII doses for treating bleeds, 10 for surgery/procedure, 9 for usual prophylaxis, 10 for OTP, and 4 doses of emicizumab.

Source: adapted from – BLA 125720/0.108, Applicant Response to FDA IR, p.11

Subjects with zero bleeds and zero factor VIII or emicizumab infusions during EEP

The Applicant had proposed to include information in the labeling on the proportion of the 134 subjects in both cohorts who had zero bleeds during each of three years after ROCTAVIAN treatment (56%, 63%, and 60%, respectively) and the proportion of subjects receiving zero FVIII infusions (72%, 70%, and 58%, respectively). I communicated that bleeding episodes and use of factor VIII or emicizumab should be considered together and we should consider only the Rollover cohort. The Applicant revised the labeling to read

In the rollover population, 65 of 112 patients (58%) had zero bleeds in Year 1 including 5 patients that used exogenous factor VIII or emicizumab, 74 of 112 patients (66%) had zero bleeds in Year 2 including 8 patients that used exogenous factor VIII or emicizumab, and 69 of 110 patients (63%) had zero bleeds in Year 3 including 12 patients that used exogenous factor VIII or emicizumab.

I was concerned with missing data, especially in later years, and requested the Applicant to only include subjects without any missing data and only proportions of subjects meeting both the criteria of zero bleeds and zero treatments during the EEP years. I also requested to include the proportion of zero bleeds at baseline for context. The Applicant chose not to include information for later years, and included only information for the first year. Below is what the Applicant proposed with light editing for clarity.

Of all patients without any missing information in the rollover population, 23/73 (32%) patients had zero bleeds during baseline

while receiving factor VIII prophylaxis, and 48/92 (52%) patients had zero bleeds without any factor VIII or emicizumab infusions during the first year after ROCTAVIAN treatment, starting from Day 33 (EEP start day).

FDA decides not to include this information in the package insert.

Reviewer Comment #9

It appears there is a substantial amount of missing data. Some of the missing data might have been caused by the COVID-19 pandemic. It is unknown whether they would qualitatively impact the study results. This information came days within action due date so this cannot be evaluated prior to the action due date. However, as the effect size, compared to no treatment, is substantial. I do not expect the biases that may be caused by missing data to completely negate the treatment effect, especially during the first two years after treatment.

6.1.11.2 Analyses of Secondary Endpoints

In this subsection, I will describe and summarize the time course of FVIII:C, measured by chromogenic assay in the central lab. For more comprehensive analyses, including FVIII:C by other assays, please refer to the clinical pharmacology review memo.

Here are a few technical considerations:

- I summarize only the data at study visits corresponding to Weeks 26, 52, 104, and 156 here, approximating Month 6, Years 1, 2, and 3, respectively.
- I requested imputation of data that may be different from the data used by other review disciplines. For example, for Week 156 FVIII:C, I requested the Applicant to report the values for the Week 156 visit, and if it was missing or confounded, impute an unconfounded value that is observed at a later timepoint. In the case that there is no unconfounded value from a later timepoint, zero should be imputed. Imputed values were noted.
- Because there are multiple ways to define quantiles (except for the median), I chose to report the order statistics instead of quantiles to avoid potential confusion.
- For many subjects, the FVIII:C time course shows a sawtooth pattern with a general declining trend instead of a monotone pattern, which might have been due to use of corticosteroids to recover transgenic FVIII expression over the time course, based on communications with colleagues.

- I have decided to use the raw data instead of using the smoothed versions by taking median/mean of several observations at several visits within a short time-interval as provided by the Applicant.
- At this time, the relationship between transgenic FVIII:C level and innate FVIII:C level (or that from exogenous replacement products) is unknown. The Applicant had referred to subjects being in the moderate HA range based on transgenic FVIII:C level in interactions with the FDA. I will consider relative magnitude and time trend, without mapping transgenic FVIII:C level to HA severity, based on considerations and findings summarized previously.
- The descriptive statistics in this subsection provides a qualitative instead of a precise quantitative assessment of time trends.

Table 16 summarizes the Pearson's correlations between FVIII:C at the four timepoints. Weeks 104 and 156 has the highest correlation at 0.95, followed by that between Weeks 26 and 52 at 0.90. The other correlations are similar, ranging between 0.77 and 0.82. Spearman's rank correlations, not shown here, shows similar pattern with slightly lower numerical values.

Figure 3 shows the FVIII:C scatterplots at pairs of the 4 timepoints. There is substantial decline over time except for the following two pairs of time points. Week 52 shows a decline from Week 26, but not as dramatic as the other pairs. Week 156 also shows a less dramatic decline which might be due to the scale of the plots (all plots are kept at the same scale) and the fact that the FVIII:C at this two timepoints are concentrated on the lower end. I will explore this aspect in what follows. Overall, Figure 3 shows that FVIII:C decline substantially over time; Week 26 FVIII:C does not predict similar FVIII:C at Week 104 (Year 2) or later timepoints. Week 26 FVIII:C was proposed to be used as the candidate surrogate endpoint in the original BLA for ABR.

Figure 4 plots the time course of FVIII:C. Because a compressed scale would mask patterns at the lower end of the scale, I split subjects based on whether their Week 156 FVIII:C was greater than the median (8.25 IU/dL). In addition to a general trend of declining FVIII:C for essentially all subjects, the right panel reveals that the decline can be dramatic for a substantial proportion of subjects. On the other hand, 50% of the subjects has FVIII:C \geq 8.3 IU/dL for the Week 156 visit, a level considered to be in the mild HA category if it was for innate FVIII:C levels.

Table 17 provides the order statistics of the Rollover cohort. This table summarizes the distribution of FVIII:C at each timepoint. For example, the maximum FVIII:C (order statistic of the 112th ranked subject at each time point) at the four timepoints are 367.3, 231.2, 187.1, and 217.7 IU/dL, respectively. The 56th ranked FVIII:C (50% percentile) at each timepoint are 38.4, 24.0, 11.6, and 8.2 IU/dL, respectively. A total of 22 subjects (20%) had 0.0 of FVIII:C reported or imputed for the Week 156 visit (not shown in the table).

Table 16. Pearson's correlation between FVIII:C at Weeks 26, 52, 104 and 156 (Rollover cohort)

	Week 26	Week 52	Week 104	Week 156
Week 26	-	0.90	0.78	0.77
Week 52	-	-	0.82	0.79
Week 104	-	-	-	0.95
Week 156	-	-	-	-

Figure 3. Scatterplots of FVIII:C at Weeks 26, 52, 104, and 156, with identity line $y=x$ (Rollover cohort)

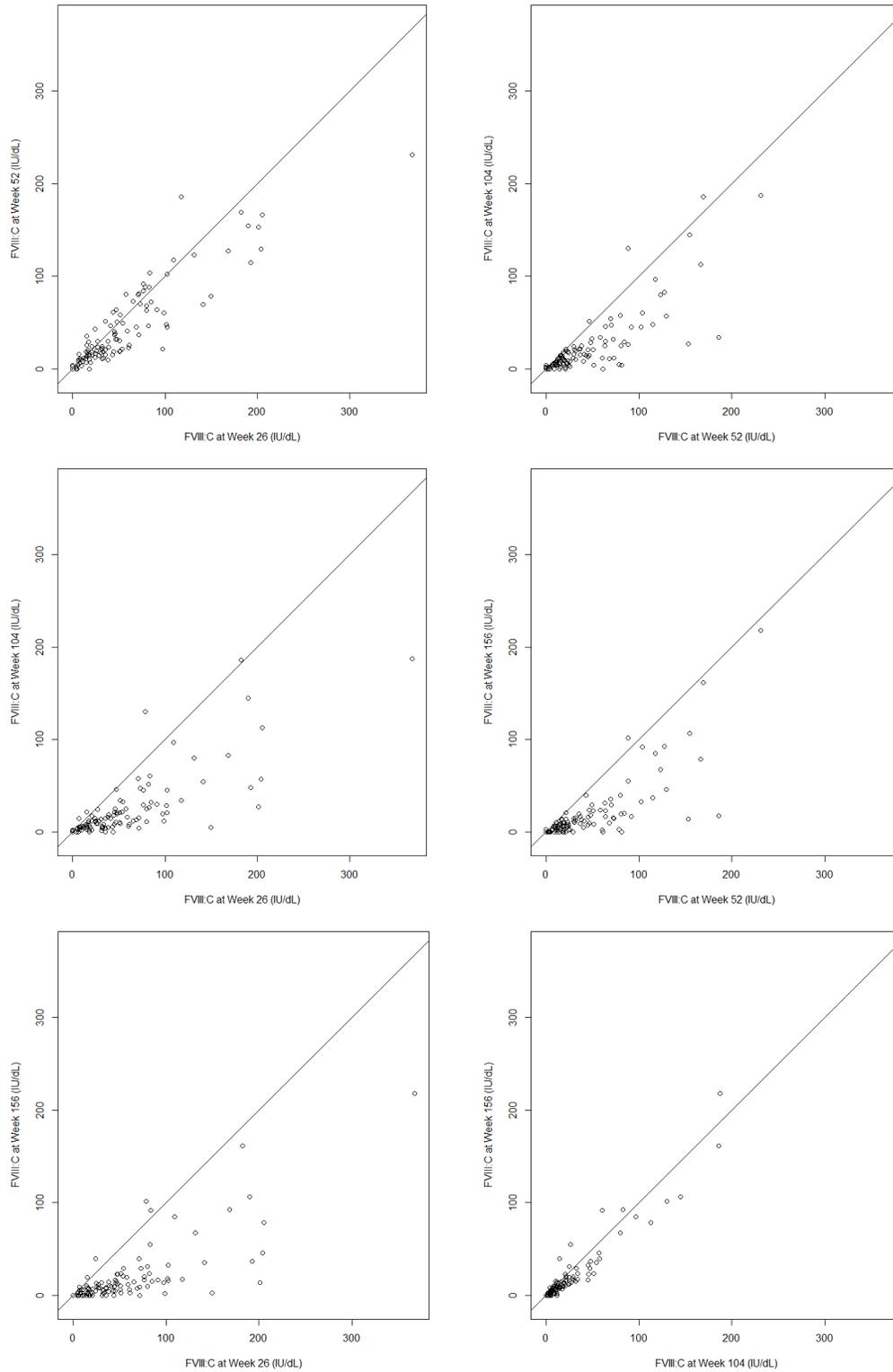


Figure 4. FVIII:C at Weeks 26, 52, 104, and 156 by subjects (Rollover cohort). Left panel for Week 156 FVIII:C greater than the median and right panel for less than the median.

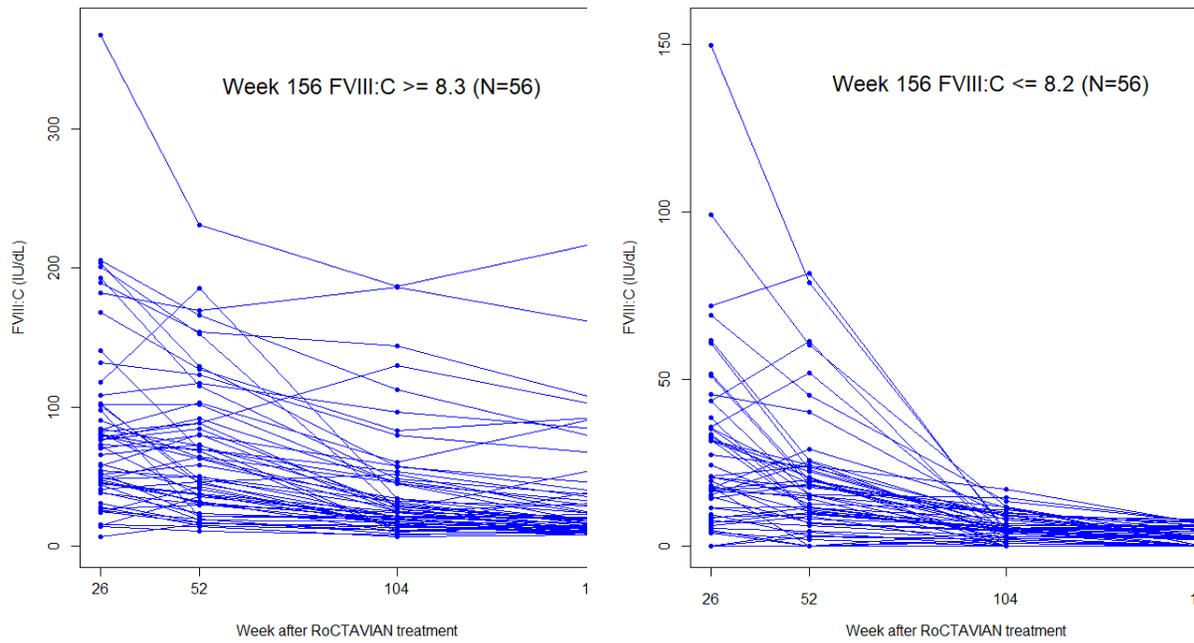


Table 17. Order statistics of FVIII:C at Weeks 26, 52, 104, and 156 (Rollover cohort)

Rank of FVIII:C among the 112 Subjects	Proportion of Subjects with FVIII:C \leq the Order Statistic	Week 26	Week 52	Week 104	Week 156
6	5%	0.0	0.0	0.0	0.0
10	9%	4.8	3.0	0.0	0.0
20	18%	11.6	9.8	3.0	0.0
30	27%	17.3	14.3	5.0	2.7
40	36%	25.2	18.1	6.7	4.6
50	45%	32.7	21.5	9.4	6.9
56	50%	38.4	24.0	11.6	8.2
60	54%	43.5	28.9	11.9	8.9
70	62%	50.9	40.1	16.2	12.6
80	71%	69.1	51.7	21.3	16.2
90	80%	81.9	72.4	30.0	23.0
100	89%	108.9	102.1	51.6	39.6
110	98%	203.9	169.2	144.4	106.3
112	100%	367.3	231.2	187.1	217.7

6.1.11.3 Subpopulation Analyses

ABR by race

Table 18 summarizes ABR by race. The 95% CI is provided as a way to gauge level of uncertainty but should not be construed as formal statistical inference.

Contrary to the "White" or "Asian" subjects, the Black subjects had an increase of mean ABR from baseline to EEP at 2.0 to 3.5 bleeds/year with a 95% CI of (-2.9, 5.9)

bleeds/year, not meeting the non-inferiority margin of 3.5 bleeds/year. I do not consider this as definite evidence that NI does not hold in the Black subjects, as this analysis is exploratory and the sample size (n=14) is small. In addition, the mean EEP ABR of 3.5 bleeds/year is considerably lower than untreated patients with severe HA, indicating effectiveness of ROCTAVIAN in the Black subjects.

Table 18. ABR by race (Rollover cohort: N=112)

Race	N	Baseline ABR Mean (SD) (Bleeds/year)	EEP ABR ¹ Mean (SD) (Bleeds/year)	Mean Difference in ABR (95% CI) (Bleeds/year)
White	78	5.6 (6.8)	2.1 (5.3)	-3.5 (-5.2, -1.8)
Asian	17	7.5 (9.3)	3.0 (8.4)	-4.5 (-9.8, 0.8)
Black or African American	14	2.0 (2.9)	3.5 (7.2)	1.5 (-2.9, 5.9)
Native Hawaiian or Pacific Islander	1	7.7 (-)	0.0 (-)	-
Not Provided	2	1.0 (1.5)	13.4 (5.6)	-

SD: Standard Deviation. CI: Confidence Interval.

¹A total of 13 subjects used factor VIII replacement products or emicizumab during EEP for prophylaxis. An ABR of 35 bleeds/year was imputed for these periods.

ABR by country/territory

Table 19 summarizes ABR by countries or territories. The six countries or territories with at least 10 (range: 10 to 18) subjects are listed individually, while the rest with a range of subjects from 1 to 6 are combined for a total of 24 subjects.

The USA had a mean (SD) baseline ABR of 5.7 (8.7) bleeds/year and a mean (SD) EEP ABR of 4.4 (9.3) bleeds/year, giving a mean difference in ABR of -1.3 (95% CI: -7.8, 5.0) bleeds/year. While the upper bound is greater than the non-inferiority margin of 3.5 bleeds/year, I do not consider this as definite evidence that NI does not hold in the USA, as this analysis is exploratory and the sample size is small (n=16). It is notable that Taiwan had a mean EEP ABR of 1.4 bleeds/year compared to a mean baseline ABR of 9.6 bleeds/year, and for South Africa these numbers are 1.0 and 6.5 bleeds/year, respectively, showing dramatic effects in these two areas compared to the rest of the world.

Table 19. ABR by country/territory (Rollover cohort: N=112)

Country/Territory	N	Baseline ABR	EEP ABR ¹	Mean Difference
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		Mean (SD) (Bleeds/year)	Mean (SD) (Bleeds/year)	in ABR (95% CI) (Bleeds/year)
Brazil	18	1.9 (3.0)	2.1 (5.3)	0.3 (-2.3, 2.7)
United States of America	16	5.7 (8.7)	4.4 (9.3)	-1.3 (-7.8, 5.0)
South Africa	16	6.5 (8.5)	1.0 (2.1)	-5.5 (-10.2, -0.8)
Great Britain	15	4.9 (3.7)	1.9 (4.5)	-3.0 (-6.2, 0.2)
Australia	13	3.3 (3.1)	1.5 (2.5)	-1.8 (-4.4, 0.8)
Taiwan	10	9.6 (10.5)	1.4 (2.0)	-8.2 (-15.9, -0.4)
Other	24	6.6 (7.1)	4.3 (8.9)	-2.3 (-5.8, 1.2)

SD: Standard Deviation. CI: Confidence Interval.

¹A total of 13 subjects used factor VIII replacement products or emicizumab during EEP for prophylaxis. An ABR of 35 bleeds/year was imputed for these periods.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The safety database for ROCTAVIAN consists of data on 170 subjects with severe HA treated with ROCTAVIAN in one of the five ongoing interventional studies (Figure 1 and Table 1).

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The 170 treated subjects were followed up from 0.03 to 5.5 years, with a total post-infusion exposure of 401.8 patient-years, by the 2-year DCO. One more year of FU data on the 134 subjects in Study 301 were provided with the 3-year update report. I will first summarize results on the 2-year data package, followed by additional information on serious adverse events (SAEs) provided in the 3-year report.

In this section I will consider two safety analysis populations:

- All Treated Population (n=170) is defined as all subjects from any of the five clinical studies included in this Class 2 resubmission who received any dose of ROCTAVIAN.
- Proposed Label Population (n=160) is defined as any subject who received ROCTAVIAN at the dose of 6E13 vg/kg, and who was AAV5 TAb-negative at the time of Screening. This population includes 7 patients from Study 201, 134 patients from Study 301, and 19 patients from Study 303, with a median FU of 162 (range: 2 to 275) weeks. Note that subjects in the three studies, as well as in the two cohorts in Study 301, had used different IS regimens. Therefore, the final labeling may include a labeling population different from what is proposed by the Applicant. Nonetheless, this does not materially affect the safety review in this memo, i.e., death, SAEs, and malignancies. Please refer to the clinical review memo for a comprehensive safety review.

Table 20 summarizes demographic data by the two safety analysis populations. Subjects in the Proposed Label Population had a mean (SD) age of 31.1 (9.9) years, with a range of 18-70 years. This was similar to the All Treated Population, which had a mean of 31.4 (9.9) years. Approximately 50% of subjects in each population were under 30 years of age, and approximately 10% were aged 50 or older (including 1 subject > 65 years old). Approximately 75% of subjects were White.

Table 20. Demographics of the safety analysis populations

	Proposed Label (N=160)	All Treated (N=170)
Age at enrollment, years		
Mean (Standard Deviation)	31.1 (9.9)	31.4 (9.9)
Median	30.0	30.0
Minimum, Maximum	18, 70	18, 70
Age at enrollment, n (%)		
18 to < 30 years	79 (49.4)	83 (48.8)
30 to < 50 years	68 (42.5)	74 (43.5)
≥ 50 years	13 (8.1)	13 (7.6)
Race, n (%)		
Asian	21 (13.1)	22 (12.9)
Black or African American	16 (10.0)	17 (10.0)
Native Hawaiian or Pacific Islander	1 (0.6)	1 (0.6)
White	119 (74.4)	127 (74.7)
Not provided due to privacy rules	3 (1.9)	3 (1.8)

Source: Adapted from - BLA 125720/0/69, Study 301 Summary of Clinical Safety, p.67, Table 2.7.4.1.3.1.1

8.4 Safety Results

8.4.1 Deaths

One subject (b) (6) from Israel in the Study 301 RO cohort died (b) (6) on Study Day 669 (Week 95, Month 22). During the study, the subject was hospitalized three times (b) (6). The subject had not received any immunosuppressant therapy at any time during the study. The Investigator assessed that this event is unrelated to ROCTAVIAN.

8.4.2 Nonfatal Serious Adverse Events

SAEs in the all treated populations reported by the 2-year DCO

Sixty SAEs (in 33 subjects) have been reported in the All Treated Population by the 2-year DCO for this Class 2 resubmission. Fifty-one of the 60 SAEs occurred in subjects in the Proposed Label Population.

Rectal hemorrhage SAEs have been reported in 3 subjects. SAEs reported in 2 subjects included Alanine aminotransferase increased, anaphylactic reaction, arthropathy, diarrhea, gastroenteritis, hemophilic arthropathy, hypersensitivity, and post-procedural hemorrhage. The following SAEs were reported once in the All Treated Population: acetabulum fracture, apnoea, arthritis, cataract, (b) (6), coronary artery disease, crohn's disease, depression, diabetes mellitus, diverticulum, haemoperitoneum, hand fracture, head injury, hypertension, hyperuricaemia, infection, influenza, influenza a virus test positive, joint stiffness, lower limb fracture, macular hole, major depression, nephrolithiasis, non-cardiac chest pain, pain, peripheral swelling, periprosthetic fracture, pneumonia, pneumonia cytomegaloviral, presyncope, pyrexia, rash maculo-papular, retinal detachment, skin laceration, steroid diabetes, traumatic haematoma, traumatic haemorrhage, and upper respiratory tract infection.

Seven SAEs (in 4 subjects) were assessed by the investigators as possibly related to use of CS or other immunosuppressant therapy (single events of rectal hemorrhage, pneumonia, influenza A virus test positive, hypertension, CMV pneumonia, steroid diabetes, and diabetes mellitus).

Eight SAEs were assessed as related to treatment with ROCTAVIAN by the investigators:

- Study 201 (b) (6) ; 4E13 vg/kg) – Grade 2 pyrexia
- Study 203 (b) (6) ; 6E13 vg/kg, AAV5 TAb+) – Grade 2 hypersensitivity
- Study 301 (b) (6) ; 6E13 vg/kg) – Grade 2 maculo-papular rash and Grade 2 presyncope
- Study 301 (b) (6) ; 6E13 vg/kg) – Grade 3 hypersensitivity
- Study 301 (b) (6) ; 6E13 vg/kg) – Grade 3 ALT increased
- Study 301 (b) (6) ; 6E13 vg/kg) – Grade 3 anaphylactic reaction
- Study 301 (b) (6) ; 6E13 vg/kg) – Grade 3 ALT increased

All treatment-related SAEs had resolved as of the 2-year DCO.

Additional SAEs from Study 301 between 2-year and 3-year DCO

Fifteen SAEs (in 11 subjects) were newly reported after the 2-year DCO as part of the 3-year DCO in Study 301. In addition, one AE reported with an onset prior to the 2-year DCO was reassessed as serious during this period. These 16 SAEs (in 12 subjects) are

listed below. The investigators assessed these SAEs not related to treatment with ROCTAVIAN. All ages reported are the subject's age as study entry.

1. (b) (6) (32-year-old White male; Rollover cohort). Study Day 1203 (3.3 years). Serious Grade 3 left muscle hemorrhage covering the groin and thigh (Resolved)
2. (b) (6) (32-year-old White male; Rollover cohort). Study Day 820 (2.2 years). Serious Grade 3 appendicitis (Resolved)
3. (b) (6) (27-year-old male of unreported race; Rollover cohort). Study Day 822 (2.3 years). Serious Grade 3 hematoma of the left iliacus muscle and left latissimus dorsi. FVIII activity level (CSA) was 19 IU/dL. The investigator assessed the SAE as related to increased physical activity.
4. (b) (6) (21-year-old White male; Rollover cohort). Serious Grade 4 B-Cell Type Acute Leukemia (Ongoing); Serious Grade 3 presyncope (Resolved); Serious Grade 2 hyponatremia (Resolved)
5. (b) (6) (22-year-old White male; Rollover cohort). Study Day 860 (2.4 years). Serious Grade 3 infection of wisdom tooth (Resolved)
6. (b) (6) (41-year-old White male; Rollover cohort). Study Day 867 (2.4 years). Serious Grade 4 (b) (6) (Resolved)
7. (b) (6) (24-year-old White male; Directly Enrolled cohort). Study Day 1403 (3.8 years). Serious Grade 2 joint swelling after rolling ankle during a misstep (Resolved with Sequelae)
8. (b) (6) (56-year-old White male; Rollover cohort). Study Day 973 (2.7 years). Serious Grade 3 arthropathy (Resolved)
 - a. His pre-operative FVIII activity levels were 47.3 IU and 37.9 IU. Not sure why two values. Possibly from two different assays.
9. (b) (6) (22-year-old White male; Rollover cohort). Study Day 946 (2.6 years). Serious Grade 3 muscle hemorrhage of the left leg psoas muscle (Resolved)
10. (b) (6) (36-year-old Asian male; Rollover cohort). Study Day 862 (2.4 years). Serious Grade 2 rectal hemorrhage (Resolved)
 - a. FVIII activity level was noted to be 30 pre-infusion, and 78 post-infusion (units not reported). The investigator noted that this was considered a Grade 2 event because the subject was hemodynamically stable and had no drop in hemoglobin.
11. (b) (6) (39-year-old White male; Rollover cohort): Serious Grade 3 Osteoarthritis; Serious Grade 3 Joint Effusion; Serious Grade 3 Hemophilic Arthropathy (All Events Resolved)

12. (b) (6) (32-year-old White male; Rollover cohort). Serious Grade 1 Dermal Cyst (Resolved)
- a. Note: this event was reported as non-serious Grade 1 in October 2020, prior to the 2-year DCO, but was reassessed as serious during the incremental analysis period between the two DCOs following the subject's hospitalization for worsening of the cyst.

8.4.8 Adverse Events of Special Interest

For Adverse Events of Special Interest (EOSI), I will summarize the result on malignancies. Please refer to the clinical review memo for additional EOSIs. The list of additional EOSIs for ROCTAVIAN includes

- Abnormal liver tests
- Infusion-associated events, including infusion-related reactions, hypersensitivity, anaphylactic, or anaphylactoid reactions
- Thromboembolic events
- Development of anti-FVIII inhibitors (neutralizing antibodies)
- Horizontal transmission to third parties
- Germline transmission

Malignancies

Malignancy in relation to vector integration is an important potential risk for all AAV-based gene therapies, including ROCTAVIAN. Two cases of malignancies were reported after treatment with ROCTAVIAN. The Applicant concluded that it was unlikely or very unlikely that ROCTAVIAN played a role in the development of malignancies in these two subjects.

- Subject (b) (6) was a 42-year-old male in the 6E13 vg/kg dose cohort of Study 201. The subject was diagnosed with acinic cell carcinoma of the tail of the parotid gland, a Grade 2 SAE, on Week 293 (November 2021) for a lump on his right neck that had been present since approximately October 2020 (Weeks 234-237).
- Subject (b) (6) was a 21-year-old White male treated with ROCTAVIAN at a US site in Study 301. He was diagnosed with a serious Grade 4 B-Cell Type Acute Leukemia (B-ALL). Starting around Day 764 (Month 25), the subject began experiencing vague back pain followed by intermittent fevers and night sweats. From Month 29 to Month 32, he had an unintended weight loss of 7 kg, a drop in hemoglobin, and elevated inflammatory markers. On Day 1079 (Month

35), a bone marrow biopsy and aspirate were performed which led to the diagnosis of serious Grade 4 B-ALL.

9. ADDITIONAL STATISTICAL ISSUES

None notable

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

ROCTAVIAN is an investigational one-time single-dose gene therapy for the treatment of adults with severe hemophilia A (HA). ROCTAVIAN consists of AAV5 capsids containing a transgene encoding the B-domain deleted SQ form of the human coagulation factor VIII under the control of a liver-specific promoter.

This class 2 BLA submission includes data on 170 subjects with severe HA who were treated with ROCTAVIAN at one of four dose levels (6E12, 2E13, 4E13, or 6E13 vg/kg) in one of five ongoing clinical trials. The maximum follow-up was 5.5 years post-treatment. The efficacy database consists of the 134 subjects treated in Study 301, and the safety database includes the 170 subjects treated in the five ongoing trials.

Study 301 is an ongoing phase 3, single-arm, multi-regional trial investigating the safety and efficacy of a single dose of 6E13 vg/kg of ROCTAVIAN in adult male HA subjects with residual FVIII levels ≤ 1 IU/dL, without detectable pre-existing antibodies to the AAV5 capsid, and without a documented history of a detectable FVIII inhibitor. Subjects must have been on prophylactic FVIII replacement therapy for at least 12 months prior to study entry. After intravenous infusion of ROCTAVIAN, subjects may continue exogenous prophylactic FVIII replacement therapy for 4 weeks, a time when ROCTAVIAN was expected to manifest its effect. Subjects would then remain in Study 301 for 5 years, and then be transferred to a long-term follow-up (FU) study for a total FU of 15 years post treatment. Study follow-up visits are weekly through Week 36, then biweekly through Week 52, then every 4 weeks in Year 2, and every 6 weeks in Years 3-5. Subjects deemed to experience treatment failure would follow an abbreviated visit schedule after Week 52 by attending visits every 12 weeks and end-of-year visits during Years 2-5. The data cut-off date was set so that all treated subjects in Study 301 had at least 3 years of FU post treatment.

Study 301 consisted of two cohorts: the Directly Enrolled (DE) cohort (N=22, with 2 HIV-positive subjects) and the Rollover cohort (N=112, no HIV-positive subjects). There are two differences between the two cohorts. First, they differ in how baseline data were collected: RO subjects had completed approximately 6 months of participation in a non-interventional study where bleed episodes and FVIII product use data were prospectively collected to serve as baseline prior to their entry into Study 301, whereas baseline data for the DE subjects were retrospectively collected. The second difference is in the

immunosuppression (IS) regimen, which is more extended in the RO cohort. The RO cohort is the primary efficacy analysis set and the DE cohort is supportive with about one more year of FU than the RO cohort.

The primary objective was to demonstrate non-inferiority (NI) in annualized bleeding rate (ABR) after ROCTAVIAN treatment during the efficacy evaluation period (EEP) compared to ABR with FVIII prophylaxis during baseline, in the RO cohort. All bleeding episodes, regardless of treatment, were counted towards ABR. 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. The primary efficacy analysis was an NI comparison between the EEP ABR and baseline ABR in the RO cohort, with an NI margin of 3.5 bleeds/year on the mean difference between the ABRs.

Secondary efficacy objectives included assessment of other endpoints, e.g., FVIII:C level and usage of exogenous FVIII replacement therapy, at various timepoints, and further descriptive characterization of bleeding episodes.

The primary efficacy analysis yielded an estimate of the mean ABR difference (EEP - Baseline) of -2.8 bleeds/year with a 95% confidence interval of (-4.3, -2.1) bleeds/year, therefore meeting the NI success criterion which required the upper bound of the CI to be less than 3.5, indicating the effectiveness of ROCTAVIAN. The mean (standard deviation, SD) of Baseline ABR was 5.4 (6.9) bleeds/year, and was 2.6 (6.2) bleeds/year for EEP ABR. The total EEP for all RO subjects was 342.8 person-years. A total of 13 subjects used factor VIII products or emicizumab for prophylaxis during the EEP for a total of 14.4 person-years, with a median start time at 2.2 (range: 0.1 to 3.3) years. For the primary analysis, an ABR of 35 bleeds/year was imputed for these 14.4 person-years when subjects were on prophylaxis during EEP.

Most RO subjects (92/112, 82.1%) who received ROCTAVIAN in Study 301 also received corticosteroids to suppress the immune system for the gene therapy to be effective and safe, with a median duration of 8.0 (range: 0.7 to 27.2) months. For the DE cohort, 14/22 (63.6%) subjects also received corticosteroids for the same purpose, with a median duration of 5.1 (range: 1.8 to 18.1) months.

In the RO cohort, 5 subjects (4.5%) did not respond to ROCTAVIAN treatment and 17 subjects (15.2%) lost response to ROCTAVIAN treatment over a median time of 2.3 (range: 1.0 to 3.3) years. In the DE cohort, 1 subject (45%) did not respond and 6 subjects (27.3%) lost response over a median time of 3.6 (range: 1.2 to 4.3) years.

FDA Office of Plasma Protein Therapeutics reviewers have concluded that transgene FVIII protein (circulating in plasma of ROCTAVIAN treated subjects) is different from the endogenous human FVIII protein (in normal pooled plasma which is used as a reference standard in clinical FVIII activity assays), and is also different from those of XYNTHA/REFACTO concentrate (FVIII exogenous replacement products). As such,

transgenic FVIII:C levels should not be mapped to severity of HA using criteria developed based on endogenous human FVIII protein, i.e., a transgenic FVIII:C level between 1 and 5 IU/dL does not mean the subject's phenotype was converted to moderate HA.

Different assays and different agents yield different readings of FVIII:C from the plasma sample after ROCTAVIAN treatment. In this review, I used the FVIII:C levels measured by the chromogenic substrate assay at a central lab. For most RO subjects, FVIII:C experienced substantial decline over time. The 50% percentile was 38.5 IU/dL at Week 26 visit, 24.0 at Week 52, 11.6 at Week 104, and 8.2 IU/dL at Week 156 visit. A total of 22 subjects (20%) had 0.0 of FVIII:C reported or imputed for the Week 156 visit.

Regarding safety, there was one death (b) (6). One subject was diagnosed with acinic cell carcinoma of the tail of the parotid gland. Another subject was diagnosed with B-cell type acute leukemia. The Applicant assessed these events as unrelated to ROCTAVIAN. A joint statement by the European Haemophilia Commission, the World Federation of Hemophilia, and the National Hemophilia Foundation reported that, as of September 13, 2022, there had been four reports of cancer (the other two being a liver cancer and a tonsil cancer in studies of other products) in participants of any hemophilia gene therapy trial.

10.2 Conclusions and Recommendations

The efficacy results of Study 301 provided sufficient statistical evidence to support the non-inferiority of ROCTAVIAN treatment to factor VIII prophylaxis in terms of ABR during the efficacy evaluation period starting around Day 33 with a median follow up of 3.1 (range: 1.8 to 3.8) years after ROCTAVIAN treatment. The majority of patients who received ROCTAVIAN also received corticosteroids to suppress the immune system for the gene therapy to be effective and safe. The data submitted constitute substantial evidence of effectiveness, and I recommend approval of ROCTAVIAN. Treatment response to ROCTAVIAN may decrease over time.