

MSAC Application 1751

Valoctocogene roxaparvovec gene therapy for congenital haemophilia A

Applicant: BioMarin Pharmaceutical Australia Pty Ltd

PICO Confirmation

Summary of PICO/PPICO criteria to define question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Table 1 PICO for AAV5 DetectCDx™ to determine eligibility for valoctocogene roxaparvovec for the treatment of severe haemophilia A

Component	Description
Population	<p>Adult patients (≥18 years) with severe congenital haemophilia A defined by residual FVIII levels of <0.01 IU/mL or <1% of normal activity</p> <p>and who also meeting the following criteria:</p> <ul style="list-style-type: none"> • no active inhibitors to FVIII • no form of active hepatitis or severe liver disease.
Prior tests	<p>Factor VIII inhibitor titre testing.</p> <p>Liver function tests and imaging ± liver disease assessment by hepatic specialist (intervention)</p>
Intervention	<p>Test: AAV5 DetectCDx™, a companion diagnostic intended for use with valoctocogene roxaparvovec (Roctavian™) to assess eligibility for treatment.</p> <p>Patients without pre-existing antibodies to AAV5 (i.e. test negative for anti-AAV5 antibodies) as determined by results of the proposed test (AAV5 DetectCDx™) are eligible for:</p> <p>Therapeutic intervention: valoctocogene roxaparvovec (Roctavian™) (with or without additional on-demand FVIII therapy and/or pre-procedural prophylaxis)</p>
Comparator/s	<p>Test: No testing (i.e. no additional tests)</p> <p>Therapy</p> <p>Comparator 1: Prophylactic FVIII replacement therapy (with or without additional on-demand and/or preprocedural prophylaxis FVIII therapy)¹</p> <p>Comparator 2: Emicizumab (with or without additional on-demand and/or preprocedural prophylaxis FVIII therapy)¹</p>
Clinical utility standard (for the AAV5 DetectCDx™)	<p>Test: Clinical trial assay</p>

¹ Emicizumab can be used in patients with congenital haemophilia A with FVIII inhibitors and in patients with moderate congenital haemophilia A without FVIII inhibitors. These patient cohorts should be excluded for the purpose of this comparative assessment.

Component	Description
Outcomes	<p>Test:</p> <ul style="list-style-type: none"> • Test reliability <ul style="list-style-type: none"> ○ intra-observer or intra-instrument variability/agreement ○ inter-observer or inter-instrument variability/agreement ○ within-patient concordance of the AAV5 DetectCDx™ test • Test concordance compared to CTA <ul style="list-style-type: none"> ○ positive percentage agreement ○ negative percentage agreement • Change in clinical management • Adverse events <p>Therapy:</p> <p><u>Effectiveness/efficacy</u></p> <ul style="list-style-type: none"> • Bleeding frequency (includes ABR and proportion of patients with zero bleeds; all bleeds, treated bleeds, treated target joint bleeds, treated spontaneous bleeds, treated traumatic bleeds) • Categorisation of patients according to FVIII concentration and ABR pre-treatment and following intervention, reported over time. • Mean FVIII activity • Time in between intervention and returning to prophylaxis (where applicable) <p><u>Safety</u></p> <ul style="list-style-type: none"> • Adverse events, including procedural complications • Serious adverse events • Acute peri-infusion adverse events • Long-term adverse events (e.g. immunogenicity, thrombosis, hepatotoxicity, hepatocellular carcinoma) • Laboratory indicators of safety (e.g. coagulation, inflammatory markers, serology, haematology) • Formation of post-treatment FVIII inhibitors • Liver function tests (ALT elevation etc.) • Anaphylactic reactions <p><u>Health system/resource utilisation:</u></p> <ul style="list-style-type: none"> • Change in exogenous FVIII replacement therapy utilisation, reported over time post-intervention as compared to baseline (reporting prophylaxis and on-demand treatment separately) • Amount of emicizumab avoided • Costs associated with intervention and comparator treatments

Component	Description
	<ul style="list-style-type: none"> • Costs associated with adverse events for intervention and comparator treatments <p><u>Quality of life:</u></p> <ul style="list-style-type: none"> • Health-related QoL indicators such as EQ-5D, SF-36, haemophilia wellbeing index, Haemo-QoL-A, PROBE questionnaire
Assessment questions	<p>What is the comparative safety, effectiveness, cost-effectiveness and total costs of AAV5 DetectCDx™ testing and treatment with valoctocogene roxaparvovec versus no testing and treatment with standard of care (FVIII replacement therapy or emicizumab) in adult patients (≥18 years) with severe congenital haemophilia A and without inhibitors to FVIII, severe liver disease or active hepatitis?</p> <p><i>Assessment questions per the assessment framework:</i></p> <p><u>Direct evidence</u></p> <ol style="list-style-type: none"> 1) Does use of the AAV5 DetectCDx™ test to determine eligibility for valoctocogene roxaparvovec result in superior health outcomes in patients with haemophilia A when compared to no testing and standard treatment (FVIII replacement therapy or emicizumab)? <p><u>Linked evidence</u></p> <ol style="list-style-type: none"> 2) What is the concordance of the findings from the AAV5 DetectCDx™ test compared to the CTA? <i>and</i> What is the within-patient concordance of the AAV5 DetectCDx™ test? 3) Does the result of the AAV5 DetectCDx™ test lead to a change in patient management compared to no testing? 4) What impact does valoctocogene roxaparvovec have on patient health outcomes relative to prophylactic FVIII replacement therapy and emicizumab? 5) Do differences in patient management resulting from AAV5 DetectCDx™ use lead to changes in FVIII levels? 6) Are the observed changes in FVIII levels and FVIII usage associated with a change in health outcomes (reduced ABR, improved QoL) and how strong and durable is the association? 7) What are the physical and psychological health risks associated with AAV5 DetectCDx™ testing compared to no testing? 8) Are there any adverse health events associated with use of valoctocogene roxaparvovec based on the result of AAV5 DetectCDx™ testing, relative to standard treatment?

Abbreviations: AAV5 = adeno-associated virus serotype 5; ABR = annualised bleeding rate, CTA = clinical trial assay; EQ-5D-5L = EuroQol 5-dimension health-related quality of life questionnaire – 5 levels; FVIII = factor VIII; Haemo-QoL-A = haemophilia-specific quality of life questionnaire for adults; IU = international unit; QoL = quality of life

Purpose of application

The codependent application (received from BioMarin Pharmaceutical Australia Pty Ltd by the Department of Health and Aged Care) requested:

- assessment of AAV5 DetectCDx™ to determine patient eligibility for a single treatment with valoctocogene roxaparvovec
- public funding of valoctocogene roxaparvovec for haemophilia A.

The application is not seeking public funding for the AAV5 DetectCDx™ test and confirms that the applicant will facilitate testing (including covering costs associated with the test) at no cost to the Australian healthcare system. This is subject to reconsideration if an onshore test becomes available; however, an onshore test is considered unlikely in the near future. The applicant has confirmed that the test cost will still be covered by BioMarin in the case of a positive result (excluding the patient from treatment with valoctocogene roxaparvovec) (applicant communication, 20 February 2024).

A Schedule 4 proposal for public funding through the National Blood Agreement (the Agreement) of valoctocogene roxaparvovec has been submitted to the National Blood Authority (NBA). Public funding for blood products and blood-related products is facilitated through the Agreement and managed by the NBA on behalf of federal, state and territory governments (National Blood Authority). Schedule 4 of the Agreement prescribes the process for initiation, evaluation and implementation of national blood supply change proposals. As part of this process, an evidence-based evaluation by the Medical Services Advisory Committee (MSAC) may be requested.

Valoctocogene roxaparvovec (Roctavian™) has received orphan approval status from the Therapeutic Goods Administration (TGA) but has not yet been listed on the Australian Register of Therapeutic Goods (ARTG). The applicant advises that approval is expected by REDACTED (applicant communication, 20 February 2024). The application claimed that compared to standard care with prophylactic factor VIII (FVIII) replacement therapy or emicizumab (the comparator), the proposed intervention valoctocogene roxaparvovec has:

- superior efficacy outcomes—reduction in annualised bleeding rate (ABR) and improved quality of life (QoL) due to reduced treatment burden and improved health outcomes
- non-inferior safety outcomes.

PICO criteria

Population

The intended population proposed for the codependent technology is described below.

Test population

Adult patients (≥ 18 years) with severe congenital haemophilia A defined by residual FVIII levels of < 0.01 IU/mL or $< 1\%$ of normal activity, and who also meeting the following criteria:

- no active inhibitors to FVIII
- no form of active hepatitis or severe liver disease.

Treatment population

Patients without pre-existing antibodies to AAV5 (i.e. test negative for anti-AAV5 antibodies) as determined by results of the proposed test (AAV5 DetectCDx™) are eligible for the therapeutic intervention: valoctocogene roxaparvovec (with or without additional on-demand FVIII therapy).

Disease characteristics

Congenital haemophilia is a group of bleeding disorders resulting from pathogenic variants of the clotting factor genes. There are 2 main types of congenital haemophilia: congenital haemophilia A is caused by a deficiency of coagulation FVIII and accounts for the majority of cases (80–85%), congenital haemophilia B is caused by a deficiency of coagulation factor IX (FIX) and accounts for around 15% of cases (Australian Haemophilia Centre Directors' Organisation & National Blood Authority (AHCDO & NBA), 2016; Srivastava, Alok et al. 2020). The proposed intervention is specifically for treatment of congenital haemophilia A. Congenital haemophilia A almost exclusively affects males (due to the disease being X-linked), with females often being carriers typically expressing a mild or asymptomatic phenotype.

The primary symptom of haemophilia A is excessive and abnormal bleeding. The vast majority of bleeds occur internally, with approximately 70–80% of bleeds occurring in the joints, known as haemarthrosis (AHCDO & NBA 2016). Recurrent bleeding, particularly haemarthrosis, is a significant cause of morbidity and reduced QoL in patients with haemophilia. Blood from recurrent bleeding into the joint space causes inflammation, leading to damage to the cartilage and other joint structures. Over time, this can lead to chronic pain, stiffness and decreased range of motion. In severe cases, joint damage can result in disability and the need for joint replacement surgery (AHCDO & NBA 2016). Bleeding sites can be categorised as serious (joints, mucus membranes, muscles) or life-threatening (intracranial, gastrointestinal) (AHCDO & NBA 2016).

In patients with haemophilia A, bleeding phenotype tends to correlate with FVIII concentration (Table 2). Lower endogenous FVIII plasma concentrations are indicative of more severe forms of haemophilia A. FVIII $< 1\%$ of the normal concentration is classified as severe disease, 1–5% is moderate disease and 5– $< 40\%$ is considered mild disease (AHCDO & NBA 2016). Patients with mild haemophilia A are unlikely to experience spontaneous bleeding or severe bleeding outside of a surgical or physical trauma setting (AHCDO & NBA 2016). Those with moderate disease may experience occasional spontaneous bleeding and prolonged bleeding with minor trauma or surgery (AHCDO & NBA 2016). Patients with severe disease are likely to experience regular spontaneous bleeding into the joints and muscles and from other internal sources in the absence of an identifiable cause (AHCDO & NBA 2016). Some patients with severe haemophilia A may

experience 30–50 spontaneous internal bleeds per year resulting in complications and a reduced QoL (AHCDO & NBA 2016).

Table 2 Relationship of bleeding severity to clotting factor level in haemophilia A

Severity	FVIII level		Symptoms
	FVIII concentration	FVIII % of normal activity	Bleeding episodes
Severe	<1 IU/dl (<0.01 IU/ml)	<1% of normal	Spontaneous bleeding into joints or muscles or other organs, predominantly in the absence of identifiable haemostatic challenge
Moderate	1–5 IU/dl (0.01–0.05 IU/ml)	1–5% of normal	Occasional spontaneous bleeding; prolonged bleeding with minor trauma or surgery
Mild	5–40 IU/dl (0.05–0.40 IU/ml)	5–<40% of normal	Severe bleeding with major trauma or surgery; spontaneous bleeding rare

Abbreviations: FVIII = factor VIII; IU = international unit
Source: AHCDO & NBA 2016, Table 1-1

Prevalence

According to the World Federation of Hemophilia’s most recent global report (2022) there are approximately 208,957 people diagnosed with haemophilia A worldwide, although this is likely an underestimate (World Federation of Hemophilia 2022). The estimated prevalence for males with haemophilia A is 17.1 per 100,000 males (World Federation of Hemophilia 2022). According to the NBA’s 2021–2022 Australian Bleeding Disorders Registry (ABDR), 2,621 people in Australia have haemophilia A, with 742 of those having severe disease, 248 having moderate disease and 1,441 having mild disease, and the remaining 190 cases having disease of unknown severity (National Blood Authority 2023a).

Treatment and management

The primary treatment for haemophilia A involves intravenous (IV) injection of FVIII replacement therapy using either plasma-derived or recombinant factor concentrates (AHCDO & NBA 2016). The replacement therapy can be given on demand when bleeds occur (used more commonly in mild cases) or as a regular prophylactic measure to ensure FVIII plasma levels are somewhat controlled; however, management is patient-specific and may differ according to individual circumstances and disease (AHCDO & NBA 2016). Individuals receiving regular FVIII prophylaxis may still require additional on-demand replacement (e.g. for break-through bleeding events or prior to surgery). In Australia, most patients receiving treatment for haemophilia A will receive care via dedicated and highly specialised haemophilia treatment centres (HTCs) usually co-located within hospitals (AHCDO & NBA 2016). HTCs encompass a multitude of specialist health professionals (haematologists, nurses, psychosocial workers, physiotherapists, laboratory technicians etc.) with expertise in haemophilia care and management (AHCDO & NBA 2016).

Guidelines recommend that patients with severe forms of haemophilia A undergo regular intravenous prophylactic treatment, ideally using concentrates with an extended half-life (AHCDO & NBA 2016; Srivastava, Alok et al. 2020). While plasma-derived versions were traditionally common, in recent years recombinant human factor FVIII has become the more popular choice. The exact dose and dosage schedule is determined by the formulation selected for treatment. A ‘typical’ example of a prophylactic dosing schedule would be the Malmö protocol: 25–40 IU/kg per dose administered 3 times per week, or the Utrecht protocol: 15–30 IU/kg per dose administered 3 times per week (AHCDO & NBA 2016; Srivastava, Alok et al. 2020).

Emicizumab (Hemlibra™) is a more recent prophylactic intervention for treatment of haemophilia A (not for on-demand treatment; on-demand intravenous FVIII replacement may still be required for breakthrough bleeding events or prior to surgery). Emicizumab is a recombinant humanised bi-specific monoclonal antibody that binds to clotting factors IXa and X simultaneously, thus holding the molecules together. This then acts as a substitute scaffolding, mimicking the role of the deficient FVIIIa, and acts as a cofactor for factor IXa in activating factor X (Kitazawa et al. 2012; Muto et al. 2014). Emicizumab is approved for use in many countries, including Australia. It was approved by the TGA and subsequently added to the ARTG early in 2018 (Therapeutic Goods Administration n.d.). At its August 2019 meeting, MSAC considered emicizumab for routine prophylaxis in patients with moderate to severe congenital haemophilia A without factor VIII inhibitors, and it supported funding via the NBA (MASC application 1579) (Medical Services Advisory Committee 2019b). At this same meeting, MSAC also considered emicizumab for routine prophylaxis in haemophilia A with factor VIII inhibitors, and similarly supported funding via the NBA for this indication (MSAC application 1510.1) (Medical Services Advisory Committee 2019a).

Like FVIII replacement therapy, emicizumab is administered within an HTC. While FVIII replacement therapy and emicizumab are both used as prophylactic treatments, only emicizumab is appropriate for use in patients with a history of FVIII inhibitors (essentially rendering FVIII replacement therapy useless) (Srivastava, Alok et al. 2020). Since the inclusion of emicizumab on the National Product Price List in 2020–2021, demand for FVIII products has decreased by 45.6% (National Blood Authority 2023a).

Dosage guidelines for emicizumab recommend a weekly subcutaneous (s.c.) loading dose of 3 mg/kg for 4 weeks, followed by one of the following: 1.5 mg/kg s.c. once per week, 3 mg/kg s.c. once every 2 weeks, or 6 mg/kg s.c. once every 4 weeks (Therapeutic Goods Administration n.d.).

The treatment burden and pain associated with haemophilia A treatment can result in poor treatment adherence and suboptimal clinical outcomes (AHCDO & NBA 2016; Srivastava, Alok et al. 2020). Poor adherence to prophylaxis has the potential to be especially dangerous, as missing an infusion can cause clotting factor levels to fall below a protective trough level, causing an increased risk of bleeding (Srivastava, Alok et al. 2020). There is also a high risk of breakthrough and spontaneous bleeding between infusion periods (Srivastava, Alok et al. 2020).

In addition to the health burden attributable to haemophilia A there is a long-term treatment burden that often interferes with education, employment and work productivity, and impacts psychosocial health (AHCDO & NBA 2016). The disease is also associated with substantial use of non-haemophilia treatment-related healthcare resources such as physician, outpatient and emergency room visits, and hospitalisations due to spontaneous or traumatic bleeds.

While current treatments for haemophilia A are safe and effective for many patients, disadvantages associated with current treatments exist, resulting in an unmet clinical need. Treatment duration and dosage schedules can be a burden of particular concern. Treating haemophilia A can be a time-consuming process, with FVIII therapy requiring intravenous infusions 2–4 times per week and emicizumab injections being administered subcutaneously 1–4 times per month (Srivastava, Alok et al. 2020; Therapeutic Goods Administration n.d.). Reducing the treatment burden would improve overall QoL for patients and their support systems. Furthermore, patients with more severe haemophilia A report chronic pain that impacts their daily lives in the form of physical limitations that make it difficult to participate in physical and social activities, resulting in an overall decrease in health and wellbeing (AHCDO & NBA 2016). Currently available treatment options cannot deliver sufficiently high sustained FVIII concentrations to provide stable

and consistent protection from bleeds. The peak and trough nature of treatments and the need for regular treatment are major limitations of the current therapy. New treatments are needed to improve patient and clinical outcomes and reduce or prevent disease progression. This gap in treatment, combined with advancements in medical technology, has resulted in the development of novel gene therapies to provide a potential improvement in haemophilia A management.

Patient eligibility for the proposed intervention

Test

Pre-existing immunity against the viral vector used (adeno-associated virus serotype 5 [AAV5]) may reduce the efficacy of the proposed treatment due to neutralising antibodies acting on the viral vector before delivery of the gene to the target cells (MSAC 1751 PICO Set 1, p3). Therefore, an AAV5 antibody test must be performed to determine treatment eligibility. The eligibility criteria for the test state that adult patients (≥ 18 years) with severe haemophilia A as classified by residual FVIII levels of < 0.01 IU/mL ($< 1\%$ of normal activity) may be eligible for valoctocogene roxaparvovec. Those with no active FVIII inhibitors and without active hepatitis or severe liver disease are eligible for treatment (April 2024 PASC meeting).²

Note, while patients with active hepatitis or severe liver disease need to be ruled out prior to being eligible for the AAV5 DetectCDx™, this is not a requirement for the current management of patients with congenital haemophilia A (MSAC 1751 PICO Set 1, p18).

Therapeutic intervention

Adult patients (≥ 18 years) with severe haemophilia A as classified by residual FVIII levels of < 0.01 IU/mL ($< 1\%$ of normal activity) (Table 1) may be eligible for valoctocogene roxaparvovec. Of those patients, only the subset who test negative to anti-AAV5 antibodies on the AAV5 DetectCDx™ test are eligible for treatment. FVIII inhibitor-level testing for haemophilia A can be done using various tests. The guidelines suggest use of the Nijmegen–Bethesda assay because it has higher sensitivity and specificity than other common alternatives (AHCDO & NBA 2016).

PASC asked for clarification around the definition of ‘no inhibitors’ in the proposed population, focusing on whether this excludes patients with a history of inhibitors or only those with active inhibitors. The applicant clarified that patients with a history of inhibitors but without current inhibitors could theoretically benefit from the treatment, thus the applicant prefers not to exclude these patients from the proposed population. However, for the ADAR, only patients with no active inhibitors and no history of inhibitors would be included, given evidence is only available for this patient group. PASC noted the absence of evidence for patients with a history of inhibitors and notes that the applicant intends to seek MSAC consideration of whether the evidence for patients with no history of inhibitors translates to those with a history of but without active inhibitors. PASC raised concerns around the assay and its use in classifying those with or without inhibitors and questioned whether the definition of ‘no inhibitors’ in the proposed population needs to specify the level (e.g. < 0.6 Bethesda units as in trial) and/or number of testing occasions (e.g. on 2 occasions as was done in the trial). PASC considered this would require further clarification in the assessment phase.

Valoctocogene roxaparvovec should not be administered to patients with active acute or uncontrolled chronic infections, known significant hepatic fibrosis (stage 3 or 4 on the Batts-Ludwig scale or equivalent) or cirrhosis, or mannitol hypersensitivity (BioMarin Pharmaceutical 2023). Patients with radiological liver

² At the April 2024 meeting, PASC noted the eligible population could be defined as patients with no active inhibitors.

abnormalities or liver function test abnormalities (see Prior tests) should be referred to a hepatologist to assess eligibility. Patients with any of the following were excluded from the key phase III trial: detectable pre-existing antibodies to the AAV5 capsid; current or prior history of factor VIII inhibitor (patients were required to test negative [<0.6 Bethesda Units] in a Nijmegen modified Bethesda assay on 2 occasions); active infection; chronic or active hepatitis B or C; immunosuppressive disorder including human immunodeficiency virus (HIV) infection; significant liver dysfunction; substantial liver fibrosis; liver cirrhosis; history of arterial or venous thromboembolic events; serum creatinine ≥ 1.4 mg/dL; and active malignancy (BioMarin Pharmaceutical 2023; Ozelo et al. 2022).

The target patient population for valoctocogene roxaparvovec seems to be consistent with the sample populations included in clinical trials (Mahlangu et al. 2023; Ozelo et al. 2022; Pasi et al. 2020), thus the selected population seems appropriate.

Prior tests

To be eligible for the intervention, patients must test negative to FVIII inhibitors and anti-AAV5 antibodies (BioMarin Pharmaceutical 2023). Patients should be assessed using the proposed companion diagnostic (AAV5 DetectCDx™), and factor VIII inhibitor titre testing be performed.

Liver health assessment must be undertaken, including liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transferase [GGT], alkaline phosphatase [ALP], total bilirubin and international normalized ration [INR]), ultrasound imaging and laboratory assessments for liver fibrosis (BioMarin Pharmaceutical 2023). Radiological liver abnormalities and/or liver function abnormalities (ALT, AST, GGT, ALP or total bilirubin >1.25 times the upper limit normal [ULN] or INR ≥ 1.4) do not automatically exclude patients from treatment; however, consultation with a hepatologist is recommended to assess eligibility (BioMarin Pharmaceutical 2023).

The application noted that eligibility assessments, including blood tests for liver function and hepatitis screening, and liver ultrasound (equivalent to tests funded under MBS items 69475, 66512 and 55037, respectively), would be covered within the operation of the HTC (MSAC 1751 PICO Set 1, Cost information attachment). The application further noted that some patients may require a fibroscan, for which an equivalent MBS item does not exist.

Patients should also be assessed on their ability to receive corticosteroids/immunosuppressives, as these are often required post-treatment in response to liver enzyme elevations (BioMarin Pharmaceutical 2023).

PASC noted the prior tests (used to define the population eligible for the intervention or comparator) include assessment of FVIII activity and past/current inhibitor(s), liver function tests and imaging including liver fibrosis ultrasound (not MBS reimbursed), and, potentially, assessment by a hepatic specialist to determine if any liver disease is present before treatment. PASC considered the need for stronger eligibility exclusions for prior tests to be explored in the ADAR.

PASC queried if patients needed to be genotype tested as some genotypes are known to have higher risk of developing inhibitors. The applicant suggested this would not be necessary, as patients have already been exposed to FVIII without developing inhibitors.

Intervention

Proposed test

The investigative technology component of the codependent technology is the AAV5 DetectCDx™ test, which is a companion diagnostic test intended for use with valoctocogene roxaparvovec (MSAC 1751 PICO Set 2, p2). The purpose of the anti-AAV5 antibody test is to determine patient eligibility to receive valoctocogene roxaparvovec treatment. Pre-existing immunity against the viral vector (AAV5) may reduce the efficacy of the proposed treatment due to neutralising antibodies acting on the viral vector before delivery of the gene to the target cells (MSAC 1751 PICO Set 1, p3).

The test uses a bridging immunoassay to detect antibodies to AAV5 in human sodium citrated (3.2%) plasma specimens (MSAC 1751 PICO Set 2, p3). The AAV5 DetectCDx™ uses a combination of concurrently conducted screening and confirmatory steps to detect antibodies specific for AAV5 capsid. The screening step assesses the presence of anti-AAV5 antibodies; the confirmatory step determines if the electrochemiluminescence signal is specific. In the confirmatory step, samples are pre-incubated with unlabelled capsid (AAV5 confirmatory reagent) to compete for any anti-AAV5 antibodies. If AAV5-binding antibodies are present, they will be bound by the unlabelled AAV5 capsid, resulting in a reduced electrochemiluminescence signal in the confirmatory step when compared to the screening step (MSAC 1751 PICO Set 2, p3). A positive result in the screening step is confirmed in the confirmatory step.

Cut points for the screening and confirmatory assays—used to determine the screen index (SI) and confirm index (CI)—were based on the statistical analysis of a set of samples negative for anti-AAV5 antibodies. This yielded a 5% false positive rate for the screening step and a 1% false positive rate for the confirmatory step (ARUP Laboratories n.d.).

A test result of ‘detected’ indicates the presence of anti-AAV5 antibodies. A negative result, denoted as ‘not detected’, indicates that anti-AAV5 antibodies were not detected in the screening step, or that the confirmatory step did not confirm the presence of anti-AAV5 antibodies (MSAC 1751 PICO Set 2, p3). Based on the result, patients are either eligible to begin treatment with valoctocogene roxaparvovec (result: not detected) or ineligible (result: detected), in which case they will need to continue with alternative treatments, including FVIII replacement therapy or emicizumab (MSAC 1751 PICO Set 2, p18).

Description of the therapeutic intervention

Valoctocogene roxaparvovec (Roctavian™), manufactured by BioMarin Pharmaceuticals, is an AAV5-based gene therapy intervention for haemophilia A designed to compensate for the lack of FVIII protein expression in haemophilia A patients. Gene therapy induces expression of the B-domain-deleted SQ form of a recombinant human factor VIII (hFVIII-SQ) under the control of a liver-specific promoter (MSAC 1751 PICO Set 1, p5). Liver cell nuclei actively transcribe the DNA to produce FVIII proteins that are secreted into the bloodstream, resulting in endogenous FVIII production and expression (Ozelo et al. 2022). Ideally, the FVIII proteins are released into the bloodstream in similar numbers as would be present in a healthy patient without haemophilia A, thereby reducing the risk of bleeding (Ozelo et al. 2022). Due to the nature of the gene therapy treatment, valoctocogene roxaparvovec is offered as a one-off infusion, with results expected to be permanent (Ozelo et al. 2022). Valoctocogene roxaparvovec is designed to be used as a replacement for other prophylactic haemophilia A treatments such as FVIII replacement therapy and emicizumab. It is important to note that treatment with valoctocogene roxaparvovec currently excludes patients from receiving any future form of gene therapy for haemophilia, due to patients seroconverting

and thus testing positive to AAV antibodies, which would exclude them from gene therapies using the same or cross-reactive viral vectors (BioMarin Pharmaceutical 2023).

PASC expressed concerns around this treatment excluding patients from future gene therapies using this viral vector. The applicant noted that while this is currently the case, this may not be an issue in the future.

Delivery of proposed medical service

Haemophilia A patients are primarily managed within Australia's HTC specialist network, specifically designed to ensure comprehensive and appropriate care for haemophilia patients (AHCDO & NBA 2016). Five primary HTCs, or 'hubs'—one each in Adelaide, Brisbane, Melbourne, Perth and Sydney—have been selected as the primary HTCs administering the treatment (MSAC 1751 PICO Set 1, pp5-6). Patients will be assessed for eligibility for valoctocogene roxaparvovec at hub and/or spoke HTCs, and haematologists within the hub and/or spoke HTC will order the proposed AAV5 DetectCDx™ test (MSAC 1751 PICO Set 2, p9).

The AAV5 DetectCDx™ test is only performed by an international laboratory, ARUP Laboratories in Salt Lake City, Utah, USA (MSAC 1751 PICO Set 2, p3). Blood samples would be collected by the hub and/or spoke HTC, centrifuged and the plasma frozen within 2 hours, and the frozen sample then shipped to the ARUP laboratory (MSAC 1751 PICO Set 2, p9). Patients living remote to an HTC hub will be able to access eligibility assessment, screening and long-term monitoring at their local HTC, but will be required to travel to a hub to receive valoctocogene roxaparvovec. Haematologists and hub HTCs will be solely responsible for administering valoctocogene roxaparvovec, with support provided by haematologists at spoke HTCs for the broader management of patients (MSAC 1751, PICO Set 1, p7). The exact patient care pathway will differ according to individual health needs and required levels of care. According to the applicant, the test cost will be entirely covered by BioMarin Pharmaceuticals at no cost to the Australian healthcare system or consumer (MSAC 1751, PICO Set 1, Cost information attachment).

PASC noted the applicant's expert advice that the consent process is an in-depth discussion not just about eligibility but also about the patient's capacity to cope with the intervention and its intensive follow-up over the first 6 months. The informed consent process also required an explanation of all therapeutic options (not just gene therapies) and is done several times before enrolment to a gene therapy.

PASC noted the proposed hub and spoke model of care, where treatment can only be delivered at a hub HTC, as opposed to delivery at both hub and spoke centres. PASC considered this may result in a high barrier to care, due to patients being required to attend a hub centre to receive the intervention. This is of particular concern for rural or regional patients who may need to travel great distances and who may have limited access to sufficient follow-up care. The applicant acknowledged this concern and that these are issues that will need to be discussed between the patient, the clinical team, and the hub and spoke centres prior to treatment.

PASC questioned if the HTCs would incur additional costs due to implementation and provision of the intervention and noted these costs should be addressed in the ADAR.

Patients deemed eligible for treatment, will then attend an authorised HTC to receive a single dose of valoctocogene roxaparvovec. Dosage is 6×10^{13} vector genomes (vg) per kilogram of body weight, administered as a single IV infusion. Infusion time depends on the infusion volume and rate, as well as patient response, taking from 2 to 5 hours or longer in some cases. Patients are monitored for adverse events for up to 3 hours post-infusion (BioMarin Pharmaceutical 2023).

Administration steps for valoctocogene roxaparvovec are as follows (BioMarin Pharmaceutical 2023):

1. The patient is examined on the day of infusion to ensure freedom from active, acute illness.
2. An IV catheter or butterfly needle is inserted into a suitable peripheral vein (e.g. median cubital vein) and flushed with saline.
3. Valoctocogene roxaparvovec (Roctavian™) is prepared and infused as a pure solution at a dose of 6×10^{13} vg/kg over a dose-dependent time using an appropriate infusion pump. The infusion rate starts at 1 ml/min, increasing by 1 ml/min every 30 minutes up to a maximum of 4 ml/min.
4. The patient's vital signs (pulse, blood pressure, respiration rate, temperature) are monitored every 15 minutes during the infusion.

Materials needed for administration of valoctocogene roxaparvovec include (BioMarin Pharmaceutical 2023):

- flow rate-controlled syringe pump
- syringes for valoctocogene roxaparvovec administration (total number will depend on the patient's dose volume and the syringe pump used)
- 18- to 21-gauge sharp needles
- high-volume, in-line, low protein-binding infusion filter (pore size 0.22 microns) with maximum operating pressure adequate for the syringe pump settings
- syringe for priming and flushing the infusion line (0.9% sodium chloride solution)
- gauze/tape/transparent dressing
- sharps disposal container.

Training and qualification requirements

The application (MSAC 1751 PICO Set 1, p7) suggested training and accreditation of clinical and other professional staff at the authorised HTCs as part of a proposed roadmap for implementation of gene therapy for haemophilia in Australia. The application expected that the Australian Haemophilia Centre Directors' Organisation (AHCDO) will establish training and accreditation requirements prior to the introduction of valoctocogene roxaparvovec.

Estimated utilisation

According to the application (MSAC 1751 PICO Set 1, Estimated utilisation attachment), approximately 2,500 people in Australia are currently seeking long-term treatment for haemophilia A. This estimate was based on the 2019–2020 ABDR annual report. The most recent version (2020–2021) reported that 2,621 people in Australia have haemophilia A—742 have severe disease, 248 have moderate disease, 1,441 have mild disease and the remaining 190 cases are of unknown severity (National Blood Authority 2023a). Of the 742 with severe haemophilia A, this includes individuals of all ages, not just adults. The ABDR annual report states 112 patients with haemophilia A of all ages have inhibitors (National Blood Authority 2023a).

Test

The utilisation calculation provided in the application for the AAV5 DetectCDx™ suggested that 42% of adult patients with severe haemophilia A may be considered for testing to determine eligibility for valoctocogene roxaparvovec gene therapy (MSAC 1751, PICO Set 2, Estimated utilisation attachment). The calculation is based on the estimation that 75% of patients have no history of FVIII inhibitors (Srivastava, A. et al. 2013), 76% do not have active hepatitis or severe liver disease, (Qvigstad et al. 2018) and 74% of adults with severe haemophilia A in the 2020 ABDR were using prophylactic FVIII replacement therapy.

Calculations provided in the application suggested that between 2024 and 2027 approximately 200–210 patients per year would be considered for AAV5 testing for the purpose of determining eligibility for valoctocogene roxaparvovec.

Intervention

The overall estimated eligible population for valoctocogene roxaparvovec gene therapy at the time of application was approximately 27% of adults with severe haemophilia A (MSAC 1751, PICO Set 2, Estimated utilisation attachment). This calculation was based on the percentages reported above for the test population, combined with an estimation that 64.3% of patients tested for anti-AAV5 antibodies will have no pre-existing antibodies to AAV5 and will be eligible for treatment (based on a BioMarin study published in Klamroth et al. (2022) that reported a mean global prevalence of anti-AAV5 antibodies of 35.7% in adults). Calculations provided in the application suggested that between 2024 and 2027, approximately 130–140 patients would be eligible for valoctocogene roxaparvovec.

PASC noted that the eligible patient population may be higher than estimated, as a proportion of paediatric patients will turn 18 years of age each year and become eligible for the proposed codependent technology (i.e. the incident testing population). It was suggested that uptake may be higher in the incident population, as these paediatric patients transitioning to adult care may be less likely to have hepatitis and/or liver failure.

The applicant provided no estimates for expected uptake of valoctocogene roxaparvovec and advised that they are engaging with AHCD0 to inform it of the potential uptake (to be clarified in the assessment report). Given the novelty of this treatment it is unlikely that all those eligible will seek the treatment immediately.

Comparator(s)

Test

The proposed comparator for the AAV5 DetectCDx™ test is 'no testing', as testing for pre-existing antibodies to AAV5 is not part of the current treatment algorithm. Furthermore, AAV5 antibody testing is not currently available or funded in Australia. In the absence of the proposed test, patients would not be tested for anti-AAV5 antibodies and would continue to receive standard medical treatment with FVIII replacement therapy or emicizumab (testing for pre-existing antibodies to AAV5 is a prerequisite to determine eligibility for the intervention).

Intervention

The proposed comparators for valoctocogene roxaparvovec are FVIII replacement therapy (prophylactic use) and emicizumab, each with or without additional on-demand FVIII therapy. In the absence of valoctocogene roxaparvovec, patients would be treated with standard care consisting of either FVIII replacement therapy or emicizumab as routine prophylactic treatments, with the potential for additional FVIII replacement therapy on-demand if required. The application (MSAC 1751 PICO Set 1, p11) suggested that while the effect of valoctocogene roxaparvovec persists, patients would not receive FVIII replacement therapy or emicizumab as routine prophylactic treatments. The proposed intervention would not fully replace FVIII replacement therapy as an on-demand treatment to control breakthrough or trauma-related injury. Both FVIII replacement therapy and emicizumab are publicly funded through the NBA (National Blood Authority 2023b).

PASC confirmed emicizumab and prophylaxis with FVIII replacement (both with/without on demand FVIII replacement therapy) are appropriate comparators.

PASC asked the applicant if there are data available to inform the comparator excluding those with liver disease and to inform outcomes for emicizumab excluding those with inhibitors/moderate severity disease. The applicant advised that this group can be teased out from the available data in the assessment. In addition, the applicant's expert advised that there are multiple reasons for the gradual increase in uptake of emicizumab over time, including patient preference.

Emicizumab can be used in patients with congenital haemophilia A with FVIII inhibitors and in patients with moderate congenital haemophilia A without FVIII inhibitors. These patient cohorts should be excluded for the purpose of any comparative assessment.

Clinical utility standard (for codependent investigative technologies only)

According to the application (MSAC 1751 PICO Set 2, p6), the test used in the clinical trials for valoctocogene roxaparvovec—the clinical trial assay (CTA)—is different from the proposed AAV5 DetectCDx™ test. Therapeutic outcomes are based upon patient selection determined using the CTA, therefore this test is the appropriate clinical utility standard for this codependent assessment. The AAV5 DetectCDx™ test, on the other hand, is the test being assessed for use in clinical practice.

Differences between the CTA and the AAV5 DetectCDx™ test are a modification of the assay incubation time, and a change in the capsid concentration (MSAC 1751 PICO Set 2, p6). The application (MSAC 1751 PICO Set 2, pp12-17) provided relevant analytical performance studies used to validate the AAV5 DetectCDx™ test (Summary of evidence section). The ADAR (applicant developed assessment report) should include an assessment of the differences between the CTA and the AAV5 DetectCDx™ test and an assessment of the accuracy and performance of the AAV5 DetectCDx™ test compared to the CTA.

The US Food and Drug Administration reviewed the existing precision studies and deemed the AAV5 DetectCDx™ test valid and acceptable for detecting AAV5 antibodies for the purpose of assessing eligibility for treatment with valoctocogene roxaparvovec (U.S. Food and Drug Administration). The AAV5 DetectCDx™ is also authorised for use in Europe (MSAC 1751 PICO Set 2, p3).

PASC noted that the proposed test assay has been approved internationally for the proposed use. PASC noted the proposed test will need to be compared to the clinical utility standard, which in this case is the clinical trial assay.

Outcomes

The following list identifies core outcomes to assess when evaluating the codependent technology (AAV5 test and valoctocogene roxaparvovec gene therapy) for the treatment of haemophilia A.

PASC noted and accepted the applicant's advice which suggested amendments to the draft outcomes, including:

- *change ABR to bleeding frequency (which includes ABR and proportion of patients with zero bleeds)*
- *addition of*
 - *mean FVIII activity*
 - *time between intervention and returning to prophylaxis (where applicable)*

- *amount of emicizumab avoided.*

AAV5 DetectCDx™ outcomes

- Test reliability
 - intra-observer or intra-instrument variability/agreement
 - inter-observer or inter-instrument variability/agreement
- Test concordance compared to CTA
 - positive percentage agreement
 - negative percentage agreement
 - within-patient concordance of the AAV5 DetectCDx™ test
- Change in clinical management
- Adverse events

Therapy outcomes

Effectiveness/efficacy

- Bleeding frequency (includes ABR and proportion of patients with zero bleeds; all bleeds, treated bleeds, treated target joint bleeds, treated spontaneous bleeds, treated traumatic bleeds)
- Categorisation of patients according to FVIII concentration and ABR pre-treatment and following intervention, reported over time.
- Mean FVIII activity
- Time between intervention and returning to prophylaxis (where applicable)

Safety

- Adverse events, including procedural complications
- Serious adverse events
- Acute peri-infusion adverse events
- Long-term adverse events (e.g. immunogenicity, thrombosis, hepatotoxicity, hepatocellular carcinoma)
- Laboratory indicators of safety (e.g. coagulation, inflammatory markers, serology, haematology)
- Formation of post-treatment FVIII inhibitors
- Liver function tests (ALT elevation etc)
- Anaphylactic reactions

Health system/resource utilisation

- Change in exogenous FVIII replacement therapy utilisation reported over time post-intervention as compared to baseline (reporting prophylaxis and on-demand treatment separately)
- Amount of emicizumab avoided
- Costs associated with adverse events for intervention and comparator treatments
- Costs associated with intervention and comparator treatments:
 - appointments
 - administration of IV infusions
 - consumables
 - hospital stay
 - follow-up
 - monitoring
 - subsequent on-demand/prophylactic therapy required

Quality of Life

- Health-related QoL indicators such as:
 - EuroQol 5-dimension questionnaire (EQ-5D) (Srivastava, Alok et al. 2020)
 - 36-item short form health survey (SF-36) (Srivastava, Alok et al. 2020)
 - haemophilia wellbeing index (Srivastava, Alok et al. 2020)
 - haemophilia-specific quality of life questionnaire for adults (Haemo-QoL-A) (Srivastava, Alok et al. 2020)
 - Patient Reported Outcomes Burdens and Experiences (PROBE) questionnaire (Srivastava, Alok et al. 2020)

Key outcomes (ABR, categorisation of patients according to FVIII concentration and ABR pre-treatment and following intervention, change in exogenous FVIII replacement therapy utilisation over time) are consistent with the outcomes and results in the key phase III clinical trial (Mahlangu et al. 2023; Ozelo et al. 2022). Health-related QoL in the key phase III trial (GENEr8-1; NCT03370913) was assessed using the Haemo-QoL-A and EQ-5D-5L instruments (O'Mahony et al. 2023; Ozelo et al. 2022), which aligns with the suggested tools. Additional patient reported outcomes assessed in the trial were the haemophilia activities list (HAL) and the work productivity and activity questionnaire (O'Mahony et al. 2023; Ozelo et al. 2022): haemophilia specific (WPAl+CIQ:HS). It should be noted that the key phase III trial referenced by the applicant is single-arm, thus any comparisons between the intervention/test and comparators are likely to be indirect.

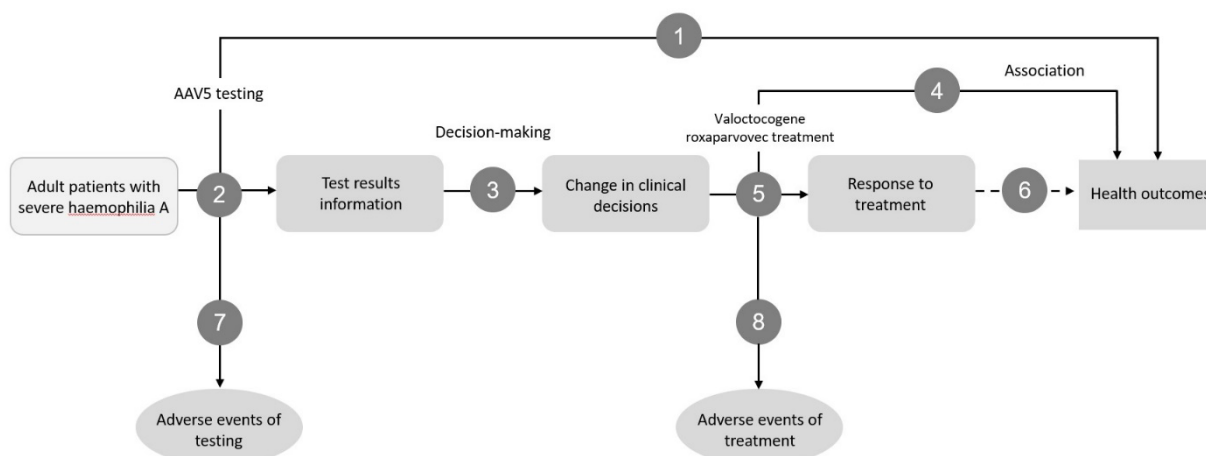
PASC noted concerns around the uncertain durability of the treatment effect, which will need to be addressed in the ADAR. The applicant's expert advised that recent 4-year follow-up data from the pivotal study showed that the biggest decline in durability of FVIII activity occurs between the first- and second-year post-treatment. Beyond the second year the decline is minimal—almost zero between years 3 and 4. The applicant confirmed durability of treatment effect will be explored in the ADAR, including via sensitivity analysis in the economic evaluation. PASC noted the applicant's expert advice that patients can engage in physical activity when above 16–18 units of FVIII activity, and that the data showed minimal decline after 2 years. Identifying when a reduction in FVIII activity occurs may be informative for payment timing in a pay-for-performance agreement.

Assessment framework (for investigative technologies)

Because the application made a claim of superiority, the assessment must show an improvement in health outcomes. The result of the AAV5 DetectCDx™ test could result in a change in treatment (access to valoctocogene roxaparvovec) for patients who test negative to anti-AAV5 antibodies, which would impact health and clinical outcomes for the patient.

In circumstances where direct evidence is unavailable, evidence needs to be provided at each step of the assessment framework. Figure 1 shows the research questions that need assessing at each step to assess the AAV5 DetectCDx™ test. Each number in the framework corresponds to one or more research questions that must be answered to support the clinical claim.

Figure 1 Assessment framework showing the links from the test population to health outcomes



Abbreviations: AAV5 = adeno-associated virus serotype 5.

Notes: 1: Direct from test-to-health-outcomes evidence; 2: test accuracy, 3: change in diagnosis/treatment/management; 4: influence of the change in management on health outcomes; 5: influence of the change in management on intermediate outcomes; 6: association of intermediate outcomes with health outcomes; 7: adverse events due to testing; 8: adverse events due to treatment.

Direct evidence

- 1) Does use of the AAV5 DetectCDx™ test to determine eligibility for valoctocogene roxaparvovec result in superior health outcomes in patients with haemophilia A when compared to no testing and standard treatment (FVIII replacement therapy or emicizumab)?

Linked evidence

- 2) What is the concordance of the findings from the AAV5 DetectCDx™ test compared to the CTA? *And* What is the within-patient concordance of the AAV5 DetectCDx™ test?
- 3) Does the result of the AAV5 DetectCDx™ test lead to a change in patient management compared to no testing?
- 4) What impact does valoctocogene roxaparvovec have on patient health outcomes relative to prophylactic FVIII replacement therapy and emicizumab?
- 5) Do differences in patient management resulting from AAV5 DetectCDx use lead to changes in FVIII levels?
- 6) Are the observed changes in FVIII levels and FVIII usage associated with a change in health outcomes (reduced ABR, improved QoL), and how strong and durable is the association?
- 7) What are the physical and psychological health risks associated with AAV5 DetectCDx™ testing compared to no testing?
- 8) Are there any adverse health events associated with use of valoctocogene roxaparvovec based on the result of AAV5 DetectCDx™ testing, relative to standard treatment?

The overarching assessment question for this application is ‘What is the comparative safety, effectiveness, cost-effectiveness and total costs of AAV5 DetectCDx™ testing and treatment with valoctocogene roxaparvovec versus no testing and treatment with standard of care (FVIII replacement therapy or emicizumab) in adult patients (≥18 years) with severe congenital haemophilia A and without inhibitors to FVIII, severe liver disease or active hepatitis?’

PASC noted that patient relevant outcomes are always preferred over surrogate outcomes, and durability of treatment effect is of significant interest. PASC also noted that there will be a linked evidence approach used in the assessment, as there is no direct evidence between the intervention and comparators.

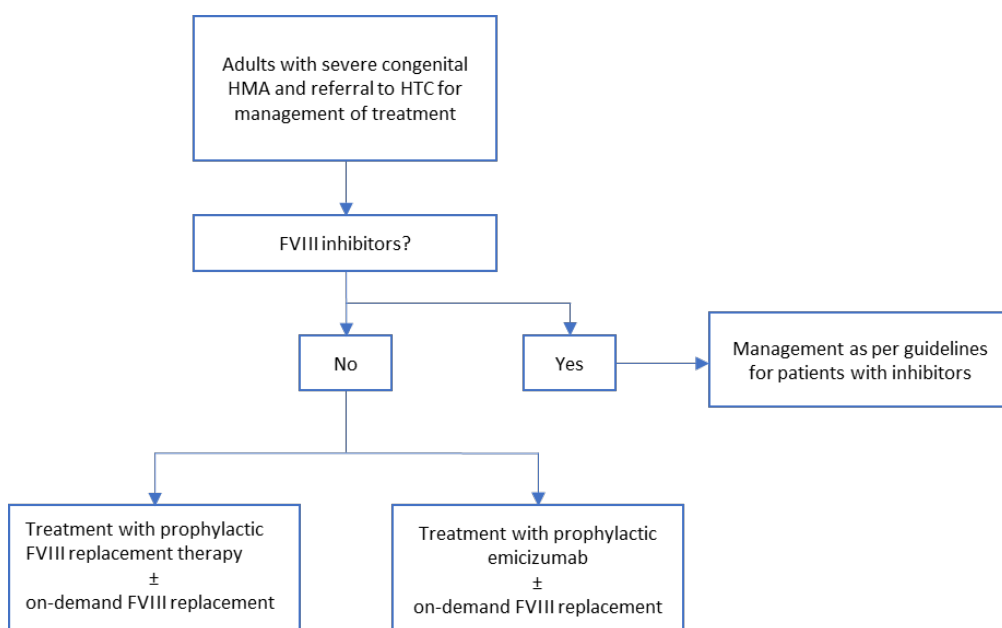
Clinical management algorithms

Current clinical management

The current clinical management for patients with haemophilia A (Figure 2) is guided by disease severity (as measured by FVIII clotting activity) (AHCDO & NBA 2016). Patients with mild or moderate haemophilia A are not relevant for this PICO; the proposed intervention would be available only for patients with severe haemophilia A. Most patients with severe haemophilia A typically receive prophylactic treatment with either FVIII replacement therapy or emicizumab (AHCDO & NBA 2016). Clinical management differs for patients who have or who develop inhibitors to FVIII. The proposed intervention can only be used in patients without active FVIII inhibitors, so the specific management of patients with inhibitors will not be further discussed (AHCDO & NBA 2016).

As noted in the application, assessments for active hepatitis and severe liver disease are not a necessary requirement for the current management of patients with severe congenital haemophilia A.

Figure 2 Current clinical management algorithm for patients with severe haemophilia A without inhibitors



Abbreviations: FVIII = factor VIII; HMA = haemophilia A, HTC = haemophilia treatment centres

Note: assessments for active hepatitis and severe liver disease are not a necessary requirement under the current management algorithm.

Source: MSAC Application 1751 PICO Set 1, p19; further adjusted by the assessment group

Proposed clinical management

Under the proposed clinical management algorithm (Figure 3), patients with severe haemophilia A will be tested for FVIII inhibitors. Those testing negative will proceed to the next stage for assessment for active hepatitis or severe liver disease (patients testing positive to inhibitors will follow the appropriate management guidelines). Patients with active hepatitis or severe liver disease are ineligible for valoctocogene roxaparvovec, so will be treated with FVIII replacement therapy or emicizumab (MSAC 1751

PICO Set 1, p17). Active hepatitis or severe liver disease do not need to be ruled out for the current management strategies.

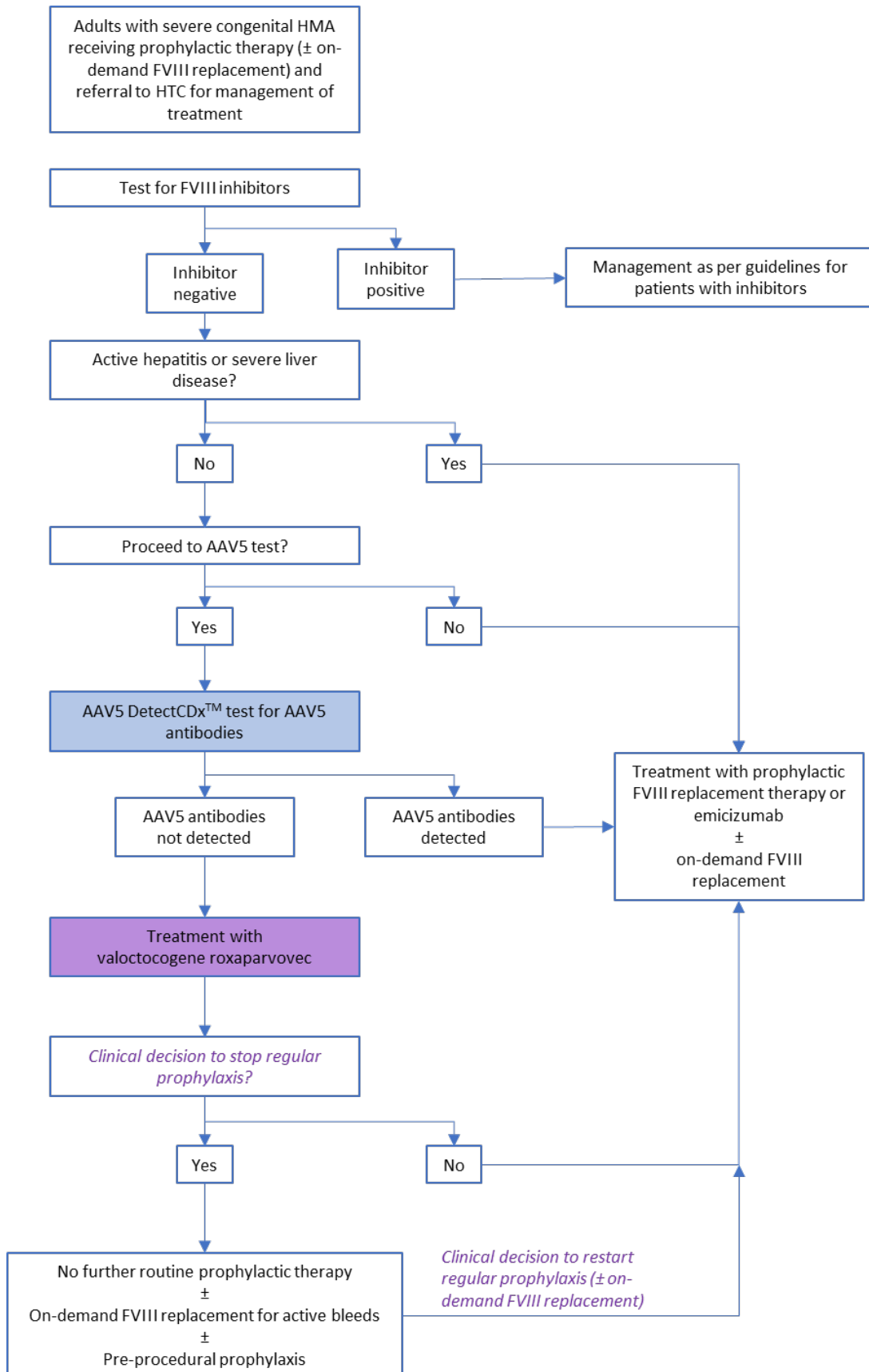
Patients without active hepatitis or severe liver disease are eligible to undergo testing for anti-AAV5 antibodies using the AAV5 DetectCDx™ test (MSAC 1751 PICO Set 1, p17). Again, this is not a requirement for current treatment strategies. Patients who test positive for anti-AAV5 antibodies are ineligible for valoctocogene roxaparvovec, so are treated with FVIII replacement therapy or emicizumab. Patients testing negative for anti-AAV5 antibodies are eligible for treatment with valoctocogene roxaparvovec.

PASC noted that the current clinical management algorithm does not include testing to exclude for liver disease and therefore current clinical care differs slightly from the proposed algorithm.

Continued prophylaxis may be required in the first few weeks after administration, as it may take time for FVIII levels to rise to levels sufficient to prevent spontaneous bleeds (BioMarin Pharmaceutical 2023). Exogenous FVIII or other haemostatic products may be required in the case of surgery, invasive procedures, trauma or bleeds in the event that FVIII activity is deemed insufficient for adequate haemostasis (BioMarin Pharmaceutical 2023). In long-term follow-up of patients treated in a phase I/II trial (n=13), the decision to return to prophylaxis was discussed with all participants with low FVIII activity levels (Symington et al. 2024). The majority of participants chose to remain off prophylaxis, with the exception of one participant who returned to prophylaxis temporarily. The application (PICO Set 1, p11) noted that durability of the valoctocogene roxaparvovec effect will be assessed in the ADAR. Change in exogenous FVIII replacement therapy utilisation over time, reported for prophylaxis and on-demand treatment separately, is also specified as an outcome for the assessment.

The application (MSAC 1751 PICO Set 1, pp18-19) suggested that overall monitoring after the use of the proposed intervention and the comparators will differ for the first 12 months and will be similar thereafter. Following administration of valoctocogene roxaparvovec, weekly liver function tests would be required for 6 months and then every 2–4 weeks for a further 6 months. FVIII levels would be assessed as needed.

Figure 3 Proposed clinical management algorithm for patients with severe haemophilia A without inhibitors



Abbreviations: AAV5 = adeno-associated virus serotype 5; FVIII = factor VIII; HMA = haemophilia A; HTC = haemophilia treatment centres
 Source: MSAC Application 1751 PICO Set 1, p20; further adjusted by the assessment group

Proposed economic evaluation

The proposed economic evaluation considers the applicant’s claims that AAV5 DetectCDx™ testing and treatment with valoctocogene roxaparvovec has superior effectiveness outcomes (reduction in ABR for all bleeds/no treated joint bleeds, improved QoL) and non-inferior safety compared to the standard care of no testing and prophylactic FVIII replacement therapy or emicizumab (MSAC 1751 PICO Set 1, p12). Based on the clinical claim made in the application, a cost effectiveness/cost utility analysis is appropriate for an economic evaluation of the codependent technology (Table 3).

Table 3 Classification of comparative effectiveness and safety of valoctocogene roxaparvovec compared with standard care (prophylactic FVIII replacement therapy or emicizumab) and suitable economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	Uncertain ^a	Non-inferior ^b	Superior
Inferior	Health forgone; need other supportive factors	Health forgone possible; need other supportive factors	Health forgone; need other supportive factors	? Likely CUA
Uncertain ^a	Health forgone possible; need other supportive factors	?	?	? Likely CEA/CUA
Non-inferior ^b	Health forgone; need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

Abbreviations: CEA = cost-effectiveness analysis; CMA = cost-minimisation analysis; CUA = cost-utility analysis

Notes:

? = reflects uncertainties and any identified health trade-offs in the economic evaluation as a minimum in a cost-consequences analysis

a = uncertainty covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detection of clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or comparative safety considerations

b = an adequate assessment of non-inferiority is the preferred basis for demonstrating equivalence

Green cell signifies appropriate economic evaluation type based on the clinical claim

PASC noted the applicant’s pre-PASC response proposed a simplified economic evaluation comparing the proposed intervention to emicizumab only (comparisons against both prophylactic FVIII replacement therapy and emicizumab would still be presented in the clinical evidence review). The simplified economic evaluation was proposed on the basis that emicizumab is superior to FVIII replacement therapy (MSAC Application 1579); therefore, if the proposed intervention is cost effective compared to emicizumab, by extension the intervention should also be cost effective compared to FVIII replacement therapy. PASC had concerns with this proposal. PASC noted emicizumab has not fully replaced FVIII replacement therapy and patients may be on FVIII replacement therapy, emicizumab or a mix of therapies.

The applicant suggested the ‘main’ driving factor for the economics is the time to return to prophylaxis, which indicates the amount of prophylaxis that can be avoided. The applicant also suggested it is unlikely the results would be significantly impacted by investigating patients who have switched between multiple treatments or who use a combination of both; there is also little data on this topic. PASC noted the ADAR would need to provide evidence that time to return to prophylaxis is the main driver of the economic evaluation.

While PASC noted the applicant’s proposed approach would simplify the economic analysis, PASC considered that standard medical therapy (prophylactic FVIII replacement therapy) should still be included as a comparator in the economic evaluation because not all eligible patients would use emicizumab; and if

the proposed therapy stops being effective, MSAC will be interested to know the incremental benefit above standard therapy for those patients.

PASC enquired about the proposed product price. The applicant noted it is dependent on the economic model and will be addressed in the ADAR.

PASC noted that under the current model of care, patients are unlikely to see any out-of-pocket (OOP) costs for treatment. Additionally, PASC noted there may be OOP costs to the individual with respect to transport to/from spoke and hub HTC (i.e. non-healthcare cost such as private travel to access healthcare).

PASC confirmed the clinical claim for this application was a superiority claim and that the appropriate economic evaluation type would therefore be a cost effectiveness analysis/cost utility analysis.

Proposal for public funding

The application is seeking funding for valoctocogene roxaparvovec through the National Blood Agreement (the Agreement). Public funding for blood products and blood-related products is facilitated through the Agreement and managed by the NBA on behalf of federal, state and territory governments (National Blood Authority n.d.).

PASC noted that there is uncertainty among some state and territory governments as to whether gene therapies that are proposed as an alternative treatment to therapies currently funded under the Agreement can be considered a blood-related product as defined in the Agreement and whether such therapies are therefore in scope of the Agreement or would be better suited to being classified as a highly specialised therapy under the National Health Reform Agreement. PASC noted Departmental advice that despite this uncertainty, the gene therapies undergoing MSAC assessment are currently being treated as a blood-related product that will be funded via the Agreement.

The application (MSAC 1751 PICO Set 1, Cost information attachment) noted that pricing for valoctocogene roxaparvovec (Roctavian™) is still being discussed and this will be provided in the final ADAR. The application (MSAC 1751 PICO Set 1, Cost information attachment) further stated that the infusion, which would take place at an HTC, would be covered within the operational costs of the HTC. Eligibility assessments specific to valoctocogene roxaparvovec (blood tests for liver function and hepatitis screening, liver ultrasound, fibroscan in some patients) would also be covered within the operations of the HTC. Although these costs may not fall to the NBA, they reflect additional costs that would be incurred by the healthcare system and, as such, should be captured in the economic and financial analyses. Regarding the AAV5 DetectCDx™ test, the application claimed (MSAC 1751 PICO Set 2, Cost Information attachment) that the full cost of the test will be covered by the applicant (BioMarin Pharmaceuticals) and no costs will be incurred by consumers or the Australian health system.

Haematologists at hub HTCs will be responsible for administering valoctocogene roxaparvovec (MSAC 1751 PICO Set 1, p7). Specialists at HTCs will provide a referral for the proposed test for patients being considered for treatment (MSAC 1751 PICO Set 2, p8).

Summary of public consultation input

Consultation feedback was received from 3 organisations. The 3 organisations that submitted input were:

- Thrombosis and Haemostasis Society of Australia and New Zealand (THANZ)
- Haematology Society of Australia and New Zealand (HSANZ)
- Haemophilia Foundation Australia (HFA)

The consultation feedback received was supportive. Overall, valoctocogene roxaparvovec was considered an additional viable therapeutic option for eligible patients with severe haemophilia A.

Clinical need and public health significance

The main benefits of public funding that were received in the consultation feedback included significantly decreased rates or no episodes of bleeding, the ability to avoid regular injections for prophylactic recombinant FVIII (rFVIII) or emicizumab, fewer hospital visits, a longer-term treatment effect, and the opportunity to live 'haemophilia free'. The consultation feedback generally considered that treatment would provide significant physical and mental health benefits due to lesser focus on treatment burden, and it would improve the ability to focus and participate in family, work and recreation (including physical activity) and ultimately produce significant improvements in quality of life.

The main disadvantages of public funding that were received in the consultation feedback were the variable treatment effect and the unknown durability of the treatment benefit. There is variability in FVII levels, with some people producing near-normal levels of FVIII after treatment and others having low levels (<5% of normal) and possibly needing prophylaxis or emicizumab. HFA indicated the possibility of negative psychological issues due to disappointing outcomes of the treatment. Other potential disadvantages include access disparity for regional areas, close monitoring following treatment, adverse effects of treatment, potential to disengage from healthcare, patients not receiving the appropriate level of healthcare, and impacts on identity.

Other services identified in the consultation feedback as being needed to be delivered included availability of required ancillary services (including AAV testing), appropriate regulated laboratory facilities and technical staff, and training programs to handle the vector and gene infusions. The consultation feedback noted some compliant treatment facilities are already available in Australia. The feedback advocated to ensure psychosocial and psychological support and long-term gene therapy registry follow-up.

Indication(s) for the proposed medical service and clinical claim

The consultation feedback strongly agreed with the proposed population, noting the exclusion of patients with developed inhibitors.

The consultation feedback strongly agreed with recombinant FVIII and emicizumab as the proposed comparators, indicating they are the standard of care for prophylaxis in these patients.

The consultation feedback ranged from agreeing to disagreeing with the proposed clinical claim. THANZ highlighted the variability in response and durability of FVIII expression after the therapy and noted the lack of direct evidence to claim superiority over current standard of care.

Cost information for the proposed medical service

The consultation feedback agreed with the proposed service descriptor.

Given there was no proposed pricing in the application, THANZ and HSANZ indicated the proposed fee should factor in the durability of treatment response and need for prophylaxis following the gene therapy.

Consumer Feedback

HFA described the impact of haemophilia A, including frequent injections, deteriorating veins, joint problems (arthritis, dexterity problems), disruption to normal life by medical appointments and hospitalisations, reduced energy, and needing to be cautious about physical activity. HFA highlighted that minor bleeds can cause pain and stiffness.

PASC noted that feedback was received from 3 organisations: Thrombosis and Haemostasis Society of Australia and New Zealand (THANZ), Haematology Society of Australia and New Zealand (HSANZ), and Haemophilia Foundation Australia (HFA).

All organisations were broadly supportive of the proposed intervention, but they noted some possible adverse events, including the need for frequent monitoring, and transaminitis that can impair FVIII expression; up to 80% of patients will need corticosteroids in the short term post-treatment. Feedback indicated a need for psychosocial support, such as in the case of disappointing outcomes. The feedback also indicated that while the intervention may achieve FVIII levels in the mild range the duration is unknown, and there may be significant variability in patient response, possibly leading to a return to prophylaxis. There was some disagreement with the claim of superiority, this being deemed uncertain based on indirect evidence. Feedback also indicated that community expectations are that valoctocogene roxaparvovec would be publicly funded in Australia.

Next steps

PASC advised that, upon ratification of the post-PASC PICO, the application can proceed to the Evaluation Sub-Committee (ESC) stage of the MSAC process.

PASC noted the applicant has elected to progress its application as an ADAR. PASC noted that the next ADAR lodgement deadline is in June, for the October 2024 ESC and November 2024 MSAC meetings. The applicant indicated it is not intending to lodge an ADAR for consideration at the REDACTED ESC and REDACTED MSAC meetings.

Applicant Comments on Ratified PICO

The Applicant had no comment.

References

ARUP Laboratories n.d., 'AAV5 total antibody assay for ROCTAVIAN (valoctocogene roxaparvovec-rvox) eligibility in hemophilia A ', https://www.accessdata.fda.gov/cdrh_docs/pdf19/P190033C.pdf.

Australian Haemophilia Centre Directors' Organisation & National Blood Authority 2016, 'Guidelines for the management of haemophilia in Australia', <https://www.blood.gov.au/system/files/HaemophiliaGuidelines-interactive-updated-260317v2.pdf>.

BioMarin Pharmaceutical 2023, 'Roctavian prescribing information', https://www.biomin.com/wp-content/uploads/2023/06/ROCTAVIAN-Prescribing-Information_US.pdf.

Kitazawa, T, Igawa, T, Sampei, Z, Muto, A, Kojima, T, Soeda, T, Yoshihashi, K, Okuyama-Nishida, Y, Saito, H, Tsunoda, H, Suzuki, T, Adachi, H, Miyazaki, T, Ishii, S, Kamata-Sakurai, M, Iida, T, Harada, A, Esaki, K, Funaki, M, Moriyama, C, Tanaka, E, Kikuchi, Y, Wakabayashi, T, Wada, M, Goto, M, Toyoda, T, Ueyama, A, Suzuki, S, Haraya, K, Tachibana, T, Kawabe, Y, Shima, M, Yoshioka, A & Hattori, K 2012, 'A bispecific antibody to factors IXa and X restores factor VIII hemostatic activity in a hemophilia A model', *Nat Med*, vol. 18, no. 10, pp. 1570–4.

Klamroth, R, Hayes, G, Andreeva, T, Gregg, K, Suzuki, T, Mitha, IH, Hardesty, B, Shima, M, Pollock, T, Slev, P, Oldenburg, J, Ozelo, MC, Stieltjes, N, Castet, SM, Mahlangu, J, Peyvandi, F, Kazmi, R, Schved, JF, Leavitt, AD, Callaghan, M, Pan-Petes, B, Quon, DV, Andrews, J, Trinh, A, Li, M & Wong, WY 2022, 'Global seroprevalence of pre-existing immunity against AAV5 and other AAV serotypes in people with hemophilia A', *Hum Gene Ther*, vol. 33, no. 7–8, pp. 432–41.

Mahlangu, J, Kaczmarek, R, von Drygalski, A, Shapiro, S, Chou, S-C, Ozelo, MC, Kenet, G, Peyvandi, F, Wang, M, Madan, B, Key, NS, Laffan, M, Dunn, AL, Mason, J, Quon, DV, Symington, E, Leavitt, AD, Oldenburg, J, Chambost, H, Reding, MT, Jayaram, K, Yu, H, Mahajan, R, Chavele, K-M, Reddy, DB, Henshaw, J, Robinson, TM, Wong, WY & Pipe, SW 2023, 'Two-year outcomes of valoctocogene roxaparvovec therapy for hemophilia A', *New England Journal of Medicine*, vol. 388, no. 8, pp. 694–705.

Medical Services Advisory Committee 2019a, 'Public Summary Document for Application No. 1510.1 – Emicizumab for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with haemophilia A with factor VIII inhibitors ', <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1510.1-public>.

Public Summary Document for Application No. 1579 – Emicizumab for routine prophylaxis to prevent or reduce frequency of bleeding episodes in patients with haemophilia A without factor VIII inhibitors ', 2019 <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1579-public>.

Muto, A, Yoshihashi, K, Takeda, M, Kitazawa, T, Soeda, T, Igawa, T, Sakamoto, Y, Haraya, K, Kawabe, Y, Shima, M, Yoshioka, A & Hattori, K 2014, 'Anti-factor IXa/X bispecific antibody (ACE910): hemostatic potency against ongoing bleeds in a hemophilia A model and the possibility of routine supplementation', *J Thromb Haemost*, vol. 12, no. 2, pp. 206–13.

National Blood Authority 2023a, 'Australian Bleeding Disorders Registry (ABDR) annual report 2021–22', <https://blood.gov.au/system/files/documents/ABDR%20Annual%20Report%202021-22%20FINAL.pdf>.

National Blood Authority 2023b, *What blood products are supplied – National Product Price List*, <https://blood.gov.au/national-product-price-list>.

O'Mahony, B, Dunn, AL, Leavitt, AD, Peyvandi, F, Ozelo, MC, Mahlangu, J, Peerlinck, K, Wang, JD, Lowe, GC, Tan, CW, Giermasz, A, Tran, H, Khoo, TL, Cockrell, E, Pepperell, D, Chambost, H, López Fernández, MF, Kazmi, R, Majerus, E, Skinner, MW, Klamroth, R, Quinn, J, Yu, H, Wong, WY, Robinson, TM & Pipe, SW 2023, 'Health-related quality of life following valoctocogene roxaparvovec gene therapy for severe hemophilia A in the phase 3 trial GENER8-1', *J Thromb Haemost*, vol. 21, no. 12, pp. 3450–62.

Ozelo, MC, Mahlangu, J, Pasi, KJ, Giermasz, A, Leavitt, AD, Laffan, M, Symington, E, Quon, DV, Wang, JD, Peerlinck, K, Pipe, SW, Madan, B, Key, NS, Pierce, GF, O'Mahony, B, Kaczmarek, R, Henshaw, J, Lawal, A, Jayaram, K, Huang, M, Yang, X, Wong, WY & Kim, B 2022, 'Valoctocogene roxaparvovec gene therapy for hemophilia A', *N Engl J Med*, vol. 386, no. 11, pp. 1013–25.

Pasi, KJ, Rangarajan, S, Mitchell, N, Lester, W, Symington, E, Madan, B, Laffan, M, Russell, CB, Li, M, Pierce, GF & Wong, WY 2020, 'Multiyear Follow-up of AAV5-hFVIII-SQ Gene Therapy for Hemophilia A', *N Engl J Med*, vol. 382, no. 1, pp. 29–40.

Qvigstad, C, Tait, RC, Rauchensteiner, S, Berntorp, E, de Moerloose, P, Schutgens, RE, Holme, PA & Group, obotAW 2018, 'The elevated prevalence of risk factors for chronic liver disease among ageing people with hemophilia and implications for treatment', *Medicine*, vol. 97, no. 39, p. e12551.

Srivastava, A, Brewer, AK, Mauser-Bunschoten, EP, Key, NS, Kitchen, S, Llinas, A, Ludlam, CA, Mahlangu, JN, Mulder, K, Poon, MC, Street, A & Hemophilia, TGWGTWFO 2013, 'Guidelines for the management of hemophilia', *Haemophilia*, vol. 19, no. 1, pp. e1–e47.

Srivastava, A, Santagostino, E, Dougall, A, Kitchen, S, Sutherland, M, Pipe, SW, Carcao, M, Mahlangu, J, Ragni, MV, Windyga, J, Llinás, A, Goddard, NJ, Mohan, R, Poonnoose, PM, Feldman, BM, Lewis, SZ, van den Berg, HM, Pierce, GF, panelists, tWGftMoH & co-authors 2020, 'WFH guidelines for the management of hemophilia, 3rd edition', *Haemophilia*, vol. 26, no. S6, pp. 1–158.

Symington, E, Rangarajan, S, Lester, W, Madan, B, Pierce, GF, Raheja, P, Robinson, TM, Osmond, D, Russell, CB, Vettermann, C, Agarwal, SK, Li, M, Wong, WY & Laffan, M 2024, 'Long-term safety and efficacy outcomes of valoctocogene roxaparvovec gene transfer up to 6 years post-treatment', *Haemophilia*, vol. 30, no. 2, pp. 320–30.

U.S. Food and Drug Administration n.d., 'Summary of safety and effectiveness data (SSED) ', https://www.accessdata.fda.gov/cdrh_docs/pdf19/P190033B.pdf

World Federation of Hemophilia 2022, 'World Federation of Hemophilia report on the annual global survey 2022', *World Federation of Hemophilia*, <https://elearning.wfh.org/resource/report-on-the-annual-global-survey-2022/>.