ROCTAVIAN®▼
(valoctocogene roxaparvovec)
Solution for intravenous infusion

BRINGING THE GENE THERAPY JOURNEY TO LIFE

Wednesday 7th February 2024
17:30–18:45 CET

Panorama 1,
The Messe Frankfurt,
Frankfurt, Germany

AGENDA

17:30	**Welcome and Introduction**	Professor Johannes Oldenburg
17:35	**Starting the Gene Therapy Journey**	Professor Margareth Ozelo
17:55	**Gene Therapy in Haemophilia: Long Term Outcomes**	Professor Johannes Oldenburg
18:10	**Patient Experience of Gene Therapy**	Dr Priyanka Raheja
18:30	**Discussion**	All Faculty
18:40	**Summary and Close**	Professor Johannes Oldenburg

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. ROCTAVIAN® is indicated 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).

BIOMARIN®

Abbreviated Prescribing Information (PI) (INTL):
ROCTAVIAN® ▼ (valoctocogene roxaparvovec)
Refer to Summary of Product Characteristics for full information.

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Presentation: ROCTAVIAN® 2 x 10^{13} vector genomes/mL solution for infusion. Valoctocogene roxaparvovec is a gene therapy medicinal product that expresses the B domain deleted SQ form of human coagulation factor VIII (hFVIII SQ). It is a non-replicating recombinant adeno associated virus serotype AAV5 based vector containing the cDNA of the B domain deleted SQ form of human coagulation factor VIII gene under the control of a liver specific promoter. Valoctocogene roxaparvovec is produced in a baculovirus expression system that derived from cells of *Spodoptera frugiperda* (Sf9 cell line) by recombinant DNA technology. **Therapeutic indications:** ROCTAVIAN® is indicated 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). **Posology:** Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia and/or bleeding disorders. Administer in a setting where personnel and equipment are immediately available to treat infusion related reactions. ROCTAVIAN® should only be administered to patients who have demonstrated absence of anti AAV5 antibodies by a validated assay. The recommended dose of ROCTAVIAN® is 6 × 10^{13} vector genomes per kilogram (vg/kg) body weight, administered as a single intravenous infusion. *Patient's dose in millilitres (mL):* Body weight in kg multiplied by 3 = dose in mL. *Number of vials to be thawed:* Patients dose volume (mL) divided by 8 = number of vials to be thawed (round up to next whole number of vials). *Discontinuation of factor VIII concentrates/haemostatic agents:* Consider patient's factor VIII activity levels are sufficient to prevent spontaneous bleeding episodes, and the duration of effect of factor VIII concentrates/haemostatic agents. *Hepatic Impairment:* The safety and efficacy of valoctocogene roxaparvovec in patients with hepatic disorders have not been established. Valoctocogene roxaparvovec is contraindicated in patients with acute or uncontrolled chronic hepatic infections, or in patients with known significant hepatic fibrosis, or cirrhosis. This medicinal product is not recommended for use in patients with other hepatic disorders. **Administration:** Intravenous infusion. Do not infuse as an intravenous push or bolus. Begin at an infusion rate of 1 mL/min, which can be increased every 30 minutes by 1 mL/min to up to a maximum rate of 4 mL/min. The infusion rate may be slowed or interrupted if the patient develops an infusion related reaction. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Active infections, either acute or uncontrolled chronic; or patients with known significant hepatic fibrosis, or cirrhosis. **Warnings and precautions:** *Traceability:* Record name and batch number of the administered product. *Patients with pre-existing antibodies to the AAV5 vector capsid:* Anti AAV5 antibody formation can take place after natural exposure. As it is not yet known whether or under what conditions valoctocogene roxaparvovec can be safely and effectively administered in the presence of anti AAV5 antibodies, this medicinal product is not indicated for use in patients with detectable anti AAV5 antibodies. *Hepatic disorders and hepatotoxic substances:* Safety and efficacy of ROCTAVIAN® in these circumstances have not been established. The efficacy of valoctocogene roxaparvovec relies on hepatocellular expression of hFVIII SQ. It is not known to what extent a reduced number of transducible liver cells (e.g., due to cirrhosis) or loss of transduced liver cells over time (e.g., due to active hepatitis or exposure to hepatotoxic agents) may affect the therapeutic effect of valoctocogene roxaparvovec. This medicinal product is not recommended in patients with other hepatic disorders, hepatic laboratory abnormalities (ALT, AST, GGT, or total bilirubin above 1.25 times ULN based on at least 2 measurements, or INR of 1.4 or above) or in patients with a history of hepatic malignancy. Patients should be screened for hepatic malignancy prior to prescribing valoctocogene roxaparvovec. Before using this medicinal product in patients with any hepatic disorder or receiving potentially hepatotoxic medications, physicians should consider the potential for reduced therapeutic effect and more serious hepatic reactions and the potential need to change concomitant medicinal products, allowing time for a washout period as needed. The effect of alcohol consumption on the magnitude and duration of the therapeutic effect is not known. In clinical studies, some ALT elevations have been attributed to alcohol consumption. It is recommended that patients abstain from consuming alcohol for at least one year after administration of this medicinal product and, thereafter limit alcohol use. *Hepatic reactions:* Following administration of valoctocogene roxaparvovec, the majority of patients (82%) experienced hepatic reactions indicated by an increase in ALT; some of these reactions were temporally associated with decreased expression of the factor VIII transgene protein. ALT and factor VIII activity levels should be monitored after valoctocogene roxaparvovec administration, and corticosteroid treatment should be instituted in response to ALT elevations as needed, to control hepatic reactions and prevent or mitigate a potential reduction in transgene expression. *Factor VIII assays:* Factor VIII activity produced by ROCTAVIAN® in human plasma is higher if measured with one stage clotting assays (OSA) compared to chromogenic substrate assays (CSA). For routine clinical monitoring of factor VIII activity levels, either assay may be used. When switching from haemostatic products (e.g., emicizumab) prior to valoctocogene roxaparvovec therapy, physicians should refer to the relevant product information to avoid the potential for factor VIII activity assay interference during the transition period. *Hepatic function and factor VIII monitoring:* A baseline assessment of liver health (including liver function tests within 3 months and recent fibrosis assessment using either imaging modalities, such as ultrasound elastography, or laboratory assessments, within 6 months) should be obtained before administration of ROCTAVIAN®. It is recommended that the hepatic function is evaluated through a multidisciplinary approach with involvement of a hepatologist to best adjust the monitoring to the patient's individual condition. It is recommended (where possible) to use the same laboratory for hepatic testing at baseline and monitoring over time, particularly during the timeframe for corticosteroid treatment decision making, to minimise the impact of inter laboratory variability. After administration, the patient's ALT and factor VIII activity levels should be monitored according to the table below.

	Measurements	Timeframe	Monitoring frequency[a]
Before administration	Liver function tests	Within 3 months prior to infusion	Baseline measurement
	Recent fibrosis assessment	Within 6 months prior to infusion	
After administration	ALT and factor VIII activity[b]	First 26 weeks	Weekly
		Weeks 26 to 52 (Year 1)	Every 2 to 4 weeks
		Year 1 to end of Year 2	• Every 3 months for patients with factor VIII activity levels > 5 IU/dL • Consider more frequent monitoring in patients with factor VIII activity levels ≤ 5 IU/dL and consider the stability of factor VIII levels and evidence of bleeding.
		After Year 2	• Every 6 months for patients with factor VIII activity > 5 IU/dL • Consider more frequent monitoring in patients with factor VIII activity levels ≤ 5 IU/dL and consider the stability of factor VIII levels and evidence of bleeding.

[a] Weekly monitoring is recommended, and as clinically indicated, during corticosteroid tapering. Adjustment of the monitoring frequency may also be indicated depending on the individual situation.
[b] Monitoring of ALT should be accompanied by monitoring of AST and CPK, to rule out alternative causes for ALT elevations (including potentially hepatotoxic medications or agents, alcohol consumption, or strenuous exercise).

To assist in the interpretation of ALT results, monitoring of ALT should be accompanied by monitoring of aspartate aminotransferase (AST) and creatine phosphokinase (CPK) to help rule out alternative causes for ALT elevations (including potentially hepatotoxic medicinal products or agents, alcohol consumption, or strenuous exercise). Based on patient's ALT elevations, corticosteroid treatment may be indicated (see Corticosteroid treatment). Weekly monitoring is recommended, and as clinically indicated, during corticosteroid tapering. It should be ensured the availability of the patient for frequent monitoring of hepatic laboratory parameters and factor VIII activity after administration. If a patient returns to prophylactic use of factor VIII concentrates/haemostatic agents for haemostatic control, consider following monitoring and management consistent with instructions for those agents. An annual health check up should include liver function tests. *Corticosteroid treatment:* If a patient's ALT rises above 1.5 × baseline in the absence of an alternative cause for the ALT elevation, a corticosteroid regimen should be promptly initiated at a daily dose of 60 mg prednisone (or equivalent dose of another corticosteroid) for 2 weeks. The daily corticosteroid dose can be gradually tapered in a stepwise manner according to the table below. Patients with baseline ALT levels between > ULN to 1.25 × ULN should initiate the corticosteroid regimen described in the table below if their ALT increases above 1.5 × baseline.

	Regimen (prednisone or equivalent dose of another corticosteroid)
Starting dose[a]	60 mg daily for 2 weeks
Tapering[b]	40 mg daily for 3 weeks 30 mg daily for 1 week 20 mg daily for 1 week 10 mg daily for 1 week

[a] If ALT continues to rise or has not improved after 2 weeks, increase the corticosteroid dose up to a maximum of 1.2 mg/kg, after ruling out alternative causes for ALT elevation.
[b] Tapering of corticosteroids can start after 2 weeks if ALT levels remain stable and/or earlier when ALT levels start to decline. The taper may be individualised based on the course of hepatic function, taking into account the patient's medical condition, corticosteroid tolerance, and potential for withdrawal symptoms.

If corticosteroids are contraindicated, other immunosuppressive therapy could be considered. Physicians should also consider discontinuing corticosteroids in cases where corticosteroids are ineffective or not tolerated. *Infusion related reactions:* Infusion related reactions to valoctocogene roxaparvovec can have multiple manifestations (such as skin, mucosal, respiratory, gastrointestinal and cardiovascular manifestations, and pyrexia) and may require reduction in infusion rate, interruption of infusion, pharmacologic intervention, and prolonged observation. Patients should be monitored during and after the infusion for possible acute infusion reactions. Instructions should be provided when discharging the patient to seek medical attention in case of a new or recurrent reaction. *Risk of thrombotic events:* Patients should be evaluated before and after administration of valoctocogene roxaparvovec for risk factors for thrombosis and general cardiovascular risk factors. *Contraceptive measures in relation to transgene DNA shedding in semen:* Male patients should be informed on the need for contraceptive measures for them and their female partners of childbearing potential. *Immunocompromised patients:* Safety and efficacy of this medicinal product in these patients have not been established. Use in immunocompromised patients is based on prescriber judgment, taking into account the patient's general health and potential for corticosteroid use post-valoctocogene roxaparvovec treatment. *HIV positive patients:* Given the risk of hepatotoxicity and/or effect on factor VIII expression, the HIV patient's existing antiretroviral therapy regimen should be carefully evaluated prior to initiating treatment and following treatment with valoctocogene roxaparvovec. The physician treating the HIV infection should be consulted to consider whether a less hepatotoxic antiretroviral therapy regimen could be available and suitable for the patient, and if indicated, switch the patient to the new antiretroviral therapy regimen whenever feasible. *Patients with active infections:* It is possible that such infections affect the response to valoctocogene roxaparvovec and reduce its efficacy and/or cause adverse reactions. Therefore, this medicinal product is contraindicated in patients with such infections. If there are signs or symptoms of acute or uncontrolled chronic active infections, treatment must be postponed until the infection has resolved or is controlled. *Patients with factor VIII inhibitors, monitoring for inhibitors:* Patients who have or had inhibitors (neutralising antibodies) to factor VIII were excluded from participation in the clinical studies. It is not known whether or to what extent such inhibitors affect the safety or efficacy of valoctocogene roxaparvovec. All patients remained negative for factor VIII inhibitors at all time points evaluated post infusion. ROCTAVIAN® is not indicated for use in patients with a history of factor VIII inhibitors. *Repeat treatment and impact to other AAV-mediated therapies:* It is not yet known whether or under what conditions valoctocogene roxaparvovec therapy may be repeated, and to what extent cross reacting antibodies could interact with the capsids of AAV vectors used by other gene therapies, potentially impacting their efficacy. *Risk of malignancy as a result of vector integration:* ROCTAVIAN® can also insert into DNA of other human body cells. The clinical relevance of individual integration events is not known to date, but it is acknowledged that individual integration events could potentially contribute to a risk of malignancy. So far, no cases of malignancies associated with ROCTAVIAN® treatment have been reported. If a malignancy occurs, the marketing authorisation holder should be contacted to obtain instructions on collecting patient samples for integration site analysis. *Long-term follow up:* Patients are expected to be enrolled in a registry to follow haemophilia patients for 15 years, to substantiate the long term efficacy and safety of this gene therapy. *Sodium content:* This medicinal product contains 29 mg sodium per vial, equivalent to 1.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult. **Interaction with other medicinal products:** Prior to valoctocogene roxaparvovec administration, the patient's existing medicinal products should be reviewed to determine if they should be modified to prevent anticipated interactions described in this section. Patients' concomitant medications should be monitored after valoctocogene roxaparvovec administration, particularly during the first year, and the need to change concomitant medicinal products based on patient's hepatic status and risk should be evaluated. When a new medication is started, close monitoring of ALT and factor VIII activity levels (e.g., weekly to every 2 weeks for the first month) is recommended to assess potential effects on both levels. *Isotretinoin:* Isotretinoin can modulate the expression of some genes. Isotretinoin is not recommended in patients who are benefiting from ROCTAVIAN®, as it may impact factor VIII expression. The use of non isotretinoin treatments should be considered. *Hepatotoxic medicinal products or substances:* Before administering valoctocogene roxaparvovec to patients receiving potentially hepatotoxic medicinal products or using other hepatotoxic agents (including alcohol, potentially hepatotoxic herbal products and nutritional supplements) and when deciding on the acceptability of such agents after treatment with valoctocogene roxaparvovec, physicians should consider that they may reduce the efficacy of valoctocogene roxaparvovec and increase the risk for more serious hepatic reactions, particularly during the first year following valoctocogene roxaparvovec administration. *Interactions with agents that may reduce or increase plasma concentrations of corticosteroids:* Agents that may reduce or increase the plasma concentration of corticosteroids (e.g., agents that induce or inhibit cytochrome P450 3A4) can decrease the efficacy of the corticosteroid regimen or increase their side effects. *Vaccinations:* Prior to valoctocogene roxaparvovec infusion, ensure that the patient's vaccinations are up to date. The patient's vaccination schedule may need to be adjusted to accommodate concomitant immunomodulatory therapy. Live vaccines should not be administered to patients while on immunomodulatory therapy. **Fertility, pregnancy and lactation:** *Women of child-bearing potential:* No dedicated animal fertility/embryofoetal studies have been conducted to substantiate whether the use in women of childbearing potential and during pregnancy could be harmful for the new born child. Moreover, no data are available to recommend a specific duration of contraceptive measures in women of childbearing potential. Therefore, ROCTAVIAN® is not recommended in women of childbearing potential. *Contraception after administration to males:* In clinical studies, after administration of ROCTAVIAN®, transgene DNA was temporarily detectable in semen. For 6 months after administration of ROCTAVIAN® treated patients of reproductive potential and their female partners of childbearing potential must prevent or postpone pregnancy using double barrier contraception, and men must not donate semen. *Pregnancy:* Experience regarding the use of this medicinal product during pregnancy is not available. Animal reproduction studies have not been conducted with ROCTAVIAN®. It is not known whether this medicinal product can cause foetal harm when administered to a pregnant woman or can affect reproductive capacity. ROCTAVIAN® should not be used during pregnancy. *Fertility:* No non clinical or clinical studies were performed to evaluate the effect of valoctocogene roxaparvovec on fertility. **Effects on ability to drive and use machines:** Infusion of valoctocogene roxaparvovec may have a minor influence on the ability to drive and use machines. Because of potential adverse reactions such as temporary presyncope, dizziness, fatigue, and headache that have occurred shortly after valoctocogene roxaparvovec administration, patients should be advised to use caution when driving and operating machinery until they are certain that this medicinal product does not adversely affect them. **Overdose:** There is no experience with accidental infusion of too high a dose volume. If considered necessary, treatment of an overdose should be symptomatic and supportive. Receiving higher doses than recommended may result in higher factor VIII activity levels and may theoretically be associated with increased risk of thrombotic events. **Summary of the safety profile:** The most common adverse reactions to ROCTAVIAN® were increases in ALT (82%), AST (69%), and LDH (57%) and CPK (44%), nausea (37%), and headache (35%). The following adverse reactions described are based on a total of 141 patients from Studies 270 201 and 270 301, all dosed at 6 × 1013 vg/kg for up to 275 weeks. **Tabulated list of adverse reactions:** Adverse reactions are listed below by MedDRA system organ class and by frequency. Frequencies are defined as very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from available data).

MedDRA System organ class	Adverse reaction	Frequency
Infections and infestations	Flu like symptoms	Common
Blood and lymphatic system disorders	Factor VIII activity levels above ULN[a]	Very common
Immune system disorders	Hypersensitivity reaction[b]	Common
Nervous system disorders	Headache	Very common
	Dizziness[b]	Common
	Presyncope[b]	Uncommon
Cardiac disorders	Increased blood pressure[b]	Common
Respiratory, thoracic and mediastinal disorders	Dyspnoea[b]	Uncommon
Gastrointestinal disorders	Nausea, vomiting, abdominal pain, diarrhoea	Very common
	Dyspepsia	Common
Hepatobiliary disorders[c]	ALT increased, AST increased, GGT increased, bilirubin increased, and LDH increased	Very common
Skin and subcutaneous tissue disorders	Rash[d], pruritus[b]	Common
Musculoskeletal and connective tissue disorders	CPK increased	Very common
	Myalgia	Common
General disorders and administration site conditions	Fatigue[e]	Very common
	Infusion related reaction[f]	Common

[a] One or more instances of factor VIII activity levels > 170 IU/dL (ULN of the CSA used) or > 150 IU/dL (ULN of the OSA used). See Description of selected adverse reactions.
[b] Considered an adverse reaction only during first 48 hours after infusion.
[c] Reflects laboratory abnormalities above the ULN.
[d] Rash includes maculopapular rash and urticaria.
[e] Fatigue includes lethargy and malaise.
[f] Infusion related reactions includes manifestations such as skin, mucosal, and respiratory tract (including urticaria, pruritus, maculopapular rash, sneezing, coughing, dyspnoea, rhinorrhoea, watery eyes, and tingling throat), gastrointestinal (including nausea and diarrhoea), cardiovascular (including increased blood pressure, hypotension, tachycardia, and presyncope) and musculoskeletal (including myalgia and lower back pain), as well as pyrexia, rigours, and chills).

Special precautions for storage: Store and transport frozen at ≤ -60 °C. ROCTAVIAN® must remain frozen until the patient is ready for treatment to ensure viable product is available for patient administration. Once thawed, do not refreeze. Store in the original carton in order to protect from light. Store upright. Once thawed, chemical and physical in use stability after thawing has been demonstrated for 10 hours at 25 °C, including hold time in intact vial, preparation time into the syringes, and time for infusion (see section 6.6). If necessary, an intact vial (stopper not yet punctured) that has been thawed can be stored refrigerated (2 °C to 8 °C) for up to 3 days, upright and protected from light (e.g., in the original carton). From a microbiological point of view, the product should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user. **Marketing authorisation holder:** BioMarin International Limited. Shanbally, Ringaskiddy, County Cork, P43 R298 Ireland. **Marketing authorisation number:** EU/1/22/1668/001 Detailed information on this medicinal product is available on the website of the European Medicines Agency: http://www.ema.europa.eu/ **Date of first authorisation:** August 2022. **Date of latest SmPC:** July 2023. ROCTAVIAN® is a trademark of BioMarin Pharmaceutical Inc. from whom further information is available. **Date of PI revision:** July 2023. **Legal classification:** Prescription-Only Medicine.

Healthcare professionals should report adverse events in accordance with their local requirements. Adverse events should also be reported to BioMarin on + 1 415 506 6179 or drugsafety@bmrn.com