MSAC Application 1751

Valoctocogene roxaparvovec for Haemophilia A

PICO Set 1

PICO set 1: Valoctocogene roxaparvovec for haemophilia A

Population

Describe the population in which the proposed health technology is intended to be used:
Haemophilia A (HA) is a genetic bleeding disorder caused by changes in the coagulation factor VIII (FVIII) (F8) gene resulting in a deficiency of the coagulation factor VIII (FVIII). As an X-linked congenital bleeding disorder, the vast majority of affected individuals are male with a reported incidence in Australia of approximately 11.5 per 100,000 males (Australian Haemophilia Centre Directors' Organisation [AHCDO] 2016). The characteristic phenotype in haemophilia is the bleeding tendency with severity of bleeding directly correlated to the level of clotting factor (Table 1). In the most severe cases, bleeding episodes most commonly occur internally into the joints or muscles leading to painful, progressive, and irreversible joint damage, however some bleeds can be life threatening, such as intracranial or gastrointestinal bleeds and require immediate treatment (Srivastava 2020). Bleeding may occur spontaneously without trauma or injury. Untreated, bleeding may result in permanent damage to muscles and joints, chronic pain, and death (AHCDO, 2016).

One of the most common clinical manifestations and debilitating complications of bleeding in haemophilia A is joint damage, also known as haemophilic arthropathy. Joint damage in haemophilia A occurs as a result of recurrent bleeding into the joint space. The blood 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 (Knobe & Bernstorp 2011). Prophylactic treatment with FVIII therapy does decrease frequency of bleeding and therefore may slow the progression of joint disease; however, it does not reverse established joint damage (AHCDO, 2016).

<u>Diagnosis</u>

Accurate diagnosis of patients with haemophilia is imperative to ensure appropriate management. Diagnosis of haemophilia typically involves the following:

- Clinical history / physical signs of unusual bleeding
- Family history of bleeding problems
- Blood test for clotting factor VIII
- Genetic testing that identifies a variant in the F8 gene that causes haemophilia.

Patients presenting with a clinical history of easy bruising in early childhood, spontaneous bleeding, excessive bleeding following surgery / trauma, family history of bleeding may be suspected of having haemophilia. A definitive diagnosis of haemophilia A is made based on laboratory assay results that demonstrate a deficiency of FVIII (AHCDO 2016). These tests are typically undertaken at the Haemophilia Treatment Centre (HTC).

According to the Haemophilia Foundation Australia (HFA), genetic testing takes place via specialist clinical genetics service, with the patient usually referred through an HTC. Diagnosis is usually confirmed by specialists at an HTC. There are currently 18 HTCs in Australia distributed across states and territories.

Severity

The severity of haemophilia A is determined by the levels of residual FVIII (Table). A normal FVIII concentration is considered to be within the range of 50-150 IU/dl (0.5-1.5 IU/ml), while patients with severe haemophilia A have FVIII levels of <1 IU/dl (or <1% of normal activity). These patients not only experience bleeding in relation to trauma or surgery, but they also suffer from recurrent, spontaneous, and sub-clinical bleeding episodes which occur in the absence of any identifiable haemostatic challenge. Untreated, patients with severe haemophilia A can suffer from 30-50 bleeds per year and may also experience significant complications, including frequent joint bleeds, leading to arthropathy, pain and reduced health-related quality of life (Manco-Johnson, 2013).

Table 1 Relationship of bleeding severity to clotting factor level

	FVIII level		
Severity	Concentration	% of normal activity	Bleeding episodes
Severe	< 1 IU/dl (< 0.01 IU/ml)	<1% of normal	Spontaneous bleeding into joints or muscles, 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-< to <40% of normal	Severe bleeding with major trauma or surgery. Spontaneous bleeding is rare

Source: AHCDO, 2016, Table 1-1

Treatment

For patients with severe haemophilia A, the world haemophilia federation (WHF) strongly recommend prophylaxis to prevent bleeds at all times and is standard of care for all patients with severe haemophilia (Srivastava 2020). This recommendation is consistent with the guidelines for the management of haemophilia in Australia (AHCDO 2016). The FVIII utilisation data from 2019-2020 provided in Figure 1 demonstrates that the majority of prophylactic treatment with FVIII was for patients with severe haemophilia A, with the remaining utilisation predominantly in moderate patients (8%) and minimal utilisation in those with mild severity (1%).

Since the inclusion of emicizumab on the National Product Price List (NPPL) in 2020-21, the demand for FVIII products decreased by 45.6% (National Blood Authority [NBA] annual report 2021-2022).

Figure 1 Volume (IU) of product (including EHL products) issued for haemophilia A patients, by severity and treatment regimen in 2019-20

	Mild	Moderate	Severe	Unknown**	Total**
HMA (IU FVIII Products)†	**6,080,290**	**17,071,750**	**160,231,850**	**22,250**	**183,406,140**
On Demand	3,698,790	4,168,750	11,878,250	22,000	19,767,790
Prophylaxis	1,806,500	12,882,000	141,601,750		156,290,250
Tolerisation	445,000		6,629,500		7,074,500
Unknown*	130,000	21,000	122,350	250	273,600

Source: Australian Bleeding Disorders Registry (ABDR) report 2019-20, Table 18. Abbreviations: EHL; extended half-life

† FVIII Products included are Advate, Xyntha, Adynovate, Eloctate and Biostate

* This represents a blank/not completed/empty field for the treatment regimen in the ABDR

** The total in this table combines the values for patients with mild, moderate and severe conditions. The severity of a patient's condition is not always known at initial presentation. This table includes product issues to patients with unknown severities.

Assessment of inhibitory antibodies to FVIII

The development of inhibitory antibodies to non-endogenous FVIII is a severe complication and one of the main challenges for treating physicians in the management of patients with severe haemophilia A. In patients with inhibitory antibodies to FVIII, the body's immune system recognises the therapeutically administered factor as a foreign protein, which in turn stimulates the production of antibodies. These inhibitors, immunoglobulin G (IgG) antibodies, neutralise the clotting factors. Haemostasis may still be achieved in patients that have low titre inhibitor although increased doses of FVIII concentrates may be necessary. In contrast, if the inhibitor titre is high, FVIII replacement is completely ineffective and bleeding continues (AHCDO 2016).

Patients with severe haemophilia are associated with a relatively high risk of developing the inhibitor, higher than those with moderate disease. A systematic review by Wight and Paisley (2003) reports a prevalence rate of 13% among those with severe cases. Presence of inhibitors makes treatment with replacement factor concentrates difficult, as such patients on FVIII therapy should be screened for the development of inhibitors. The confirmation of inhibitors, and quantification of the titre is performed via laboratory test, using the Nujmegen-modified Bethesda assay (AHCDO 2016).

Consideration of antibodies against adeno-associated virus (AAV) in the context of gene therapy

Pre-existing immunity against adeno-associated virus (AAV) may reduce the efficacy of AAV gene therapy due to the potential for neutralising antibodies to act on the vector before the delivery of the functional gene to the target cell. The mean global prevalence of AAV5 immunity in adults has been reported at 35.7% with considerable geographic variability (Klamroth 2022). Although AAV5 immunity is considered to be a serotype with very low neutralising antibody prevalence, a wide range of estimates between 4% to 50% have been reported (Mingozzi 2013; Li 2012; Boutin 2010; Erles 1999; Halbert 2006). As discussed in more detail below, valoctocogene roxaparvovec will be limited to those without AAV5 detected antibodies. For more details regarding the process involving the AAV5 antibody test (eg, AAV5 DetectCDx™), refer to the AAV5 PICO set.

Clinical need for a gene therapy in the management of haemophilia A

Haemophilia A is well-suited for a gene therapy approach as the clinical manifestations are directly attributable to the deficiency of a single gene product (FVIII) and the severity is inversely correlated with FVIII activity. As discussed in more detail in sections to follow, the current management of patients with severe haemophilia A consists of prophylactic treatment with FVIII therapy or emicizumab. These options are associated with a high treatment burden, with FVIII infusions 2–4 times per week and subcutaneous injections with emicizumab once per week to once every 4 weeks. Relative to these treatments, the once-off single infusion of valoctocogene roxaparvovec has been demonstrated to improve health related quality of life and provides an opportunity to live a significant period of time without thinking about or planning their life around their next treatment. Relative to these treatments, valoctocogene roxaparvovec is also expected to reduce bleeds which in turn would be expected to further improve a person's quality of life. The ability to achieve haemostatic efficacy while freeing patients from the burden of repeated treatment administrations and associated adherence issues is an important and transformative characteristic of valoctocogene roxaparvovec. Thus, reimbursing valoctocogene roxaparvovec for the proposed patient population will address the unmet clinical need of a treatment option that is associated with reduced treatment burden, superior efficacy and quality of life relative to current options.

Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed health technology, describing how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the technology:
Adults with severe haemophilia A without a history of FVIII inhibitors and pre-existing antibodies to AAV5, without active hepatitis or severe liver disease.

As discussed above, these patients are diagnosed, assessed and managed at the HTC. AAV5 antibody testing must be ordered by healthcare professionals at the HTC and performed by an overseas laboratory (ARUP) (for details refer to the AAV5 PICO set).

Provide a rationale for the specifics of the eligible population:
The proposed population is consistent with the eligibility for enrolment in the clinical trial program for valoctocogene roxaparvovec, where patients are required to have haemophilia A with residual FVIII levels of ≤1 IU/dL classifying them as severe according to Australian Haemophilia management guidelines (AHCDO, 2016).

Consistent with the current clinical evidence, eligibility to valoctocogene roxaparvovec is proposed for adult patients without pre-exiting antibodies to AAV5 (Ozelo 2022). Furthermore, patients with a history of FVIII inhibitors were excluded from the clinical trial (Ozelo 2022).

Additionally, consistent with the clinical evidence, and suggested eligibility criteria in the AHCDO roadmap for implementation of gene therapy for haemophilia in Australia (AHCDO 2022), access to valoctocogene roxaparvovec is proposed to be limited to patients without active hepatitis or severe liver disease, because the introduced F8 gene is under the control of a liver-specific promoter.

AHCDO is a national, not for profit organisation that brings together medical directors of HTCs and other clinicians involved in the care of persons with bleeding disorders in Australia. The AHCDO roadmap is further discussed in the 'Intervention' section.

Intervention

Name of the proposed health technology:
The proposed intervention is infusion of ROCTAVIAN™ (valoctocogene roxaparvovec), a gene therapy that uses an AAV5 vector to deliver a healthy copy of the F8 gene to the liver.

Describe the key components and clinical steps involved in delivering the proposed health technology:
The recommended dose of Roctavian is 6×10^{13} vector genomes per kilogram (vg/kg) administered as a single, one-time intravenous infusion.

As per the administration protocol in the pivotal study (270-301), the clinical steps involved in delivering the proposed medical service are as follows:

- The patient is examined on the day of infusion to ensure freedom from active, acute illness
- An intravenous (IV) catheter or butterfly needle is inserted into a suitable peripheral vein (for example the median cubital vein) and flushed with saline
- Roctavian is prepared and infused at a dose of 6×10^{13} vector genomes (vg) per kilogram of body weight as a pure solution over a dose-dependent time, through the catheter or

butterfly needle using an appropriate infusion pump. The infusion rate starts at 1 mL/min, and is increased every 30 minutes by 1 mL/min up to a maximum of 4 ml/min
- The patient's vital signs (pulse, blood pressure, respiration rate and temperature) are monitored every 15 minutes during the infusion

According to the draft product information (PI) for Roctavian, the infusion time depends on infusion volume, rate and patient response. Infusion time may take 2 to 5 hours or longer for a patient weighing 100 kg.

Identify how the proposed technology achieves the intended patient outcomes:
Valoctocogene roxaparvovec is an adeno-associated virus serotype 5 (AAV5) based gene therapy causing the expression of the B-domain deleted SQ form of a recombinant human factor VIII (hFVIII-SQ) under the control of a liver-specific promoter. The expressed hFVIII-SQ substitutes for the missing coagulation factor VIII needed for effective haemostasis. Following valoctocogene roxaparvovec infusion, vector DNA is transformed in vivo to form full-length, episomal transgenes that persist as the stable DNA forms that support long term production of hFVIII-SQ.

As the new F8 gene is under the control of a liver-specific promoter, only liver cells are able to activate transcription to make FVIII protein which is then secreted into the bloodstream (Ozelo 2022). Treatment with valoctocogene roxaparvovec provides endogenous FVIII production with constant FVIII expression.

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?
Yes

ROCTAVIAN™ (valoctocogene roxaparvovec)

Explain whether it is essential to have this trademark component or whether there would be other components that would be suitable:
Roctavian is the brand name of the gene therapy, and like all other products on the NPPL, the proposed listing will be brand-specific.

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient (For example: accessibility, dosage, quantity, duration or frequency):
Yes

Provide details and explain:
As proposed in the AHCDO roadmap for implementation of haemophila gene therapy in Australia, it is anticipated that valoctocogene roxaparvovec will be administered once only as a single intravenous administration by a haematologist at a hub HTC trained in the delivery of the gene therapy (AHCDO 2022). [More details of hub HTCs are provided below]. The dosage is 6×10^{13} vg per kilogram of body weight.

The AHCDO roadmap proposes a hub and spoke model of care for the administration of gene therapy in Australia. While it is the spoke centre's responsibility to identify and screen patients for selection, the decision of which patients to treat is shared by the hub and spoke centres, and the hub is responsible for the administration of gene therapy (Table 2).

The map provided in Figure 2 shows AHCDO's proposed distribution of hub and spoke centres for haemophilia gene therapy across Australia. One expert hub centre in five key states (red boxes) has been identified for gene therapy treatment of adult patientswith the remaining seven HTCs representing spoke centres. It should be noted that AHCDO did not consider paediatric treatment centres because gene therapy for patients younger than 18 years of age is not anticipated in the foreseeable future.

Given the administration of valoctocogene roxaparvovec will only occur once per patient, AHCDO consider that the five hub centres, with support of the spoke centres, will be able to meet the demand, and be capable of delivering the service to all eligible patients.

Figure 2 AHDCO's assessment of current HTCs as potential gene therapy sites

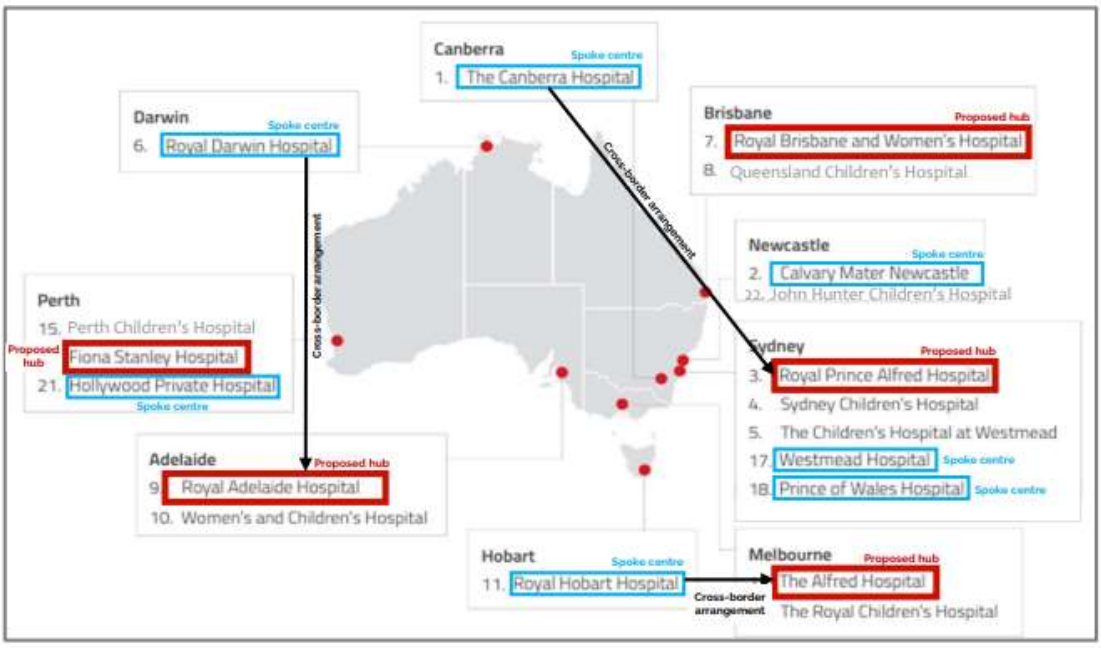

Table 2 Key steps in the proposed model of care

Stage	Description	Hub activity	Spoke activity	Shared activity
Identification	Identification of haemophilia patients that are eligible to undergo gene therapy. This stage includes patient education and initial discussions about risks, benefits, side effects, and the end-to-end treatment process		✓	
Screening	Assessment of relevant clinical factors against eligibility criteria to inform the decision to proceed with gene therapy		✓	
Decision	Patients provide enhanced consent to undergo gene therapy. Clinician approval to treat with gene therapy is facilitated via a Clinician Advisory Group with hub and spoke representatives			✓
Supply	Prescription, ordering, storage, and compounding (if applicable) of gene therapy products	✓		
Administration	Administration of gene therapy to eligible haemophilia patients as a day procedure (with option of overnight stay if clinically indicated or if travel home exceeds 3 hours), including pre-infusion preparations and post-infusion monitoring	✓		
Monitoring	Twelve months of testing (initially on a weekly basis) and monitoring for patients who have received gene therapy, with check-ups at regular intervals thereafter. This stage also includes management of adverse events should they occur		✓	✓*

* Routine patient monitoring will be primarily managed by spoke centres. Should any adverse events arise, a shared care approach between the hub and spoke site will be needed.
Source: AHCDO roadmap to gene therapy (2022)

If applicable, advise which health professionals will be needed to provide the proposed health technology:
Haematologists at hub HTCs will be solely responsible for administering valoctocogene roxaparvovec.

If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:
Not applicable.

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:
As discussed above, haematologists at hub HTCs will be solely responsible for administering valoctocogene roxaparvovec with support provided by haematologists at spoke HTCs in the broader management of these patients.

Is there specific training or qualifications required to provide or deliver the proposed service, and/or any accreditation requirements to support delivery of the health technology?
Yes

Provide details and explain:
Valoctocogene roxaparvovec infusion will be provided at five hub HTCs by highly specialised experts. As discussed above, AHCDO has provided a roadmap for the implementation of gene therapy for haemophilia in Australia (AHCDO 2022). The roadmap also recommends training and accreditation of clinicians and other healthcare professionals at hub centres for the implementation of gene therapy in Australia and it is expected that AHCDO will establish the training and accreditation requirements prior to the introduction of valoctocogene roxaparvovec.

Indicate the proposed setting(s) in which the proposed health technology will be delivered:
☐ Consulting rooms
☐ Day surgery centre
☐ Emergency Department
☐ Inpatient private hospital
☐ Inpatient public hospital
☐ Laboratory
☒ Outpatient clinic
☐ Patient's home
☐ Point of care testing
☐ Residential aged care facility
☐ Other (please specify)

The proposed service will be provided in the outpatient setting at hub HTCs, in public setting.

Is the proposed health technology intended to be entirely rendered inside Australia?
Yes

Please provide additional details on the proposed health technology to be rendered outside of Australia:
Not applicable

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service:

Please provide a name for your comparator:
The nominated comparators to treatment with valoctocogene roxaparvovec are *prophylactic FVIII replacement therapy and emicizumab*.

Please provide an identifying number for your comparator (if applicable):
Not applicable.

Please provide a rationale for why this is a comparator:
Both comparators are currently listed on the NPPL and reimbursed via the NBA for patients with severe haemophilia A.

Current Australian guidelines for the management of haemophilia (AHCDO 2016) recommend treatment based on the severity of disease. For patients with severe haemophilia A, the recommended standard of care for patients is prophylactic FVIII replacement therapy, with the aim of maintaining trough FVIII levels >1% to minimise the number of spontaneous bleeding episodes (Srivastava 2020, Collins 2009). Patients on prophylactic treatment with FVIII therapy typically require intravenous infusions 2-3 times per week to maintain target trough levels.

Emicizumab is funded via the NBA NPPL *"to prevent or reduce the frequency of bleeding episodes in: patients with haemophilia A with inhibitors, and patients with severe (FVIII <1%) or moderate (FVIII 1-4%) haemophilia A without inhibitors"*[1].

On demand FVIII treatment is not recommended for severe patients due to the high risk of bleeds. This is reflected in the utilisation of FVIII products by severity as reported in the Australian blood disorders registry report (2019-2020) in which 88.4% of FVIII product was used for prophylactic treatment in patients with severe disease (Figure 1). While 7.4% of FVIII products were used 'on demand', this utilisation likely reflects treatment of breakthrough bleeds and/or use during surgical procedures consistent with current guidelines. The AHCDO Clinical statement for emicizumab also recognises that a subpopulation of severe patients relies on treatment on demand over prophylactic FVIII therapy due to poor venous access and that the availability of emicizumab through the NBA NPPL, provides the opportunity to move from on demand to prophylactic therapy.

Consequently, it is proposed that prophylactic treatment with FVIII replacement therapy or emicizumab are the appropriate comparators for valoctocogene roxaparvovec.

Prophylactic treatment with FVIII therapy

As shown in Table 3, there are currently five FVIII products listed on the NPPL (effective 1 July 2023), of which four are recombinant imported products (Advate, Adynovate, Eloctate, Xyntha) and one is plasma-derived, domestic product (Biostate). According to the ACDCO (2016) guidelines, recombinant FVIII is the treatment of choice for haemophilia A in Australia.

[1] https://www.ahcdo.org.au/documents/item/475 (accessed 16 February 2023)

Two of the products are extended half-life (EHL) (Eloctate and Adynovate) – and the remaining products are standard half-life (SHL) (Advate and Xyntha). According to the Public Summary Document (PSD) from Application 1511 (July 2018) seeking inclusion of EHL product on the NPPL, "*MSAC concluded from the evidence available that there was little clinically important improvement in patient outcomes between the two types of products, but accepted that EHL products would reduce dosing frequency*" with EHL products recommended for listing on a cost-minimisation basis. In their deliberation, *"MSAC acknowledged that even one less dose per week would be valuable to patients"* (MSAC Application 1511, Public Summary Document, July 2018).

Biostate is the only plasma-derived FVIII available on the NPPL – it is mainly indicated for use as prophylactic treatment with FVIII therapy in patients with von Willebrand disease in addition to haemophilia A. The total usage of the SHL products and Biostate for prophylactic treatment with FVIII therapy in haemophilia A in the 2019-2020 period shows that Biostate only represents 2% of the SHL market. To this end, Biostate is not a relevant prophylactic FVIII product for comparison with valoctocogene roxaparvovec in haemophilia A.

Due to confidential pricing, prices are not known for recombinant FVIII products (see Table 3), with the exception of Biostate, which is not an appropriate comparator product in haemophilia A as discussed above.

Vials of factor concentrates are available in dosages ranging from 250 to 3000 units each. In the absence of an inhibitor, each unit of FVIII per kilogram of body weight infused intravenously will raise the plasma FVIII level by about 2 IU/dL, with the patients' dose calculated by multiplying their weight in kilograms by the factor level in IU/dL desired, multiplied by 0.5 (AHCDO 2016).

For example: 70 kg × 40 (IU/dL level desired) × 0.5 = 1400 units of FVIII

FVIII should be infused by slow intravenous injection at a rate not exceeding 3 ml/minute in adults, according to the Product Information (PI). Subsequent doses of FVIII are based on the half-life of FVIII levels and on the recovery observed in the patient.

A summary of dosing recommendations for prophylactic treatment with FVIII therapy, as per the Australian approved PI for relevant recombinant FVIII products is provided below, showing that SHL products are administered more frequently (3-4 times per week) compared with EHL (twice per week):

- **Advate:** For prevention of bleeding episodes, doses between 20 to 40 IU of factor VIII per kg body weight every other day (3 to 4 times weekly) may be utilised. In some cases, especially in younger patients, shorter dose intervals or higher doses may be necessary.
- **Adynovate:** For long term prophylactic treatment with FVIII therapy, the recommended dose is 40 to 50 IU per kg bodyweight of adynovate twice weekly in 3 to 4-day intervals. Dose and/or frequency should be adjusted to provide the necessary coverage to prevent bleeding. In some cases, doses up to 60 IU per kg may be used.
- **Eloctate:** For individualised prophylactic treatment with FVIII therapy, the recommended regimen is 50 IU/kg every 3-5 days. The dose may be adjusted based on patient response in the range of 25-65 IU/kg. For weekly prophylactic treatment with FVIII therapy, the recommended dose is 65 IU/kg can be used.
- **Xyntha:** For routine prophylactic treatment with FVIII therapy to prevent or reduce the frequency of spontaneous musculoskeletal haemorrhage in patients with haemophilia A, doses of 10 to 50 IU of factor VIII per kg body weight should be given at least twice a week. Xyntha has been administered prophylactically in a pivotal clinical trial in adolescent and adult previously treated patients at a dose of 30 ± 5 IU/kg given 3 times weekly.

Table 3 FVIII products listed on the NPPL, on 1 July 2023

Product Type	Name	Presentation	Supplier	Price
Factor VIII (recombinant - imported) Standard half-life	Advate	250 IU	Takeda Pharmaceuticals Australia	#
		500 IU		
		1000 IU		
		1500 IU		
		2000 IU		
		3000 IU		
Factor VIII (recombinant - imported) Extended half-life	Adynovate	500 IU	Takeda Pharmaceuticals Australia	#
		1000 IU		
		1500 IU		
		2000 IU		
		3000 IU		
Factor VIII (recombinant - imported) Extended half-life	Eloctate	250 IU	Sanofi-Aventis	#
		500 IU		
		1000 IU		
		2000 IU		
		3000 IU		
Factor VIII (plasma-derived - domestic) Standard half-life	Biostate	250 IU	CSL Behring	$256.76*
		500 IU		$513.54*
		1000 IU		$1,027.07*
FVIII (recombinant - imported) Standard half-life	Xyntha	250 IU	Pfizer Australia Pty Ltd	#
		500 IU		
		1000 IU		
		2000 IU		
		3000 IU		

Price not disclosed
*The price does not include the starting plasma provided to CSL Behring by the Australian Red Cross Lifeblood.
Source: https://www.blood.gov.au/national-product-price-list (accessed 10 October 2023)

Prophylactic treatment with emicizumab

Emicizumab is an alternative prophylactic treatment for haemophilia A with a different mechanism of action from FVIII replacement therapy that was listed on the NBA NPPL in November 2020 (refer to AHCDO clinical statement regarding emicizumab[2]). Emicizumab is administered as a subcutaneous (SC) injection, with a loading dose of 3 mg/kg once weekly for 4 weeks, followed by a maintenance dose from Week 5, either:

- 1.5 mg/kg once weekly, or
- 3 mg/kg every two weeks, or
- 6 mg/kg every four weeks

The maintenance dose should be selected based on the physician and patient/caregiver dosing regimen preference to support adherence (Emicizumab Product Information). Although patients treated with emicizumab no longer require prophylactic treatment with FVIII replacement therapy, it is still associated with a significant burden of treatment requiring 1–4 subcutaneous injections per month. Furthermore, on demand FVIII replacement therapy may still be required to treat spontaneous bleeds (Oldenburg, 2017, Mahlangu, 2018).

[2] https://www.ahcdo.org.au/documents/item/475 (accessed 11 October 2023)

According to the most recent NBA annual report (2021-22), the demand for FVIII has decreased by 45.6% since 2019-20 before emicizumab was introduced. Based on the proposed population described above, and current utilisation, emicizumab is therefore considered a secondary comparator to valoctocogene roxaparvovec.

Pattern of substitution – Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator?

☐ None – used with the comparator
☐ Displaced – comparator will likely be used following the proposed technology in some patients
☐ Partial – in some cases, the proposed technology will replace the use of the comparator, but not all
☒ Full – subjects who receive the proposed intervention will not receive the comparator

Please outline and explain the extent to which the current comparator is expected to be substituted:

While the effect of valoctocogene roxaparvovec is maintained, subjects will not receive the comparator interventions (ie, prophylactic treatment with FVIII therapy and emicizumab). The durability of the effect of valoctocogene roxaparvovec will be assessed in the ADAR.

Outcomes

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

The key outcomes for the assessment of valoctocogene roxaparvovec in the proposed population include:

Type	Outcome	Outcome description
Health benefits	Annualised bleeding rate (ABR), including all bleeds, treated bleeds, treated target joint bleeds, treated spontaneous bleeds and treated traumatic bleeds	Valoctocogene roxaparvovec leads to a reduction in annualised bleeding relative to baseline (ie, FVIII)
Health benefits	Proportion of patients with zero bleeding events (treated bleeds, all bleeds)	Valoctocogene roxaparvovec leads to increased proportions of patients with zero bleeds relative to baseline (ie, FVIII)
Health benefits	Change in factor VIII activity (and severity category) over time	Valoctocogene roxaparvovec results in sustained expression of FVIII activity that provides haemostatic control relative to baseline (ie, FVIII)
Health benefits	Quality of life	Valoctocogene roxaparvovec leads to improved quality of life relative to baseline (ie, FVIII)
Health harms	Adverse events including procedural complications	Adverse events which may cause harm to health have been observed with valoctocogene roxaparvovec
Resource utilisation	Change in exogenous FVIII replacement therapy / FVIII infusion rate	Valoctocogene roxaparvovec treatment leads to a reduction in use of FVIII relative to baseline (ie, FVIII)

Additionally, a *post hoc* analyses exploring potential associations between FVIII activity levels during Week 49-52 and baseline or demographic characteristics or post-infusion characteristics will be presented in the ADAR.

Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:
Not applicable as valoctocogene roxaparvovec is not a test.
For outcome description of major and minor health outcomes for valoctocogene roxaparvovec, see table above.

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)?
☒ Superior
☐ Non-inferior
☐ Inferior

Please state what the overall claim is, and provide a rationale:
Valoctocogene roxaparvovec is expected to be associated with superior effectiveness (reduction in bleeds and improved quality of life) and non-inferior safety versus prophylactic treatment with FVIII therapy and emicizumab in patients with severe haemophilia A.

Rationale:
Relative to prophylactic treatment with FVIII therapy and emicizumab, valoctocogene roxaparvovec will reduce mean ABR due to constant FVIII expression and lack of trough related bleeding (Ozelo 2022, Mahlangu 2018). A matching adjusted indirect comparison (MAIC) demonstrated ABR for all bleeds was statistically significantly lower with valoctocogene roxaparvovec than emicizumab, and significantly higher proportions of patients had no treated joint bleeds and no treated bleeds than with emicizumab. Furthermore, valoctocogene roxaparvovec is expected to improve the quality of life of patients with severe haemophilia A compared with treatment with prophylactic treatment with FVIII therapy and emicizumab, given the treatment burden associated with these therapies (FVIII infusions 2–4 times per week; emicizumab subcutaneous injections 1-4 times per month) versus a once-off treatment with valoctocogene roxaparvovec (Krumb 2021).

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?
Not applicable.

Identify how the proposed technology achieves the intended patient outcomes:
Haemophilia A is caused by mutations in the F8 gene which provides instructions for producing the FVIII clotting factor. Because of these mutations, in patients with haemophilia A, either the FVIII protein does not function correctly, or an insufficient amount is produced, which in turn results in delayed blood clotting. The characteristic phenotype in haemophilia is the bleeding tendency with severity of bleeding directly correlated to the level of clotting factor. Following infusion with valoctocogene roxaparvovec, a recombinant F8 gene is delivered preferentially to hepatocytes via the tissue tropism of the AAV5 vector. By delivering a functional F8 gene, FVIII production is restored to an effective level, without peaks and troughs, thereby decreasing the risk of bleeding, and minimising the need for FVIII to treat bleeds. As described above, clinical evidence supports the claim of reduction in bleeding outcomes with valoctocogene roxaparvovec relative to prophylactic treatment of FVIII therapy and emicizumab.

Reducing bleeds relative to prophylactic use of FVIII and emicizumab could in turn be expected to improve a person's quality of life: the patients may be less anxious about having a bleeding

event requiring medical attention or progressing to irreparable joint damage and disability. The patients will also have improved quality of life with valoctocogene roxaparvovec as a direct consequence of reduction in joint damage.

Furthermore, patients receiving a single infusion of valoctocogene roxaparvovec gene therapy would be expected to have a better quality of life compared with prophylactic treatment with FVIII therapy and emicizumab due to reduced treatment burden (FVIII requires intravenous infusions 2–3 times weekly [104–156 infusions/ year]; emicizumab requires 1-4 subcutaneous injections per month [12–48 injections/year]).

For some people, compared with the comparator(s), does the test information result in:

- **A change in clinical management?**
- **A change in health outcome?**
- **Other benefits?**

Not applicable.

Please provide a rationale, and information on other benefits if relevant:
Not applicable.

In terms of the immediate costs of the proposed technology (and immediate cost consequences, such as procedural costs, testing costs etc.), is the proposed technology claimed to be more costly, the same cost or less costly than the comparator?
☒ More costly
☐ Same cost
☐ Less costly

Provide a brief rationale for the claim:
Valoctocogene roxaparvovec is a single administration treatment that is associated with a higher upfront cost however, considering it displaces chronic treatment with the comparators over time, significant cost savings will be anticipated given the reduced FVIII utilisation and need to manage of bleeding events. A cost-effectiveness model will be provided in the ADAR along with the justification for the unit price of valoctocogene roxaparvovec.

Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology.

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
1.	**Study 270-201** NCT02576795 Phase 1 / 2, OL, dose escalation study Follow up to 5 years available Ongoing	Pasi (2021). Persistence of haemostatic response following gene therapy with valoctocogene roxaparvovec in severe haemophilia A.	Participants, male adults with severe HA (FVIII≤1 IU/dL) without pre-existing antibodies to AAV5, and without FVIII inhibitors, were enrolled in one of four cohorts, and received one single IV infusion, at a dose based on body weight (N=15). The primary endpoints were safety and determining the dose of valoctocogene roxaparvovec required to achieve FVIII activity levels ≥5% at Week 16 post-infusion. The results demonstrated the optimal dose of valoctocogene roxaparvovec to be $6x10^{13}$ vg/kg. This dose was subsequently used in the phase III trial, Study 301. The study demonstrated transgene expression and haemostatic response for up to 5 years in individuals with HA and an acceptable safety profile.	https://pubmed.ncbi.nlm.nih.gov/34378280/	2021
2.	**Study 270-301 (GENEr8-1)** NCT03370913 Phase 3, OL, SA 104 weeks follow up available Ongoing	Ozelo 2022 Valoctocogene roxaparvovec gene therapy for haemophilia A	Valoctocogene roxaparvovec was administered at a dose of $6x10^{13}$ vg/kg (n=134) to male adults with severe HA (FVIII≤1 IU/dL) who have been on prophylactic FVIII for ≥ 1 year; without a history of FVIII inhibitors and without AAV5 antibodies. The reduction from baseline in bleeding episodes demonstrated a marked clinical benefit of valoctocogene roxaparvovec. The majority (88%) of ITT subjects responded to treatment through 52 weeks post treatment. Valoctocogene roxaparvovec was able to significantly reduce ABR by 85% with a total reduction of 4.48 (10.36) (median –1.77) bleeding episodes/year (p-value <0.0001). Analyses of FVIII activity levels over 52 weeks indicated successful endogenous FVIII production. Treatment with valoctocogene roxaparvovec resulted in significant and clinically meaningful improvements in QoL as assessed by the Haemo-QoL-A and the EQ-5D-5L at 52 weeks relative to baseline. Single infusions of 6 $x10^{13}$ vg/kg have been generally well tolerated with an acceptable safety profile.	https://pubmed.ncbi.nlm.nih.gov/35294811/	2022
		Mahlangu 2023	The two year follow up of the GENEr8-1 study showed durability of effect, with the mean annualised treated bleeding rate decreased by 84.5% from baseline (P<0.001) among the participants. At 2 years post-infusion, no new safety signals had occurred and no new serious adverse events related to treatment had emerged.	https://www.nejm.org/doi/10.1056/NEJMoa2211075	2023

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
3.	**Study 270-902** Natural history study, non-interventional 6 months follow up	Kenet 2021 Real-World Rates of Bleeding, Factor VIII Use, and Quality of Life in Individuals with Severe Haemophilia A Receiving Prophylaxis in a Prospective, Noninterventional Study	The study reports real-world data from a global cohort on regular prophylactic therapy FVIII therapy in individuals with severe HA (N=293). In the AAV5 negative cohort (n=193) the median ABR bleeds per year for treated bleeds was 2.39. For the AAV5 negative cohort (n=196), mean (SD) annualised FVIII utilisation during the baseline period was 3908.10 (1797.87) IU/kg/year (median 3582.71), compared with 3942.87 (1738.53) IU/kg/year (median 3746.28) during the on-study period [data from AAV5 negative cohort on file, CSR]. This real-world study illustrates the limitations of FVIII prophylaxis in individuals with severe HA. Patients with AAV5 negative status from this study could enrol in Study 301.	https://pubmed.ncbi.nlm.nih.gov/34945255/	2021
5	**270-814** Retrospective, comparative, MAIC	Astermark 2023 Matching-adjusted indirect comparison of bleeding outcomes in severe haemophilia A: Comparing valoctocogene roxaparvovec gene therapy, emicizumab prophylaxis, and FVIII replacement prophylaxis	This study is a retrospective unanchored, indirect comparison of valoctocogene roxaparvovec and emicizumab prophylaxis, that utilised IPD from the ongoing phase III clinical trial 270-301 along with aggregate publicly available data from HAVEN 3 for emicizumab (Mahlangu 2018). MAIC methods were used to adjust for between-trial imbalances between the study cohorts based on the distribution of reported subject characteristics (i.e., covariates). After MAIC weighting, ABR for all bleeds was statistically significantly lower with valoctocogene roxaparvovec than emicizumab (RR 0.55 [95% CI: 0.33–0.93]), and statistically significantly higher proportions of participants had no treated joint bleeds and no treated bleeds with valoctocogene roxaparvovec relative to emicizumab.	https://onlinelibrary.wiley.com/doi/full/10.1111/hae.14818	2023

AAV5, Adeno-Associated Virus Type 5; ABR, Annualised bleeding rate; FVIII, exogenous factor VIII; HA, haemophilia A; OL, open label; SA, single arm; SD, standard deviation;

Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your application). Do not attach full text articles; this is just a summary.

	Type of study design	Title of research (including any trial identifier if relevant)	Short description of research (max 50 words)	Website link to research (if available)	Date
1.	**270-303** GENEr8-3 / NCT04323098 Phase 3b, SA, OL	Study to evaluate the efficacy and safety of valoctocogene roxaparvovec, with prophylactic steroids in Haemophilia A (GENEr8-3)	This study aims to evaluate the efficacy and safety of valoctocogene roxaparvovec, with prophylactic steroids in HA in an expected sample of 22 patients.	NA	Estimated completion date: January 2027
2.	**270-205** NCT04684940 Phase 1 / 2, SA, OL	Safety, tolerability, and efficacy study of valoctocogene roxaparvovec in haemophilia A with active or prior inhibitors	This Phase I/II clinical study aims to evaluate the safety and efficacy of valoctocogene roxaparvovec in patients with severe HA and inhibitors to FVIII. Part A of the study will involve subjects who have active inhibitors to FVIII, and Part B involve subjects with a prior history of inhibitors. Expected sample of 20 patients.	NA	Estimated completion date: February 2029
3.	**270-203** NCT03520712 Phase 1 / 2, SA, OL	Gene Therapy Study in Severe A Patients with Antibodies Against AAV5 (270-203)	This study aims to determine the safety of valoctocogene roxaparvovec in severe HA patients with pre-existing antibodies against AAV5.	NA	Estimated completion date: November 2027
4	**270-804** Retrospective, comparative, PSMA	Protocol Title: Comparative effectiveness of valoctocogene roxaparvovec and prophylactic Factor VIII replacement using data from 270-301 and 270-902: application of propensity score methodologies	IPD from 270-301 and 270-902 will be utilised to construct a PSMA, comparing valoctocogene roxaparvovec with FVIII. Cohorts will be compared for ABR and proportion patients with zero bleeds, with a follow up of 12 months.	NA	Estimated completion date: 2023

AAV5, Adeno-Associated Virus Type 5; ABR, annualised bleeding rate; FVIII, exogenous factor VIII; HA, haemophilia A; IPD, individual patient data; OL, open label; MAIC, matched adjusted indirect comparison; PSMA, propensity score matched analysis; SA, single arm.

Algorithms

Preparation for using the health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:
The clinical management algorithm of patients with severe haemophilia A, including required tests to determine eligibility for valoctocogene roxaparvovec is provided in Figure 4

The following will occur prior to treatment with valoctocogene roxaparvovec:

- Diagnosis of haemophilia A established based on clinical history, family history of bleeding and confirmed by a blood test for coagulant FVIII and genetic testing via the HTC.
- The severity of haemophilia A is assessed.
- Patient assessed for history of inhibitors to FVIII
- Patient assessed for active hepatitis or severe liver status.
- Patients assessed for AAV5 antibody status via the AAV5 DetectCDx™ test (see AAV5 PICO set).

According to local experts[3], a process of shared decision making for gene therapy with valoctocogene roxaparvovec will take place, from early discussion to infusion, as part of an existing comprehensive care model.

Following these assessments, patients diagnosed with severe haemophilia A, who do not have a history of inhibitors, who do not have active hepatitis or severe liver disease, and are otherwise considered suitable candidates for treatment with valoctocogene roxaparvovec by their treating physicians, will undergo AAV5 antibody testing to confirm eligibility.

Patients without detectable AAV5 antibodies will be eligible for treatment with valoctocogene roxaparvovec. It is expected that the majority of tested patients without detectable AAV5 antibodies will receive valoctocogene roxaparvovec. Patients with AAV5 antibodies will continue prophylactic treatment with FVIII replacement therapy or emicizumab.

It is expected that all patients with severe haemophilia A at the time of eligibility for valoctocogene roxaparvovec would have received prior prophylactic treatment.

Is there any expectation that the clinical management algorithm before the health technology is used will change due to the introduction of the proposed health technology?
Yes

The main difference in the algorithm with the introduction of the proposed health technology is the need for testing of AAV5 antibody status. This is not a requirement for access to FVIII and emicizumab as per the current management algorithm of patients with severe haemophilia A without inhibitors (Figure 3).

[redacted] *Note. The AAV5 test is not available in Australia as it was assessed as unviable to set up testing of AAV5 in Australia given the small patient numbers and highly specialised nature of the test* (refer to the AAV5 PICO set).

[3] Five experts were consulted, including four from HTCs (NSW, QLD, VIC, WA) and one from a spoke centre (ACT).

Additionally, active hepatitis or severe liver disease need to be ruled out prior to patients being eligible for valoctocogene roxaparvovec; this is not a necessary requirement for the current management of patients with haemophilia A.

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:
As detailed above, the main difference in terms of the clinical management algorithm prior to the use of the proposed health technology vs the comparator health technology is the requirement to test AAV5 antibody status to assess eligibility for valoctocogene roxaparvovec and the assessment of hepatitis and liver function.

Use of the health technology

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:
No other healthcare resources are used. The infusion will take place at the HTC, with no additional costs incurred in administering the treatment (ie covered within the operation of the HTC).

Explain what other healthcare resources are used in conjunction with the comparator health technology:
No other healthcare resources are used. Initiation of prophylactic treatment with FVIII therapy and emicizumab take place at the HTC (ie covered within the operation of the HTC).

Describe and explain any differences in the healthcare resources used in conjunction with the proposed health technology vs. the comparator health technology:
Not applicable.

Clinical management after the use of health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the proposed health technology:
and

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, *after* the use of the comparator health technology:
and

Describe and explain any differences in the healthcare resources used *after* the proposed health technology vs. the comparator health technology:
Overall, monitoring after the use of the proposed intervention, valoctocogene roxaparvovec, and the comparators, prophylactic treatment with FVIII therapy and emicizumab, will differ for the first 12 months, and will be similar thereafter.

According to local expert advice and in line with the Summary of Product Characteristics (SmPC) awarded by the European Medicines Agency, the monitoring requirements for the proposed intervention and its comparators for the first 12 months are as follows:

- Valoctocogene roxaparvovec: weekly liver function tests (LFTs) for 6 months; then LFTs every 2–4 weeks until 12 months; FVIII levels are assessed as needed.
- Emicizumab: Patients are assessed at week 1, week 5, at 3 months, at 6 months and then yearly after that.
- Prophylactic FVIII replacement therapy: similar to emicizumab.

Algorithms

Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology:

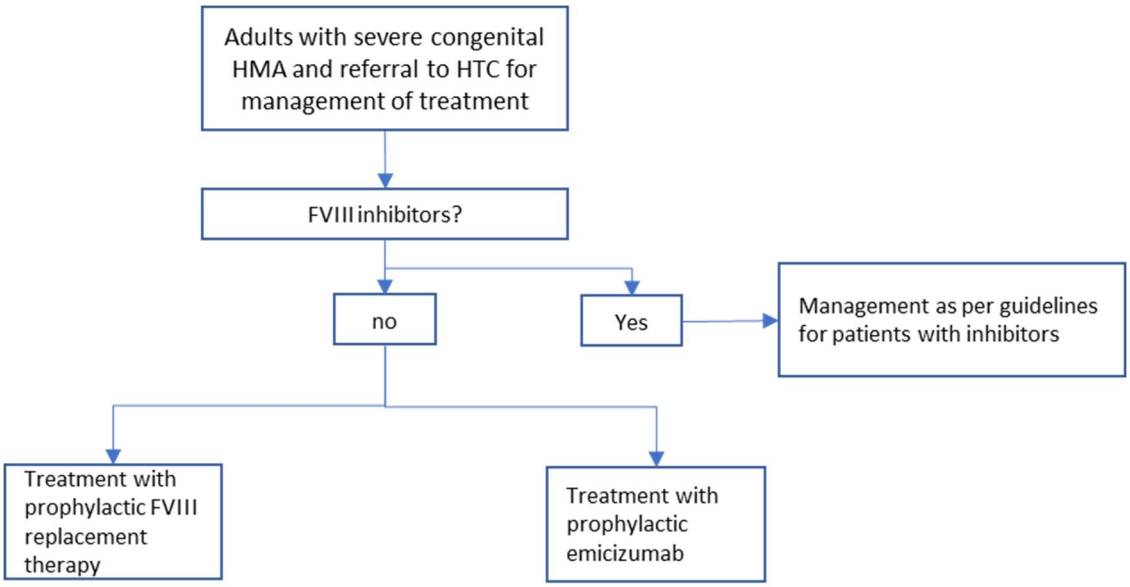

Figure 3 Current clinical management algorithm for patients with severe haemophilia A without inhibitors

Source: Simplified and adapted from emicizumab MSAC Application 1579 Public Summary Document (PSD)

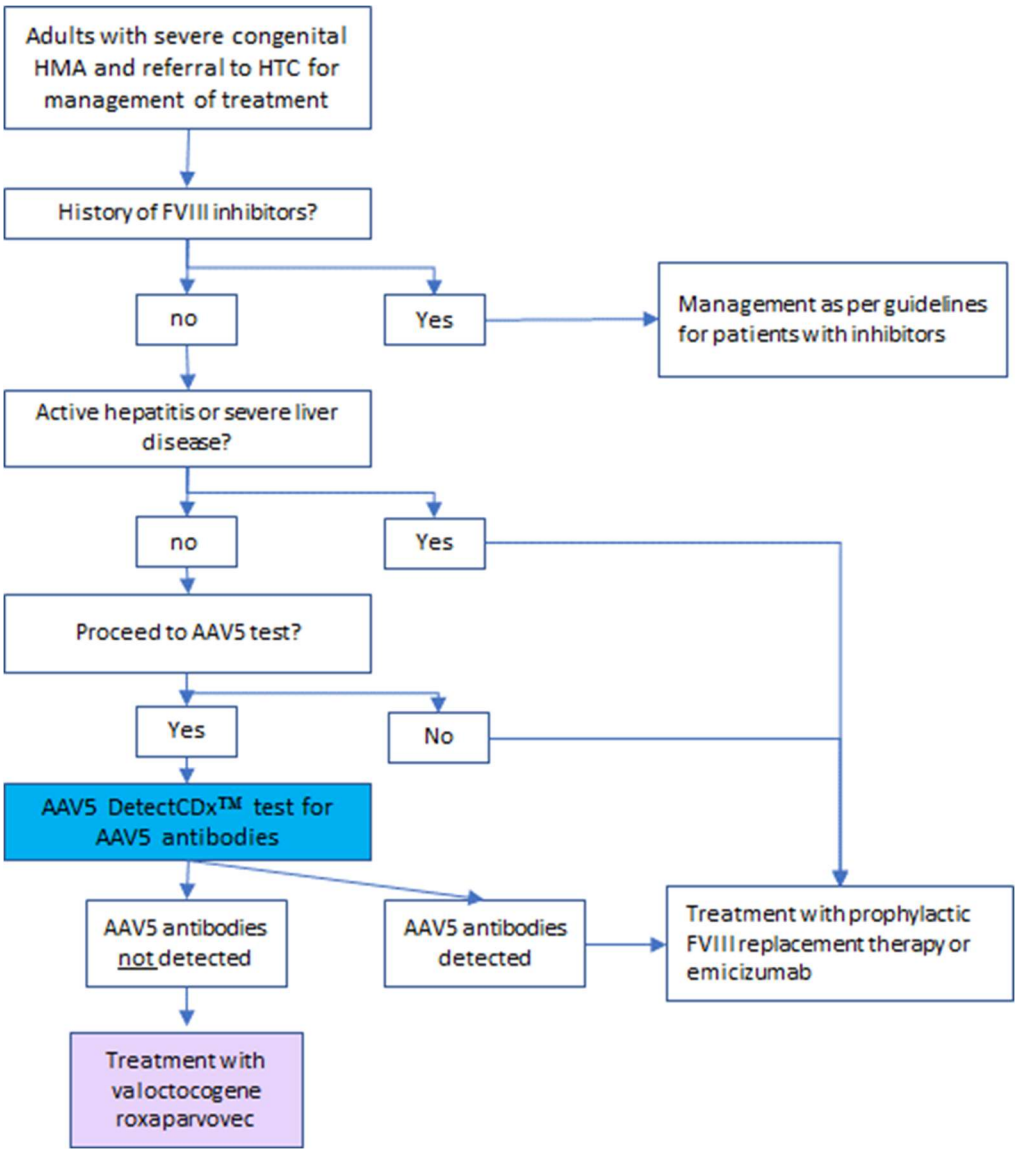

Figure 4 Proposed clinical algorithm with the introduction of valoctocogene roxaparvovec in the management of patients with severe haemophilia A

HA, haemophilia A; AAV5, adeno-associated virus serotype 5