Valoctocogene Roxaparvovec: First Approval

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Abstract
Valoctocogene roxaparvovec (ROCTAVIAN™) is a gene therapy being developed by BioMarin Pharmaceutical Inc. for the treatment of haemophilia A. In August 2022, valoctocogene roxaparvovec was granted conditional marketing authorization in the EU for the treatment of severe haemophilia A [congenital factor VIII (FVIII) deficiency] in adults without a history of FVIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5). This article summarizes the milestones in the development of valoctocogene roxaparvovec leading to this first approval for severe haemophilia A.

1 Introduction
Haemophilia A is an inherited X-linked bleeding disorder caused by a deficiency of coagulation factor VIII (FVIII) [1]. To prevent spontaneous bleeding, joint disease and disability, the management of haemophilia A has traditionally focused on replacement of the missing FVIII. However, standard replacement recombinant FVIII products have a short half-life, require frequent intravenous infusions and can lead to the development of neutralizing antibodies (inhibitors) against FVIII. Extended half-life FVIII products and subcutaneous non-factor therapies have been developed in an attempt to address these challenges. In addition, gene therapy is being investigated as a potential new treatment paradigm for haemophilia A [1].

Valoctocogene roxaparvovec (ROCTAVIAN™) is a gene therapy being developed by BioMarin Pharmaceutical Inc. for the treatment of severe haemophilia A [2]. In March 2016, valoctocogene roxaparvovec received orphan drug designation in the EU [3] and the USA [4]. Access to Priority Medicines (PRIME) regulatory support was granted by the European Medicines Agency in February 2017 [5] and breakthrough therapy designation was granted by the US FDA in October 2017 [6]. The US FDA granted a regenerative medicine advanced therapy designation to valoctocogene roxaparvovec in March 2021 [7]. Based on positive results from a phase III trial (GENEr8-1), valoctocogene roxaparvovec received conditional approval in the EU on 24 August 2022 for the treatment of severe haemophilia A (congenital FVIII deficiency) in adults without a history of FVIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5) [2, 8]. Conversion to a
standard marketing authorization is contingent on the provision of additional data from ongoing clinical trials [2]. The recommended dosage of valoctocogene roxaparvovec is $6 \times 10^{13}$ vector genomes per kg of body weight (vg/kg), administered as a single intravenous infusion [8]. The initial rate of infusion is 1 mL/min, which can be increased in 1 mL/min increments every 30 min to a maximum of 4 mL/min [8].

Valoctocogene roxaparvovec is under regulatory review in the USA for the treatment of haemophilia A. It is currently undergoing phase III clinical development for haemophilia A in multiple countries worldwide, including Australia, Brazil, Israel, South Africa, South Korea, Taiwan and the UK.

### 1.1 Company Agreements

In February 2013, BioMarin Pharmaceutical Inc. licensed a factor VIII gene therapy programme for haemophilia A from University College London and St. Jude Children’s Research Hospital [9].

Complete Response Letter, MAA Marketing Authorization Application, PDUFA Prescription Drug User Fee Act, PRIME PRIority MEdicines, RMAT Regenerative Medicine Advanced Therapy

### 2 Scientific Summary

#### 2.1 Pharmacodynamics

Valoctocogene roxaparvovec is produced in a baculovirus expression system derived from the *Spodoptera frugiperda* cell line by recombinant DNA technology [8]. The AAV5-based gene therapy vector expresses the B domain-deleted SQ version of a recombinant human FVIII (hFVIII-SQ), under the control of a liver-specific promotor. The expressed hFVIII-SQ replaces the missing coagulation factor VIII required for effective homeostasis. After valoctocogene roxaparvovec infusion, vector DNA forms full-length, episomal transgenes that support long-term production of hFVIII-SQ [8].

Single intravenous injections of valoctocogene roxaparvovec were associated with dose-dependent expression of hFVIII-SQ in mice and primates [10, 11]. These levels of hFVIII-SQ were therapeutic, normalizing the bleeding phenotype in haemophilic mice and correcting the prolonged...
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bleeding time to the same extent as exogenously administered recombinant hFVIII-SQ [10]. Long-term expression of hFVIII-SQ was associated with the formation of full-length circular episomes in liver tissue; this was seen as early as 1 week after dosing and increased over 6 months [11]. In cynomolgus monkeys with pre-existing anti-AAV5 antibodies, valoctocogene roxaparvovec was associated with reduced liver transduction and a ≈ 75% reduction in peak plasma concentrations of hFVIII-SQ, while no reduction was observed in animals with only non-antibody transduction inhibitors [12].

The potential for germline transmission in male mice treated with a single intravenous dose of valoctocogene roxaparvovec was low (< 5% with a 99.2% confidence level) [13]. Transgene DNA was detected in the liver and testes of all treated males (confirming successful transduction), but no transgene DNA was detected in any of the tested offspring [13].

Chronic prednisolone administration did not regulate FVIII expression in mice receiving a single intravenous dose of valoctocogene roxaparvovec [14]. Hepatic hFVIII-SQ DNA, RNA, and plasma hFVIII-SQ protein expression and activity increased dose-dependently, with or without prednisolone. There were no significant elevations of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) in response to prednisolone [14].

### 2.2 Pharmacokinetics

Following a single intravenous infusion of valoctocogene roxaparvovec, vector DNA was identified in the saliva, urine, stool and semen [8]. Vector DNA concentrations peaked between 1 and 9 days after infusion, followed by a subsequent steady decline. In 141 evaluable patients who received valoctocogene roxaparvovec in GENEr8-1 (Sect. 2.4.1) or the dose-escalation study (Sect. 2.4.2), encapsidated (i.e. potentially infectious) vector DNA was detectable in plasma up to 10 weeks after infusion. Vector DNA was cleared in semen (100% of patients), urine (100%), saliva (99%) and stool (84%). The maximum time to clearance was 36, 8, 26 and 88 weeks, respectively. The magnitude and duration of shedding were not associated with FVIII activity [8].

### Features and properties of valoctocogene roxaparvovec

| Alternative names | AAV5-hFVIII-SQ; BMN-270; factor-VIII-gene-therapy-BioMarin; ROCTAVIAN |
| Class | Gene therapies; antihaemorrhagics; blood coagulation factors |
| Mechanism of action | Factor VIII replacements; gene transference |
| Route of administration | Intravenous infusion |
| Pharmacodynamics | Dose-dependent expression of hFVIII-SQ, which replaces missing coagulation factor VIII; long-term hFVIII-SQ expression associated with formation of full-length circular episomes in the liver |
| Pharmacokinetics | Vector DNA identified in saliva, urine, stool and semen following therapy (peak concentrations seen after 1–9 days); magnitude and duration of shedding not associated with FVIII activity |
| Most frequent adverse events | Increased ALT, increased AST, increased LDH, nausea, headache |
| ATC codes |  |
| WHO ATC code | B02B-D02 (coagulation factor VIII) |
| EphMRA ATC code | B2D1 (factor VIII) |

AAV5 adeno-associated virus serotype 5, ALT alanine aminotransferase, AST aspartate aminotransferase, hFVIII-SQ B domain-deleted SQ version of recombinant human factor VIII, LDH lactate dehydrogenase

### 2.3 Drug Interactions

No in vivo drug interaction studies have been conducted with valoctocogene roxaparvovec [8]. Due to potential effects on FVIII expression, the use of isotretinoin is not recommended in patients who have been treated with valoctocogene roxaparvovec. Some potentially hepatotoxic medications and other hepatotoxic agents (e.g. alcohol) may decrease the efficacy of valoctocogene roxaparvovec and increase the risk of serious hepatic reactions. All patients should be up to date with scheduled vaccinations prior to valoctocogene roxaparvovec infusion. If possible, vaccination schedules should be adjusted to accommodate concomitant immunomodulatory therapy; live vaccines should not be administered to patients receiving concomitant immunomodulatory therapy [8].

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2.4 Therapeutic Trials

2.4.1 Phase III GENEr8-1 Trial

Valoctocogene roxaparvovec increased FVIII activity and reduced bleeding rates and FVIII concentrate use in men with severe haemophilia A participating in the open-label, multicentre, phase III GENEr8-1 trial (NCT03370913) [15]. All patients were aged ≥ 18 years with severe congenital haemophilia A (FVIII activity level ≤ 1 IU/dL), did not have pre-existing anti-AAV5 antibodies or a history of development of FVIII inhibitors, and had been receiving FVIII prophylaxis for ≥ 1 year. A total of 134 patients were enrolled and received a single intravenous infusion of valoctocogene roxaparvovec 6 × 10^{13} vg/kg. All patients continued to receive FVIII prophylaxis through 4 weeks after infusion; thereafter, FVIII was administered as required. The primary endpoint of change from baseline in FVIII activity at 49 to 52 weeks after infusion (as measured by chromogenic substrate assay) was analyzed in the modified intention-to-treat (mITT) population. The secondary endpoints of change from baseline in annualized FVIII concentrate use and annualized number of treated bleeding episodes after week 4 were analyzed in the rollover population of patients from a non-interventional study with ≥ 6 months of prospectively collected data on FVIII usage and bleeding [15].

Through week 54, the mean or median FVIII activity level was ≤ 3 IU/dL in the low- and intermediate-dose cohorts [16]. In the high-dose cohort, the mean or median FVIII activity level was > 5 IU/dL between weeks 2–9; this level increased to normal (> 50 IU/dL) after week 20 and was maintained one year after infusion. Among patients in the high-dose cohort who had previously received FVIII prophylaxis (n = 6), the median annualized bleeding rate decreased from 16 events/year at baseline to 1 event/year after infusion. Median annualized FVIII use decreased from 138 to 0 infusions/year after week 2 [16].
The beneficial effects of valoctocogene roxaparvovec on annualized bleeding rates and prophylactic FVIII use were sustained over the longer term (up to 5 years), including in a fourth cohort of patients who received valoctocogene roxaparvovec 4 × 10^{13} \text{vg/kg} (n = 6) [17, 18]. The clinical benefits valoctocogene roxaparvovec were also associated with improved quality of life (QOL) over 4–5 years, as assessed using the haemophilia-specific health-related QOL questionnaire for adults [18].

2.5 Adverse Events

A single intravenous infusion of valoctocogene roxaparvovec had an acceptable safety profile in men with severe haemophilia A [15–18]. In a pooled analysis of patients from GENER8-1 and the dose-escalation study who received valoctocogene roxaparvovec 6 × 10^{13} \text{vg/kg} (n = 141), the most commonly reported adverse reactions were increased ALT levels (80%), increased AST levels (67%), increased lactate dehydrogenase levels (54%), nausea (37%) and headache (35%) [8]. Half of all ALT increases above the upper limit of normal (ULN) occurred within 26 weeks of infusion, with 34% occurring during weeks 27–52. The median duration of increased ALT > ULN was 2 weeks and the median time to reduction in ALT (i.e. first reduction of ≥ 10 IU/L or ALT ≤ ULN) following an increase in corticosteroid dose or a new corticosteroid course was 8 days. Overall, 8% of patients experienced transient infusion-related reactions within 6 h of infusion; the median time to onset was 1 h and the median duration of symptoms was 1 h [8].

Through week 54 in the dose-escalation study (Sect. 2.4.2), which was primarily designed to evaluate safety, the most common (incidence > 30%) adverse events were increased ALT levels (78%), arthralgia (67%), back pain (44%), increased AST levels (33%), fatigue (33%) and productive cough (33%) [16]. Most adverse events were mild or moderate in severity. All ALT increases were asymptomatic and resolved without sequelae [16]. The safety profile of valoctocogene roxaparvovec remained acceptable over 2–3 years [17] and 4–5 years [18] of follow-up.

Patients participating in GENER8-1 and the dose-escalation study were required to screen negative for anti-AAV5 antibodies and FVIII inhibitors at baseline [8]. All patients remained negative for FVIII inhibitors during the 3 years after infusion of valoctocogene roxaparvovec [19]. All patients seroconverted to anti-AAV5 antibody positive within 8 weeks of infusion; anti-AAV5 antibody titres peaked at week 40 and remained durable during 1.5–2.5 years of follow-up. There was no association between FVIII cellular immune responses and changes in ALT or FVIII activity [19].

2.6 Companion Diagnostic

An AAV5 total antibody assay is being developed by ARUP Laboratories and BioMarin Pharmaceutical Inc. as a companion diagnostic for valoctocogene roxaparvovec [20]. The AAV5 total antibody assay is a blood test designed to identify patients with haemophilia A who are most likely to respond to AAV5-based gene therapy with valoctocogene roxaparvovec. The companion diagnostic is currently under regulatory review in the USA [20].

2.7 Ongoing Clinical Trials

In addition to the ongoing phase III GENER8-1 (NCT03370913) and phase I/II (NCT02576795) trials described in Sect. 2.4, a number of other clinical trials are currently underway. The open-label, single-arm, phase III GENER8-2 (NCT03392974) and GENER8-3 (NCT04323098) trials are evaluating the efficacy and safety of valoctocogene roxaparvovec in patients with haemophilia A. Two phase I/II trials are currently recruiting patients and plan to evaluate the safety, tolerability and efficacy of valoctocogene roxaparvovec in severe haemophilia A patients with active or prior inhibitors (NCT04684940) or pre-existing antibodies against AAV5 (NCT03520712).

3 Current Status

Valoctocogene roxaparvovec received its first approval on 24 August 2022 in the EU for the treatment of severe haemophilia A (congenital factor VIII deficiency) in adults without a history of factor VIII inhibitors and without detectable antibodies to AAV5 [2].

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Declarations

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