

MSAC Application 1728

**Etranacogene dezaparvovec for the treatment
of congenital haemophilia B**

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 etranacogene dezaparvec for the treatment of congenital haemophilia B (cHMB)

Component	Description
Population	<p>Adult patients (≥ 18 years) with severe cHMB or moderately severe cHMB defined as:</p> <ul style="list-style-type: none"> severe cHMB: FIX activity $< 1\%$; FIX concentration < 0.01 IU/mL subgroup of patients with moderate cHMB, defined as moderately severe disease: FIX activity $1-2\%$; FIX concentration < 0.02 IU/mL <p>who also meet the following criteria:</p> <ul style="list-style-type: none"> anti-AAV5 neutralising antibody titre $< 1:700$ no inhibitor formation against expressed FIX protein
Intervention	Etranacogene dezaparvec (HEMGENIX®)†
Comparator/s	Standard of care for cHMB with no gene therapy
Outcomes	<p>Outcome measures to be considered for inclusion:</p> <p><u>Efficacy/effectiveness outcomes:</u></p> <ul style="list-style-type: none"> annualised bleed rates (overall, categorised bleed severity, and site/type specific) over time endogenous FIX activity concentration and trough FIX activity over time Change in patient disease categorisation over time Fix utilisation occurrence and resolution of target joint bleeding central venous access no longer required events of central venous access-related sepsis or thrombosis <p><u>Safety outcomes:</u></p> <ul style="list-style-type: none"> acute peri-infusion adverse effects long-term adverse events (e.g. thrombosis, hepatitis, hepatocellular carcinoma) laboratory indicators of safety (e.g. coagulation, inflammatory markers, serology, haematology) formation of post-infusion FIX inhibitors formation of anti-AAV5 NABs in relation to suboptimal therapeutic effect or intervention failure <p><u>HRQoL outcomes:</u></p> <ul style="list-style-type: none"> EQ-5D-5L SF-36 HWBI HAEMO-QoL-A PROBE questionnaire HAL FISH

Component	Description
	<p data-bbox="379 159 740 192"><u>Healthcare system outcomes:</u></p> <ul data-bbox="427 197 1318 304" style="list-style-type: none"> <li data-bbox="427 197 1230 230">• costs associated with intervention and comparator treatments <li data-bbox="427 235 1318 304">• costs associated with adverse events for intervention and comparator treatments
Assessment questions	What is the comparative safety, comparative effectiveness, cost-effectiveness and total costs of etranacogene dezaparvovec (HEMGENIX®) versus standard of care with no gene therapy in adult patients (≥18 years) with severe or moderately severe cHMB?

Abbreviations: **AAV5** = adeno-associated virus 5; **anti-AAV5 NAb**s = anti-adeno-associated virus 5 neutralising antibodies; **cHMB** = congenital haemophilia B; **EQ-5D-5L** = EuroQol 5-dimension health-related quality of life questionnaire–5 levels; **FISH** = functional independence score in haemophilia; **FIX** = factor IX; **HAEMO-QoL-A** = haemophilia-specific quality of life questionnaire for adults; **HAL** = haemophilia activities list; **HRQoL** = health-related quality of life; **HWBI** = haemophilia wellbeing index; **IU** = international units; **PROBE** = patient reported outcomes, burdens and experiences; **PROMS** = patient-reported outcome measures; **SF-36** = 36-item short form health survey

Note: † Eligible patients allowed to receive a single course of treatment per lifetime.

Purpose of application

An application requesting public funding of Hemgenix (etranacogene dezaparvovec [HEMGENIX®]) for congenital haemophilia B (cHMB) was received from CSL Behring (Australia) Pty Ltd by the Department of Health and Aged Care.

Public funding for blood and blood-related products is facilitated via the National Blood Agreement and managed by the National Blood Authority (NBA) on behalf of all governments (Applicant 2023c). Schedule 4 of the Agreement provides for evidence-based evaluation and advice to governments to support decisions regarding changes to products funded under the national blood arrangements, including assessment by the MSAC where required (Applicant 2023c). A Schedule 4 proposal for funding was submitted to the NBA on 30 June 2022 (Applicant 2023c).

Under the Agreement, the Jurisdictional Blood Committee (JBC) provides advice to all Health Ministers on which products should be included on the National Products Price List (NPPL) (Applicant 2023c). This is typically based on a Cycle 1 Multi Criteria Assessment (MCA) which provides a description of the proposal, followed by an outline of the PICO, and a high-level literature review. JBC may also refer the submission to MSAC for an evidence-based health technology assessment of clinical effectiveness, cost-effectiveness and safety (Applicant 2023c).

Following submission of the Schedule 4 to the NBA, an MSAC application form was lodged by the applicant to initiate PICO development in parallel to the Schedule 4 assessment (Applicant 2023c).

The applicant claims (Applicant 2023c) that compared to standard of care with no gene therapy, the proposed intervention (Hemgenix) has:

- superior efficacy outcomes: annualised bleed rates (overall, categorised bleed severity, and site/type specific) over time, Reduction in FIX utilisation
- endogenous FIX activity concentration and trough FIX activity over time, occurrence and resolution of target joint bleeding, central venous access no longer required, events of central venous access-related sepsis or thrombosis
- non-inferior and acceptable safety outcomes: acute peri-infusion adverse effects, long-term adverse events (e.g. thrombosis, hepatitis, hepatocellular carcinoma), laboratory indicators of safety (e.g. coagulation, inflammatory markers, serology, haematology), formation of post-infusion FIX inhibitors and formation of anti-AAV5 NAb in relation to suboptimal therapeutic effect or intervention failure
- superior health-related quality of life (HRQoL) outcomes: EQ-5D-5L (EuroQol 5-dimension health-related quality of life questionnaire–5 levels), SF-36 (36-item short form health survey), HWBI (haemophilia wellbeing index), HAEMO-QoL-A (haemophilia-specific QoL questionnaire for adults), PROBE (patient reported outcomes, burdens and experiences) questionnaire, HAL (haemophilia activities list), FISH (functional independence score in haemophilia).

PICO criteria

Population

Disease characteristics

Congenital haemophilia is a rare bleeding disorder caused by deficiencies in coagulation factors as a result of mutations in clotting factor genes (Srivastava et al. 2020). There are 2 main types of congenital haemophilia, with type A (HMA) accounting for 80–85% of the total prevalent population and type B (HMB) around 15% (Srivastava et al. 2020). A much rarer form known as type C is estimated to occur in less than 5% of cases. Congenital HMB (cHMB) is characterised by partial or complete deficiency in the activity of essential coagulation factor IX (FIX) due to X-linked heritable variants of the *HMB* gene. It occurs primarily in males, with females typically being carriers with a mild or absent phenotype.

Acquired HMB, due to the formation of anti-FIX antibodies occurring in an individual without cHMB, is out of scope of this application.

Most bleeding occurs internally, with intra-articular, intramuscular, intracerebral and mucocutaneous bleeds considered severe (AHCDO & NBA 2016). Repeated bleeding, especially joint bleeds (haemarthrosis), is a major cause of significant morbidity and decreased quality of life (QoL) in people living with HMB (AHCDO & NBA 2016). Although infrequent, intracranial and gastrointestinal bleeding, and bleeding into the neck and throat, can be life-threatening (AHCDO & NBA 2016). For patients with cHMB, bleeding tendency correlates with FIX concentrations, so cHMB-associated severity and risk of bleeding is classified according to endogenous plasma FIX concentrations. FIX concentrations <1% is classified as severe disease, 1–5% is moderate disease and >5–40% is mild disease (Srivastava et al. 2020). However, individuals may exhibit severe bleeding irrespective of FIX concentrations and require use of FIX for ongoing prophylaxis. It should also be noted that a subgroup of patients in the moderate severity categories has been specifically defined for the purpose of this PICO. Patients who have FIX concentrations between 1–2% (<0.02 IU/mL) are considered as “moderately severe”, and this is a definition which is used in clinical trials (ClinicalTrials.gov 2022b). Besides the FIX concentrations, patients with moderately severe cHMB experience frequent spontaneous bleeding, and their bleeding management may require more aggressive and intensive treatments. Table 2 shows the classification of cHMB according to clinical severity, based on FIX clotting activity, symptoms and usual age of diagnosis.

Table 2 Classification of congenital haemophilia B

Clinical severity	FIX clotting activity	Symptoms	Usual age of diagnosis
Severe	<1% (<0.01 IU/mL)	Frequent spontaneous bleeding	Age ≤2 years
Moderately severe	1–≤2% (<0.02 IU/mL)	Excessive and/or prolonged bleeding after minor injuries, surgery or tooth extractions, <i>used in the HOPE-B trial*</i>	
Moderate	1–5% (0.01–0.05 IU/mL)	Rare spontaneous bleeding Excessive and/or prolonged bleeding after minor injuries, surgery or tooth extractions	Age <5-6 years
Mild	>5–<40% (>0.05–0.4 IU/mL)	No spontaneous bleeding Excessive and/or prolonged bleeding after major injuries, surgery or tooth extractions	Often later in life, depending on haemostasis challenges

Abbreviations: FIX = factor IX; IU = international units

Notes: * = Not part of historical haemophilia categorisation but was used as an inclusion criterion in the HOPE-B trial (ClinicalTrials.gov 2022b).

Sources: ClinicalTrials.gov (2022b); Konkle and Nakaya Fletcher (1993); Srivastava et al. (2020)

Prevalence

cHMB is a rare disease. In 2021, the World Federation of Haemophilia estimated the total number of patients with cHMB to be 37,998 worldwide (World Federation of Hemophilia 2021). The global prevalence is estimated to be 3.8/100,000 males, with 1.1/100,000 males categorised with severe disease (World Federation of Hemophilia 2021).

According to the Australian Bleeding Disorders Registry (ABDR), in 2020–2021 the national prevalence of cHMB was 601 individuals, of whom 129 had moderate disease and 111 had severe disease (NBA 2021).

Treatment and management

The mainstay of treatment for cHMB consists of intravenous (IV) FIX replacement therapy, using either plasma-derived or recombinant factor concentrates administered on demand when bleeds occur or prophylactically as regular ongoing infusions (AHCDO & NBA 2016). Optimal management is highly nuanced and patient specific. Local and international clinical guidelines summarise a constantly evolving treatment landscape and evidence base (AHCDO & NBA 2016; Srivastava et al. 2020). In Australia, most people living with cHMB receive care via a dedicated haemophilia treatment centre (HTC), typically located within a hospital (Haemophilia Foundation Australia 2023). HTCs comprise a team of specialist health professionals (haematologists, nurses, psychosocial workers, physiotherapists, laboratory services etc.) with expertise in managing and treating cHMB to ensure that all care needs are met (Haemophilia Foundation Australia 2023).

Guidelines recommended that patients with severe cHMB, or moderate cHMB with a severe phenotype, should receive routine prophylaxis with recombinant FIX concentrate, preferably using an extended half-life (EHL) formulation (AHCDO & NBA 2016). Over the last 30 years, recombinant products (e.g. BeneFIX) have largely replaced plasma-derived FIX replacement products (e.g. MonoFIX) (NBA 2023). For routine prophylaxis, EHL products such as ALPROLIX (administered weekly or every 10 days) have become increasingly common in the last 5 years (NBA 2023). For on-demand treatment when a bleed occurs, the initial dose of ALPROLIX for a minor/moderate (30-60 IU/kg) and major (100 IU/kg) bleeds with repeat dosing and duration depending on individual clinical response, severity of FIX deficiency, location/extent of bleeding and pharmacokinetic profile (Sanofi 2021). Although the introduction of EHL products has decreased the total number of injections, FIX replacement injections are still frequent and lifelong, potentially leading to poor venous access, blood clots, inflammation and secondary infections (Srivastava et al. 2020).

Treatment complexity and pain associated with FIX injections (e.g. via a Portacath) can result in poor adherence, leading to poor clinical outcomes. It is estimated that more than a quarter of people living with cHMB in Australia are not optimally adherent to treatment (Brennan et al. 2020; Srivastava et al. 2020). Poor adherence to prophylaxis may be especially dangerous, as missing an infusion can cause clotting factor levels to fall below the individual protective trough level, causing an increased risk of bleeding (Srivastava et al. 2020). Between infusion periods, patients are at high risk of breakthrough, spontaneous bleeding (Srivastava et al. 2020). Long term, treatment burden combined with the negative effects of haemophilia can interfere with education, employment and productivity at work. cHMB is also associated with a substantial use of non-FIX treatment healthcare resources, including physician visits, outpatient visits, emergency room visits and hospitalisations due to spontaneous bleeds or traumatic bleeds from surgery.

Current unmet needs for cHMB include treatments that provide long-term bleeding control without risk of inhibitor development, and those that eliminate the burden of frequent injections and improve QoL. Severe cHMB patients or moderate cHMB patients with high frequency of spontaneous bleeding events

experience chronic pain, with most reporting that haemophilia impacts their daily lives (AHCDO & NBA 2016). Physical limitations caused by cHMB can make it difficult for patients to participate in social activities, leading to substantial effects on mental wellbeing, particularly among younger people living with the condition (AHCDO & NBA 2016). Currently available treatment options cannot deliver sufficiently high sustained FIX concentrations to provide protection from bleeds and resolve these issues. The peak and trough nature of treatments and the need for regular IV infusions are major limitations of the current therapy. New treatments are needed to improve patient and clinical outcomes and reduce or prevent progression of the disease, ultimately improving the humanistic and economic burdens of cHMB. This gap in the treatment landscape combined with advancements in medical technology generated the development of novel gene therapies to provide a potential improvement for cHMB management.

Patient eligibility for the proposed intervention

Adult patients with cHMB (≥ 18 years) classified as having FIX activity and FIX concentration of severe cHMB ($< 1\%$; < 0.01 IU/mL) or moderately severe cHMB ($1\text{--}2\%$; < 0.02 IU/mL) may be eligible for Hemgenix (Konkle & Nakaya Fletcher 1993; Thornburg 2021). Of these, only patients with anti-AAV5 NAb titre $< 1:700$ and who have not formed inhibitors against the FIX protein will be eligible for treatment (Applicant 2023c, 2023e).

The test for determining the level of inhibitors against FIX protein is carried out for some patients with severe cHMB, and those patients with evidence of emergent FIX ineffectiveness (Miller 2018). For FIX inhibitor detection, clot-based functional assays and antibody detection assays (enzyme-linked immunosorbent assay; ELISA) are most commonly used (Miller 2018). While continuing improvement of these tests are ongoing, these tests are validated testing methods and widely used in laboratories to help patients and clinicians to understand the FIX inhibitor levels.

In comparison, the detection of anti-AAV5 NAb for the proposed gene therapy is more complex. Due to the existing neutralising antibodies, patients would be less likely to benefit from the gene therapy. Therefore, it is important to accurately assess whether patients with cHMB have pre-existing anti-AAV5 NAb before commencing Hemgenix. Reviews and analyses of the test performance data on the anti-AAV5 NAb assays are limited in the existing literature due to the assay novelty. However, a recent available FDA clinical review memo reported that the assay used in the Hemgenix clinical trial was “neither valid nor reliable” (FDA 2022). Also, the HOPE-B study (Pipe et al. 2020) reported that 21 out of 54 subjects were positive for anti-AAV5 NAb (also confirmed by the response from the applicant), and the subject with high NAb did not express the transgene and continued to have multiple bleeding events after the treatment (Applicant 2023b). Information surrounding the status of the FDA application for the anti-AAV5 NAb assay specific for Hemgenix is not available. To date, one clinical laboratory has published a media release regarding the FDA approval of a non-Hemgenix anti-AAV5 NAb assay (ARUP Laboratories 2020). The $< 1:700$ titre threshold for pre-existing NAb was selected based on results obtained in the HOPE-B study, where $1:678$ was the second highest titre whilst also being effective up to this level (Applicant 2023d; Pipe et al. 2023). No response was observed in the highest titre of $1:3212$ (Applicant 2023d; Pipe et al. 2023). Further information and discussion are provided below in the intervention section.

Clinical evidence is only available for Hemgenix in patients ≥ 18 years; **REDACTED**.

In adult patients with cHMB, the objective of Hemgenix therapy is to enable FIX production at a level high enough to allow for discontinuation of routine prophylactic FIX replacement therapy and to greatly reduce the need for on-demand FIX therapy (Thornburg 2021). Therefore, those who have been receiving a stable dose of regular FIX prophylaxis and have not formed inhibitors to FIX replacement therapy may be eligible for treatment (Applicant 2023c).

PASC noted the application specified that the proposed eligible patient population for Hemgenix will include adult cHMB patients ≥ 18 years **REDACTED**. PASC questioned whether it is possible that a different age threshold related to developmental stage rather than the standard ≥ 18 years (i.e. adults) may be appropriate. This query will need to be addressed when MSAC Application 1728 is progressed to the Applicant Developed Assessment Report (ADAR) phase.

PASC noted the application stated that the proposed eligible patient population for Hemgenix will include cHMB patients with no inhibitor formation against expressed FIX protein. PASC questioned whether the population inclusion criteria of 'no inhibitor formation against expressed FIX protein' needs to be more clearly defined in terms of test results. This query will need to be addressed when MSAC Application 1728 is progressed to the ADAR phase.

PASC noted that the proposed eligible patient population for Hemgenix will include cHMB patients with an anti-AAV5 NAb titre of $< 1:700$. PASC noted that pre-existing anti-AAV5 NAb may compromise the effectiveness of Hemgenix and that the applicant pre-PASC response stated that in the HOPE-B trial, 21 of the 54 patients were positive for anti-AAV5 NAb (titre range: 1:8.7 – 1:3,212). The short-term and long-term pharmacodynamic response according to pre-exposure anti-AAV5 titre from these 54 patients, and FDA-mandated post-market study, should be reported in a future submission. One patient with an anti-AAV5 NAb titre of 1:3,212 received Hemgenix but did not express the transgene and continued to have bleeding events. **REDACTED**. PASC noted the FDA approved Hemgenix product label stating that "Currently, there is no validated neutralizing anti-AAV5 antibody assay.", and was supportive of the department's policy position that the anti-AAV5 NAb test is an essential codependent test related to Hemgenix and the importance of onshore anti-AAV5 NAb testing to allow for regulatory oversight. PASC also questioned whether the AAV5 NAb threshold may be amended as further data becomes available.

REDACTED. PASC noted that should CSL Behring choose not to proceed with a codependent application, MSAC Application 1728 as it stands will not be able to progress to an ADAR assessment.

PASC noted that ongoing clinical trials of Hemgenix exclude cHMB patients with active hepatitis infection, severe liver or lung disease and uncontrolled human immunodeficiency virus (HIV). PASC questioned whether it would be appropriate to also specify these exclusion criteria in the population description. The applicant clarified that in some cases patients with well-controlled HIV were allowed to participate in the studies. The other exclusion criteria will need to be addressed when MSAC Application 1728 is progressed to the ADAR phase.

PASC considered whether the current eligibility criteria based on FIX activity sufficiently reflects clinical disease severity and FIX utilisation as there is variability in clinical presentation due to other disease modifiers. Some patients categorised as having moderate haemophilia with FIX activity between 2-5% require prophylaxis treatment and therefore may benefit from Hemgenix but are not eligible under the proposed descriptor. PASC suggested that eligibility thresholds could be explored in a sensitivity analysis in the assessment.

Intervention

Description of the intervention

Etranacogene dezaparvovec (proprietary product HEMGENIX® [Hemgenix] manufactured by CSL Behring, also known as AMT-061, CSL222 or EtranaDez) is a gene therapy infusion treatment designed to introduce a copy of the human FIX gene to address the lack of functional FIX protein expression in a patient with cHMB (CSL Behring LLC 2022; Thornburg 2021). The infusion consists of a recombinant adeno-associated

virus 5 (AAV5) vector that includes a gene cassette containing the FIX Padua variant under the control of a liver-specific promoter (CSL Behring LLC 2022; Thornburg 2021). The FIX Padua variant is a hyperactive transgene associated with elevated FIX concentrations and activates FIX at a faster rate than endogenous FIX (Thornburg 2021). Provided as a sterile solution in 10 mL glass vials at a concentration of approximately 1×10^{13} genome copies per millilitre (gc/mL), Hemgenix is administered as a single-dose IV infusion into a peripheral vein (CSL Behring LLC 2022).

After infusion, Hemgenix preferentially targets liver cells, where vector DNA is released into the nucleus, instructing the cell to produce FIX (CSL Behring LLC 2022; Thornburg 2021). Following transduction, functional FIX is produced at near-normal to normal levels that circulate in the body, reducing the risk of bleeding (CSL Behring LLC 2022; Thornburg 2021). As Hemgenix delivers a functional gene that acts as a blueprint for FIX, the treatment is offered as a one-off infusion with effects anticipated to last a lifetime.

Four published or ongoing clinical trials have investigated the use of Hemgenix for cHMB. One phase I/II trial (NCT02396342) has been completed with results posted (ClinicalTrials.gov 2022a; Miesbach et al. 2018). An extension of this trial is currently ongoing, estimated for completion in May 2026 (NCT05360706) (ClinicalTrials.gov 2023b). One phase IIb trial (CT-AMT-061-01; NCT03489291) has published interim 26-week results and will be completed in September 2023 (ClinicalTrials.gov 2023a; Von Drygalski et al. 2019). The phase III trial HOPE-B (NCT03569891) is also ongoing, with estimated study completion in March 2025 (ClinicalTrials.gov 2022b). This trial has resulted in a number of published abstracts, but peer-reviewed publications are unavailable as yet (Miesbach et al. 2022; Pipe et al. 2020).

The applicant (CSL Behring) submitted an application to the Therapeutic Goods Administration (TGA) on 24 February with the proposed indication as follows (Applicant 2023a):

REDACTED

Delivery of proposed medical service

People living with cHMB are managed within Australia's network of specialist HTC, which deliver a model of comprehensive care to ensure the needs of haemophilia patients are met (Haemophilia Foundation Australia 2023). Prevention and treatment are provided in a coordinated way by a multidisciplinary team with specialised expertise (Haemophilia Foundation Australia 2023). The complex provision of care frequently differs from patient to patient, meaning a single clinical pathway cannot be followed (Applicant 2023c).

The first step in delivering Hemgenix requires establishing patient eligibility and suitability for treatment. This involves a combination of clinical and laboratory assessments including age, gender, clinical severity/FIX activity level and previous exposure to FIX replacement therapy (ClinicalTrials.gov 2022a, 2022b, 2023a, 2023b). Assessment of anti-AAV5 NAb status would be an additional step to current clinical care for this population (Applicant 2023c, 2023e). It is proposed that those with anti-AAV5 NAb titre $<1:700$ will be eligible for treatment with Hemgenix (Applicant 2023c, 2023e). **REDACTED**. In late February 2023, a media release has reported that a specific premarket approval of total antibody assay for AAV5-based gene therapy has been filed by FDA (Cision PR Newswire 2020). However, this test is the companion diagnostic assay for a specific gene therapy for severe HMA (Cision PR Newswire 2020). This information has not been verified through official FDA channels, possibly due to the documentations yet to be made available for public access. The applicant did not specify whether the assay will be conducted using kits available in the market (e.g. the aforementioned assay, non-specific for Hemgenix) or any specific assay as a companion test for Hemgenix only. **REDACTED**.

Assessment of suitability for Hemgenix, administration of the therapy and subsequent follow-up, is expected to be conducted exclusively within an established HTC setting with appropriate Hemgenix dosing capabilities (Applicant 2023c; Haemophilia Foundation Australia 2023). Patients will receive counselling and education within a multidisciplinary care model (AHCDO & NBA 2016). For eligible, suitable patients, Hemgenix would be administered by IV infusion at a dose of 2×10^{13} gc/kg over 1–2 hours in an outpatient setting (CSL Behring LLC 2022). Patients would be closely monitored for tolerance and detection of immediate adverse events for approximately 3 hours after administration (CSL Behring LLC 2022). Longer-term follow-up for assessment of safety and treatment response would be determined by the treating specialist haematologist, consistent with regulatory advice (AHCDO & NBA 2016). Under no circumstances, would patients receive a second course of treatment (CSL Behring LLC 2022).

Supplies and materials for administration

Materials needed for the administration of Hemgenix include (CSL Behring LLC 2022):

- winged IV needle or catheter set
- infusion pump
- 0.2 micron in-line filter
- antiseptic skin preps
- 70% isopropyl alcohol wipes
- gauze/tape/transparent dressing
- sharps disposal container
- virucidal agent spill kit.

Training and qualification requirements

CSL Behring, manufacturer of Hemgenix, will work with Australian HTCs to provide appropriate education and training in administration of Hemgenix (Applicant 2023c). **REDACTED**.

Estimated utilisation

The applicant reports that **REDACTED** adults living with severe cHMB and **REDACTED** living with moderately severe disease were enrolled in the ABDR in 2019–2020 (Applicant 2023c; NBA 2020). Of these, **REDACTED** with severe disease and **REDACTED** with moderately severe disease had been receiving prophylaxis therapy with FIX concentrates (**REDACTED**) (Applicant 2023c). A small number of additional patients with baseline FIX $\leq 2\%$ and eligible for but not receiving prophylaxis therapy may also be eligible for treatment with Hemgenix (Applicant 2023c). Therefore, prevalence in the proposed population is expected to number between **REDACTED** and **REDACTED** in total, as at 2019–2020 (Applicant 2023c). It is expected that most of these patients will meet the treatment eligibility criterion of anti-AAV5 NAb titre of $< 1:700$. The applicant did not provide details on how the number of patients in the subgroup with FIX concentrations between 1–2% (defined as “moderately severe”) was derived. Therefore, the validity of this data could not be verified. The applicant stated that the number was obtained via a data request from the ABDR (Applicant 2023c). The applicant highlighted that **REDACTED** of **REDACTED** patients (**REDACTED**) enrolled in the CT-AMT-061-01 (NCT03489291) or HOPE-B (NCT03569891) studies had a titre of $< 1:700$ at baseline, providing an indication of the proportion of patients likely to be eligible for treatment with Hemgenix (Applicant 2023c; ClinicalTrials.gov 2022b, 2023a).

The ongoing incident population, comprising adolescents with severe or moderately severe disease requiring prophylaxis who transition to adulthood, is expected to average **REDACTED** new patients per year (Applicant 2023c).

Given the novelty of gene therapy, it is unlikely that all of those eligible would seek immediate treatment upon its availability. Targeted research and consultation will be required to estimate the likely uptake curve for the intervention; however, given the limited patient population and one-time nature of the therapy, utilisation is unlikely to exceed **REDACTED** patients per year at any time over the next 5 years. This would also reduce sharply as the prevalent population is treated.

The applicant notes that leakage outside of the highly restricted patient population and specialised treatment setting is highly unlikely to occur (Applicant 2023c). Furthermore, patients will be managed by a very small number of specialised haematologists under well-established governance frameworks, ensuring appropriate and quality use.

REDACTED.

PASC noted that as mentioned in the ‘Clinical Implementation Plan’ of gene therapy for haemophilia in Australia developed by The Australian Haemophilia Centre Directors’ Organisation (AHCDO), issues around access and resourcing demands are likely to be the greatest risks to implementation. This includes accessibility issues and potential workforce shortages. Additionally, PASC highlighted further requirements in the care model which would typically involve ‘patient monitoring’, including but not limited to, weekly liver function tests for 3 months, check-ups at regular intervals for 12 months, corticosteroid treatment, annual liver ultrasounds and psychosocial support. PASC advised that national and local program coordination would be required, including mental health and other supports.

PASC noted there is uncertainty in the projected uptake rate of Hemgenix.

PASC queried how FIX inhibitor development post-Hemgenix would be managed, to which the clinical experts responded that this is relatively uncommon in HMB, in practice occurs within the first 150 exposure days of FIX replacement therapy (which will have occurred in all eligible patients) and has not been reported in response to any gene therapy product. It was discussed that Hemgenix inserts the Padua variant using a gain in function mutation which is very similar to wild-type FIX and has not had any observed impact on inhibitor development.

PASC queried the length of time that the AAV5 virus vector remains active in the patient and if there were any safety issues related to this. The applicant advised they would provide a response after consulting with **REDACTED**.

Comparator(s)

The comparator proposed by the applicant is no gene therapy. In the absence of Hemgenix, eligible patients would be managed with standard of care, including FIX replacement therapies for prophylaxis treatment as routine management plus on-demand and procedural prophylaxis to control for elevated risk of bleeding event. The proposed therapy has the potential to reduce the need for FIX replacement therapy or even make FIX replacement therapy obsolete. However, whether patients could completely come off the prophylaxis treatment is a multifaceted decision-making process. This decision is unlikely to be solely reliant on some biometric results such as FIX concentrations or bleeding frequencies.

Various FIX replacement therapies used in the background standard of care are currently funded for certain cHMB patients through the NBA (NBA 2023). Available FIX replacement therapies include plasma-derived FIX replacement products (e.g. MonoFIX), recombinant products (e.g. BeneFIX) and EHL formulations (e.g. ALPROLIX) (NBA 2023).

PASC confirmed the comparator, standard of care for cHMB with no gene therapy (i.e. prophylactic FIX replacement therapy) was appropriate. PASC noted that Hemgenix will not completely replace (but may reduce) the use of FIX replacement therapy.

Outcomes

As outlined by the applicant, the following list presents the core outcomes to assess when evaluating Hemgenix for the treatment of cHMB (Applicant 2023c):

Efficacy/effectiveness outcomes:

- annualised bleed rates (overall, categorised bleed severity and site/type specific) over time
- endogenous FIX activity concentration and trough FIX activity over time
- change in patient disease categorisation over time
- FIX utilisation
- occurrence and resolution of target joint bleeding
- central venous access no longer required
- events of central venous access-related sepsis or thrombosis

Safety outcomes:

- acute peri-infusion adverse events
- long-term adverse events (e.g. thrombosis, hepatitis, hepatocellular carcinoma)
- laboratory indicators of safety (e.g. coagulation, inflammatory markers, serology, haematology)
- formation of post-infusion FIX inhibitors
- formation of anti-AAV5 NAb in relation to suboptimal therapeutic effect or intervention failure

These outcomes are consistent with previously published and ongoing clinical trials (ClinicalTrials.gov 2022a, 2022b, 2023a, 2023b; Miesbach et al. 2018; Von Drygalski et al. 2019).

HRQoL outcomes (Srivastava et al. 2020):

- EuroQol 5-dimension health-related quality of life questionnaire–5 levels
- 36-item short form health survey
- haemophilia wellbeing index
- haemophilia-specific quality of life questionnaire for adults
- patient-reported outcome measures
- patient reported outcomes, burdens and experiences questionnaire
- haemophilia activities list
- functional independence score in haemophilia

Healthcare system outcomes:

- costs associated with intervention and comparator treatments:
 - appointments
 - administration of IV infusions
 - consumables
 - hospital stay
 - follow-up
 - monitoring
 - subsequent on-demand/prophylactic therapy required
- costs associated with adverse events for intervention and comparator treatments

PASC agreed with the proposed outcomes. PASC noted that a patient could have their central venous access removed temporarily or permanently for a number of reasons that may not be directly related to the effectiveness of Hemgenix. Therefore, PASC suggested amending 'removal of central venous access' to 'central venous access no longer required', to reduce ambiguity and capture the intent that central venous access was no longer required for intravenous prophylaxis FIX replacement therapy.

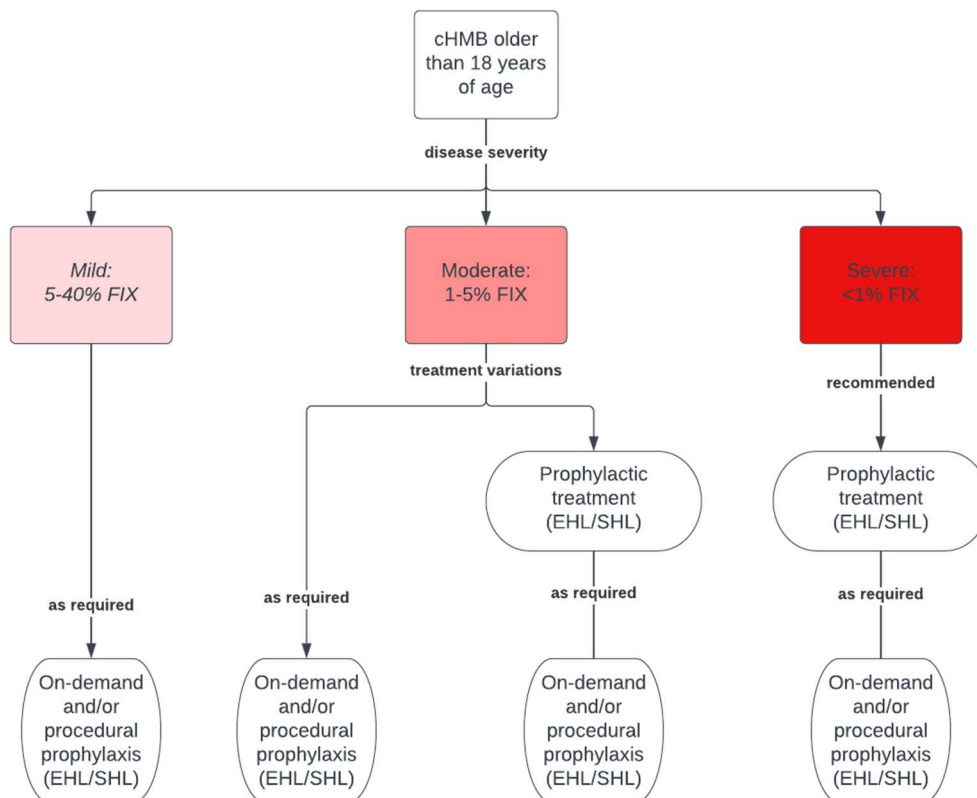
PASC considered that there is a need for long term follow up in a registry, and noted that the Australian Bleeding Disorders Registry (ABDR) is building in a gene therapy specific module to assess long term efficacy and safety. In parallel, the World Federation of Haemophilia has established a world-wide gene therapy registry assessing long-term outcomes among patients with haemophilia A and B.

Clinical management algorithms

Current and proposed clinical management algorithms for cHMB in Australia are provided in Figure 1 and Figure 2.

Current treatment approaches in Australia are guided by disease severity (as measured by FIX clotting activity) although bleeding phenotype, individual patient circumstances and preferences also play an important role (AHCDO & NBA 2016). Patients with mild cHMB are not relevant to this PICO for assignment of the intervention but are relevant for the outcome as patients are anticipated to move to a lower disease severity category following the intervention. They are shown in the algorithm to ensure the disease severity categories are complete. Patients with more severe disease typically receive routine FIX prophylaxis, usually with a recombinant EHL product (AHCDO & NBA 2016). For moderate patients, treatment variations may exist depending on the frequency of the simultaneous bleeding events. Prophylaxis treatment may still be required for patients with moderate cHMB who are in the more severe spectrum within this severity category. Short-term/procedural prophylactic therapy is recommended for all patients prior to surgical or dental procedures or other foreseeable occasional events for which there is an elevated bleeding risk (AHCDO & NBA 2016). Irrespective of prophylaxis, most patients will require at least occasional on-demand treatment for a bleeding event (AHCDO & NBA 2016). For this reason, the connection between prophylaxis treatment and on-demand/procedural prophylactic therapy boxes are not directional. They could be carried out concurrently depending on patients' need. It should be noted that the intensity of different treatment regimens (prophylaxis treatment or otherwise) would be different across different individuals. Therefore, the terminal nodes at the end of each branch are specific to those patient subgroups in terms of FIX usage frequency, dosage and occasions.

Figure 1 Current clinical management algorithm for haemophilia B in Australia



Abbreviations: cHMB = congenital haemophilia B; FIX = factor IX; EHL = extended half-life recombinant FIX replacement therapy; SHL = standard half-life recombinant FIX replacement therapy

Sources: Developed using AHCDO and NBA (2016); Applicant (2023c); Dolan et al. (2018); Medical Services Advisory Committee (MSAC) (2018)

As described previously, the clinical indication for Hemgenix is adult patients with moderately severe or severe cHMB ($\leq 2\%$ FIX) without FIX inhibitors, who are currently receiving FIX prophylaxis at a stable dose and have pre-existing anti-AAV5 NAb titre $<1:700$. As noted previously, the patient subgroup characterised as “moderately severe” cHMB is not a guideline-defined category. Therefore, the proposed clinical management pathway has attempted to avoid using this terminology but be more specific on how these population subgroups are technically defined. Further, the patients’ eligibility is determined by three criteria, as outlined in the algorithm. Two of them are related to the treatment efficacy (NAb and inhibitor tests) and the other one is related to patient choice following informed consent. These three criteria do not have priorities, and all of them would co-determine whether Hemgenix could be applicable to patients. They are formed in a row only for presentation convenience purposes. Patients in the mild category, as well as the relationship between prophylaxis treatment and on-demand/procedural prophylaxis, are similarly handled in the proposed pathway compared to the current pathway.

The proposed intervention has several impacts on the current clinical management pathway.

- Firstly, the patient subgroup with 1–2% FIX would be more explicitly managed under the Hemgenix treatment pathway. These patients might still fall back to the FIX prophylaxis regimen due to being ineligible for or choosing not to receive Hemgenix.
- Secondly, there are uncertainties of whether patients could completely come off prophylaxis treatment with Hemgenix. The clinical decision of ceasing prophylaxis treatment is likely to be multifaceted, based on patients bleeding frequencies, risks, lifestyle, and other individual circumstances. Once coming off the prophylaxis treatment, those patients would be managed

Proposed economic evaluation

The proposed economic evaluation for Hemgenix treatment of cHMB considers the applicant's claims that compared to standard of care with no gene therapy, the proposed intervention (Hemgenix) has:

- superior efficacy outcomes: annualised bleed rates (overall, categorised bleed severity, and site/type specific) over time, endogenous FIX activity concentration and trough FIX activity over time, change in patient disease categorisation over time, FIX utilisation, occurrence and resolution of target joint bleeding, central venous access no longer required and events of central venous access-related sepsis or thrombosis
- non-inferior and acceptable safety outcomes: acute peri-infusion adverse effects, long-term adverse events (e.g. thrombosis, hepatitis, hepatocellular carcinoma), laboratory indicators of safety (e.g. coagulation, inflammatory markers, serology, haematology), formation of post-infusion FIX inhibitors and formation of anti-AAV5 NABs in relation to suboptimal therapeutic effect or intervention failure
- superior HRQoL outcomes (e.g. EQ-5D-5L, SF-36, HWBI, HAEMO-QoL-A, PROBE questionnaire, HAL, FISH)

Based on the clinical claims, as per Table 3, a cost-effectiveness and/or cost-utility analysis would be appropriate for the economic evaluation of Hemgenix treatment of cHMB.

Table 3 Classification of comparative effectiveness and safety of Hemgenix, compared with gene therapy, and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	Uncertain ^a	Noninferior ^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
Noninferior ^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, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or comparative safety considerations.

^b Adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

PASC noted that the applicant's pre-PASC response updated the clinical claim for HRQoL from non-inferior and acceptable HRQoL to superior HRQoL. In addition, the relevant type of economic evaluation should be CEA/CUA under the non-inferior safety and superior effectiveness outcomes.

Proposal for public funding

Public funding for blood and blood-related products is facilitated via the National Blood Agreement and managed by the NBA on behalf of all governments (Applicant 2023c). Schedule 4 of the Agreement provides for evidence-based evaluation and advice to governments to support decisions regarding changes to the NPPL (Applicant 2023c). **REDACTED.** Following this submission, an MSAC application form was lodged by the applicant to initiate PICO development in parallel to the Schedule 4 assessment (Applicant 2023c).

The applicant claims that Hemgenix will substantially reduce healthcare resource utilisation due to elimination or significant reduction in the need for FIX prophylaxis in most cHMB patients. This will reduce the overall resourcing pressure on the healthcare system over time (Applicant 2023c). As a one-time infusion, Hemgenix will incur a high up-front treatment cost compared to the current standard of care, which comprises high ongoing costs spread over regular intervals throughout a lifetime (Applicant 2023c). Over the long term, Hemgenix is expected to compound cost-savings, ultimately relieving direct budget pressure on the NBA by reducing FIX clotting factor usage for adults living with severe and moderately severe cHMB (Applicant 2023c). Hemgenix will also likely reduce healthcare resource use, including physician visits, outpatient visits, emergency room visits, and hospitalisations for spontaneous bleeds, and for traumatic bleeds from surgery (Applicant 2023c).

REDACTED. A final price and overall budget impact model will be provided at the time of full submission for consideration by MSAC (Applicant 2023e).

PASC acknowledged the proposal for public funding via the National Blood Arrangements and the clear impact to the demand of current products used in the treatment of cHMB patients.

PASC noted that providers would be specialist haematologists.

Summary of public consultation input

Consultation Feedback

PASC noted and welcomed consultation input from 3 professional organisations, 1 consumer organisation and 1 medical professional. The organisations that submitted input were:

- Royal Brisbane and Women's Hospital Haemophilia Treatment Centre (RBWH-HTC)
- Australian Haemophilia Nurses Group (AHNG)
- Thrombosis and Haemostasis Society of Australia and New Zealand (THANZ)
- Haemophilia Foundation Australia (HFA)

The consultation feedback received was all supportive of public funding for MSAC Application 1728.

Clinical need and public health significance

- The main benefits of public funding received in the consultation feedback included the improvement of quality of life for patients, carers and families and reduced demand on health systems.
- The main disadvantages of public funding received in the consultation feedback were related to psychological impacts of both response and non-response to treatment, the lack of long term data, and the clinical follow up and lifestyle changes post-intervention.

- Other services identified in the consultation feedback as being needed to be delivered before or after the intervention included AAV antibody testing, psychosocial support, gene therapy coordinator, national haemophilia clinicians' group, dietician, pathology services, and education for haemophilia treatment staff.

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

- The consultation feedback strongly agreed with the proposed population(s).
 - THANZ stated that moderately severe to severe Haemophilia B patients have the most to benefit from the proposed treatment.
 - RBWH-HTC states that it is important for women who are affected with moderately severe to severe haemophilia B are included
- The consultation feedback strongly agreed with the proposed comparator(s).
- The consultation feedback strongly agreed with the clinical claim.
 - THANZ stated that most of the adverse events of gene therapy relate to immediate side effects, i.e. related to transfusion.

Descriptor for the proposed medical service

- The consultation feedback ranged from agreeing to strongly agreeing with the proposed service descriptor.

Additional comments

The ANHG queried whether the use of steroids is part of the treatment pathway and whether a formal process of screening or consent is required. Multiple respondents queried the funding mechanism and whether funding would be provided by States or the Commonwealth. The ANHG queried how this would affect patients who travel interstate for treatment.

The ANHG stated that the hub and spoke model is not mentioned in the application form.

PASC noted the feedback was generally supportive, emphasising the importance of addressing the burden of disease as well as the opportunity to reduce healthcare utilisation in the population. Issues of access via the existing HTC system ('hub and spoke' approach) were raised as well as the additional services that would be required (e.g. mental health, psychosocial support before, during and after [including for those found to be ineligible], education, dietician) for cHMB patients.

PASC also noted the feedback from an individual specialist suggested that funding would be better managed via the Pharmaceutical Benefits Scheme (PBS) as per other AAV vector gene therapies; whereas the RBWH-HTC feedback stated that it is imperative to fund Hemgenix treatment via the NBA pathway.

Next steps

The applicant confirmed that the assessment should proceed as an ADAR.

PASC noted that, as discussed earlier, the department has advised the applicant that in order to progress the application, the applicant must submit a co-dependent application to allow the anti-AAV5 NAb test to be evaluated in parallel to Hemgenix. PASC noted that should CSL Behring choose not to proceed with a codependent application, that MSAC Application 1728 as it stands will not be able to proceed to the evaluation stage.

Applicant comment on the ratified PICO Confirmation

CSLB is working with the Department and MSAC to resolve any remaining issues and progress the application at the earliest possible opportunity.

REDACTED.

References

AHCDO & NBA 2016, *Guidelines for the management of haemophilia in Australia*, <<https://www.blood.gov.au/system/files/HaemophiliaGuidelines-interactive-updated-260317v2.pdf>>.

Applicant 2023a, *Application 1728: CSL Behring responses to Pre-PASC PICO questions*, April 2023.

2023b, *Application 1728: Responses to Pre-PASC teleconference questions*.

2023c, *Application form for Application 1728*.

2023d, *PASC Meeting Teleconference with Assessment Group, Department of Health and Applicants for 1728 on 14 April 2023*.

2023e, *Teleconference with Assessment Group, Department of Health and Applicants for 1728 on 21 February 2023*.

ARUP Laboratories 2020, *FDA Files ARUP Laboratories' AAV5 CDx for Hemophilia A Gene Therapy Treatment*, viewed 17 March 2022, <<https://www.aruplab.com/news/2-20-2020/aav5-cdx-hemophilia-gene-therapy-treatment>>.

Brennan, Y, Parikh, S, McRae, S & Tran, H 2020, 'The Australian experience with switching to extended half-life factor VIII and IX concentrates: On behalf of the Australian Haemophilia Centre Directors' Organisation', *Haemophilia*, vol. 26, no. 3, pp. 529-35.

Cision PR Newswire 2020, *FDA Files ARUP Laboratories' AAV5 CDx for Hemophilia A Gene Therapy Treatment*, viewed 17 March 2023, <<https://www.prnewswire.com/news-releases/fda-files-arup-laboratories-aav5-cdx-for-hemophilia-a-gene-therapy-treatment-301008793.html>>.

ClinicalTrials.gov 2022a, *NCT02396342: Trial of AAV5-hFIX in Severe or Moderately Severe Hemophilia B*, viewed 17 Feb 2023, <<https://clinicaltrials.gov/ct2/show/NCT02396342>>.

2022b, *NCT03569891: HOPE-B: Trial of AMT-061 in Severe or Moderately Severe Hemophilia B Patients*, viewed 17 Feb 2023, <<https://clinicaltrials.gov/ct2/show/NCT03569891>>.

2023a, *NCT03489291: Dose Confirmation Trial of AAV5-hFIXco-Padua*, viewed 17 Feb 2023, <<https://clinicaltrials.gov/ct2/show/NCT03489291>>.

2023b, *NCT05360706: Study of AAV5-hFIX in Severe or Moderately Severe Haemophilia B*, viewed 17 Feb 2023, <<https://clinicaltrials.gov/ct2/show/NCT05360706>>.

CSL Behring LLC 2022, *Hemgenix Prescribing Information*, viewed 16 Feb 2023, <<https://labeling.cslobehring.com/PI/US/Hemgenix/EN/Hemgenix-Prescribing-Information.pdf>>.

Dolan, G, Benson, G, Duffy, A, Hermans, C, Jiménez-Yuste, V, Lambert, T, Ljung, R, Morfini, M & Zupančič Šalek, S 2018, 'Haemophilia B: Where are we now and what does the future hold?', *Blood Reviews*, vol. 32, no. 1, pp. 52-60.

FDA 2022, *Clinical Review Memo, November 22, 2022 - HEMGENIX*, viewed 17 March 2023, <<https://www.fda.gov/media/164332/download>>.

Haemophilia Foundation Australia 2023, *Haemophilia Treatment Centres*, <<https://www.haemophilia.org.au/support-services/treatment-services?state=all>>.

Konkle, BA & Nakaya Fletcher, S 1993, 'Hemophilia B', in MP Adam, DB Everman, GM Mirzaa, RA Pagon, SE Wallace, LJH Bean, KW Gripp & A Amemiya (eds), *GeneReviews*(®), University of Washington, Seattle, Seattle (WA).

Medical Services Advisory Committee (MSAC), DoH, Australian Government 2018, *PICO Confirmation - Application 1511: Extended half-life clotting factor concentrates for the treatment of haemophilia A and B*, <[http://www.msac.gov.au/internet/msac/publishing.nsf/Content/C3B4D8FB345D71C4CA2581BD00141E25/\\$File/1511_Ratified_PICO_accessible.pdf](http://www.msac.gov.au/internet/msac/publishing.nsf/Content/C3B4D8FB345D71C4CA2581BD00141E25/$File/1511_Ratified_PICO_accessible.pdf)>.

Miesbach, W, Leebeek, F, Recht, M, Key, N, Lattimore, S, Castaman, G, Coppens, M, Cooper, D, Slawka, S & Verweij, S 2022, 'Final analysis from the pivotal phase 3 Hope-B gene therapy trial: stable steady-state efficacy and safety of etranacogene dezaparvovec in adults with severe or moderately severe hemophilia B', *Haemophilia*, vol. 28, no. S1, p. PO143.

Miesbach, W, Meijer, K, Coppens, M, Kampmann, P, Klamroth, R, Schutgens, R, Tangelder, M, Castaman, G, Schwäble, J, Bonig, H, Seifried, E, Cattaneo, F, Meyer, C & Leebeek, F 2018, 'Gene therapy with adeno-associated virus vector 5-human factor IX in adults with hemophilia B', *Blood*, vol. 131, no. 9, pp. 1022-31.

Miller, CH 2018, 'Laboratory testing for factor VIII and IX inhibitors in haemophilia: A review', *Haemophilia*, vol. 24, no. 2, pp. 186-97.

NBA 2020, *Australian Bleeding Disorders Registry (ABDR) Annual Report 2019-20*, <<https://www.blood.gov.au/sites/default/files/ABDR-Annual-Report-2019-20-FINAL.pdf>>.

2021, *Australian Bleeding Disorders Registry (ABDR) Annual Report 2020-21*, viewed 16 March 2023, <<https://www.blood.gov.au/sites/default/files/ABDR-Annual-Report-2020-21%20FINAL.pdf>>.

2023, *What Blood Products are Supplied – National Product Price List*, viewed 17 Feb 2023, <<https://www.blood.gov.au/national-product-price-list>>.

Office of the Gene Technology Regulator 2023, *About the OGTR*, viewed 3 March 2023, <<https://www.ogtr.gov.au/about-ogtr>>.

Pipe, SW, Leebeek, FWG, Recht, M, Key, NS, Castaman, G, Miesbach, W, Lattimore, S, Peerlinck, K, Van der Valk, P, Coppens, M, Kampmann, P, Meijer, K, O'Connell, N, Pasi, KJ, Hart, DP, Kazmi, R, Astermark, J, Hermans, CRJR, Klamroth, R, Lemons, R, Visweshwar, N, von Drygalski, A, Young, G, Crary, SE, Escobar, M, Gomez, E, Kruse-Jarres, R, Quon, DV, Symington, E, Wang, M, Wheeler, AP, Gut, R, Liu, YP, Dolmetsch, RE, Cooper, DL, Li, Y, Goldstein, B & Monahan, PE 2023, 'Gene Therapy with Etranacogene Dezaparvovec for Hemophilia B', *New England Journal of Medicine*, vol. 388, no. 8, pp. 706-18.

Pipe, SW, Recht, M, Key, NS, Leebeek, FWG, Castaman, G, Lattimore, SU, Van Der Valk, P, Peerlinck, K, Coppens, M, O'Connell, N, Pasi, J, Kampmann, P, Meijer, K, von Drygalski, A, Young, G, Hermans, C, Astermark, J, Klamroth, R, Lemons, RS, Visweshwar, N, Crary, S, Kazmi, R, Symington, E, Escobar, MA, Gomez, E, Kruse-Jarres, R, Kotowski, A, Quon, D, Wang, M, Wheeler, AP, Sawyer, EK, Verweij, S, Colletta, V, Bajma, N, Gut, R & Miesbach, WA 2020, 'First data from the phase 3 HOPE-B gene therapy trial: efficacy and safety of etranacogene dezaparvovec (AAV5-Padua hFIX variant; AMT-061) in adults with severe or moderate-severe hemophilia B treated irrespective of pre-existing anti-capsid neutralizing antibodies', *Blood*, vol. 136, no. Supplement_2, pp. LBA-6-LBA-.

Sanofi 2021, *Australian product information – ALPROLIX (eftrenonacog alfa) (rhu) powder and solvent for solution for injection*, viewed 3 March 2023, <<https://secure.guillink.com.au/gc/ws/sw/pi.cfm?product=swpalpro>>.

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 2020, 'WFH Guidelines for the Management of Hemophilia, 3rd edition', *Haemophilia*, vol. 26 Suppl 6, pp. 1-158.

Thornburg, CD 2021, 'Etranacogene dezaparovec for hemophilia B gene therapy', *Therapeutic Advances in Rare Disease*, vol. 2, p. 26330040211058896.

Von Drygalski, A, Giermasz, A, Castaman, G, Key, NS, Lattimore, S, Leebeek, FWG, Miesbach, W, Recht, M, Long, A, Gut, R, Sawyer, EK & Pipe, SW 2019, 'Etranacogene dezaparovec (AMT-061 phase 2b): normal/near normal FIX activity and bleed cessation in hemophilia B', *Blood Adv*, vol. 3, no. 21, pp. 3241-7.

World Federation of Hemophilia 2021, *World Federation of Hemophilia Report on the Annual Global Survey 2021*, viewed 17 Feb 2023, <<https://www1.wfh.org/publications/files/pdf-2324.pdf>>.