Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1728 – Etranacogene dezaparvovec for the treatment of Haemophilia B

Applicant: **CSL Behring (Australia) Pty Ltd.**

Date of MSAC consideration: **1-2 August 2024**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

An application requesting funding under the national blood arrangements of etranacogene dezaparvovec (also known as Hemgenix®, AMT-061 and CSL222 or EtranaDez) for the treatment of moderately severe and severe haemophilia B was received from CSL Behring (Australia) Pty Ltd by the Department of Health and Aged Care.

This application also assessed a 9-point cell-based anti-adeno-associated virus type 5 (anti-AAV5) neutralising antibodies (NAb) assay for prediction of response to Hemgenix. Funding was not sought for this test. Assessment of the assay was requested by the PICO Confirmation Advisory Sub-Committee (PASC).

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC did not support public funding of the gene therapy etranacogene dezaparvovec (Hemgenix) for the treatment of adult patients with moderately severe or severe congenital haemophilia B. MSAC noted the limited low certainty clinical evidence indicated that Hemgenix may be effective for some patients in the short term but considered that there was substantial inter-individual variability in the patient response to Hemgenix. Although a lifetime benefit was claimed, MSAC considered the clinical evidence (3-year follow-up) was insufficient to substantiate the long-term safety and effectiveness of Hemgenix. MSAC noted that pre-existing neutralising antibodies against the viral vector (anti-AAV5 neutralising antibodies) used to deliver Hemgenix impacts the effectiveness of Hemgenix. MSAC considered the neutralising antibody test was essential for determining patient eligibility to Hemgenix, but noted this test has not been validated. MSAC also considered that the cost effectiveness of Hemgenix compared to factor IX replacement therapy was highly uncertain due to the uncertainties in both the clinical evidence and the oversimplified economic model which had inherent limitations. As such, MSAC considered the proposed very high price for Hemgenix was not cost-effective. MSAC considered that the estimated utilisation may be erroneously low given the prevalent pool of potentially eligible individuals but this was uncertain as there may be potential system and supply capacity constraints. In addition, patient acceptance with current alternative treatments and other near market and emergent treatments, such as subcutaneously administered anti–tissue factor pathway inhibitors, may increase treatment choice and therefore impact the uptake of Hemgenix. Therefore, MSAC consider the utilisation and financial impact of Hemgenix was uncertain. MSAC also noted that Hemgenix is only provisionally approved for use in Australia by the Therapeutic Goods Administration.

MSAC considered any re-application would need to provide additional longer-term clinical evidence, including evidence for the neutralising antibody test (consistent with post-marketing registration requirements), revised economic and financial analyses, a significantly reduced price, and details for a proposed risk sharing arrangement.

Consumer summary

This application from CSL Behring (Australia) Pty Ltd requested funding of Hemgenix under the national blood arrangements for adults with moderately severe and severe congenital haemophilia B.

Haemophilia is a bleeding disorder where a person's blood does not clot properly, which can result in excessive internal and external bleeding. Congenital haemophilia B is a rare type of haemophilia that is caused by a lack of blood clotting protein, specifically the factor IX blood clotting protein. In patients with congenital haemophilia B, there is a problem with the factor IX gene that results in the liver producing low amounts of factor IX. The severity of a patient's condition worsens with lower levels of factor IX. Patients with congenital haemophilia B can receive replacement factor IX either on a routine basis as a prophylactic (preventative) and/or as on-demand (as needed) treatment. The replacement factor IX is administered via injections into a vein (intra-venous).

Hemgenix is a viral-based gene therapy – this means that an inactive virus (that can't reproduce) is used to deliver a copy of the factor IX gene into the liver cells, which enables the liver cells to produce the factor IX blood clotting protein. Hemgenix is delivered to a patient via a single intra-venous infusion.

MSAC noted that the clinical studies indicated that some patients responded well to Hemgenix, but others did not. Some patients who did respond still needed factor IX replacement treatment, but not as much as before receiving Hemgenix. Some patients also had more bleeds after Hemgenix than they did before receiving Hemgenix. Further, MSAC noted that one patient initially appeared to respond but then later on the effect appeared to reduce and the patient needed routine factor IX replacement again. MSAC did not know whether the effect may wane over time for other patients as MSAC only had 3-year follow-up data from a small number (54) of patients to consider. The limitations in the study design also increased the uncertainty in the claimed benefit of Hemgenix. MSAC considered that longer term follow-up data would be better to determine whether Hemgenix continues to work and is comparatively safe in the long term.

MSAC noted that if someone has a high level of antibodies that neutralise the virus that is used to deliver the factor IX gene, then Hemgenix did not work. MSAC considered it important that people are tested for neutralising antibodies before treatment with Hemgenix but noted that further studies are needed to validate the test for the neutralising antibodies. Further, MSAC noted that after receiving Hemgenix, all patients had high levels of neutralising antibodies, which would then prevent people from receiving another similar gene therapy later, even if Hemgenix doesn't work for them or if it works for only a short time. As such, MSAC agreed with consultation input that it was important for patients to receive counselling to understand the risks and benefits when considering Hemgenix.

MSAC noted the proposed price of Hemgenix was very high, which MSAC did not consider to be justified. When the very high cost for Hemgenix was considered in the context of uncertain clinical benefit in comparison to the current treatments, Hemgenix was not demonstrated to be good value for money. The budget impact was also very high, even though some costs were not included. MSAC also noted that the number of patients who may use Hemgenix was very uncertain due to a number of factors such as potential system and supply capacity, patient acceptance with current alternative treatments, and other new treatments that may become available (and increase treatment choice) in the near future. As such, MSAC considered the financial impact was also very uncertain.

Consumer summary
MSAC also noted that Hemgenix only has provisional approval from the Therapeutic Goods Administration (TGA), this means that the TGA approval for Hemgenix is currently time-limited for up to a maximum of 6 years. The continued approval of Hemgenix after this provisional approval period depends on the submission of additional data from ongoing studies to the TGA to confirm the longer-term benefit of Hemgenix. **MSAC's advice to the Commonwealth Minister for Health and Aged Care** MSAC did not support funding Hemgenix under the national blood arrangements. MSAC considered that the short-term effectiveness was highly variable, the longer-term safety and effectiveness was unknown, the lack of a validated neutralising antibody test, and the very high price together meant Hemgenix did not provide value for money and could result in a very high budget impact.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this application from CSL Behring (Australia) Pty Ltd sought funding of etranacogene dezaparvovec (Hemgenix) for the treatment of adult patients with moderately severe and severe congenital haemophilia B (cHMB) under the national blood arrangements.

MSAC noted that Hemgenix is an adeno-associated virus type 5 (AAV5) gene therapy that is intended to enable the liver to produce factor IX (FIX) clotting protein. A single infusion of 2×10^{13} genome copies per kilogram of body weight is administered to the patient. MSAC noted that Hemgenix is provisionally registered by the TGA and that the proposed price for Hemgenix was $redacted for a single infusion.

MSAC noted that the consultation feedback was mostly supportive of the treatment. MSAC noted a consumer survey conducted by the Haemophilia Foundation Australia, indicated that consumers had expressed concerns about gene therapy, especially regarding safety and adverse events (AEs), how long the treatment lasts and associated failure rates, and the fact that they may not be able to access any similar future therapy if Hemgenix doesn't work. The survey indicated that patients are currently hesitant to choose gene therapy but are open to it as an option in the future. As such, consultation feedback highlighted the importance of counselling as patients need to understand the risks and benefits when considering Hemgenix.

MSAC noted the proposed population included patients with severe cHMB (endogenous FIX activity less than 1%) or moderately severe cHMB (endogenous FIX activity 1–2%) who are currently receiving replacement FIX prophylaxis. MSAC also noted that the PICO had included that patients must also have an anti-AAV5 neutralising antibody (NAb) level of <1:700 (on a 7-point assay), but this was removed from the proposed eligibility criteria in the Applicant Developed Assessment Report (ADAR). MSAC considered specifying an anti-AAV5 NAb titre threshold was an important eligibility criterion as Hemgenix was not effective in a patient who had a high anti-AAV5 NAb titre. However, MSAC noted that the anti-AAV5 NAb test, which is currently only performed in the United States (US), is not yet validated. Further, the US Food and Drug Administration (FDA) approval for Hemgenix[1] mandates that a number of post-market studies must be conducted, including studies to validate the anti-AAV5 NAb test and to assess the association between the

[1] US FDA Approval Letter (Nov 2022) - Hemgenix Biologics Licence Application Approval - https://www.fda.gov/media/163466/download?attachment

effectiveness of Hemgenix and pre-existing anti-AAV5 NAb. The TGA's provisional approval for Hemgenix is also reliant on further follow-up data to lead to full registration.

MSAC noted that the clinical evidence for Hemgenix was informed by three single-arm observational studies (i.e. low certainty evidence), and that the HOPE-B study (n = 54) provided the main supporting evidence. Measured outcomes from the HOPE-B study included annualised bleeding rate (ABR), uncontaminated FIX activity (i.e. FIX activity tested off FIX prophylaxis), FIX use after treatment, AEs, EQ-5D-5L and Haem-A-QoL scores. MSAC noted the ADAR had presented 3-year data from the HOPE-B study and that the applicant's pre-MSAC response provided some 4-year data but stated that these data were not yet cleaned and the early analyses were unconfirmed and no conclusions made. Further, due to the late provision, these 4-year data were not evaluated as part of the MSAC assessment process.

MSAC noted the AEs reported for Hemgenix (36 month follow up data) included abnormal liver function tests, infusion reactions, bleeds, the development of anti-AAV5 antibodies and neoplasms. MSAC noted the development of NAbs, which would preclude any future treatment with AAV5- or of a cross-reactive AAV species- based gene therapy, was of particular concern for consumers. MSAC considered that as at 36 months, the claim that Hemgenix had non-inferior safety compared to standard of care (i.e. routine prophylaxis with FIX replacement therapy) was reasonable. However, MSAC agreed with ESC that the comparative long-term safety of Hemgenix was unknown and uncertain, as the assessed HOPE-B study data are only available for 3 years post-treatment.

MSAC considered that the reduction in the average ABR for the whole patient cohort (from 4.19 pre-treatment to 1.52 post-treatment) indicated that Hemgenix was effective at 3 years follow up for a sub-group of patients. That is, while MSAC noted the short-term evidence indicated a reduction in ABR post-Hemgenix for some patients, MSAC agreed with ESC that there was substantial inter-individual variability in response. MSAC noted the applicant's pre-MSAC response argued that the variability in the ABR was not substantial and was reflective of the heterogenous population that was evaluated. MSAC noted the tornado plot depicting the ABR for each patient highlighted the extent of the inter-individual variability (Section 12, Figure 1). Some patients not only had more bleeds post-Hemgenix treatment but also had more serious bleeds post-treatment than they did prior to Hemgenix treatment. In addition, some patients had no bleeds before or after Hemgenix. As such, MSAC considered it problematic to interpret the treatment effect (median ABR) for the whole cohort. MSAC also noted that the tornado plot depicting the post-treatment FIX replacement therapy use demonstrated that, even though responders may not have required routine prophylactic FIX replacement therapy, 32/54 patients still required some FIX infusions after Hemgenix so it could not be considered curative (Section 12, Figure 3). MSAC again noted that while the average number of FIX infusions for the whole patient cohort was reduced (from an average of 44.1 to 1.7 FIX infusions per patient)), there was inter-individual variability. MSAC also noted that there was evidence of waning effectiveness with one of the patients developing late loss of efficacy although the applicant's pre-MSAC response redacted. MSAC noted the lack of data for joint bleeding measurements and use of central venous lines and line access.

Regarding patient quality of life, MSAC noted that there was no change in EQ-5D-5L, and although Haem-A-QoL scores were improved, it is uncertain whether this represented a meaningful improvement.

Overall, MSAC considered that, in the short-term, Hemgenix appeared to have superior effectiveness for a subgroup of patients and while Hemgenix may potentially be life changing for this subgroup, this was based on low certainty evidence. MSAC concluded that there was substantial variation in patient response, with no identifiable pattern or ability to predict the

subgroup of patients for whom Hemgenix would be effective. Further, due to the short study follow-up, the long-term effectiveness of Hemgenix was highly uncertain. The inability to predict who will respond to Hemgenix and the uncertainty the long-term effectiveness are important issues for consumers who, as noted earlier, are hesitant to try a gene therapy as they may not be able to access any similar future therapy if the response to Hemgenix is suboptimal.

MSAC agreed with ESC's concerns regarding the economic evaluation, including that the model was too simplistic (two health states: alive and dead), and that the method and duration of extrapolation based on FIX activity created high uncertainty. MSAC did not accept the applicant's claim that a severe health state was not required because younger cHMB patients are well treated with the current standard of care and typically do not progress to a severe health state. MSAC noted that while this emphasised how well patients are being managed with the current standard of care (i.e. prophylactic FIX replacement therapy), some patients are still experiencing joint bleeds and damage, which is able to be modelled as demonstrated in other published models. MSAC did not consider it reasonable that the outcomes for a novel gene therapy with uncertain long-term safety and effectiveness to be extrapolated out over 25 years, based on 36 months of data. MSAC considered a shorter time horizon would be more appropriate. MSAC also agreed with ESC that FIX activity is a surrogate outcome and the correct cutoff level(s) was uncertain. MSAC noted the applicant's pre-MSAC response asserted that a FIX activity of between 3-5% provides sufficient bleeding protection. However, MSAC considered that the applicant's response did not satisfactorily address the uncertainty and validity regarding the binary application of FIX activity using a single threshold set at 3%, which was a driver of outcomes (e.g. utilisation of FIX replacement therapy) that created high uncertainty in the downstream cost savings.

MSAC noted that the incremental cost-effectiveness ratio (ICER) was approximately $redacted per quality-adjusted life-year (QALY) gained after 3 years, approximately $redacted per QALY gained at 8 years, but dominant after 25 years. MSAC noted that when the effective prices for the comparator FIX replacement therapies were applied, the ICERs increased and Hemgenix was no longer dominant over the 25-year time horizon:

- Step 1 – 3-year study data–based time horizon: $redacted per QALY gained
- Step 2 – 8-year time horizon: $redacted per QALY gained
- Step 3 – 25-year time horizon: $redacted per QALY gained.

MSAC noted additional sensitivity analyses, conducted by the Department using effective prices for the comparator FIX replacement therapies, indicated the approximate prices to reach dominance were:

- $redacted at redacted years
- $redacted at redacted years
- $redacted at redacted years.

MSAC also noted that, to reach an ICER of $100,000 after 3 and 5 years, the price for Hemgenix would need to be reduced to approximately $redacted and $redacted, respectively.

MSAC noted that the applicant's pre-MSAC response stated that a lower price for Hemgenix that would be required to achieve an ICER of <$100,000 per QALY over a 5-year time horizon was not commercially feasible, but MSAC considered that the price of $redacted was not justified and was not cost-effective.

MSAC noted that the financial impact used a mixed epidemiology and market-share approach. MSAC noted that although a cHMB register exists to help inform the number of potential eligible patients, there is uncertainty regarding how many patients would have the treatment. MSAC

noted the ADAR assumed a low uptake rate of redacted% and the applicant's pre-MSAC response reiterated the uptake would be low and that the risk of a higher uptake is low based on the uptake rate observed in France and United States of America (USA). MSAC acknowledged that the uptake may be low (noting potential system and supply capacity, patient acceptance with current alternative treatments, and other near market and emergent treatments) but whether uptake would be as low as redacted% was uncertain. MSAC also noted that the financial impact analysis did not account for the additional services that would be required post-treatment. Overall, MSAC considered the financial impact analysis and the claimed cost-savings were highly uncertain.

MSAC noted the pre-MSAC response stated that other countries, including Canada and the United Kingdom (UK), have supported funding for Hemgenix. However, MSAC noted that the Canadian Reimbursement Recommendation[2] specified that a significant price reduction was required, and Hemgenix might not yet be available to patients. MSAC also noted that in the UK, Hemgenix was not recommended for routine funding through the National Health Service (NHS) but is currently accessible through the Innovative Medicines Fund (IMF) with a managed access agreement[3]. MSAC considered it important that the details of these listings be revealed before attempting to replicate international considerations, as many of them have managed access and outcome-based agreements. MSAC also noted that Hemgenix uptake has been very low due to other therapies on the horizon (for example, the subcutaneously administered anti-tissue factor pathway inhibitors Concizumab and Marstacimab), system barriers and current comfortability with available prophylaxis options. Additionally, MSAC reiterated that the TGA has only listed Hemgenix provisionally.

MSAC recalled that it previously supported funding for Luxturna (a gene therapy for patients with inherited retinal dystrophies) at its November 2020 meeting (see Public Summary Document for MSAC application 1623[4]). This approval was based on data from a randomised controlled trial with 7-year follow-up. Additionally, there were no other treatment options for these patients, and if left untreated, the outcome was blindness. MSAC also noted that its support for listing Luxturna depended on a detailed risk-sharing arrangement subject to many conditions, and a price reduction. MSAC also recalled that, at the time, it was advised to consider alternative ways to price gene therapies, given the very high requested fees.

Overall, MSAC did not support public funding for Hemgenix for the treatment of adult patients with moderately severe or severe cHMB on the basis that the comparative safety, effectiveness, cost-effectiveness and total cost of Hemgenix was highly uncertain. Although the limited low certainty clinical evidence indicated that Hemgenix appeared to be effective for a subgroup of patients in the short-term, there was substantial inter-individual variability, and the evidence was insufficient to substantiate the long-term comparative safety and effectiveness of Hemgenix. Further, MSAC considered anti-AAV5 NAb testing important for determining patient eligibility to Hemgenix but that further evidence to validate this test was required. MSAC considered the proposed price for Hemgenix was not justified, in that it was too high and not found to be cost-effective. MSAC also considered the estimated utilisation and financial impact to be highly uncertain. MSAC considered the provisional registration of Hemgenix in Australia added further

[2] CADTH Reimbursement Recommendation Etranacogene Dezaparvovec (Hemgenix), Canadian Journal of Health Technologies, May 2024, 4:(5) - https://www.cadth.ca/etranacogene-dezaparvovec

[3] UK Managed Access Agreement, Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B (ID3812) https://www.nice.org.uk/guidance/ta989/documents/supporting-documentation-2

[4] http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1623-public

uncertainty. MSAC noted there are emergent subcutaneously administered monoclonal antibody treatment options for people with cHMB.

MSAC considered any re-application would need to provide:

- a significantly reduced proposed price
- additional longer-term clinical evidence from HOPE-B study
- evidence on anti-AAV5 NAb assay performance, validity, reproducibility and clinically meaningful threshold (consistent with post-marketing registration requirements)
- evidence on FIX consumption, activity, presence/extent of FIX inhibitors after Hemgenix treatment for a minimum of 2 years follow-up
- evidence on all healthcare use after Hemgenix treatment for a minimum of 2 years follow-up.
- a codependent application for Hemgenix with anti-AAV5 NAb testing, including an updated proposed population eligibility criteria that specifies an appropriate anti-AAV5 titre threshold (as above)
- provide a revised economic evaluation with a new structure that includes health states related to natural history, addresses ESC concerns regarding the extrapolation and threshold for FIX % activity, and reduce the time horizon
- provide additional evidence to support the estimated utilisation
- provide details of a risk sharing arrangement as described by ESC.

4. Background

The Medical Services Advisory Committee (MSAC) has not previously considered etranacogene dezaparvovec for the treatment of HMB.

An AAV5-based gene therapy product for haemophilia A, valoctocogene roxaparvovec, was considered by MSAC's PICO Advisory Sub-Committee (PASC) at the April 2024 PASC meeting (application 1751)[5]. The codependent application included a PICO Set for the companion anti-AAV5 titre assay; the assay is a total antibody assay and is qualitative only (positive or negative result).

5. Prerequisites to implementation of any funding advice

Etranacogene dezaparvovec (Hemgenix) was granted provisional registration by the TGA on 15 March 2024. The provisionally registered indication, per the entry in the Australian Register of Therapeutic Goods for Hemgenix (ARTG 405360) is:

> HEMGENIX® is an adeno-associated virus vector-based gene therapy indicated for treatment of adults with haemophilia B (congenital factor IX deficiency), without a history of factor IX inhibitors, who:
> - currently use factor IX prophylaxis therapy, or
> - have current or historical life-threatening haemorrhage, or repeated, serious spontaneous bleeding episodes.

[5] http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1751-public

This decision to approve this indication has been made on the basis of short-term efficacy and safety data from the clinical trial program. Continued approval of this indication depends on confirmation of longer-term benefit from ongoing clinical trials.

The current TGA-approved provisional indication does not specify severity of cHMB. As such, patients with moderate cHMB (for example) could potentially receive Hemgenix per the TGA provisionally registered indication.

The Australian Haemophilia Centre Directors' Organisation (AHCDO) has developed the Gene Therapy Roadmap (2022) to provide a Clinical Implementation Plan that sets out AHCDO's position on the preferred approach to implementation of gene therapy for haemophilia in Australia.

Haemophilia Treatment Centres (HTCs) in Australia form part of the public hospital system, thus coordination with state and territory agencies was considered an essential pre-requisite to implementation of funding advice for this treatment.

The applicant did not seek public funding for the anti-AAV5 assay. The applicant advised that the anti-AAV5 NAb test will be run redacted. The test will not be TGA registered or listed on the Medicare Benefits Schedule (MBS), and the cost of the test will be covered by CSL Behring (Australia) Pty Ltd.

6. Proposal for public funding

Under the national blood arrangements, blood and blood-related products and services are jointly funded by the Australian Government and state and territory governments, in accordance with the National Blood Agreement (Agreement), which is administered by the National Blood Authority (NBA). Although Hemgenix does not consist of human blood or components of human blood, nor is it derived from human blood, it could be regarded as a blood-related product as defined by the Agreement, as it is proposed as an alternative therapy to the use of blood products currently funded under the national blood arrangements.

Hemgenix is infused as a single dose of 2×10^{13} genome copies per kilogram of body weight. The total number of vials in each finished pack is prepared for the dosing requirement for each individual patient based on body weight. The proposed price per Hemgenix infusion is $redacted. No rationale was provided by the applicant for this price.

The therapy will be delivered in existing HTCs to patients already familiar with and known to the NBA and who will be monitored through the Australian Bleeding Disorders Registry (ABDR). AHCDO's position is that gene therapy should be implemented via a 'Hub and Spoke' model in line with emerging international best practice; five of the existing HTCs will be designated as hubs and prescribe and administer haemophilia gene therapies nationally.

The TGA provisional registration states that Hemgenix must be prescribed and administered in a clinical treatment centre under the supervision of a haematologist or physician with experience in the diagnosis and management of HMB.

Anti-AAV5 NAb testing would be ordered, and interpreted, by the treating specialist in the HTC (a public hospital outpatient clinic). The expected turnaround time is 1–3 weeks. The commentary noted that the Australian Government will not have oversight of the adequacy of the testing facility, nor will the department be able to require the laboratory take part in any quality assurance or accreditation programs as would usually be the case for a new pathology service. Test data from Australian patients should nonetheless be made available by CSL Behring to the department to enable independent assessment of testing.

7. Population

The ADAR included a single PICO set for treatment with Hemgenix. The proposed population, as per the ratified PICO Confirmation, was adult patients (≥ 18 years) with severe cHMB or moderately severe cHMB defined as:

- severe cHMB: factor IX (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
- currently receiving stable FIX prophylactic therapy

who also meet the following criteria:

- anti-AAV5 NAb titre < 1:900 using 9-point assay (< 1:700 using 7-point assay)
- no inhibitor formation against expressed FIX protein.

The Australian Product Information for Hemgenix, approved as part of the TGA provisional registration lists additional contraindications:

- active infections, either acute or uncontrolled chronic
- known advanced hepatic fibrosis, or cirrhosis.

The commentary noted that additional contraindications in the TGA provisional registration should also be regarded as further exclusions for the assessment of Hemgenix. The AHCDO Roadmap also considers patients with severe lung disease likely to be excluded from the proposed treatment.

The ratified PICO confirmation specified that the patient population for Hemgenix met the criteria of anti-AAV5 NAb titre less than 1:700. This was based on the 7-point assay (used in the clinical studies and therefore the clinical reference standard). The ADAR stated that this is equivalent to a titre less than 1:900 based on the 9-point assay. The 9-point assay was the proposed intervention for the co-dependency.

However, the population proposed in the ADAR was adults ≥18 years of age with haemophilia B (congenital factor IX deficiency) and:

1) FIX activity ≤2% of normal; and
2) currently receiving prophylaxis with FIX concentrate for at least 2 months; and
3) whom do not have inhibitors.

The ADAR removed the anti-AAV5 NAb titre reference from the proposed population based on alignment with the TGA indication. Provisional registration was obtained from the TGA during the assessment. A cut-off titre for anti-AAV NAbs was not included in the TGA indication but there was a warning regarding use in patients with a titre above 1:900 (9-point assay) and the approval stated that baseline testing of pre-existing anti-AAV5 NAb titre is required. It was also a condition of the provisional registration that the sponsor submit studies to validate the cut-off titre. The TGA noted the effectiveness data in patients with a titre greater than 1:700 (7-point assay) was from a single patient with a titre of 1:3212 (using the clinical trial assay); in this patient, no FIX expression was observed, and recommencement of prophylaxis was needed.

The commentary noted that the removal of an anti-AAV5 NAb titre threshold from the population was inconsistent with the ratified PICO confirmation.

The applicant's pre-ESC response provided the following additional information regarding the eligibility criteria for the proposed population for funding:

- Due to the lack of validated age thresholds related to development stage and paucity of data amongst patients <18 years, the applicant considered it appropriate to retain the proposed age threshold of ≥18 years of age. The applicant supported incorporating exclusion criteria "Active infections, either acute or uncontrolled chronic" and "Patients with known advanced hepatic fibrosis, or cirrhosis" as these are aligned with the exclusion criteria for the HOPE-B study and the approved product information for Hemgenix.
- The applicant did not support including "No lung disease" as an exclusion criterion as this was not an exclusion criterion for the Hemgenix clinical studies, nor was it identified as a safety signal in the studies.

These issues were not addressed in the ADAR.

The commentary noted that PASC had noted that there are some patients categorised as having moderate (not moderately severe) haemophilia with FIX activity between 2–5% who require prophylaxis treatment and therefore may benefit from Hemgenix but are not eligible under the proposed descriptor. The commentary noted that no data were available in this population.

Treatment with the intervention was proposed as an alternative to current best supportive care, that is a stable prophylactic regimen of recombinant FIX concentrate. Treatment with Hemgenix may not completely eliminate the need for FIX replacement therapy or change the circumstances under which it would be required, but it was proposed to significantly reduce both the extent and frequency of its use.

The ADAR addressed most of the PICO elements that were prespecified in the ratified PICO confirmation. Two outcomes specified in the PICO (related to the requirement of central venous access and related sepsis or thrombosis) were not presented due to lack of data.

The ratified PICO confirmation did not include a PICO set for the anti-AAV5 NAb assay.

The test population would be adults (≥ 18 years) with severe or moderately severe cHMB considering treatment with Hemgenix.

8. Comparator

Patients not treated with gene therapy will continue to be treated with a stable prophylactic regimen of recombinant FIX concentrate. On-demand or episodic treatment with FIX is administered only at the time of a bleeding event (or event anticipated to cause bleeding). Under current procurement arrangements Alprolix (eftrenonacog alfa/extended half-life) and Benefix (nonacog alfa/standard half-life) recombinant FIX clotting factor concentrates are available, along with Monofix, a plasma derived clotting factor with minimal utilisation. All treatments for haemophilia B are currently fully funded (no patient co-payment) by all Australian governments under the national blood arrangements.

9. Summary of public consultation input

Consultation input was received from four (4) professional organisations, one (1) consumer organisation and two (2) medical professionals. The organisations that submitted input were:

- Australian Haemophilia Centre Directors' Organisation (AHCDO)
- Australian Haemophilia Nurses Group (AHNG)
- Haemophilia Foundation Australia (HFA)
- Royal Brisbane and Women's Hospital Haemophilia Treatment Centre (RBWH-HTC)

- Thrombosis and Haemostasis Society of Australia and New Zealand (THANZ).

The consultation feedback received raised some concerns but overall was supportive of Application 1728.

Benefits

- Reduced bleeding rate for a number of years post single infusion (depending on longevity of response) compared to factor IX (FIX) prophylaxis.
- Reduced treatment burden for patients who no longer require regular infusions of FIX clotting factor (when Hemgenix is effective) which has a high treatment burden and requires a commitment to incorporating the treatment into a weekly routine.
- Some individuals may attain adequate FIX levels (post-Hemgenix treatment) to permit a higher level of physical activity than provided by standard FIX prophylaxis; better chance to achieve good fitness levels, build healthier joints and lead a more normal lifestyle.
- Improvement of quality of life for patients, carers and families.
- Reduced demand on health systems with fewer hospitalisations.
- Equity of access for patients who would otherwise be unable to afford Hemgenix.

Disadvantages

- The level of FIX response (post-Hemgenix treatment) each individual person will obtain is not guaranteed meaning some patients may have a modest, poor or no response.
- Some patients may experience negative psychological impacts as a result of both unsuccessful treatment (disappointment) or successful treatment where patients may experience psychosocial adjustment issues, for example regarding the patient's identity and how they interact with other members of the family who may or may not also have haemophilia.
- Significant use of steroids to preserve the gene therapy product may be required, with associated side effects including mental health challenges, risk of diabetes and impaired glucose control, steroid-induced myopathy and osteoporosis.
- Unknown long-term effects due to the lack of long-term data for safety and effectiveness.
- Some patients may find the clinical follow up and lifestyle changes (e.g. in relation to alcohol intake, contraception and post infusion monitoring) required after receiving Hemgenix gene therapy challenging.
- Not all patients will be eligible, and some will be excluded based on seropositivity to the vector.
- Remote or regional patients may need to travel to a clinical site that can successfully administer this therapy.
- No clinical or laboratory parameters which allow the clinician to predict which patients will derive the most benefit from gene therapy.

Additional comments

AHCDO noted the proposed intervention will not wholly replace the comparator (FIX replacement therapy) as even if a patient responds to the treatment, the patient's FIX levels post-Hemgenix treatment may not be sufficient to enable management of bleeding-associated surgery or trauma. In these instances, patients may still require FIX replacement therapy.

The AHNG was interested in guidance on the use of steroids is part of the treatment pathway and whether a formal process of screening or consent is required. Other feedback highlighted the need for counselling regarding the risks and benefits, the nature of the intervention and the potential impact it may have on the patient's mental health, particularly identity, steroid-related mood effects and interaction with other family members who may or may not have haemophilia and may or may not be eligible for the intervention.

Other services identified as being needed to be delivered before or after the intervention included adeno-associated virus (AAV) antibody testing, psychosocial support, gene therapy

coordinator, national haemophilia clinicians' group, dietician, pathology services, and education for haemophilia treatment staff.

Multiple respondents queried the funding mechanism and whether funding would be provided by States or the Commonwealth. The AHNG raised the issue of costs for travel and accommodation for patients who travel interstate for treatment. It was suggested the therapy is better managed through the Pharmaceutical Benefits Scheme (PBS), as it is gene therapy, not a blood or blood-derived product.

10. Characteristics of the evidence base

Evidence for etranacogene dezaparvovec (Hemgenix)

The evidence base consisted of three single arm observational studies: two of etranacogene dezaparvovec (AMT-061) and one of its precursor gene therapy construct (AMT-060). Published indirect treatment comparisons were not used in the assessment[6].

Key features of the included evidence are summarised in Table 1.

Table 1 Key features of the included evidence for etranacogene dezaparvovec (Hemgenix)

Trial/Study	N	Study design Risk of bias[a]	Population	Intervention	Key outcome(s)[b]	Result used in economic model
Phase III AMT-061-02 (HOPE-B) NCT03569891	54	Interrupted time series (follow-up planned to 5 y, with extension to 15 y) NR, MC, OL, SA High	Adults with HMB (severe or moderate)	SOC + etranacogene dezaparvovec (2×10^{13} gc/kg)	ABR 6–18 mo post-treatment Uncontaminated FIX activity FIX utilisation AEs EQ-5D-5L Haem-A-QoL	Yes (FIX activity, ABR, SAEs, EQ-5D-5L)
Phase IIb AMT-061-01 NCT03489291	3	Case series NR, MC, OL, SA Very high	Adults with HMB (severe or moderate)	etranacogene dezaparvovec (2×10^{13} gc/kg)	FIX activity at 6 wk post-treatment	Yes (FIX activity)
Phase I/II AMT-060-01 NCT02396342	10	Case series NR, MC, OL, SA Very high	Adults with HMB (severe or moderate)	AMT-060: 5×10^{12} gc/kg 2×10^{13} gc/kg	Frequency and incidence of AEs at 1 y, 5 y	No

ABR = annualised bleed rate; AE = adverse event; EQ-5D-5L = EuroQol 5-dimension health-related quality of life questionnaire–5 levels; FIX= factor IX; gc = gene copies; Haem-A-QoL = Haemophilia Specific Quality of Life Index; HMB = haemophilia B; MC = multi-centre design; mo = month(s); N = number of participants; N/A = not applicable; NR = non-randomised design; OL = open label design; SA = single arm design; SAE = serious adverse event; SOC = standard of care; wk = week(s); y = year(s).
a Risk of bias using the IHE Quality Appraisal Checklist for Case Series Studies (2016), Institute of Health Economics, Edmonton, Canada.
b Only primary outcomes are indicated for the earlier phase studies.
Source: Commentary Table 10 of MSAC 1728 ADAR+in-line commentary.

The Phase III study, HOPE-B (N=54) provided the pivotal evidence while the other studies were deemed supportive by the ADAR. The very small number of patients (N=3) limited the value of the Phase IIb study. The Phase I/II study with the precursor gene construct was a dose-ranging study

[6] Klamroth R, Bonner A, Gomez K, Monahan PE, Szafranski K, Zhang X, Walsh S, Wang D, Yan S (2024) 'Indirect treatment comparisons of the gene therapy etranacogene dezaparvovec versus extended half-life factor IX therapies for severe or moderately severe haemophilia B', *Haemophilia*, 30(1): 75-86. doi: 10.1111/hae.14882.

that employed the target dose (2 x 10^{13} gc/kg) in half the cohort (N=5). The ADAR did not synthesise results across the studies with either a meta-analysis or narratively.

HOPE-B was an open-label, single arm study with a before-and-after design, designated an interrupted time series by the commentary. Eligible patients underwent a lead-in period of 6 months prior to treatment with Hemgenix.

The median duration of follow-up at the time of the 3-year data (provided for review) was 36.2 months (range 12.1–48.0 months). For analyses specifically using data up to the 36-month visit, this corresponds to a median post-treatment duration of 36.1 months (range 12.1–39.0 months). The median duration of the lead-in period for the 54 patients who received Hemgenix was 7.1 months (range 6.0–10.6 months).

HOPE-B patients were recruited across 33 study sites leading to a correspondingly small number of patients per site (1.6 patients per site). Although this is difficult to avoid for an orphan indication, it is likely to introduce further risk of bias and the potential for confounding.

The study was directly applicable to the clinical question; the study inclusion and exclusion criteria were aligned with the PICO population. The commentary considered the HOPE-B study was reasonably well designed but at inherently high risk of bias given the single arm, open label design.

The commentary noted the primary objective of the HOPE-B study, when it commenced, was to demonstrate the effect of Hemgenix on endogenous FIX activity at 6 months post-treatment. A series of protocol amendments were implemented after study commencement, including a change to the primary endpoint to determination of annualised bleed rate (ABR) at 52 weeks post-treatment. In the same protocol amendment, the timeframe the ABR analysis commenced was changed from post-treatment Day 21 to post-treatment Month 7. HOPE-B patients were dosed between January 2019 and March 2020. The protocol amendment was dated 28 June 2021, around 4 months prior to database lock for the 18-month analysis.

Given that investigators were not blinded to patient FIX levels and bleeds, the commentary inferred that these changes to the primary endpoint were made subsequent to post-treatment results as they emerged and therefore did not consider the primary endpoint of the study to be pre-specified.

Three main analyses were presented for this ongoing study: the prespecified interim analysis for the primary efficacy endpoint (18 months) and two additional analyses (24 months pre-specified interim analysis and 36 months post-hoc analysis). No clinical study report (CSR) is planned for the 3-year data. A final analysis will be performed at 5 years post treatment when the study concludes (in 2025).

Evidence for the anti-AAV5 NAb titre assay

The HOPE-B study also provided direct evidence for the predictive effect of the anti-AAV5 NAb assay with respect to treatment outcome (Table 2). No patients were excluded from the study based on pre-treatment anti-AAV5 NAb titre.

Table 2 Key features of the included evidence for assessing the 9-point anti-AAV5 NAb assay

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base
Correlation	Unpublished cross-sectional comparison of index test compared to clinical utility standard	☒ k=1 n=30	Not assessed
Accuracy and performance of the test (cross-sectional accuracy)	No studies (note there is no established reference standard)	☐ k=0 n=0	NA
Change in patient management	No studies	☐ k=0 n=0	NA
Predictive effect (treatment effect variation)	Comparison of outcomes in patients with pre-existing anti-AAV5 NAb and without who received etranacogene dezaparvovec	☒ k=1 n=54 (21 with pre-existing anti-AAV5 NAbs)	High

AAV = adeno-associated virus; k = number of studies; n = number of patients; NA = not applicable; NAb = neutralising antibody.

The assay used in the HOPE-B study is the clinical utility standard. The proposed assay is a modification of this assay using 9 dilutions rather than 7 to extend the reporting range. No published studies comparing the 7-point assay with the 9-point assay were presented in the ADAR. The ADAR presented data from a whitepaper produced by Precision for Medicine, the commercial supplier of the assay. No attempt was made in the ADAR to undertake a critical appraisal of this evidence. The commentary noted redacted at the relevant decision threshold (around 1 in 900 using the 9-point assay) and considered the evidence extremely limited.

This clinical utility standard was not used in AMT-060-01, the only study to exclude participants based on pre-existing anti-AAV5 NAb titre. AMT-060-01 used a green fluorescent protein (GFP) reporter; re-testing with a more sensitive luciferase reporter subsequently identified participants with preexisting neutralising antibodies. Analysis of response in these patients was the basis for not excluding ant-AAV5 Nab positive patients from HOPE-B. The assay used in each study is shown in Table 3.

Table 3 Anti-AAV5 assays and related exclusion criteria for key clinical studies

Study	anti-AAV5 NAb assay	Related study exclusion criteria
HOPE-B (AMT-061-02)	Cell-based transduction assay with a luciferase reporter. "Point-based" titres calculated using software. 7-dilution points.	No exclusions based on antibody titre.
AMT-061-01	Cell-based transduction assay with a luciferase reporter.	No exclusions based on antibody titre.
AMT-060-01	Cell-based transduction assay with a GFP reporter. Pre-defined cut-point of 29%.	Negative for pre-existing anti-AAV5 NAbs. *Re-testing of patient samples with the cell-based assay revealed all 10 patients were positive.*

AAV = adeno-associated virus; GFP = green fluorescent protein; NAb = neutralising antibody.
Source: Adapted from Commentary Table 7 of MSAC 1728 ADAR+in-line commentary.

11. Comparative safety

Etranacogene dezaparvovec (Hemgenix)

The ADAR did not report safety according to the outcomes specified in the PICO confirmation.

Acute peri-infusion adverse effects

Acute peri-infusion events were common; infusion reactions occurred in 6/54 participants (11.1%). One subject prematurely discontinued treatment infusion due to hypersensitivity and received only a partial dose (10%) of Hemgenix. Three participants required a dose interruption.

Common adverse events

Post-treatment adverse events (AEs) occurring in at least 10% of patients at three years were mostly non-specific AEs suggestive of inflammatory or flu-like symptoms. Exceptions to this were enzyme elevations of alanine aminotransferase (ALT; in 13 [24.1%] patients), aspartate aminotransferase (AST; in 9 [16.7%] patients) and creatine kinase (in 8 [14.8%] patients). The liver enzyme elevations (ALT and AST) indicate a clear reaction focused on the liver, consistent with the Hemgenix mechanism of action and class effects observed with other AAV-based gene therapies. The significance of the moderately high number of patients with creatine kinase elevations was unclear.

There were 20 AEs of COVID-19 reported during the study which was underway at the height of the pandemic. This provides context for the high post-treatment incidence of nasopharyngitis (in 15 patients [28.0%]) and other AEs consistent with respiratory illness.

Serious adverse events

At 36 months post-treatment, 22 serious AEs (SAEs) had occurred, of which seven were bleeds or bleed-related, and a further two were arthroses or similar. These were considered consistent with events for a moderate-to-severe HMB patient population. Two SAEs of note were a death described as not treatment related and a case of hepatocellular carcinoma (HCC) in a patient with multiple risk factors (including a history of both hepatitis B and C and fatty liver disease). The assessment that this HCC was not treatment related was plausible. In comparison, the SAEs in the lead-in period were mainly muscle and joint events consistent with a HMB patient population.

At 36 months post-treatment, 13 neoplasms were reported in 7 individuals. Three of these were reported as AEs of special interest (AESIs) (the HCC noted above and two basal cell carcinomas). Aside from the HCC, very limited information on the neoplasms was provided in the ADAR.

Immune response

Laboratory values were consistent with an initial post-infusion immune or inflammatory response, with an increase in some inflammatory markers, some evidence of adaptive (cell-based) immune mechanisms and a sustained a humoral (antibody-based) response. Where reported as AEs, these events were typically managed with oral corticosteroid use.

Data for AAV5 anti-capsid T-cell response were inadequate due to problems with the assay (testing performed by redacted). Data beyond 12 months were not available. It was unknown whether more data would have permitted analysis to determine whether – similar to the anti-AAV5 humoral response – adaptive immunity also played a role in determining the patient response to Hemgenix and thus durability of effect.

Post treatment, and throughout the remaining study period, all patients experienced anti-AAV5 NAb titres at the upper limits of detection. There was no relationship between these levels and treatment efficacy, however the commentary noted the very high post-treatment tires would

interfere with other AAV-based gene therapies and thus preclude access to potential future HMB treatments.

Lack of efficacy

Criteria for how lack of efficacy was determined were not described in the ADAR. Given the inconsistencies in how patients with lack of efficacy were identified and presented, the commentary considered it would have been preferable for an independent assessment to be made to determine which HOPE-B patients experienced lack of efficacy.

Three patients experienced confirmed lack of efficacy, or product failure, in the HOPE-B post-treatment period. The first received only 10% of the infusion following a hypersensitivity reaction (pre-treatment anti-AAV5 titre redacted).

The second patient had a very high pre-treatment anti-AAV5 titre (3212.3; lack of efficacy reported post-treatment Day 14). This patient would not be eligible for treatment under the population defined in the PICO confirmation but could potentially access treatment under the ADAR's proposed funding indication where anti-AAV5 titre is used as a decision-making tool rather than a criterion for access. The ADAR proposed that patients with high titres may delay treatment until a lower titre is obtained.

The third patient experienced lack of efficacy later in the study (reported on post-treatment Day redacted; pre-treatment anti-AAV5 titre redacted). The third case was not described in the ADAR but was extracted from the 3-year data. The commentary noted that data were insufficiently mature to determine whether the third patient who developed lack of efficacy was the last of a small number of non-responders or represents the first of a subgroup of patients who will go on to show waning efficacy over the long term.

Based on mean FIX activity and FIX use, the commentary identified at least one further patient who could be considered a potential candidate for lack of efficacy. The number of patients reported to lack efficacy, and the frequency with which they emerge, were key in considering the validity of the efficacy extrapolation used to inform the economic evaluation.

It may have been useful for the applicant to:

- present data according to the following 3 post-treatment groups:
    (i) those that ceased prophylaxis for the entire follow-up phase
    (ii) those that ceased but restarted prophylaxis
    (iii) those that were unable to cease regular prophylaxis (includes at the same or a reduced dose).

Conclusion regarding safety

Given the HOPE-B study design, the commentary states that rare and common AEs will not be detectable in the clinical data. The design was not comparative nor was the sample size large enough to detect events in either the lead-in or post-treatment phases unless they were very common (that is, with a cumulative one-year incidence of at least 10%). While the investigators have assessed the HOPE-B AEs for treatment-relatedness, the commentary noted that the study design did not permit a true assessment of causality.

The commentary also noted that the PICO confirmation requested long-term AEs, however the duration of follow-up for the HOPE-B patients only extended to a median of 36.1 months. Reported AEs might be considered only medium-term, given the intervention is not reversible,

patients will be excluded from further AAV-based gene therapies, and patients are eligible from 18 years of age.

In summary, clinical management of HMB in moderate or severe patients with Hemgenix had similar safety at three years post-treatment compared to standard of care. The safety profile of Hemgenix beyond three years is uncertain given the small number of patients with longer follow-up in the supplementary studies.

Anti-AAV5 NAb titre assay

Regarding direct harms, the assay did not pose additional harms compared to any other serology test.

Indirect harms of the test could include patients being excluded from treatment with Hemgenix where it would be beneficial, or conversely receiving treatment where it may not be effective or where it may be less effective.

12. Comparative effectiveness

Etranacogene dezaparvovec (Hemgenix)

Bleeds and annualised bleed rate

Summary statistics of bleeds and ABR are presented in Table 4, noting the statistically significant reduction in bleeds as measured by the rate ratio at 18, 24 and 36 months. At 36 months, the pooled unadjusted ABR for the patient cohort was 0.9 compared to 4.11 during the lead-in period.

Table 4 Summary of bleeding episodes for etranacogene dezaparvovec (Hemgenix) – HOPE-B study at 36 months

Any bleeding episode	Lead-in period (N=54)	Post treatment period (N=54)		
		Month 7-18	Month 7-24	Month 7-36
Any episode, n (%)	40 (74.1)	20 (37.0)	27 (50.0)	31 (57.4)
Zero episodes, n (%)	14 (25.9)	34 (63.0)	27 (50.0)	After 21 d: 20 (37.0) After 6 mo: 23 (42.6)
Unadjusted ABR[a]	4.11	1.08	0.99	0.90
Adjusted ABR (95% CI)	4.19 (3.22, 5.45)	1.51 (0.81, 2.82)	1.51 (0.83, 2.76)	1.52 (0.81, 2.85)
Rate ratio (post-treatment / lead-in) (95% CI) p-value		**0.36 (0.20, 0.64)** **p=0.0002**	**0.36 (0.21, 0.63)** **p=0.0002**	**0.36 (0.20, 0.66)** **p=0.0004**

ABR = annualised bleeding rate; CI = confidence interval; d = days; FIX = factor IX; mo = months.
Note: One-sided p-value ≤ 0.025 for Post-treatment/Lead-In < 1 is regarded as statistically significant.
a Unadjusted ABR is calculated as the ratio of the total (pooled) patient number of bleeds to the total (pooled) patient time of observation (in years)
Source: Table 2-20 of MSAC 1728 ADAR+in-line commentary.

The aim of the HOPE-B study's primary efficacy endpoint was to compare the adjusted ABR for the 12 months post stable FIX expression (i.e. months 7-18 post-treatment) to that from the 6-month lead-in period. The upper bound of the 95% confidence interval for the rate ratio (0.64) was less than the prespecified margin (1.8). Thus, the HOPE-B study met the non-inferiority

criterion. A secondary inferential analysis of this endpoint subsequently established superiority, while the estimated reduction in the ABR between periods was 64% (RR = 0.36).

The commentary presented bleeds as a tornado plot of bleeds per month (Figure 1) to visualise the comparison between lead-in and post-treatment periods.

The commentary noted the following:

- Nine patients had more bleeds per month in the post-treatment phase compared to the lead-in phase. Aside from the patient with confirmed lack of efficacy (redacted), this may have been due to the marked difference in duration between the phases (6 months versus 36 months).
- Patient redacted may have been an outlier, showing high bleeds in both the lead-in and post-treatment phases. Perplexingly, neither FIX activity nor FIX replacement use corresponded to the high number of post-treatment bleeds in this patient. Nevertheless, this patient's unadjusted ABR over the post-treatment period (redacted after Day 21 or redacted after Month 7) was still reduced compared to the lead-in period ABR of redacted.
- At least three patients (redacted, redacted, redacted) experienced at least 10 bleeds in the post-treatment period along with <12% mean FIX activity (or 'contaminated' FIX activity due to FIX infusion use) and moderate FIX consumption of at least 0.5–1.0 infusions per month over the three years. It was not possible to distinguish between these cases and those with confirmed lack of efficacy based on the bleed data alone. All these patients were anti-AAV5 titre positive pre-treatment (titres of redacted, redacted, redacted, respectively).

Figure 1 Tornado plot of HOPE-B lead-in bleeds per month vs. post-treatment bleeds per month (0-36 months)

Figure redacted

FIX = factor IX.
Note: **Redacted** The median lead-in for the N=54 population was 7.1 months (range 6.0 – 10.6 months). Cumulative bleeds at 36 months (not including the first 21 post-treatment days) were used, which correlated to a median post-treatment duration of 36.1 months (range12.1 – 39.0 months).
Source: Developed by the Commentary, Figure 4 of MSAC 1728 ADAR+in-line commentary.

FIX activity levels

The applicant presented FIX activity as mean values. However, the commentary noted that FIX activity values represented 'uncontaminated FIX activity', which biased this outcome towards patients who responded well to Hemgenix. Patients who required frequent FIX replacement use had fewer uncontaminated values. Data representing patients with lack of efficacy was essentially absent from the FIX activity data.

The commentary summarised changes in putative disease severity in HOPE-B patients over time based on FIX activity (Table 5).

It may have been useful for the applicant to report the transition for the severe and mod-severe population over time separately (ideally a tabular and graphical transition plot).

Table 5 Patient status over time – HMB severity after etranacogene dezaparvovec (Hemgenix)

Status / severity of HMB	Definition of severity	Patients, n (%) at baseline	Patients, n (%) at 18 mo	Patients, n (%) at 24 mo	Patients, n (%) at 36 mo
Severe	FIX <1%	44 (81)	0[a]	0[a]	0[a]
Moderate Moderately severe Moderate only	FIX 1% to <5% 1% to <2% 2% to <5%	10 (19) 10 (19) 0	1 (1.9%) 0[a] 1 (1.9%)	1 (1.9%) 0[a] 1 (1.9%)	1 (1.9%) 0[a] 1 (1.9%)
Mild	FIX 5% to <40%: 5% to <12% 12% to <40%	0	32 (59.3%) 2 (3.7%) 30 (55.6%)	31 (57.4%) 4 (7.4%) 27 (50.0%)	29 (53.7%) 3 (5.6%) 26 (48.1%)
Non-haemophilic	FIX 40% to 100%	0	17 (31.5%)	18 (33.3%)	18 (33.3%)
Death	–	–	1 (1.9%)	1 (1.9%)	1 (1.9%)
Data missing / uninterp.[b]	–	–	1 (1.9%)	1 (1.9%)	2 (3.7%)
Lack of efficacy	–	–	2 (3.7%)	2 (3.7%)	3 (5.6%)
	Total:	54 (100%)	54 (100%)	54 (100%)	54 (100%)

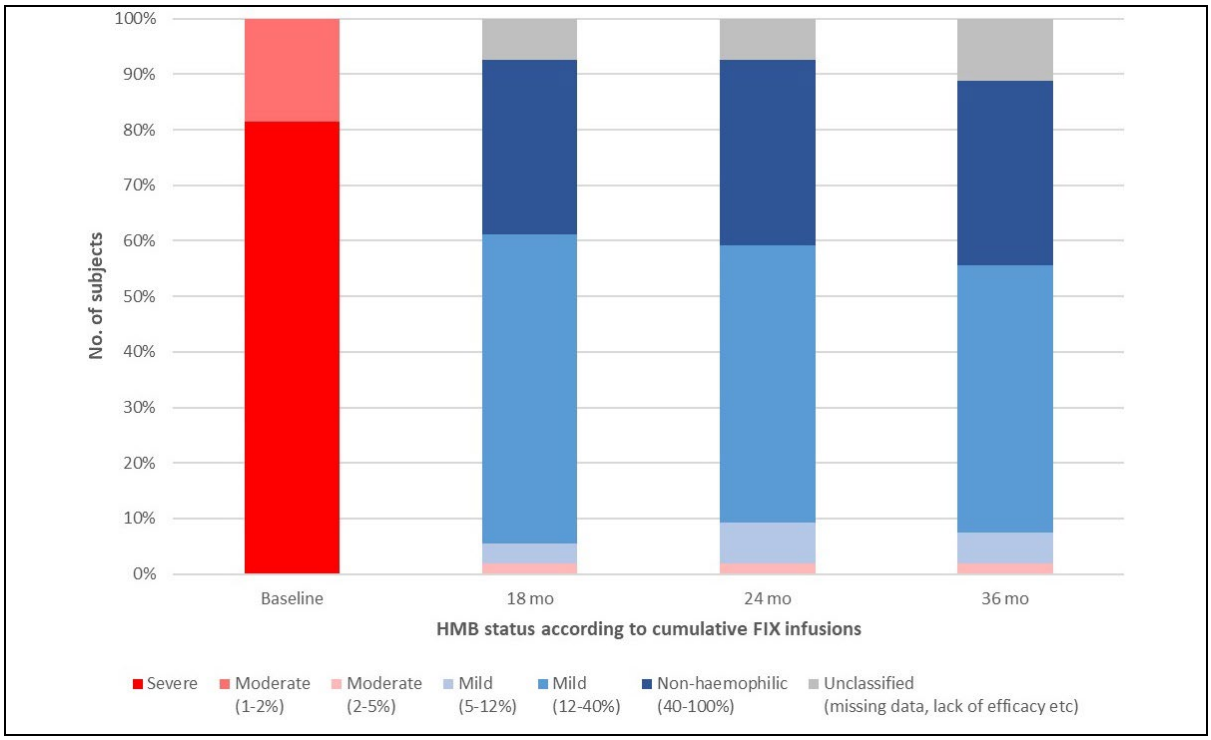
aPPT = Activated Partial Thromboplastin Time; FIX = factor IX; HMB = haemophilia B; mo = months; uninterp. = uninterpretable.
a Although FIX activity values indicate zero patients with severe or moderately severe HMB, it is unknown whether the patients with lack of efficacy ought to have been shown in these categories (noting all FIX activity values for those patients were contaminated).
b Missing due to a missed visit. Uninterpretable due to an unusually high value outside the upper limit of normal.
Source: Commentary Table 23 of MSAC 1728 ADAR+in-line commentary.

The commentary noted that the FIX activity values at baseline were imputed based on patients known disease categorisation and may have been underestimates compared with actual patient values prior to Hemgenix treatment.

Around one-third of patients could be regarded as non-haemophilic based on FIX activity (> 40%) over the 36 months. Between 50–60% of patients were in the mild HMB category. Fourteen patients (25.9%) were consistently above 40% FIX activity at all three timepoints.

A visualisation of the changes in patient severity over the course of the study was plotted in the commentary (Figure 2) to show the categories as proportions of the whole cohort (N=54), including the patients that were under-represented by the FIX activity mean values.

Figure 2 Visualisation of HOPE-B patient disposition according to severity of FIX activity at 36 months



FIX = factor IX; HMB = haemophilia B.

Source: Developed by the Commentary, Figure 5 of MSAC 1728 ADAR+in-line commentary.

FIX replacement use and prophylaxis

Post-treatment FIX replacement therapy consumption decreased significantly from the pre-treatment lead-in period (Table 6), with a percentage reduction of at least 95% at all timepoints.

It may have been useful for the applicant to report the proportion of patients who were on and off prophylaxis at each post-treatment timepoint, and separately any that ceased then returned to prophylaxis, according to pre-treatment disease severity. This description of trajectory of patient response may be informative in the development of the risk share-arrangements.

Table 6 Annualised exogenous FIX replacement therapy consumption up to 36 months (HOPE-B)

Consumption IU/year	Lead-in (N = 54)	Post-treatment period (N = 54)[a]				
		Month 0-6	Month 7-12	Month 13-18	Month 19-24	Month 25-36
Unadjusted mean (SD)	257,338.8 (149,013)	12,912.9 (37,093)	8399.1 (29,721)	8473.4 (28,761)	9589.6 (29,127)	10,529.8 (36,940)
Difference, Post-treatment – Lead-in period		Month 0-6	Month 7-18	Month 7-24	Month 7-36	Year 0-3
Unadjusted mean (SD)	-	-244,425.8 (143,457)	-248,831.4 (155,063)	-248,446.5 (154,659)	-246,969.1 (152,205)	-246,763.4 (150,421)
Adjusted mean (SE)	-	-244,425.8 (19,522)	-248,831.4 (21,101)	-248,446.5 (21,046)	-246,969.1 (20,712)	-246,763.4 (20,470)
Mean reduction	-	95%	97%	97%	96%	96%
95% CI	-	-283,582, -205,270	-291,155, -206,507	-290,660, -206,233	-288,997, -206,250	-287,820, -205,706
p-value	-	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001

CI = confidence interval; FIX = factor IX; IU= international units; SD = standard deviation; SE = standard error.
a One subject died prior to Month 19.
Source: Table 2-24 of MSAC 1728 ADAR.

Examination of the HOPE-B patient-level data showed the mean value masked variability in patient response (Figure 3).

Figure 3 Total FIX replacement use (total number of injections per patient) at 36 months – HOPE-B, excluding first 21 days post-treatment infusion (actual use; n=54)

Figure redacted

FIX = factor IX.
Source: Developed by the Commentary, Figure 6 of MSAC 1728 ADAR+in-line commentary.

The commentary visualisation of total FIX replacement use at 36 months (Figure 3) showed the three patients with confirmed lack of efficacy at the top of the chart. The late emergent case (redacted) was not so different from other patients with slightly lower FIX use (likely given the more recent onset resumption of prophylaxis). The patient fourth highest on the chart (redacted), redacted and an average dose across the post-treatment period of redacted IU/kg (redacted). This patient shared most of the features in terms of bleeds and FIX use with patient redacted who had confirmed lack of efficacy.

The applicant stated that after Hemgenix treatment, 51/54 (94.4%) subjects in the HOPE-B patient cohort discontinued and remained free of standard of care continuous FIX prophylaxis from Day 21 to Month 36 post dose. The commentary noted that data were not available in a format that allowed this claim to be confirmed, but aside from the three individuals confirmed to have lack of efficacy, this appears to be supported by the post-treatment FIX use data.

Health-related quality of life (HRQoL)

Pre- and post-treatment EuroQol 5-dimension 5 level questionnaire (EQ-5D-5L) results are presented in Table 7. The commentary noted a statistically significant difference was reported at the 24-month timepoint for the EQ-5D-5L (least squares [LS] mean difference 0.0439 (standard

error [SE] 0.01919; 95% CI: 0.0054, 0.0823; p-value 0.0132) (2-year CSR) but at no other timepoint. The ADAR did not specify a minimally clinically important difference, however a value of 0.07 is reported in the literature and at no time point was the difference in score greater than this value.

Table 7 EQ-5D-5L Index scores (HOPE-B)

	Lead-in (N=54)	Post-treatment period (N=54)[a]				Difference vs. Lead-in
		Month 12	Month 24	Month 36	Month 12-36	Month 12-36
LS mean (SE)	0.7857 (0.04088)	0.8334 (0.02581)	0.8417 (0.01976)	0.8230 (0.02726)	0.8327 (0.02160)	0.0373 (0.02084)
95% CI	0.7037, 0.8677	0.7817, 0.8852	0.8021, 0.8814	0.7683, 0.8776	0.7894, 0.8760	-0.0045, 0.0791
p-value	-	-	-	-	-	0.0395

CI = confidence interval; EQ-5D-5L = EuroQol 5-dimension 5-level questionnaire; LS = least squares; SE = standard error.
a One subject died before Month 19.
Source: Table 2-26 of MSAC 1728 ADAR+in-line commentary.

Change in HAEM-A-QoL results are presented in Table 8. At 36 months, HOPE-B patients showed a mean reduction in HAEM-A-QoL scores. The ADAR did not report a minimal clinically important difference for this instrument. The change in treatment domain may reflect a clinically meaningful reduced treatment burden of Hemgenix.

Table 8 Change from the Lead-In period in HAEM-A-QoL Index Scores (HOPE-B)

Domain, statistic	Month 12	Month 24	Month 36
Total			
LS mean (SE)	-5.50 (0.97)	-6.2 (1.19)	-6.1 (1.28)
95% CI	-7.42, -3.58	-8.6, -3.8	-8.7, -3.6
One-sided p-value	< 0.0001	< 0.0001	< 0.0001
Feelings			
LS mean (SE)	-9.42 (1.938)	-9.10 (1.957)	-9.50 (2.242)
95% CI	-13.26, -5.59	-13.02, -5.17	-14.00, -5.01
One-sided p-value	< 0.0001	< 0.0001	< 0.0001
Treatment			
LS mean (SE)	-14.88 (1.789)	-14.24 (2.103)	-13.40 (2.224)
95% CI	-18.42, -11.34	-18.46, -10.02	-17.86, -8.94
One-sided p-value	< 0.0001	< 0.0001	< 0.0001
Work / School			
LS mean (SE)	-4.99 (1.825)	-5.24 (2.192)	-5.68 (1.979)
95% CI		-9.64, -0.85	-9.65, -1.71
One-sided p-value		0.0102	0.0029
Future			
LS mean (SE)	-5.02 (1.736)	-6.57 (1.828)	-5.75 (2.094)
95% CI	-8.45, -1.58	-10.24, -2.90	-9.95, -1.55
One-sided p-value	0.0023	0.0004	0.0041

LS = least squares; SE = standard error.
Source: Table 2-27 of MSAC 1728 ADAR+in-line commentary.

Other outcomes

Data on target joints presented in the ADAR were limited.

Haemophilia Joint Health Score (HJHS) was not a specified outcome in the ratified PICO confirmation, but the commentary noted a measurable improvement was reported using this instrument. The 3-year data reported the largest improvement thus far (following statistically significant improvements at 18 and 24 months), which suggested joint health was continuing to improve at 36 months.

Conclusion regarding effectiveness

The HOPE-B study showed a significant benefit over 36 months follow-up in terms of bleeds, FIX activity and FIX use, and to a lesser extent in terms of joint health and quality of life, although there were variations in response across the cohort. The size of the effect was substantial and suggested that despite the low-level evidence - lacking in a parallel control group - treatment efficacy was supported. However, the magnitude of this benefit compared to best standard of care and the durability of these effects was uncertain.

Based on the data cut-offs from the HOPE-B 3-year data, results of visits up to 4 years should be available from redacted.

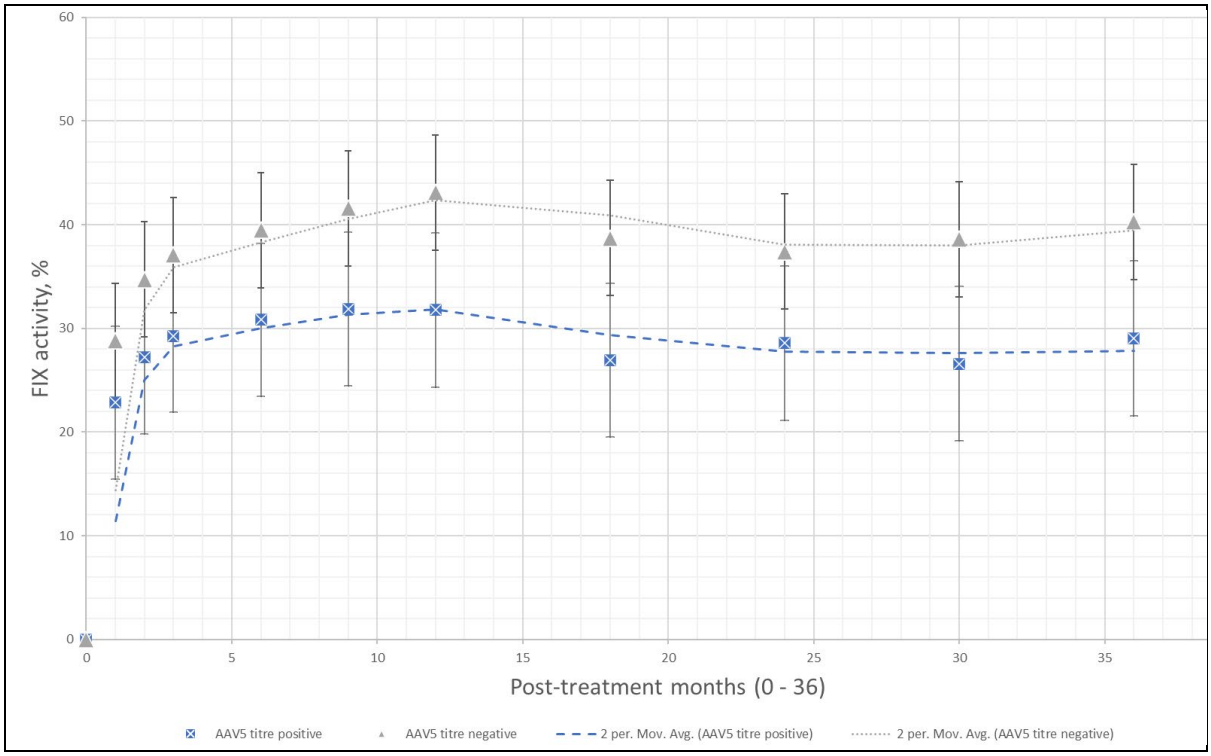
Anti-AAV5 NAb titre assay

Direct evidence

During the HOPE-B study, patients were tested for anti-AAV5 titre at screening and then at each of the monthly visits prior to Hemgenix infusion. The pre-treatment value on the day of infusion was reported as the patient's titre. Of the 54 treated participants, 21 were positive for anti-AAV5 NAbs. There was limited variability in the pre-treatment titre recorded at each visit. Where variability was observed, it is unknown if this was due to natural variability in the patient or due to the nature of the AAV5 NAb test.

Levels of endogenous FIX were numerically lower in the AAV positive titre group at all time points, but the difference was not statistically significant (Figure 4). Although linear regression indicated a trend to lower mean FIX activity in patients with higher anti-AAV5 NAb titres at baseline, this was also non-significant. Data were not available for a subgroup analysis of patients above versus those below an AAV5 titre threshold (such as 1:100 or 1:300), which may have been informative.

Figure 4 FIX activity, AAV5 titre positive vs. negative (change from baseline, LS mean % over time, with 95% CI)



AAV5 = adeno-associated virus type 5; CI = confidence interval; FIX = factor IX; LS = least squares.
Source: Developed by the Commentary, Figure 1 of MSAC 1728 ADAR+in-line commentary.

The HOPE-B study pre-specified a subgroup analysis reporting ABR change from baseline based on AAV5 NAb titre status. The unadjusted ABR for the titre negative group at 36 months was 0.63, whereas for the titre positive group it was 1.42 (Table 9). In the adjusted analyses, the rate ratio for the titre negative group was considerably lower than that for the titre positive group (and the latter did not reach significance). Excluding the patients with a very high pre-treatment titre, who would be excluded under the proposed indication, this rate ratio remains non-significant. This may partly be a function of the statistical approach to adjustment where all bleeds were included but only time within 5 half-lives of FIX treatment was included.

Table 9 Annualised bleed rate in AAV5 titre negative versus AAV5 titre positive[a] participants (HOPE-B)

Any bleeding episode	Lead-in period (N=54)	Post treatment period (N=54)		
		Month 7-18	Month 7-24	Month 7-36
AAV5 titre negative (n=33)				
Unadjusted ABR[b]	3.76	0.90	0.79	0.63
Adjusted ABR (95% CI) Primary endpoint definition	3.79 (2.55, 5.63)	0.93 (0.44, 1.98)	0.80 (0.39, 1.67)	0.64 (0.33, 1.24)
Rate ratio (adjusted ABR post-treatment / lead-in) (2-sided Wald 95% CI), p-value	-	**0.25 (0.14, 0.43) p<0.0001**	**0.21 (0.12, 0.37) p<0.0001**	**0.17 (0.10, 0.28) p<0.0001**
AAV5 titre all positive (n=21)[a]				
Unadjusted ABR[b]	4.64	1.40	1.37	1.42
Adjusted ABR (95% CI) Primary endpoint definition	4.97 (3.66, 6.75)	8.77 (1.97, 39.06)	12.59 (2.95, 53.66)	17.71 (3.98, 78.72)
Rate ratio (adjusted ABR post-treatment / lead-in) (2-sided Wald 95% CI), p-value	-	1.77 (0.41, 7.62) p=0.2232	2.56 (0.61, 10.66) p=0.0986	3.62 (0.82, 15.98) p=0.9556
AAV5 titre <3000 (n=20)[a]				
Unadjusted ABR[b]	4.84	1.13	1.18	1.30
Adjusted ABR (95% CI) Primary endpoint definition	4.30 (3.08, 6.00)	1.30 (0.63, 2.71)	1.65 (0.84, 3.26)	2.14 (0.96, 4.77)
Rate ratio (adjusted ABR post-treatment / lead-in) (2-sided Wald 95% CI), p-value	-	**0.30 (0.15, 0.62) p=0.0005**	**0.39 (0.18, 0.82) p=0.0065**	0.49 (0.21, 1.16) p=0.0532

AAV5 = adeno-associated virus type 5; ABR = annualised bleed rate; CI = confidence interval.

Note: values in bold met criteria for statistical significance.

a Two AAV5 titre positive analysis sets are shown, all titre positive (n=21) and titre <3000 (n=20) which excludes the high antibody titre individual [**redacted**]. The highest titre in the <3000 analysis was 678 (7-point assay).

b Unadjusted ABR is calculated as the ratio of the total (pooled) patient number of bleeds to the total (pooled) patient time of observation (in years).

Source: adapted from Commentary Table 6 of MSAC 1728 ADAR+in-line commentary.

Correlation of clinical utility standard against proposed test

The assay used in the HOPE-B study – the clinical reference standard – was a 7-point assay. The proposed test is a 9-point assay. The tests are undertaken in the same laboratory and use the same technical approach, differing only in the number of dilutions undertaken to extend the range. The data provided suggest that they are sufficiently well correlated, however the data are limited in size and range.

The clinical reference standard was not considered sufficiently valid or reliable by the United States Food and Drug Administration (FDA) for its purpose as a companion diagnostic. FDA's clinical review[7] of Hemgenix commented regarding the assay:

> "Assay validation for the neutralizing antibodies to AAV was performed by [the Center for Devices and Radiological Health (CDRH)]. CDRH determined that the data provided to support the assay utilized in the clinical trials and for the modified assay submitted as a

[7] https://www.fda.gov/vaccines-blood-biologics/vaccines/hemgenix

companion diagnostic in a Premarket Application (PMA) were not sufficient to support assay validation. The reported results from the assay utilized in the clinical trial should be interpreted with caution as they are not considered validated or reliable."

No pre-market authorisation was approved for this assay and it remained unapproved for the United States market.

Clinical claim

The ADAR concluded that, in comparison to continued standard care for HMB with no gene therapy, Hemgenix will provide a significant and clinically important improvement in effectiveness, with an acceptable and overall non-inferior safety profile.

The commentary separated out the clinical claims by outcome and concluded the following.

Safety:

- The use of Hemgenix resulted in inferior safety compared with standard of care for the outcomes of peri-infusion AEs and laboratory indicators of safety.
- The use of Hemgenix resulted in non-inferior safety compared with standard of care for the outcomes of medium-term AEs (up to 36 months post-infusion).
- There were patients with lack of efficacy and reduced efficacy. The sample size was too small for the factors contributing to this to be established.
- Overall, the use of Hemgenix had non-inferior safety over the period of the clinical study.

Effectiveness:

- The use of Hemgenix resulted in superior effectiveness compared with standard of care for annualised bleed rates, endogenous FIX activity, change in patient disease categorisation and FIX utilisation.
- The use of Hemgenix resulted in non-inferior effectiveness compared with standard of care over 36 months for HRQoL outcomes. The small sample size of the key study was likely to be a limitation for establishing superiority for these outcomes.
- There were insufficient data available to establish the effectiveness of Hemgenix compared with standard of care for the outcome of occurrence and resolution of target joint bleeding.
- There were no data available to establish the effectiveness of Hemgenix compared with standard of care for the outcomes of central venous access no longer required and events of central venous access-related sepsis or thrombosis.
- The use of Hemgenix in patients who were AAV5 NAb positive trended towards inferior effectiveness compared to patients who were AAV5 NAb negative, however there were insufficient data to establish the clinical relevance of this. Further patient factors may complicate this analysis.

All of the clinical conclusions were limited to a follow-up period of 36 months. The commentary noted that Hemgenix is intended for life-time treatment, is irreversible and likely precludes patients from accessing treatments in the future. Treatments for HMB (gene therapies and non-gene therapies) are likely to evolve rapidly.

13. Economic evaluation

A cost-utility analysis (CUA) was presented in the ADAR. The model was composed of two phases:

1. A short-term decision tree describing the results of a modified NAb assay with 9-point luciferase anti-AAV5 NAb assay to classify patients as suitable for genetic treatment with an AAV carrier.
2. Long-term (25 years) Markov model with two health states (alive and dead). Transition probabilities were informed by general Australian population mortality rates adjusted by a standardised mortality ratio (SMR) in HMB patients, and the outcomes reported in the HOPE-B study (FIX activity levels, annualised bleeding rates, annualised FIX consumption, HRQoL and incidence of SAEs).

An overview of the economic model is provided in Table 10.

Table 10 Summary of the economic evaluation

Component	Description
Perspective	Healthcare perspective
Population	Adult patients (≥ 18 years) with severe or moderately severe HMB (FIX activity ≤ 2%) without inhibitors, who are receiving regular prophylaxis using FIX concentrate
Prior testing	FIX inhibitor titre testing Liver health assessments (enzyme testing, hepatic ultrasound and elastography)
Intervention	Test: Improved Precision for Medicine (PfM) 9-point luciferase assay Treatment: Single IV infusion of etranacogene dezaparvovec at a dose of 2×10^{13} gc/kg
Comparator	Continuous prophylaxis with FIX replacement therapy
Type(s) of analysis	Cost utility analysis
Outcomes	Quality-adjusted life years gained
Time horizon	25 years in the model base case (versus 3 years in the HOPE-B study)
Computational method	Initial decision tree for the anti-AAV5 NAb test followed by a Markov, modelling treatment outcomes
Generation of the base case	Modelled analysis using 3-year data from the HOPE-B study, and 22 years of extrapolation of FIX activity level
Health states	Alive and dead
Cycle length	6 months
Transition probabilities	Decision tree: • Point prevalence of anti-AAV5 NAb >1:900 (9-point assay) • Probability of a false negative result using proposed assay Markov model: • General population mortality • Standardised mortality ratio for HMB • HR for death following treatment with etranacogene dezaparvovec Health indicators: • Annualised bleeding rate (events/cycle) • FIX prophylaxis proportion (% of patients) • Annualised FIX consumption (IU/cycle) • Health utilities (EQ-5D Index Score) • SAE incidence (events/cycle)
Discount rate	Annual rate of 5% for both costs and outcomes
Software	Microsoft Excel

AAV = adeno-associated virus; EQ-5D = EuroQol five-dimension questionnaire; FIX = factor IX; gc/kg = gene copies per kilogram; HMB = haemophilia B; HR = hazard ratio; IU = international units; IV = intravenous; NAb = neutralising antibodies; SAE = serious adverse event.
Source: Table 3-1 of MSAC 1728 ADAR+in-line commentary.

The commentary considered the two-health state Markov structure an oversimplification of the natural history of the disease as it did not capture the long-term consequences of HMB. For example, recurrent joint bleeding events have been shown to commonly lead to joint damage and deterioration of functional status over time that can progress to requiring joint replacement surgeries and reduced quality of life. An alternative could have been a model with health states defined by bleeding severity, which was prospectively assessed in the HOPE-B study. Published economic analyses and those considered by other health technology assessment (HTA) agencies used more complex models that included health states for joint bleeds and non-joint bleeds or for joint damage.

In the model, a patient with a FIX activity level closer to the lower limit had the same quality of life and incurred the same costs as a patient with high FIX activity. Likewise, transitions related to potential treatment failures were not incorporated in the model, which assumed uniform patient trajectories where the full consequences of expression loss were not captured. The commentary asserted that a more informative economic evaluation incorporating severity-specific and failure-specific health states directly informed by the HOPE-B study could have produced more accurate and meaningful results.

The healthcare resources and costs considered in the model were the cost of serum collection to the MBS for anti-AAV5 NAb testing, cost of Hemgenix, cost of FIX replacement therapy, cost of bleeds and cost of unspecified SAEs. The model did not consider the costs associated with determining eligibility for Hemgenix (with the exception of the cost of the anti-AAV5 NAb assay), the costs associated with post-treatment monitoring or additional costs associated with delivering the comparator.

Time horizon and extrapolation of trial results

The base case assumed a 25-year time horizon based on a published analysis[8] that aimed to estimate the long-term durability of FIX activity levels after receiving Hemgenix using data from the HOPE-B study. The published analysis was updated to include 36-month follow-up from the HOPE-B study. The extrapolation included data from 50 patients with 30 months follow-up, dropping to 10 patients with 36 months and 4 patients with 42 months.

The long-term FIX activity levels in the model were estimated using a mixed linear model with data from the HOPE-B study and AMT-061-01 study considering covariates: (1) pre-existing AAV5 NAb titres; and (2) post-infusion ALT elevations within 90 days. The extrapolation analysis excluded two patients who did not respond to Hemgenix.

A third patient experienced lack of efficacy at 857 days post-treatment. The extrapolation truncated the last FIX activity level for this patient, and thus assumed a decline of FIX activity level to around 2.5%, representing an increase from baseline. Using this analysis, 10.5% of patients fall below the 3% FIX activity threshold at 25 years. When the long-term durability analysis assumed return to baseline for this patient, the extrapolation analysis predicted 24.2% of patients fall below the 3% FIX activity threshold at 25 years.

The commentary noted that the extrapolation analysis had some important limitations. Patients requiring external FIX after treatment with Hemgenix likely had FIX activity levels contaminated

[8] Shah J, Kim H, Sivamurthy K, Monahan PE, Fries M (2023) 'Comprehensive analysis and prediction of long-term durability of factor IX activity following etranacogene dezaparvovec gene therapy in the treatment of hemophilia B', *Curr Méd Res Opin*, 39: 227–237. doi: org/10.1080/03007995.2022.2133492.

and those records were excluded from the analysis. This might lead to selective omission of data from patients responding poorly to the intervention. As a consequence:

- patients with poorer responses may have been underrepresented, overstating treatment effectiveness
- variability in responses for these patients could also have been underestimated if measurements during periods of poor response were excluded.

Additionally, the model assumed data were missing at random, while the commentary noted that missingness was probably related to treatment response, since FIX activity level records for patients requiring FIX replacement were excluded. The small number of patients and limited follow-up available in the clinical studies increased uncertainties about durability of treatment that are not accounted for in the extrapolation analysis.

Results

The results of the CUA were driven by differences in costs between the arms. During the study period, the intervention arm's costs were dominated by the higher upfront cost of Hemgenix in the first cycle, compared to the more gradual accrual of costs for FIX prophylaxis over 3 years in the comparator arm. Conversely, over the longer-term extrapolation period, the total costs were lower for the intervention arm since Hemgenix was assumed to be administered only once per patient in their lifetime and annualised FIX consumption was greatly reduced (9,590 IU/year). In contrast, the comparator arm continued to accumulate costs associated with lifelong FIX prophylaxis over the 25-year time horizon (257,339 IU/year). As a result of these differences in cost accumulation, the intervention was dominant over a lifetime horizon. Table 11 showed the total discounted average cost and QALYs per patient at different time horizons. Time horizon was a key driver of the model. In the base case analysis, the treatment effect of Hemgenix would need to last at least redacted years to become the dominant strategy compared to continuous prophylaxis.

Table 11 Results of the stepped economic analysis

Step	Etranacogene dezaparvovec (Hemgenix)	Continuous prophylaxis	Increment	ICER ($/QALY)
Step 1 – Comparative study data; Trial based; Time horizon: 3 years				
Costs	$redacted	$986,306	$redacted	$redacted
QALY	2.33	2.23	0.10	
Step 2 – Study evidence extrapolated; Time horizon: 8 years				
Costs	$redacted	$2,309,627	$redacted	$redacted
QALYs	5.50	5.23	0.27	
Step 3 – Study evidence extrapolated; Time horizon: 25 years				
Costs	$redacted	$4,714,853	-$redacted	Dominant
QALYs	11.23	10.68	0.56	

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.
Source: Table 3-9 and Commentary Table 28 of MSAC 1728 ADAR+in-line commentary.

The model results were sensitive to assumptions around costs, particularly the price of FIX therapy (Table 12).

Table 12 Key drivers of the model

Description	Method/Value	Impact Base case: ICER dominant
Time horizon	Treatment effect continued beyond 3-year study period for up to 25 years. Waning of FIX activity level extrapolated from study data.	*High, favours intervention* *Reducing the time horizon from 25 years to 3 years resulted in change of comparative cost-effectiveness from dominance (-$**redacted** per QALY) to $**redacted** per QALY.*
Annualised FIX use	FIX use in the comparator arm (257,339 IU/ patient/ year) was informed by the study and not tested in a sensitivity analysis nor adjusted by FIX consumption in the Australian cohort of HMB patients.	*High, favours intervention* *A 15% reduction of FIX use in the comparator arm increased the ICER by 47% (but still dominant).*
Cost of the comparator	Extended half-life FIX listed price of $1.42 per IU. Short half-life FIX listed price of $0.79 per IU.	*High, favours intervention* *A price reduction of extended half-life FIX of 25% increased the ICER by 70% (but still dominant).*

FIX = factor IX; ICER = incremental cost-effectiveness ratio; IU = international unit; QALY = quality-adjusted life year.
Source: compiled for the executive summary.

Sensitivity analysis

The results of key univariate sensitivity analyses are summarised below (Table 13).

The model was highly sensitive to the time horizon employed, with an average of redacted-fold increase in the ICER for each additional year modelled in the first 10 years. An alternative time horizon of 8 years was used in the sensitivity analysis, aligning with the available long-term data from the AMT-060-01 study (precursor intervention, N=10).

The model was also sensitive to assumptions around average FIX replacement consumption during the lead-in period. FIX consumption in the lead-in period informed by ABDR data for moderate patients of 196,031 IU/year/patient was tested in a sensitivity analysis performed for the commentary (the FIX consumption modelled in the base case was 257,339 IU/year/patient). When accounting for the lower FIX consumption of moderate HMB patients compared to severe HMB patients, the model predicted it would take redacted years for Hemgenix to be considered dominant.

In a sensitivity analysis performed for the commentary where the extrapolation analysis was informed by the last activity level from the patient who failed Hemgenix after 24 months (resulting in 24.2% of patients with FIX activity below 3% at 25 years), the resulting ICER was still dominant at -$redacted.

The commentary noted that the model failed to consider the full life expectancy of younger patients, as the time horizon was 25 years in the base case and extended to 79 cycles (39.5 years) in sensitivity analysis. A cohort starting at 18 years of age results in a dominant ICER (- $redacted) with redacted years of efficacy needed to reach dominance. However, this sensitivity analysis did not consider the possibility of younger patients requiring resumption of FIX prophylaxis as they age due to structural limitations of the model provided, nor their ineligibility for future treatments.

Table 13 Selected sensitivity analyses

Analysis	Incremental cost	Incremental QALY	ICER ($/QALY gained)	Time to dominance
Base case	**-$redacted**	**0.56**	**Dominant**	**redacted years**
Time horizon: 8 years	**$redacted**	0.27	**$redacted**	NA
Discount rate: 0%	-**$redacted**	0.916	-**$redacted**	**redacted** years
AFC in the lead-in period for moderate patients = 196,031 IU/year/patient	-**$redacted**	0.56	-**$redacted**	**redacted** years
Rate of FIX activity level decline: 24.2% <3% at 25 years in the extrapolation	-**$redacted**	0.53	-**$redacted**	**redacted** years
Starting age of the cohort: 18 years	-**$redacted**	0.59	-**$redacted**	**redacted** years

AFC = annualised FIX consumption; FIX = factor IX; ICER = incremental cost-effectiveness ratio; IU = international units; NA = not applicable; QALY = quality adjusted life year.
Source: Commentary Table 29 of MSAC 1728 ADAR+in-line commentary.

Table 14 Additional sensitivity analysis provided in the applicant's pre-ESC response

Analysis	Value used in the model	Description	Time horizon	ICER
Base case			25 years	-**$redacted**
Starting age of the cohort	18 years	Sensitivity analysis conducted by the evaluators	25 years	-**$redacted**
Starting age of the cohort	18 years	Additional sensitivity conducted in response to Commentary by CSL Behring	40 years	-**$redacted**
Starting age of the cohort	18 years	Additional sensitivity conducted in response to Commentary by CSL Behring*	82 years	-**$redacted**

*For this sensitivity the analysis, the model continues to assume a 1% per annum loss of response up to a time horizon of 82 years.
Source: Table 3 of MSAC 1728 Applicant's Pre-ESC Response

14. Financial/budgetary impacts

The ADAR used a mixed epidemiology and market-based approach to estimate the uptake and financial implications for the proposed introduction of Hemgenix for the treatment of HMB.

The eligible patient population was estimated from ABDR data and assumed to have a stable growth rate. The ADAR anticipated the uptake in Australia to be low with the base case being a rate of **redacted**% in Year 1, **redacted**% in Year 3 and **redacted**% in all other years. The ADAR and commentary acknowledged uncertainty in these estimates.

The AHCDO Gene Therapy Roadmap considered the capacity of hub sites to deliver gene therapy a medium level risk to implementation and proposed to model expected patient volume to inform resourcing decisions. It estimated that hubs could support a throughput of around 1 to 2 patients receiving gene therapy per week. The modelling by AHCDO was proposed to be undertaken in the short term and would be useful to inform the estimated uptake rate.

Only the costs of Hemgenix and of the comparator FIX products were included in the financial analysis. The commentary noted that the TGA and the AHCDO Roadmap both specified pre-

treatment testing and screening and post-treatment monitoring. These costs were not modelled, nor were costs of managing AEs, including corticosteroids for treating infusion-related immune response. These costs are much smaller than the treatment costs and funding may be a mix of MBS and public hospital, however their exclusion does not reflect the ongoing resources required to deliver the intervention.

The financial implications to the national blood arrangements resulting from the proposed listing of Hemgenix are summarised in Table 15. In this analysis, Hemgenix was cost-saving to the national blood arrangements by Year 9 (not shown).

Table 15 Net financial implications of etranacogene dezaparvovec (Hemgenix) to the national blood arrangements

Parameter	2025	2026	2027	2028	2029	2030
Estimated use and cost of the proposed health technology						
Number of people eligible for etranacogene dezaparvovec	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**
Number of people who receive etranacogene dezaparvovec	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**
Cost to national blood arrangements	$**redacted**	$**redacted**	$**redacted**	$**redacted**	$**redacted**	$**redacted**
Change in use and cost of other health technologies						
Total FIX cost-offsets	$**redacted**	$**redacted**	$**redacted**	$**redacted**	$**redacted**	$**redacted**
Net financial impact to national blood arrangements	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**

FIX = factor IX.

Source: Table 4-4, Table 4-5 and Table 4-9 of MSAC 1728 ADAR+in-line commentary.

Given the uncertainty regarding uptake, and the different assumptions in the ADAR compared to the AHCDO Gene Therapy Roadmap, the commentary performed a sensitivity analysis with a constant 10% uptake rate (not shown) and constant 20% (Table 16) uptake rate, noting that as patients are treated, the eligible (prevalent) population declines so the number of patients accessing treatment each year declines.

Under the 10% scenario, the initial net cost to the national blood arrangements is higher ($redacted in Year 1, with redacted patients treated) but declines thereafter due to the declining prevalent population and the accumulated offsets due to reduced FIX treatment. The scenario is cost saving in Year 8. With a higher uptake rate of 20% (Table 16), the initial net costs are higher again at $redacted in Year 1 (redacted patients treated); however, the offsets accumulate more rapidly and therefore the intervention becomes cost-saving more quickly.

Table 16 Net financial implications of etranacogene dezaparvovec (Hemgenix) to the national blood arrangements with 20% uptake rate

Parameter	2025	2026	2027	2028	2029	2030
Number of people eligible for etranacogene dezaparvovec	redacted	redacted	redacted	redacted	redacted	redacted
Number of people eligible excluding those already treated	redacted	redacted	redacted	redacted	redacted	redacted
Number of people who receive etranacogene dezaparvovec	redacted	redacted	redacted	redacted	redacted	redacted
Cost to national blood arrangements(etranacogene dezaparvovec treatment)	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Change in use of FIX	-$redacted	-$redacted	-$redacted	-$redacted	-$redacted	-$redacted
Net financial impact to national blood arrangements	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted

FIX = factor IX.
Source: Commentary Table 33 of MSAC 1728 ADAR+in-line commentary.

15. Other relevant information

Risk share proposal

The TGA has given Hemgenix provisional registration, with the Product Information stating that "continued approval of this indication depends on confirmation of longer-term benefit from ongoing clinical trials." A medicine with evidence sufficient for provisional registration only would be appropriate for funding on the basis of managed access (or other similar measures depending on the funding pathway). The extent of any uncertainty associated with immature evidence would typically be reflected in the price for such a treatment or in rebates to the Australian Government negotiated as part of a risk sharing agreement.

The applicant proposed a risk sharing agreement summarised in Table 17.

Table 17 Applicant's proposed risk-share agreement

Component	Description
redacted	redacted
redacted	redacted
redacted	redacted
redacted	redacted
redacted	redacted

Source: MSAC 1728 ADAR Table 5-1.

The applicant's assumption of an initial redacted% uptake rate resulted in a very low number of patients being treated each year from the prevalent pool of patients (redacted, redacted and redacted patients from a population of redacted in the first three years, see Table 15). If the uptake was much higher, for example 20%, this would have sizeable up-front implications to

budgets (both the Australian Government and the states/territories). This is a substantial risk that may require management under the terms of the risk sharing agreement.

The commentary considered that the risk sharing agreement should include an option for renegotiation in the event that significant new information emerges regarding either safety or efficacy, especially if this results in a modification of the TGA approved indication or contraindications. The commentary suggested a list of clinical events as the potential basis for this as well as a list of outcomes that could be considered as the basis for full or partial rebate.

Redacted. The commentary noted that, according to the HOPE-B study, stable FIX expression was not achieved until Month 7 post-infusion redacted. In the event lack of efficacy is included as an event for rebate in a risk sharing agreement, the commentary considered that a risk sharing agreement should differentiate between product failure (minimal clinical benefit across the post-treatment period) and waning efficacy (decreasing benefit after an initial response) and that it may be necessary to evaluate the two types of events at different timepoints post-treatment and potentially using different criteria.

The commentary stated that any registry should be managed by an independent party, it should be subject to mandatory reporting requirements and the Australian Government should have access to registry data. The AHCDO Gene Therapy Roadmap (2022) provides a model for this.

Redacted, it is noted that pre-treatment testing may require multiple repeat tests in patients who show either high or variable anti-AAV5 NAb titre values. Since the test is currently an unapproved companion diagnostic provided by a commercial laboratory in the United States, the commentary suggests the Australian Government consider including provisions in the risk share agreement to ensure adequate and timely access to testing for Australian patients.

Ongoing monitoring will be required to evaluate the treatment response in individual patients. The TGA provisional approval specified that Hemgenix recipients with pre-existing risk factors for HCC receive abdominal ultrasound screenings and alpha fetoprotein (AFP) monitoring annually for five years post-infusion and all patients receive weekly liver function testing for the first three months post-treatment. The commentary suggested these will need to be considered as part of any implementation plan included in the risk sharing agreement.

Organisational, legal, social, equity and ethical issues

The ADAR did not address any organisational, legal, social, equity or ethical issues. The AHCDO Gene Therapy Roadmap laid out risks to implementation, particularly:

- delays to Australian Government funding approval
- real world efficacy over the long term fails to meet expectations
- costs borne by the states and territories hinder implementation
- resource/staffing constraints at individual sites impact treatment of patients.

16. Committee-in-confidence information

Redacted

17. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- There is no evidence to support the use of Hemgenix® in patients with anti-adeno-associated virus type 5 (anti-AAV5) neutralising antibody (NAb) titre of ≥:900 on a 9-point NAbs assay (equivalent to the clinical reference standard, <1:700 on a 7-point assay). The Applicant Developed Assessment Report (ADAR) noted that the use of Hemgenix in patients who were positive for anti-AAV5 NAbs trended towards inferior effectiveness based on endogenous factor IX (FIX) activity compared to patients who were negative for anti-AAV5 NAbs.
- ESC considered the determination of pre-treatment anti-AAV5 antibody concentration to be an obligatory codependent test, given it is critical in determining patient eligibility to Hemgenix, notwithstanding the test is not validated. ESC noted the United States Food and Drug Administration (US FDA) has mandated two post-marketing studies to validate an assay for detecting anti-AAV5 antibodies, and to categorise the post-treatment bleeding risk according to pre-treatment anti-AAV5 antibody concentration.
- There is uncertainty in long term safety and effectiveness of Hemgenix therapy due to the HOPE-B study design which given the limited treatment population can only detect very common adverse events (AEs); the unrandomized study design does not allow a true assessment of causality. Furthermore, despite the claim that Hemgenix therapy offers a potential lifetime benefit, the current follow-up period from the pivotal clinical study is 3 years.
- The transition of patients from their baseline disease category to different category at each post-infusion time-point is not sufficiently well described to show the inter- and intra-individual variability in treatment response. Similarly, average measures of annualised bleeding rate obfuscates the substantial inter-individual variability in treatment response.
- Post-treatment ABR was worse among nine patients (17%) of the HOPE-B cohort.
- There is reasonable evidence of short-term efficacy with large interindividual variability. The duration of response is unknown. HOPE-B 3-year data was provided and 4-year data should also now be available. There is also a planned analysis at 5 years. MSAC may wish to consider whether to request this data before making a decision or alternatively, if MSAC supports funding of Hemgenix, the extension study data should be provided and reviewed.
- Reporting of post-infusion FIX concentration is limited to only subjects who had received no recent FIX replacement.
- Patient-level data on the 13 neoplasms observed on-study was not submitted for ESC consideration.
- A 15-year follow-up study of safety has been committed to by the sponsor. The Australian Bleeding Disorders Registry may be used to monitor the long-term safety of Hemgenix of all recipients.

Economic issues:

- ESC was concerned that the ADAR's two-state economic model (alive, dead) might not have sufficiently captured important patient-relevant events over a 25-year time horizon. Noting that relevant published economic models represented a range of approaches, ESC observed that the published models incorporated health states that more closely approximated the natural history of disease than the ADAR model.

- There are a number of uncertainties and limitations with the model including that how FIX activity levels were extrapolated and the validity of using FIX activity in a binary way as a driver of patient relevant outcomes (the annualised bleeding rate) and healthcare utilisation outcomes (FIX consumption). ESC noted that while the above outcomes were modelled as a function of FIX activity levels, other outcomes (health-related quality of life and serious adverse events) were modelled independently of the FIX activity levels, which raised questions about the logic and consistency of the model.
- Considering the model structure, data sources, and extrapolation methods, ESC was not confident that the health indicators and extrapolation used in the model were reasonable, unbiased and realistic for the Australian setting.
- The incremental cost effectiveness ratio (ICER) reported for the study based 3-year time horizon was prohibitively high ($redacted per quality adjusted life year [QALY] gained). The ICER reduced and was dominant when the model was extrapolated out to a 25-year time horizon, with dominance reached after redacted years in the base case. ESC noted that the long-term treatment benefit was assumed and had yet to be demonstrated in clinical trials.
- However, the ICERs increased when the effective prices for the FIX replacement therapies were used, such that Hemgenix was no longer dominant when the model was extrapolated out to a 25-year time horizon (ICER was $redacted per QALY gain).

Financial issues:

- The rate of uptake was uncertain (ADAR assumed an uptake rate of redacted%). Increasing the estimated uptake rate significantly increases the year 1 financial impact but the costs savings from less ongoing FIX replacement therapy results in significantly lower costs at year 6.
- More generally, higher initial uptake rates would be advantageous in terms of reducing the overall (i.e. cumulative) net impact, due to the avoidance of the costs of ongoing FIX replacement therapy.
- In addition to the uncertainty of the uptake rate, the supply-side constraints (possible global manufacturing constraints and the system's capacity to deliver the treatments) were important determinants of the adoption of Hemgenix and associated financial impacts.
- Uncertainty of the estimated financial impact was further increased due to questions regarding treatment eligibility, FIX cost offsets and additional costs not being included.
- There may be a differential lifetime reduction in FIX use following Hemgenix administration among the youngest eligible individuals (i.e. for the incident population of children with cHMB who transition to adults each year), as compared to use in the prevalent pool of older Hemgenix-eligible individuals, but earlier use is associated with greatest uncertainty of duration of effect.

Other relevant information:

- Although Hemgenix was claimed to offer lifetime benefit, there is no evidence to support the safety and effectiveness beyond three years (HOPE-B study), and among 10 patients with five-year follow-up data (Study AMT-060-01). Furthermore, the TGA only granted provisional approval which may be extended to a maximum of six years before either full registration is granted, or de-registration occurs. The uncertainty regarding long-term outcomes, and durability of response may be addressed using a combination of price and payment structures where a long-term pay-for-performance (PfP) arrangement might need to be put in place by the NBA. However, it is important to note that the duration of the PfP structure may exceed the maximum period of TGA's provisional registration, and there may need to be reconsideration of the PfP arrangement once full registration is granted.
- Initial infusion success and long-term efficacy are two separate risks that need addressing. Regarding long-term efficacy, the cohort-based and individual-based PfP options represent

different implementation challenges. In particular, ESC noted the difficulty of long-term individual data collection to inform PfP payments, and questioned the feasibility of retrospective adjustments based on cohort-level outcomes.

- ESC considered that moving forward would require:
  - consideration of the strength of existing short-term evidence
  - a decision on the acceptable level of risk regarding the extrapolation of the short-term data to inform long-term efficacy and related assumptions
  - view of an acceptable economic model structure recognising existing limitations of data and evidence to inform the model.

This above information can then be used to make a recommendation and determine the appropriate price and PfP payment structure. Several practical implementation risks would have to be considered, including the anti-AAV5 NAb titre test status, clinical monitoring and access to registry data.

ESC discussion

ESC noted that this application from CSL Behring requested public funding through the national blood arrangements for etranacogene dezaparvovec (Hemgenix®) infusion, a gene therapy for the treatment of moderately severe and severe congenital haemophilia B (cHMB). cHMB is a rare, X-linked recessive bleeding disorder that results in reduced levels of factor IX (FIX).

Hemgenix is a somatic gene therapy where an inactive adeno-associated virus type 5 (AAV5) vector is used to introduce a copy of the FIX gene into liver cells, which then produce functional FIX (of the Padua variant). The therapy is proposed to be a one-off, once-per-lifetime treatment however, patients may still require on-demand and/or procedural FIX prophylaxis after Hemgenix treatment.

ESC noted and welcomed consultation input from 3 professional organisations, 1 consumer organisation and 2 individuals (both of whom were specialists). ESC noted from the consultation feedback that there is strong support for publicly funding Hemgenix. However, none of the feedback addressed the anti-AAV5 NAb test and its effectiveness. Consultation feedback noted several possible advantages for the gene therapy, such as no ongoing injections for up to 7 years and avoiding any adverse events (AEs) associated with bleeding incidents, resulting in an improved quality of life (QoL) for the patient and their family. Feedback also identified disadvantages of the therapy such as not all patients were eligible, the need for pathology and dietitian interventions, and avoidance of alcohol, before and after Hemgenix treatment. Consultation feedback also noted the importance of genetic counselling before patients undergo such a treatment, and the importance of a robust informed consent process, to which ESC agreed. ESC specifically noted the importance of patients understanding that if they receive Hemgenix, they will develop high level of anti-AAV5 NAb post-treatment and therefore, would likely be precluded from receiving any future AAV-based gene therapies based on AAV5 (or other cross-reactive AAV species), even if Hemgenix fails or becomes ineffective. ESC also noted that the burden of treatment, patient productivity and the impact on carers were all important factors that cannot be adequately considered in a health technology assessment.

ESC noted that Hemgenix received provisional (time-limited) approval for use in Australia by the Therapeutic Goods Administration (TGA) for adults with cHMB without a history of FIX inhibitors. Continued approval (i.e. beyond the initial 2-year provisional approval period) depends on confirmation of longer-term benefit from ongoing clinical trials. Provisional registration can be granted for up to six years before transition to either full registration or de-registration.

ESC noted that the TGA provisionally approved indication for Hemgenix does not restrict use based on severity of cHMB but that in the Applicant Developed Assessment Report (ADAR), the population proposed for funding was restricted to patients with severe cHMB or a subgroup of patients with moderately severe cHMB based on FIX activity (i.e. FIX activity ≤2%).

ESC also noted that, to determine a patient's eligibility for Hemgenix, patients are tested for anti-AAV5 neutralising antibodies (NAbs), as it biologically plausible that high levels of anti-AAV5 NAbs may render the treatment ineffective. ESC noted that the anti-AAV5 NAb assay would be performed in the United States with CSL Behring covering all related costs, but that this meant the anti-AAV5 NAb assay would not be subjected to Australian regulatory requirements, quality assurance program or laboratory accreditation. ESC queried if the cost of the anti-AAV5 NAb assay is covered if the test finds the patient to be ineligible for Hemgenix infusion.

Although the TGA provisionally approved indication for Hemgenix does not specify an anti-AAV5 NAb titre threshold, ESC noted the requirement to assess a patient's anti-AAV5 NAb titre is stated in the Australian Product Information for Hemgenix. ESC noted the ADAR asserted that the anti-AAV5 NAb assay was considered a 'complementary diagnostic' by the TGA and had removed the anti-AAV5 NAb titre threshold from the eligibility criteria for the population proposed for funding. However, ESC considered the anti-AAV5 NAb assay provided information that is essential for determining the patient population for public funding for which there is evidence on the safety and effectiveness of Hemgenix. ESC considered that, as proposed in the ratified PICO Confirmation, a NAb titre of <1:700 on a seven-point assay (or <1:900 on a nine-point assay) should be retained as one of the eligibility criteria for accessing publicly funded Hemgenix (if supported by MSAC).

ESC also noted the proposed population for funding was restricted to adult patients ≥18 years old and who have no inhibitor formation against expressed FIX protein. ESC considered the restriction to patients ≥18 years old appropriate given current evidence but highlighted that treatment for patients <18 years old would be of interest to prevent future morbidity in this population. As such, future data generation (and submission) for this population was encouraged.

ESC noted the clinical evidence base consisted of three single arm observational studies, however the phase III HOPE-B study (n=54 patients with moderate to severe cHMB treated with Hemgenix) provided the pivotal evidence. The outcomes considered were annualised bleeding rate (ABR) 6–36 months post-treatment, uncontaminated FIX activity, FIX utilisation, adverse events (AEs), and EQ-5D-5L and Haem-A-QoL scores. The two other case studies where phase I/II and phase IIb studies that included very small patient numbers (n = 3 and n = 10, respectively) provided supporting evidence.

ESC noted that the trial protocol for the HOPE-B study changed over time. The primary endpoint was initially FIX activity level, then changed to ABR after trial commencement. In addition, the timeframe for the primary endpoint also changed from day 21 to month 7. However, ESC noted the applicant's pre-ESC response clarified that these amendments were based on input and support from the United States Food and Drug Administration (FDA) and considered the applicant's claim that these changes did not affect the validity of the trial results was reasonable. ESC further noted that both endpoints were published. ESC also noted that it was unclear as to how patients were initially screened for the trial and noted that the trial had more exclusion criteria (any active or history of inhibitors, abnormal liver function test results, advanced liver fibrosis [i.e. based on a high fibroscan score], HIV with CD4 <200/uL, hepatitis B or C infection, any comorbidities and previous gene therapy) than the population proposed for funding in the ADAR.

Regarding comparative safety of Hemgenix, ESC noted that there were several AEs in the HOPE-B study, including liver function test abnormalities, an infusion reaction and all patients developed anti-AAV5 NAbs. There were also 22 serious AEs; of note, 9 were in the form of bleeds, one was a death, and one was a hepatocellular carcinoma (although the ADAR reported there was no evidence of vector-related insertional mutagenesis as the aetiology). ESC also noted there were 13 neoplasms reported in 7 people. ESC noted the applicant's pre-ESC response stated all neoplasms were not treatment related and there is no known oncological risk. While ESC considered the neoplasms were likely unrelated to Hemgenix, further details are still required.

Regarding comparative effectiveness of Hemgenix, ESC noted that for patients in the HOPE-B study, the adjusted ABRs decreased from an average of 4.19 before treatment to 1.52 post-treatment (measured throughout 7–36 months post-treatment). ESC noted that the reduction in adjusted ABR, when reported as an average for the whole cohort, appeared to demonstrate Hemgenix effectiveness. However, presenting the average for the whole cohort obfuscated the substantial inter-individual variability in ABR following Hemgenix. ESC noted that a tornado plot of the ABR for each patient highlighted the extent of the inter-individual variability and in particular noted:

- the pre- and post-treatment ABR for the 3 patients that the ADAR reported to have confirmed lack of efficacy. One patient had an infusion reaction (and didn't receive the full infusion), one patient experienced lack of efficacy at day redacted, and one patient had a high anti-AAV5 NAb titre (pretreatment) and had no response.
- the patient that experienced lack of efficacy at day redacted was important as it is unclear if the patient was a late non-responder or the first of a cohort of patients with waning efficacy
- 9 patients had more bleeds per month post-treatment than before treatment
- 3 patients had 10 bleeds post-treatment, needing one infusion per month for 3 years, but were considered to be responders as per the study definition
- one patient had high bleeds both pre- and post-treatment (18 and 7 bleeds, respectively); ESC acknowledged that this may be an outlier
- one patient died, but was considered a responder, even though they were in the upper quartile for bleeds before they died.

Further, ESC noted that a tornado plot of post-treatment FIX use demonstrated that even though responders may have not required regular prophylactic FIX, 32/54 patients still required some FIX infusions after Hemgenix, with an average of 1.7 FIX infusions per patient over 3 years on-demand treatment of bleeding (reduced from an average of 44.1 infusions before Hemgenix treatment). Again, ESC noted the inter-patient variability, redacted.

ESC noted the applicant's pre-ESC response had not adequately addressed all of the data requests in the commentary and considered that it would be useful for MSAC decision-making for the applicant address these in their pre-MSAC response. ESC considered this information, such as the description of patient response trajectory would be informative for MSAC to understand when contextualising any uncertainties in the effectiveness of Hemgenix and whether the uncertainties require mitigation through a risk share arrangement (RSA).

ESC noted that the HOPE-B study also reported FIX activity levels (uncontaminated) which ESC considered a surrogate outcome but noted was a key input for the economic evaluation. ESC noted that uncontaminated FIX activity meant that any patient who received a FIX infusion within five half-lives (of the measurement timepoint) was not included at that data point, this was to ensure the FIX activity level was not confounded by recent FIX infusion. The three patients classified as non-responders were also excluded. However, ESC considered the selective nature of FIX activity observation to be biased towards the patient group who were responding well to Hemgenix. ESC also noted that for the calculation of pre- and post-treatment FIX activity, the

actual baseline (pre-treatment) values were not used; rather, the baseline values were imputed based on patients' disease categorisation. Thus, it is unknown if FIX activity was actually higher at baseline and, therefore, the accuracy in the reported median improvement in FIX activity may be uncertain.

Regarding QoL outcomes, ESC noted that the HOPE-B study reported no overall clinically meaningful change in the EQ-5D-5L after 3 years. For the Haem-A-QoL outcome (a haemophilia-specific QoL score), a statistically significant difference (reduction) was reported, but interpretation of whether this change reflects a meaningful reduction in treatment burden is uncertain because there is no minimal clinically important difference (MCID) published. ESC also noted that the study did not compare QoL in those who did not have any further FIX therapy to those who had intermittent or regular FIX prophylaxis.

Regarding the anti-AAV5 NAb assay, ESC noted that the ADAR claimed it attempted to fulfill the additional data requirements of a codependent application, but the ADAR also asserted that the anti-AAV5 NAb assay was not developed as a companion diagnostic (TGA term), and no traditional clinical performance, sensitivity or specificity studies were conducted to interrogate this. As such, ESC noted there was no information regarding diagnostic accuracy of the anti-AAV5 NAb assay (e.g. false-positive or false-negative rates, etc).

ESC noted that in the HOPE-B study, no patient was excluded from treatment based on anti-AAV5 NAb titre and that 21/54 (39%) patients were positive for anti-AAV5 NAb at baseline. ESC noted the patient with the highest titre (1:3212) did not respond to Hemgenix. ESC considered it important to note that post-treatment FIX activity levels (at all time points) were lower in patients who were positive for anti-AAV5 NAbs at baseline. The post-treatment adjusted ABR was also higher for the subgroup of patients who were positive for anti-AAV5 NAb (at baseline) compared to subgroup of patients who were negative for anti-AAV5 NAb at baseline (adjusted ABR = 17.71 and 0.64, respectively). ESC noted this was not statistically significant, but this is possibly underpowered and may be clinically important.

ESC also noted that the US Food and Drug Administration (FDA) has mandated two pivotal post-marketing requirement studies[9] to assess decreased therapeutic efficacy in the presence of pre-existing anti-AAV5 NAbs:

- The first study is to validate a sensitive assay for detecting anti-AAV5 NAbs.
- The second study will enrol 35 patients with haemophilia B, at least 10 of whom have pre-existing NAb titres ≥1:1400, to receive Hemgenix to examine the association between bleeding risk and pre-existing anti-AAV5 NAbs, once a validated assay is available.

Thus, ESC considered that the anti-AAV5 testing may serve two purposes: to assess patient eligibility for the treatment (as noted earlier) and as a prognostic marker to guide any future funding arrangements given the:

- observed trend toward lower FIX activity and higher ABR in patients with a positive anti-AAV5 NAb titre at baseline
- the lack of effectiveness associated with an anti-AAV5 NAb titre of 1:3212
- the absence of evidence for the effectiveness of Hemgenix in patients with an anti-AAV5 NAb titre >1:900 (equivalent to 1:700 in the clinical trial assay).

ESC noted the economic evaluation was a cost-utility analysis that used a Markov model with two health states: alive and dead. ESC noted that other consequences such as joint damage were not modelled, and agreed with the commentary that using only two health states might have

[9] Anguela & High (2024). Hemophilia B and gene therapy: a new chapter with etranacogene dezaparvovec. Blood Adv 8(7):1796–1803.

oversimplified the natural history of the condition. ESC disagreed with the applicant's pre-ESC response, which argued that a single "alive" state was appropriate because it was heterogeneous. ESC noted that published models on gene therapies for haemophilia all attempted to better represent the natural history of haemophilia and none used a two-state model. ESC was unable to confirm whether a more complex model would substantially alter the results of the economic evaluation. However, ESC considered that a more informed model could:

- potentially impact the incremental cost-effectiveness ratio (ICER)
- represent a more appropriate natural history of cHMB
- ensure consistency of modelled consequences
- allow more opportunity for isolating or testing input sensitivity.

Further, ESC noted that there appear to be data available to support the development of a more appropriate model structure.

ESC noted the ADAR's base case was generated using 3-year data from the HOPE-B study extrapolated out to 25 years of FIX activity level. ESC noted that FIX activity level was not applied as the driver of all consequences. The health outcome parameters were individually extrapolated and varied over time, which ESC considered was problematic. ESC noted that usually the consequences follow a key variable representing health status, such as typical healthcare cost and QoL per disease stage. The ADAR's model however, assumed that the estimated extrapolated proportion of patients with FIX <3% would return to the observed ABR of 4.11 from the lead-in period, while those remaining above this threshold would maintain an improved ABR of approximately 1.0. ESC considered that it would have been clearer had the model employed 3 health states, e.g., FIX activity >3%, FIX activity ≤3% and dead. ESC noted that such a model, while more transparent, could still be inappropriate due to FIX activity being an intermediate rather than patient-relevant outcome that forms the basis of the model. ESC considered the extrapolated FIX activity levels to estimate long-term treatment durability to be highly uncertain due to methodological issues such as potential bias that stems from the uncontaminated FIX activity data selection and how data for non-responders were accounted for. ESC noted that inclusion of data for the late non-responder altered the proportion of patients that fall below the 3% FIX activity threshold (from 10.5% in the base case to 24.2% in the commentary sensitivity analysis). Further, ESC questioned the validity of using the FIX activity level as a driver of patient relevant outcomes. While ESC noted there may be some correlation of FIX activity with disease severity, it is a surrogate outcome, was used in binary way and it was unclear whether the 3% threshold was appropriate. That is, whether the threshold should have been higher or lower. Further, the selected 3% FIX activity threshold did not align with how FIX activity is used to categorise disease severity in the guidelines.

Overall, ESC was not confident that the health indicators and extrapolation used in the model were reasonable, unbiased and realistic for the Australian setting.

As such, ESC viewed the economic evaluation as using a simplistic model that applied mortality and a constant (comparator) or adjusted for efficacy loss (intervention) outcomes post-trial to generate costs and quality-adjusted life years (QALYs). Costs included in the model were intervention delivery, FIX replacement therapy, on-demand FIX infusions and treating serious AEs. However, ESC noted that costs were not included for: prior testing (other than anti-AAV5 NAb testing), post-treatment monitoring, or deteriorating joints.

ESC noted the stepped economic analysis reported an ICER of $redacted per QALY gained when using a 3-year (study data based) time horizon. The ICER reduced to $redacted per QALY gained

when extrapolated to an 8-year time horizon and was dominant when extrapolated to a 25-year time-horizon. ESC noted the ICER became dominant at approximately redacted years.

ESC noted the key drivers of the model were the time horizon, cost of the comparator (short half-life and extended half-life FIX replacement therapy) and the annualised FIX consumption (AFC). ESC noted the applicant's pre-ESC response asserted that the appropriate time horizon should be the patient's lifetime, but the ADAR base case instead used a more conservative time horizon of 25 years. ESC considered that the duration of effect was assumed, not demonstrated.

ESC noted that when the effective prices for the FIX replacement therapies were applied, the ICERs increased and Hemgenix was no longer dominant over the 25-year time horizon:

- Step 1 – 3-year study data based time horizon: $redacted per QALY gained
- Step 2 – 8-year time horizon: $redacted per QALY gained
- Step 3 – 25-year time horizon: $redacted per QALY gained.

ESC noted that, when using the effective prices for FIX replacement therapies, the price of Hemgenix would need to be reduced to $redacted to reach dominance over a redacted-year time horizon, approximately $redacted to reach dominance in redacted years (corresponding to the base case) or $redacted to reach dominance over an redacted-year time horizon.

ESC considered that it would be useful to present MSAC with additional sensitivity analyses exploring the price (reduction) required to achieve a dominant ICER at 3 years and 5 years. In addition, sensitivity analyses exploring the price (reduction) required to achieve a lower ICER (e.g. $100,000 per QALY gained) using a 3 year and 5 year time horizon may also be informative for MSAC.

ESC also noted that the Canadian Agency for Drugs and Technologies in Health (CADTH) recommended reimbursement of Hemgenix for treatment of patients with moderately severe to severe cHMB (with an anti-AAV% titre <1:900) but this was contingent on a price reduction[10]. However, the National Institute of Health and Care Excellence (NICE) did not recommend funding Hemgenix, citing uncertain effectiveness and high costs as the reasons.

ESC noted that the financial impact estimates used a mixed epidemiology and market-share approach, but only considered the cost of Hemgenix and the comparator FIX products. ESC noted that while the prevalence of cHMB in Australia is reliably informed based on data from the Australian Bleeding Disorders Registry (ABDR), there is uncertainty regarding how many of the 253 patients that currently have cHMB would be eligible for the gene therapy. Further, ESC considered a major uncertainty was how many eligible patients would choose this therapy and noted that the uptake rate assumed in the ADAR was low (redacted%).

ESC noted that the financial analysis only considered the cost of Hemgenix or the comparator FIX replacement therapies. While ESC noted that the costs of pre-treatment testing, screening, post-treatment monitoring and managing AEs may be less material, ESC considered that these costs should have been included as they are important for understanding the overall impacts on specific healthcare budgets. The financial analysis also considered system readiness (hub-and-spoke model) as per the Australian Haemophilia Centre Directors' Organisation Gene Therapy Roadmap, which describes:

- the capacity of hub sites to deliver gene therapy (a medium level risk to implementation)
- hubs that could support a throughput of around 1–2 patients per week

[10] CADTH Reimbursement Recommendation Etranacogene Dezaparvovec (Hemgenix), Canadian Journal of Health Technologies, May 2024, 4:(5) - https://www.cadth.ca/etranacogene-dezaparvovec

- a proposal to model expected patient volumes to inform resourcing decisions.

ESC also questioned whether, in addition to the uptake rate and system readiness, global manufacturing constraints could impact on the ability to deliver the treatment to Australian patients.

ESC noted that the total financial impact to the national blood arrangements would be $redacted in year 1, decreasing to $redacted by year 6 using the commentary's corrected FIX cost offsets. However, this depends on an uptake rate of redacted% of all eligible patients, which ESC considered to be uncertain. ESC noted that if a higher uptake was assumed, for example, 20% of eligible patients received Hemgenix, the initial cost to the national blood arrangements would increase to $redacted in year 1 but would become cost-neutral faster due to less ongoing FIX replacement therapy (cost of $redacted in year 6).

ESC noted several uncertainties and limitations with the financial impact, including eligibility and uptake, system capacity to deliver the treatment, FIX cost offsets, additional costs not included and possible global manufacturing constraints. Additionally, when ESC noted the effective prices for the FIX replacement therapies were applied, cost savings were lower, the net cost was higher, and it would take longer for cost offsets to be fully realised.

ESC noted the ADAR had proposed a risk sharing arrangement. ESC considered the high proposed cost of $redacted per infused patient, coupled with the uncertain treatment success rate and uncertain durability of the effect, posed a high risk to government budgets. ESC considered redacted was not evidence based as the primary outcome in the HOPE-B study was measured at 7 months post-infusion. ESC also considered that the RSA would need to:

- mitigate uncertainty regarding the durability of effect, which is assumed, not known – for example, include a pay-for-performance arrangement. ESC considered long-term individual-based multiple payment pay-for-performance would be the preferred mechanism but noted there maybe challenges with this, but if a cohort-based mechanism was used then the ability to implement an appropriate mechanism for retrospective cost adjustment would essential.
- mitigate the long-term economic and financial uncertainty, potentially through a price reduction
- take into consideration that the TGA provisional approval for Hemgenix is time-limited (initial 2 years, up to 6 years) and continued TGA approval depends on confirmation of longer-term benefit from ongoing clinical trials
- include annual review of safety and effectiveness which ESC considered currently warranted, in particular as one patient demonstrated late loss of efficacy (just after 2 years) and is unclear if this is the last of the non-responders or the first of a cohort of patients with waning efficacy
- consider the codependency issues raised, that the available data show a non-statistical trend of decreased efficacy in patients with anti-AAV5 NAbs, and the anti-AAV5 NAb threshold needs to be better understood for the purposes of appropriately setting the eligibility criteria for defining the population for public funding in which Hemgenix is safe, effective and cost-effective.
- note that 2% of patients had an infusion reaction and could not complete the infusion, so a part payment or no payment option for these patients should be considered
- stipulate that registry data collection and provision is required, which should be independent of industry, have no restrictions on access for defined stakeholders and have mandatory reporting embedded in any agreement.

ESC noted that the applicant has committed to a 15-year follow-up study, **redacted**. ESC advised that the following information from this study should be required for any RSA:

- individualised and total use of FIX replacement for both prophylaxis and on-demand needs
- the proportion who are free of prophylaxis use each year
- ABR
- QoL
- safety
- anti-AAV5 antibody titre with FIX activity levels and AFC.

18. Applicant comments on MSAC's Public Summary Document

While CSL Behring is disappointed that Hemgenix has not been supported for public funding at the first opportunity, we are pleased that there is a clear path forward for resubmission to MSAC. We are confident in the transformative impact of Hemgenix and its long-term value to eligible patients, families and the Australian healthcare system. Hemgenix has been publicly funded already in a number of countries and as an Australian company, we are keen to support timely funded access for Australian Haemophilia B patients. We are optimistic and committed to working with MSAC and all other relevant stakeholders to help achieve this shared goal.

19. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website