



Administration of ROCTAVIAN™

(valoctocogene roxaparvovec-rvox)

ICD-10 Coordination and
Maintenance Committee Meeting

BIOMARIN®

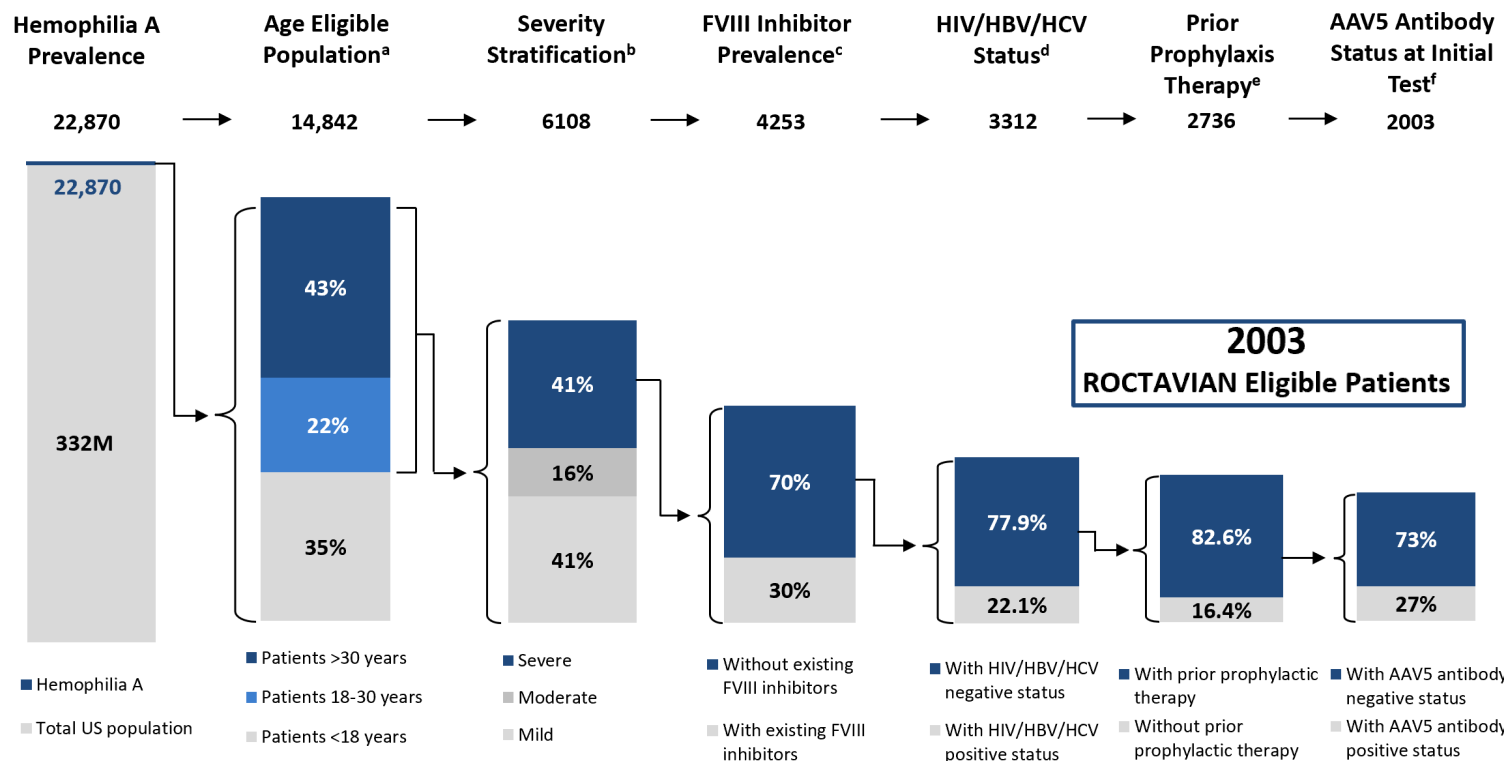
- These slides are directed to the audience of this presentation for the sole purpose of supporting the request for an ICD-10-PCS procedure code for ROCTAVIAN™ (valoctocogene roxaparvovec-rvox).
- Nothing in this presentation should be taken to be any form of promotion or advertisement of any of BioMarin's products or therapies. Please see the full Prescribing Information for additional information.



Patient Population

Indication

ROCTAVIAN™ is indicated for the treatment of adults with severe hemophilia A (congenital Factor VIII deficiency with Factor VIII activity <1 IU/dL) without antibodies to adeno-associated virus serotype 5 detected by an FDA-approved test.



^a CDC Community Count (September 2022 data cut; Source: CDC 2022⁴) was used to calculate the proportion of individuals in the 3 age categories and projected 2021 US Census data (Source: US Census 2022⁵⁷) were used to split the 11-19 age group into an 11-17 age group and an 18-19 age group.

^b BMN 270 eligible patients are those with severe disease, in age ≥18 population. Disease severity distribution by age groups is reported by CDC Community Count (September 2022 data cut; Source: CDC 2022⁴). Projected 2021 US Census data (Source: US Census 2022⁵⁷) were used to calculate proportion of individuals ≥18 years in the disease severity distribution. The proportion of individuals with severe disease was calculated as the number of individuals ≥18 years with known severe disease divided by the total number of patients ≥18 years with hemophilia A. In particular, this calculation assumes that none of the patients with unknown disease severity have severe disease.

^c This value is sourced from a severe hemophilia A population, age and gender not specified (Source: Witmer 2013⁵⁹).

^d HIV/HBV/HCV prevalence is expected to vary by age cohort. HIV/HBV/HCV negative status estimates for populations 18-30 years and >30 years of age are 100% (assumption) and 65.4% (Source: Mazepa 2016⁶⁰), respectively. The 65.4% value is sourced from a male only, severe hemophilia A and B population, born in 1983-1992. This value may underestimate the number of individuals with HIV/HCV/HSV as individuals born prior to 1983 have a higher prevalence of HIV/HCV/HSV coinfection in this study (Source: Mazepa 2016⁶⁰).

^e This value is sourced from a severe hemophilia A population treated at HTC and could be a slight over-estimation of prior prophylaxis use in a general adult hemophilia A population (Source: Croteau 2019⁶¹).

^f This value is sourced from a severe hemophilia A population, age and gender not specified (Source: Klamroth 2021⁶²).

Abbreviations: AAV5, adeno-associated virus serotype 5; CDC, Centers for Disease Control and Prevention; FVIII, factor VIII; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTC, hemophilia treatment center; US, United States.

Prior Prophylaxis is not a requirement in the US Prescribing Information

Centers for Disease Control and Prevention. Patient counts: factor VIII and factor IX - September 2022 data release 2022; Available at: <https://www.cdc.gov/ncbddd/hemophilia/communitycounts/data-reports/2022-09/table-2-factor.html>. Accessed February 27, 2023.

U.S. Census Bureau. Annual estimates of the resident population by single year of age and sex for the United States: April 1, 2020, to July 1, 2021. 2022; Available at: <https://www.census.gov/data/tables/time-series/demo/popest/2020s-national-detail.html>. Accessed April 29, 2022.

Witmer C, Young G. Factor VIII inhibitors in hemophilia A: rationale and latest evidence. *Ther Adv Hematol*. 2013;4(1):59-72.

Mazepa MA, Monahan PE, Baker JR, Riske BK, Soucie JM. Men with severe hemophilia in the United States: birth cohort analysis of a large national database. *Blood*. 2016;127(24):3073-3081.

Croteau SE, Cheng D, Cohen AJ, et al. Regional variation and cost implications of prescribed extended half-life factor concentrates among U.S. haemophilia treatment centres for patients with moderate and severe haemophilia. *Haemophilia*. 2019;25(4):668-675.

Klamroth R, Hayes G, Andreeva T, et al. Global seroprevalence of pre-existing immunity against AAV serotypes in people with hemophilia A. ISTH 2021 Virtual Congress.

Please see Important
Safety Information
throughout and in the
Prescribing Information

B:OMARIN®

Severity	Factor VIII Level %	Frequency of bleeding episode	Potential causes of bleeding episodes
Normal*	50–150% ³	No abnormal bleeding	
Mild	>5-40%	Infrequent	<ul style="list-style-type: none"> • Major trauma • Surgery • Spontaneous bleeds are rare
Moderate	1-5%	Variable	<ul style="list-style-type: none"> • Minor trauma • Surgery • Occasional spontaneous bleeding
Severe	<1%	Frequent	<ul style="list-style-type: none"> • Spontaneous bleeding • Can occur without known trauma

*The definition of a 'normal' factor level remains controversial, with the classification of individuals with FVIII between 40 and 50% remaining unresolved²

**Symptoms of hemophilia vary based on severity of disease,
but all persons with hemophilia may experience life-threatening complications**



Disease Burden

Disease management
Clinical and economic burden

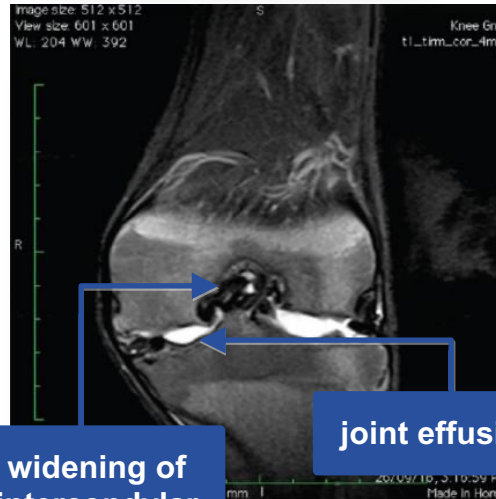
Repeated bleeds of any size can lead to the development of hemophilic arthropathy

Target joints may develop through recurrent bleeds and microbleeds, if undetected, can have long-term irreversible consequences



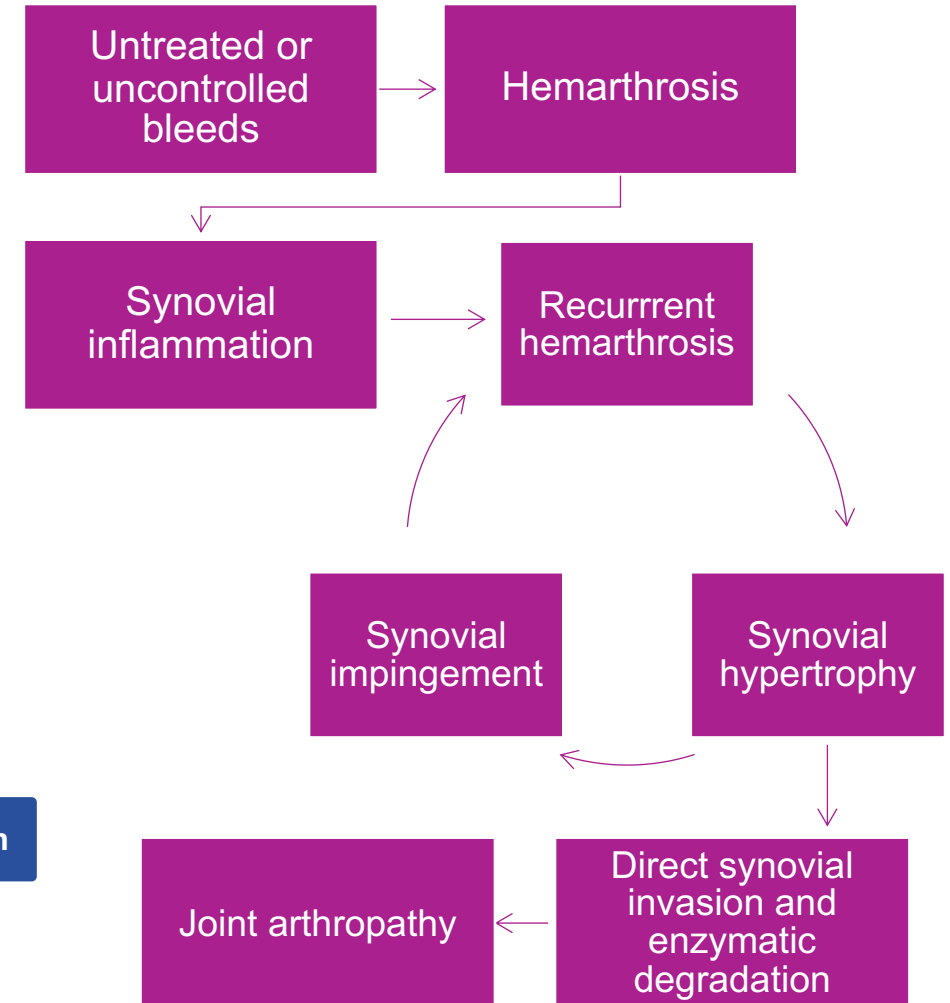
Bleeding into the synovium causes chronic inflammation (chronic synovitis) with hypertrophy of the synovium and swelling of the joint

Although uncommon with effective prophylaxis, **hemophilic arthropathy** is a cause of significant pain, disfigurement, and functional impairment, which may require surgical intervention



widening of intercondylar notch

joint effusion



Hemophilia A Management Currently Includes Episodic or

Continuous prophylaxis with exogenous FVIII	World Federation of Hemophilia (WFH) Guidelines strongly recommend that all patients with severe hemophilia should be on regular long-term prophylaxis, initiated at an early age, and prefer clotting factor concentrates in preference to cryoprecipitate or Fresh Frozen Plasma (FFP)
Continuous prophylaxis with emicizumab	WFH Guidelines state that emicizumab is an option indicated for routine prophylaxis
Prophylaxis can be individualized	<ul style="list-style-type: none">• Joint status• Bleeding phenotype• Availability of therapy• Venous access• Individual pharmacokinetics• Patient self-assessment and preference
Episodic therapy is not preferred	<ul style="list-style-type: none">• Even in countries with significant healthcare constraints, WFH Guidelines always recommend the use of prophylaxis over episodic therapy

Physical^{1–6}



A significant physical impact

- Chronic pain⁴
- Severe, debilitating arthropathy⁵
- Reduced life expectancy⁴

Infusion burden

- Substantial venous scarring due to frequent infusions, including permanent scar tissue/bruises⁶

Logistical^{5,6,12}



Time

- Follow-up and clinic visits

Infusion practicalities^{5,6}

- Treatment schedules
- Ensuring adequate medical supplies
- Levels of treatment adherence range from 44–87%¹³
- Need to travel with large quantities of treatment

Psychological^{3,6–11}



Social isolation³

- Limited activity and social participation

Impact on relationships^{9,11}

- Negative impact on relationships
- Negative impact on sex life

Reduced quality of life^{6,7}

- Anxiety and depression⁸

Economic^{4,8,14}



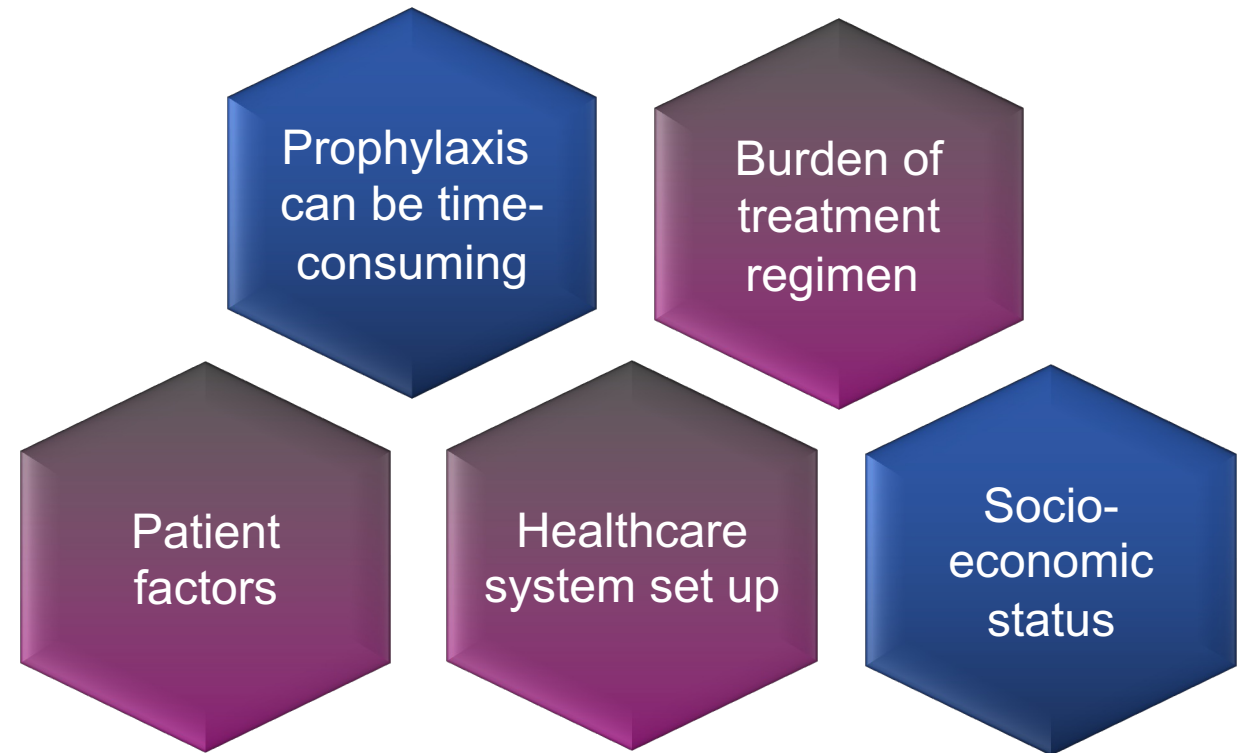
- Hospitalizations
- Outpatient visits
- Drug treatments
- Diminished work productivity or absenteeism
- Early retirement

*Burdens may vary across regions and patient populations

1. Mauser-Bunschoten EP *et al. Haemophilia* 2009;15:853–63; 2. Knobe K *et al. J Comorb* 2011;1:51–9; 3. Miesbach W *et al. Haemophilia* 2019;25:545–57; 4. Salzman R *et al. Mol Ther* 2018;26:2717–26; 5. Balkaransingh P, Young G. *Ther Adv Hematol* 2018;9:49–61; 6. Wiley RE *et al. Haemophilia* 2019;433–40; 7. Carvalhosa AM *et al. Haemophilia* 2014;20:479–85; 8. Chen SL. *Am J Manag Care* 2016;22:S126–33; 9. Cassis FRMY *et al. Haemophilia* 2014;20:e287–95; 10. Cassis FRMY *et al. Haemophilia* 2012;18:e101–14; 11. Blamey G *et al. Patient Relat Outcome Meas* 2019;10:243–55; 12. Quon D *et al. Am J Hematol* 2015;90:S17–22; 13. Lee Mortensen G *et al. Haemophilia* 2018;24:862–72; 14. Mahlangu J *et al. Haemophilia* 2019;25:382–91

- Poor adherence is associated with worse outcomes^{1,2}
 - Can result in lower trough levels^{3,4}
 - Increase risk of breakthrough bleeds^{3,4}
- Factor concentrates have an adherence rate of 58–67%⁶

Factors affecting adherence^{5–8}



1. Krishnan S *et al. Haemophilia* 2015;21:64–70; 2. McLaughlin JM *et al. Haemophilia* 2014;20:506–12; 3. Dodd C, Watts RG. *Haemophilia* 2012;18:561–7; 4. Fischer K *et al. Blood* 2013; 122:1129–36; 5. Miesbach W *et al. Haemophilia* 2019;25:545–57; 6. Thornburg CD, Duncan NA. *Patient Pref Adherence* 2017;11:1677–86; 7. Srivastava A *et al. Haemophilia* 2020;26(Suppl 6):1–158; 8. duTreil S. *J Blood Med* 2014;5:115–22



Clotting factor or bypassing agents

Up to 97% of direct healthcare
economic impacts are attributable to
the utilization
of FVIII replacement therapy¹

Real-world evidence demonstrates that
extended half-life (EHL) therapies do
not lower drug expenditures as
compared to SHL therapies, despite
the less frequent need for utilization²



Hospitalizations¹



Laboratory tests¹



Medical procedures¹



Emergency room visits¹



Other healthcare service provider visits¹

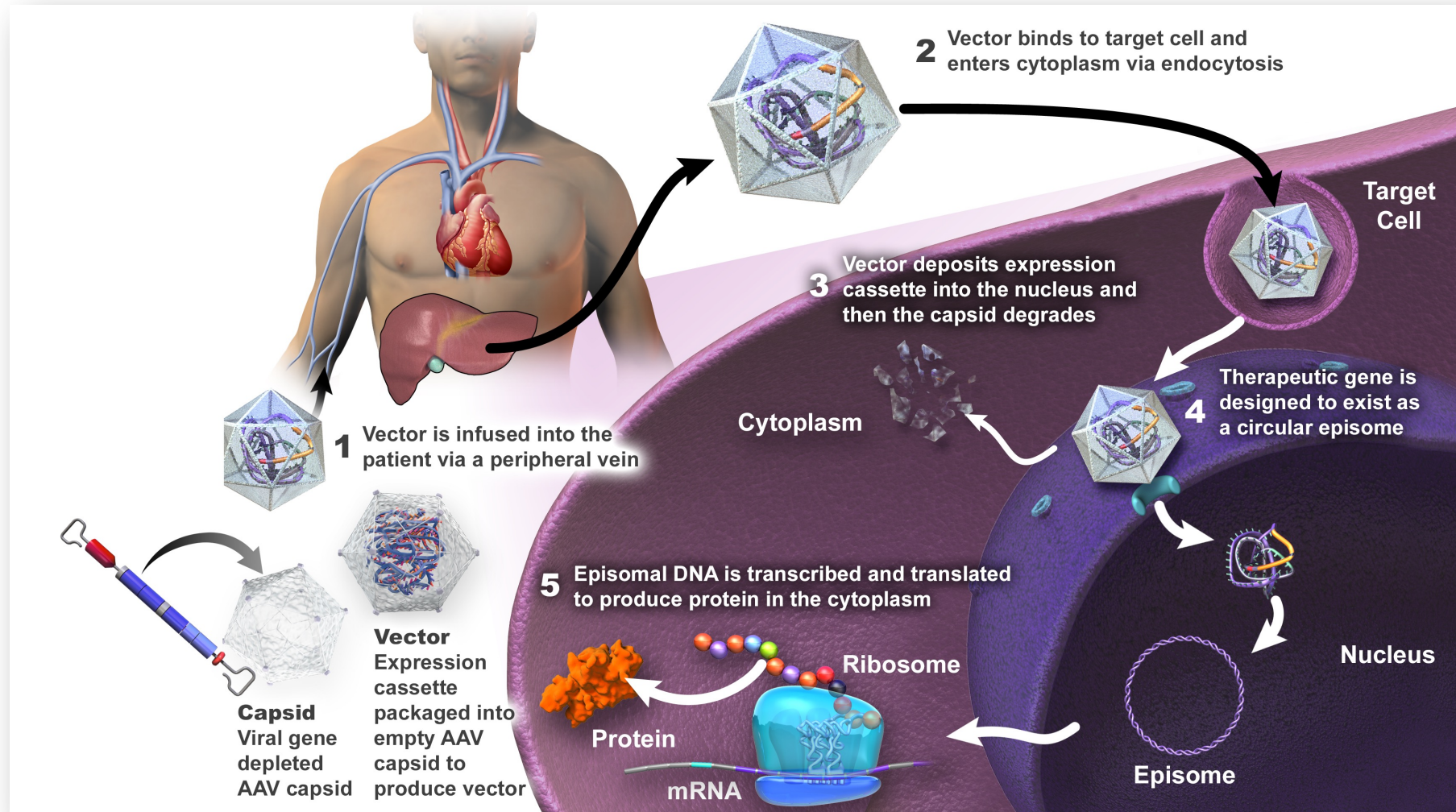


ROCTAVIAN™

Mechanism of action

Dosing

Outcomes



ROCTAVIAN™ is administered as a one-time intravenous infusion of 6×10^{13} vector genomes per kilogram body weight

Each Vial Contains



Extractable volume of not less than 8 mL; 2×10^{13} vg/mL of valoctocogene roxaparvovec-rvox)

Recommended Dose



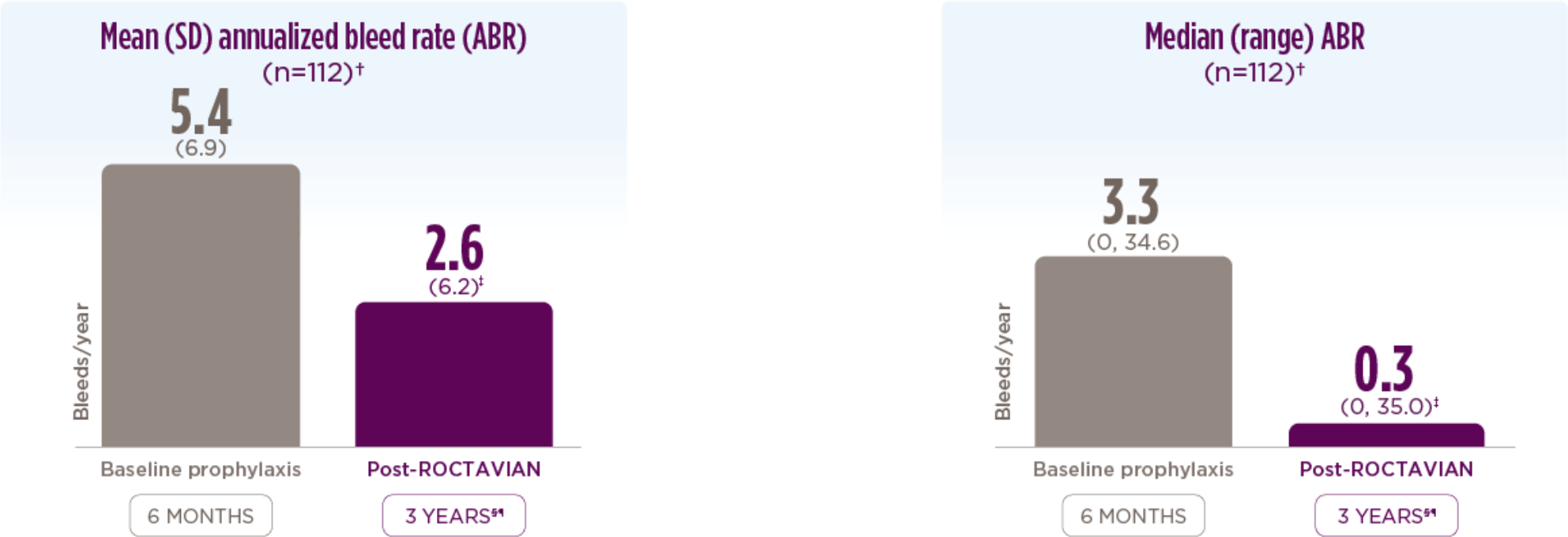
6×10^{13} vg/kg of body weight administered as a single intravenous infusion

Sample Dose Calculation



80 kg patient, 8 mL extractable volume per vial:
 $80 \text{ kg} \times (3 \text{ mL/kg}) / (8 \text{ mL/vial}) = \mathbf{30 \text{ vials}}$

Reduction in annualized bleeding rate (ABR) from baseline prophylaxis*1



SD=standard deviation.

*An NI test of the difference in ABR during the EEP following ROCTAVIAN™ administration was compared with ABR during the baseline period in the rollover population. The mean difference in ABR was -2.8 (95% CI: -4.3, -1.2) bleeds/year. The NI analysis met the prespecified margin, indicating the effectiveness of ROCTAVIAN.

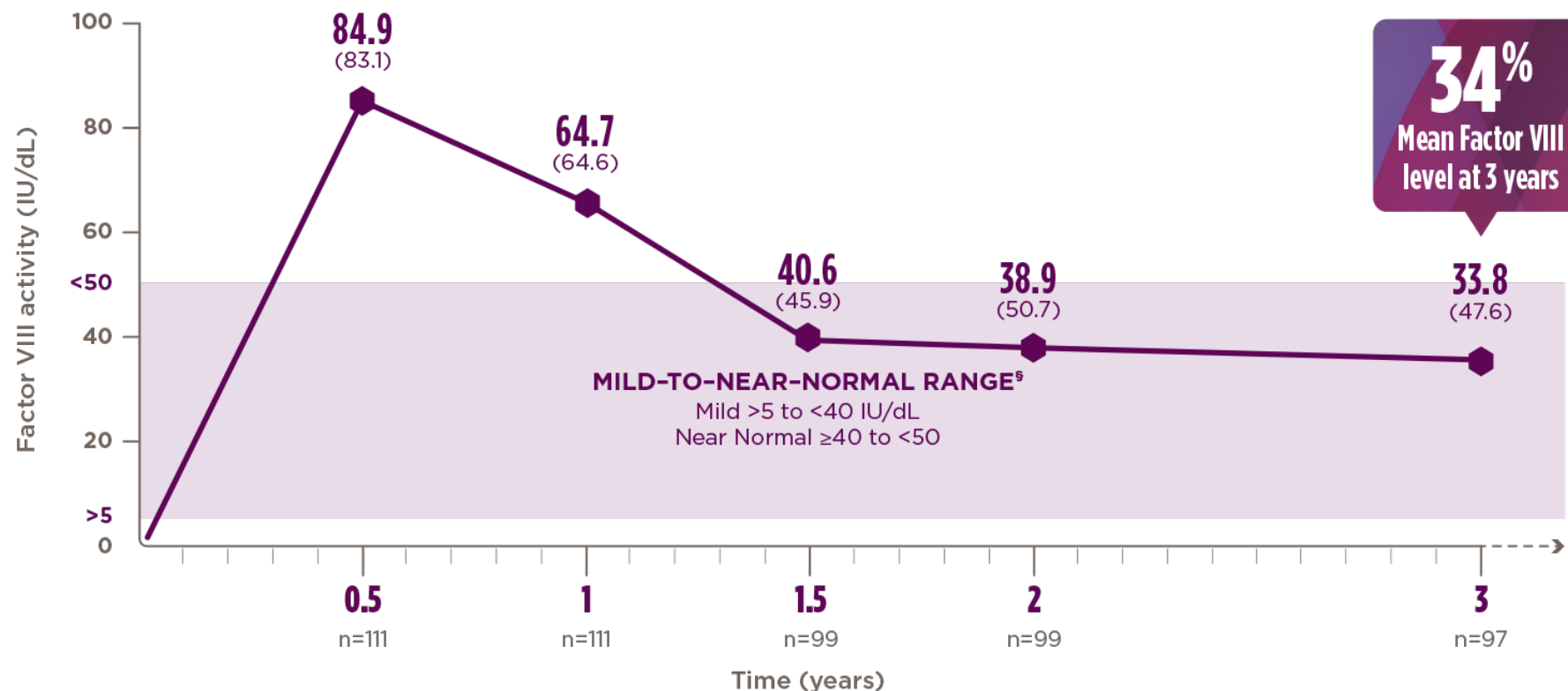
[†]Of the 134 patients who received ROCTAVIAN™ in the clinical trial, 112 patients had baseline ABR data prospectively collected during a period of ≥6 months on Factor VIII prophylaxis prior to receiving ROCTAVIAN™ (rollover population). The remaining 22 patients had baseline ABR collected retrospectively (directly enrolled population).

[‡]A total of 13 patients (12%) had used Factor VIII replacement products or emicizumab during the efficacy evaluation period for prophylaxis, with a median start time at 2.3 (range: 0.1 to 3.3) years. An ABR of 35 was imputed for the periods when these patients were on prophylaxis.

[§]The 3-year follow-up period 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.

[¶]Median duration of follow-up was 3.0 years (range: 1.7, 3.7).

Mean (SD) Factor VIII activity level, per one-stage assay†‡



Some patients had increased Factor VIII activity levels but were determined to have not responded or lost response to ROCTAVIAN™

*Median duration of follow-up was 3.0 years (range: 1.7, 3.7).

†Of the 134 patients who received ROCTAVIAN™ in the clinical trial, 112 patients had baseline ABR data prospectively collected during a period of ≥6 months on Factor VIII prophylaxis prior to receiving ROCTAVIAN™ (rollover population). The remaining 22 patients had baseline ABR collected retrospectively (directly enrolled).

‡Factor VIII activity produced by ROCTAVIAN™ in human plasma is higher if measured with one-stage assay compared to chromogenic assay. In clinical studies, there was a high correlation between one-stage and chromogenic Factor VIII activity levels across the entire range of each assay's results. For routine clinical monitoring of Factor VIII activity levels, either assay may be used. The conversion factor between the assays can be approximated based on clinical study results (central laboratory) to be: OSA=1.5xCSA.

§World Federation of Health definitions of hemophilia severity. Here, we define near-normal to normal as 40 IU/dL to ≤150 IU/dL.

- **Contraindications:** Patients with active infections, either acute (such as acute respiratory infections or acute hepatitis) or uncontrolled chronic (such as chronic active hepatitis B). Patients with known significant hepatic fibrosis (stage 3 or 4 on the Batts-Ludwig scale or equivalent), or cirrhosis, and patients with known hypersensitivity to mannitol.
- **Infusion-related reactions** including hypersensitivity reactions and anaphylaxis, have occurred. Monitor during and for at least 3 hours after ROCTAVIAN™ administration. Administer ROCTAVIAN™ in a setting where personnel and equipment are immediately available to treat infusion-related reactions. Discontinue infusion for anaphylaxis.
- **Hepatotoxicity:** Monitor alanine aminotransferase (ALT) weekly for at least 26 weeks and institute corticosteroid treatment in response to ALT elevations as required. Continue to monitor ALT until it returns to baseline. Monitor factor VIII activity levels since ALT elevation may be accompanied by a decrease in factor VIII activity. Monitor for and manage adverse reactions from corticosteroid use.
- **Thromboembolic Events:** Factor VIII activity above ULN has been reported following ROCTAVIAN™ infusion. Thromboembolic events may occur in the setting of elevated Factor VIII activity above ULN. Evaluate patients for risk of thrombosis including general cardiovascular risk factors before and after administration of ROCTAVIAN™. Advise patients on their individual risk of thrombosis in relation to their Factor VIII activity levels above ULN and consider prophylactic anticoagulation. Advise patients to seek immediate medical attention for signs or symptoms indicative of a thrombotic event.
- **Factor VIII Inhibitors and Monitoring for Inhibitors.** The safety and effectiveness of ROCTAVIAN™ in patients with prior or active Factor VIII inhibitors have not been established. Patients with active Factor VIII inhibitors should not take ROCTAVIAN™. Following administration, monitor patients for Factor VIII inhibitors (neutralizing antibodies to Factor VIII). Test for Factor VIII inhibitors especially if bleeding is not controlled, or plasma Factor VIII activity levels decrease.
- **Monitor Factor VIII** using the same schedule for ALT monitoring. It may take several weeks after ROCTAVIAN™ infusion before ROCTAVIAN™-derived Factor VIII activity rises to a level sufficient for prevention of spontaneous bleeding episodes. Exogenous Factor VIII or other hemostatic products may also be required in case of surgery, invasive procedures, trauma, or bleeds.
- **Malignancy:** The integration of liver-targeting AAV vector DNA into the genome may carry the theoretical risk of hepatocellular carcinoma development. ROCTAVIAN™ can also insert into the DNA of other human body cells. Monitor patients with risk factors for hepatocellular carcinoma (e.g., hepatitis B or C, nonalcoholic fatty liver disease, chronic alcohol consumption, nonalcoholic steatohepatitis, advanced age) with regular liver ultrasound (e.g., annually) and alpha-fetoprotein testing for 5 years following ROCTAVIAN™ administration. In the event that any malignancy occurs after treatment with ROCTAVIAN™, contact BioMarin Pharmaceutical Inc. at 1-866-906-6100.

The safety of Roctavian™ was evaluated in 134 patients in the Phase 3 study (112 rollover and 22 directly enrolled).

Adverse Reactions	Number of Patients (%), N=134	
	All Grades	≥Grade 3
Nervous system disorders		
Headache	9 (7%)	0 (0%)
Gastrointestinal disorders		
Nausea	42 (31%)	0 (0%)
Vomiting	8 (6%)	0 (0%)
Abdominal pain ^b	8 (6%)	0 (0%)
General disorders and administration site conditions		
Fatigue ^c	21 (16%)	0 (0%)
Infusion-related reactions ^d	9 (7%)	2 (1%)

^aOther adverse reactions include gastroenteritis (2 patients; 1%), rash (2 patients; 1%), diarrhea (6 patients; 4%), and dizziness (3 patients; 2%).

^bIncludes abdominal discomfort, abdominal distension, abdominal tenderness, and abdominal pain upper.

^cIncludes fatigue, lethargy, and malaise.

^dInfusion-related reactions are not under a specific system organ class and include multiple symptoms that occurred during or within 6 hours after the end of infusion.

AAV Gene Therapy Products Currently in Clinical

	Gene Therapy	AAV Vector	Institution/Company	Interventional Trial Status
Hemophilia A	Valoctocogene roxaparvovec (BMN270)	AAV5	BioMarin	Phase 3 ¹
	Giroctocogene fitelparvovec (SB-525 / PF-07055480)	AAV2/6	Sangamo Therapeutics / Pfizer	Phase 3 ²
	SPK-8011	AAV-LK03	Spark Therapeutics / Roche	Phase 3 ³
	SPK-8016	AAV	Spark Therapeutics / Roche	Phase 1/2 ³
	BAY 2599023 (DTX-201)	AAVhu37	Bayer / Ultragenyx	Phase 1/2 ⁴
	TAK-754 (BAX-888 / SHP654)	AAV8	Takeda	Phase 1/2 ⁵
	AAV2/8-HLP-FVIII-V3	AAV8	UCL / St. Jude	Phase 1 ⁶
	ASC618	AAV8	ASC Therapeutics	Phase 1/2 ⁷
	BBM-002	n/a	Institute of Hematology & Blood Diseases Hospital, Tianjin, China	Early Phase 1 ⁸
	GS001	n/a		Early Phase 1 ⁹

n/a, information not available.

1. Ozelo MC *et al.* *N Engl J Med* 2022;386:1013–25; 2. <https://www.fdanews.com/articles/209166-biomarins-roctavian-gets-ec-conditional-marketing-authorization-for-severe-hemophilia-a>; 3. <https://www.clinicaltrials.gov/ct2/show/NCT04370054>; 4. <https://www.ultragenyx.com/our-research/our-pipeline/>; 5. <https://clinicaltrials.gov/ct2/show/NCT03370172>; 6. <http://www.clinicaltrials.gov/ct2/show/NCT03001830>; 7. <https://www.clinicaltrials.gov/ct2/show/NCT04676048>; 8. <http://www.clinicaltrials.gov/ct2/show/NCT05454774>; 9. <http://www.clinicaltrials.gov/ct2/show/NCT04728841>

ROCTAVIAN™ (valoctocogene roxaparvovec-rvox) is administered as a one-time intravenous infusion of 6×10^{13} vector genomes per kilogram body weight

Roctavian™ is expected to be primarily administered in the outpatient setting

Rare instances may result in patients being admitted to the inpatient setting

Its use will be documented in the patient's medical record in the same manner as other therapies that are administered via IV infusion

Clinical documentation may also appear in the providers notes in the procedure room medical record and in the nurses' notes