Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1728.1 – Etranacogene dezaparvovec for the treatment of Haemophilia B

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

Date of MSAC consideration: **31 July 2025**

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 Agreement of etranacogene dezaparvovec (also known as Hemgenix®, AMT-061 and CSL222 or EtranaDez) for the treatment of moderately severe and severe haemophilia B (HMB) was received from CSL Behring (Australia) Pty Ltd by the Department of Health, Disability and Ageing.

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 etranacogene dezaparvovec (ED). Funding was not sought for this test as it will be undertaken and paid for by CSL overseas.

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 supported public funding of the gene therapy etranacogene dezaparvovec (ED, Hemgenix ®) for the treatment of adult patients with moderately severe or severe congenital haemophilia B. Based on the available clinical evidence, MSAC considered that ED, administered as a one-time treatment, provides clinical benefit to patients. MSAC considered that an anti-adeno-associated virus type 5 neutralising antibody assay was essential for determining patient eligibility to treatment, but raised some concern about the accuracy and validity of the proposed assay. MSAC further considered that the proposed assay threshold was based on limited data and highlighted the importance of establishing a clinically meaningful threshold to ensure that patients who access the treatment are those most likely to benefit. MSAC noted that a study is underway to refine the assay threshold. Among patients treated with ED in the key trial, approximately 94% of patients were able to cease regular (typically 1-2 times per week) prophylactic factor replacement injections, with approximately 41% of patients having no further bleeding episodes. However, MSAC noted that ED is provisionally registered in Australia and considered that the clinical evidence (4-year follow-up in the key trial) did not yet fully support the durability of treatment effect over a lifetime because the key study showed that a small number of patients experienced a lack or loss of treatment effect over time. Given the uncertainties in the long-term safety and effectiveness of ED, MSAC considered that the proposed price of $**redacted** per patient was too high. MSAC considered that the cost effectiveness of ED would be acceptable if it were cost neutral (compared to factor replacement therapy) over 10 years, and in conjunction with a pay-for-performance arrangement - a type of outcome-based risk sharing arrangement (RSA). Based on current factor replacement utilisation reported by the National Blood Authority and costs of factor replacement therapy, MSAC advised that a condition of its support was a price reduction of ED to $**redacted** per patient (approximately **redacted**% price reduction from the proposed price), in conjunction with the RSA. Under the RSA, MSAC advised for payments to be made in equal instalments over 10 years and be linked to individual patient response.

Consumer summary

This reapplication from CSL Behring (Australia) Pty Ltd requested funding of etranacogene dezaparvovec (ED, trade name Hemgenix ®) under the National Blood Agreement for adults with moderately severe or severe congenital haemophilia B. MSAC did not recommend ED for public funding when it considered the original application (MSAC 1728) in August 2024 because it wanted to see longer-term data showing that the treatment is effective, safe and better value for money than current treatment.

Haemophilia is a bleeding disorder where a person's blood does not clot properly, which can result in excessive bleeding. Congenital haemophilia B is a rare type of haemophilia that is caused by a lack of the blood clotting protein factor IX (FIX). 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. 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 needed lifelong and is administered via injections into a vein (intravenous).

ED is a viral-based gene therapy. This means that an inactive virus (that cannot reproduce) is used to deliver a healthy copy of the factor IX gene into the liver cells. This new gene helps the liver cells to produce the factor IX blood clotting protein. ED is a one-off treatment. It is given to the patient as an intravenous infusion.

MSAC noted that the clinical studies indicated that most of the patients responded well to ED, but others did not. Some patients who did respond still needed some factor IX replacement treatment, but not as much as before receiving ED. A small number of patients had no benefit with the treatment. MSAC considered that the clinical evidence (4-year follow-up in the key trial) did not yet show how well the treatment would work over a lifetime. This is because the key study showed that a small number of patients lost the treatment effect over time. A small number of patients did not experience any treatment effect.

Similar to the first time it considered this application in August 2024, MSAC noted that if someone has a high level of antibodies that neutralise the virus that is used to deliver the factor IX gene, ED did not work. MSAC considered it important that people are tested for neutralising antibodies before treatment with ED. MSAC noted that further studies are needed to ensure the test for the neutralising antibodies is accurate. Further, MSAC noted that, after receiving ED, all patients will have high levels of antibodies that will attack similar inactive viruses used for gene therapies. This would then prevent people from receiving another similar gene therapy lifelong if ED does not work for them or if it works for only a short time. For the same reason, ED cannot be given to a patient for a second time if it does not work well the first time.

MSAC noted that the applicant proposed a slightly lower price for ED than in the previous application, however it was still very high. Given the uncertainty of long-term safety and effectiveness beyond 4 years, MSAC considered the proposed price not justified. The budget impact was also very high.

MSAC advised that its support was conditional on a price reduction of ED in conjunction with a pay-for-performance arrangement - a type of outcome-based risk sharing arrangement (RSA). Under this agreement, MSAC advised for payments to be made in equal instalments over 10 years and be linked to how long and how well individual patients respond to treatment.

MSAC's advice to the Commonwealth Minister for Health, Disability and Ageing

MSAC supported the public funding of ED under the National Blood Agreement, provided the price per patient is reduced and a pay for performance arrangement – a type of outcome-based RSA is in place. MSAC considered that ED provides clinical benefit to patients and reduces disease burden. MSAC considered that the RSA proposed in the application was designed to address key uncertainties such as treatment failure, variability in patient

Consumer summary
response, durability of effect, and the high cost to governments. MSAC noted that this model aligns payments with treatment outcomes and incentivises ongoing patient monitoring.

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

MSAC noted that this re-application from CSL Behring requested public funding through the National Blood Agreement for etranacogene dezaparvovec (ED, trade name: 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 clotting factor IX (FIX).

ED is a somatic gene therapy in which 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 once-per-lifetime treatment.

MSAC recalled that it had not supported the initial application for ED at its August 2024 meeting (MSAC 1728). MSAC considered that the limited, low-certainty clinical evidence indicated that ED may be effective for some patients in the short term, but considered that there was substantial inter-individual variability in the patient response to ED. MSAC considered the available clinical evidence, including 3-year follow-up data, to be insufficient to substantiate the long-term safety and effectiveness of ED. Furthermore, MSAC considered the neutralising antibodies (NAb) test essential for determining patient eligibility for ED but noted the test has not been validated. MSAC further considered the cost-effectiveness of ED compared to FIX replacement therapy to be highly uncertain, due to both the limitations of the clinical evidence and the oversimplified economic model.

MSAC noted that consultation feedback from the Australian Haemophilia Centre Directors' Organisation (AHCDO) and Haemophilia Foundation Australia (HFA) was supportive for the public funding of ED. HFA highlighted results from the 2024 Haemophilia gene therapy snapshot survey indicating that haemophilia patients preferred a permanent solution (i.e. a cure) that prevents bleeds and joint damage, with no need for ongoing treatment, and minimal side effects. Patients also sought reduced treatment burden, including less frequent and less painful administration; fewer hospital visits; and faster recovery. Patients preferred treatment outcomes that increase their quality of life, enabling participation in daily activities, work, education, sport and travel. The survey also highlighted that there was substantial concern among people with haemophilia regarding current gene therapies and long-term effectiveness and safety. AHCDO emphasised the importance of explicitly discussing with eligible patients the need for ongoing, long-term safety and efficacy monitoring post-treatment, which will be conducted through scheduled clinical reviews and laboratory tests.

The applicant was granted a hearing. At the hearing, representatives of the applicant highlighted the positive impact ED had on patients and their quality of life. At the hearing (and in their pre-MSAC response), the applicant's representatives asserted that the collective evidence presented in the applicant-developed assessment report (ADAR), along with a newly published study on AAV-mediated gene therapy[1], demonstrates stable and lasting efficacy of ED. MSAC noted that the newly published study was a Phase 1 trial involving 10 patients with severe haemophilia B, who received a single administration of scAAV2/8-LP1-hFIXco gene therapy. This AAV-mediated gene therapy showed sustained clinical benefit over a 13-year period. MSAC considered that while both therapies, scAAV2/8-LP1-hFIXco and ED use liver-directed AAV vectors to deliver a codon-

[1] Reiss UM, Davidoff AM, Tuddenham EGD, et al. Sustained Clinical Benefit of AAV Gene Therapy in Severe Hemophilia B. *N Engl J Med*. 2025;392(22):2226-2234. doi:10.1056/NEJMoa2414783

optimised FIX transgene, no assessment has been presented nor considered regarding whether the results of the former is applicable to the latter.

MSAC noted that the proposed population for ED was restricted to adult patients ≥18 years old with severe (FIX activity ≤1% of normal) or moderately severe (FIX activity ≤2% of normal) cHMB who have no inhibitor formation against FIX protein, and who are found to have an anti-adeno-associated virus type 5 (anti-AAV5) neutralising antibody (Nab) titre of <1:900 on a 9-point anti-AAV5 NAb assay. MSAC noted that in this reapplication, anti-AAV5 NAb assay testing was included as an eligibility requirement to access ED, as patients with high NAb titres may have limited or no response to AAV5-based therapy. While the HOPE-B study used a 7-point assay for anti-AAV5 NAb testing, the applicant has proposed to use a 9-point assay in clinical practice. MSAC noted that the proposed anti-AAV5 NAb testing would be performed overseas, with patient serum sent to the United States (with a turnaround time of 2–3 weeks), and with no Australian oversight. MSAC noted that the cost of the anti-AAV5 NAb testing would be borne by the applicant. MSAC also acknowledged the need for effective therapies in the paediatric haemophilia population and noted the current evidence gap for this subgroup.

With regards to the proposed test, MSAC acknowledged Food and Drugs Administration's (FDA's) notification that a post-marketing requirement 'to validate a sensitive and accurate assay for the detection of anti-AAV5 neutralizing antibodies, specifically to detect anti-AAV5 NAb titres up to 1:1400 or higher' has been considered fulfilled by the FDA. MSAC noted that there is no reference standard currently available to determine the accuracy of the anti-AAV5 NAb testing and considered that the data presented in the ADAR to support test accuracy was limited, based on a small sample size and limited titre range. MSAC noted that aside from FDA notification, the only new information provided in this reapplication related to test turnaround time, test failures and updated predictive value data for treatment response at 48 months. MSAC also noted that some patients in the key HOPE-B study had titres that varied above 1:700 prior to treatment but were <1:700 on infusion day. MSAC considered it uncertain whether the source of this variability was due to test variability or inherent patient variability. MSAC noted that in their pre-MSAC response the applicant stated that in the case of a false positive result, the patient may be tested again in the future (at no cost to Government), as their NAb titre can decrease over time. MSAC considered that the uncertain performance of the assay could lead to misclassification, potentially leading to inappropriate exclusion or inclusion of patients for treatment.

MSAC noted that the proposed 1:900 assay threshold with the 9-point was based on limited data and emphasised the importance of establishing a clinically meaningful threshold to ensure that patients who access treatment are those most likely to benefit. MSAC noted that there is an evidence gap for patients with titres between 1:900 to 1:4417 on the 9-point assay (corresponding to 1:700 and 1:3212 in the 7-point assay), who may be inappropriately excluded. MSAC noted that in their pre-MSAC response the applicant argued that the seroprevalence of patients with titres above 1:900 was low (2.6% for serum dilutions of 1:80 and 0% for serum dilutions of 1:400 and beyond in one study)[2] and therefore considered that the absolute likelihood of patients in this titre range to be very low. MSAC noted that the additional published evidence for the test cited in the pre-MSAC response came from two posters, however MSAC considered this level of evidence insufficient to fully validate the test. MSAC considered that better evidence on the performance of the assay (including the appropriate threshold) was needed from the FDA mandated clinical trial currently undergoing recruitment of patients with pre-treatment AAV5 NAbs (NCT06003387). MSAC noted that study completion is expected in 2028.

MSAC noted that the clinical evidence for ED was informed by three single-arm observational studies (i.e. low certainty evidence). The Phase III HOPE-B study (n = 54 patients with severe or

[2] Chhabra A, Bashirians G, Petropoulos CJ, et al. Global seroprevalence of neutralizing antibodies against adeno-associated virus serotypes used for human gene therapies. *Mol Ther Methods Clin Dev*. 2024;32(3):101273. Published 2024 May 29. doi:10.1016/j.omtm.2024.101273

moderately severe cHMB treated with ED, data presented up to 4 years in the ADAR) provided the main evidence for treatment outcomes, while results from the two other studies were considered supportive evidence. MSAC noted that the ADAR did not provide any data on the comparative safety between ED and current standard of care. In regards to safety of treatment with ED, MSAC noted that, in the short term, some patients developed transaminitis, requiring high-dose steroids, which may be required for a prolonged period and carry associated side effects. Potential longer-term safety considerations of ED include a possible increased malignancy risk potentially due to vector integration into the patient genome. MSAC noted that at 4 years post-treatment in the key HOPE-B trial, 16 neoplasms (7 of which were malignant) were reported, although no clear causality has yet been established. MSAC also noted that animal studies had identified a risk of hepatocellular carcinoma in mice injected with AAV vectors[3], although it remains unclear whether more recent viral vector modifications have mitigated this risk. MSAC also noted that patients treated with AAV gene therapies retain high levels of neutralising antibodies through follow-up (even up to 10 years[4]), and noted that this would prevent patients receiving any AAV-mediated therapies in the future, if needed. Overall, MSAC considered that based on the available information, ED appears to have an acceptable safety profile; however, considered that the safety of ED beyond 4 years remains uncertain due to the limited number of subjects with longer follow-up in the two supporting studies.

Regarding the effectiveness of ED treatment, MSAC noted from the ADAR and the applicant's post-hoc analysis of the HOPE-B data in the pre-MSAC response that although relative differences in treatment effectiveness were observed between the baseline NAb-positive (NAb titre >0 - 3000) and NAb-negative subgroups, both demonstrated efficacy across primary and secondary outcomes. MSAC noted that in the key HOPE-B trial 22/54 (40.7%) patients had no bleeding episodes from Months 7 to 48 post-treatment, although 14/54 (25.9%) patients had also reported no bleeds in the 6-month lead-up to treatment. MSAC considered that zero bleeding episodes may signify a functional cure for these patients during the 4-year time period, however queried if patients in this group received additional exogenous FIX if levels had declined over the 4 years. MSAC also noted that 51/54 (94.4%) patients did not require routine FIX prophylaxis (defined in the study as having been contaminated by exogenous FIX during any contiguous 3-month period) from Months 7 to 48 post-treatment. While MSAC considered that ED was effective in majority of the patients, some patients experience a lack or loss of efficacy to treatment. Of the 3 patients that returned to FIX prophylaxis, one had a high level of NAb titre (3,212.3) and would be ineligible for therapy under the proposed eligibility criteria, one experienced a hypersensitivity reaction to the infusion and received only 10% of the dose, and one patient (pre-treatment NAb titre of 98.5) lost efficacy due to unknown reasons at approximately 29 months. MSAC noted that, while hypersensitivity reactions to ED may occur in clinical practice, as observed in one patient in the key trial, the ADAR did not include any risk mitigation strategies to address this issue. MSAC further noted that 32/54 (59.3%) patients continued to experience some bleeding post-treatment, with significant inter-individual variability. MSAC also noted that 50% of patients still required FIX replacement during Months 7-48 post treatment, although the amount of FIX required was significantly reduced compared to pre-treatment levels.

MSAC reviewed the health-related quality of life (HRQoL) data from the HOPE-B study, noting that two tools – HAEM-A-QoL and EQ-5D-5L – were presented in this application. MSAC noted that the applicant, in their pre-MSAC response and during the hearing, emphasised that the QoL benefits associated with ED including improvement in chronic pain, disability, social activities, education and travel are not fully captured through the available HRQoL measuring tools. However, MSAC noted that the EQ-5D-5L does include relevant domains such as pain/discomfort, usual activities and anxiety/depression. MSAC considered that while a small benefit in HRQoL was observed

[3] A Donsante, DG Miller, Y Li, C Vogler, EM Brunt, DW Russell, MS Sands (2007). AAV vector integration sites in mouse hepatocellular carcinoma. Science 317(5837):477. DOI: 10.1126/science.1142658

[4] Reiss UM, Davidoff AM, Tuddenham EGD, et al. Sustained Clinical Benefit of AAV Gene Therapy in Severe Hemophilia B. *N Engl J Med*. 2025;392(22):2226-2234. doi:10.1056/NEJMoa2414783

using the aforementioned tools, the magnitude of the effect was not consistent with a transformational therapy as claimed by the applicant. MSAC noted consultation feedback from HFA indicated that many haemophilia patients have been waiting for a permanent solution (i.e. a cure). MSAC considered that while ED gene therapy is effective (to varying magnitudes) in a majority of patients, it may not represent a cure for all patients.

MSAC noted that the reapplication included a revised economic model - a Markov model based on joint bleed severity using the Petersson Score and with a 15-year time horizon. MSAC noted that ED treatment is dominant in the 15-year base case analysis of the ADAR. However, MSAC agreed with ESC that the 15-year time horizon lacked justification and that the assumptions of long-term treatment durability were not well-supported by the available clinical data. MSAC agreed with ESC's advice that a 10-year horizon would be more appropriate, **redacted**.

MSAC noted that the incremental cost-effectiveness ratio (ICER) was $**redacted** per quality-adjusted life year (QALY) at 10 years (extrapolated) for the ED price proposed by the applicant of $**redacted** per patient. MSAC considered this ICER to be too high and not cost effective considering the substantial heterogeneity in treatment response, lack of randomised controlled trial evidence on effectiveness with currently available therapy and uncertainty of the long-term safety and effectiveness of ED. MSAC noted that the main drivers of the ICER were the high cost of ED, the relatively high ongoing costs for FIX, and the relatively small QALY difference in relation to costs. MSAC agreed with ESC that the cost-effectiveness of ED would be acceptable if it were cost neutral compared to the comparator (FIX replacement therapy) at 10 years, and in conjunction with a comprehensive pay for performance arrangement – a type of outcome-based RSA.

MSAC noted that FIX usage in the ADAR was based on HOPE-B study data; however, data from the Australian Bleeding Disorders Registry (ABDR) suggested that lower FIX consumption would be required for a comparable Australian patient cohort, with annual FIX usage at 216,050 IU/yr/patient (based on the 2023-2024 data) - 16% lower than in the HOPE-B study. Using Australian FIX utilisation data, effective FIX prices at the time of ADAR lodgement, and a 10 year time-horizon, MSAC considered that price of ED would need to be reduced to $**redacted** per patient (i.e. a **redacted**% reduction from the applicant proposed price) in order to be cost neutral at 10 years.

MSAC noted the financial impact based on the cost neutral ED price, effective FIX prices and Australian FIX utilisation using ABDR data:

- in year 1, the financial impact would be **$redacted** to the National Blood Agreement, comprising **$redacted** to states and territories and **$redacted** to the Australian Government
- in year 6, the financial impact would increase to **$redacted** to the National Blood Agreement, comprising **$redacted** to states and territories and **$redacted** to the Australian Government.

MSAC noted that the ADAR's financial impact did not include some healthcare resource costs including multidisciplinary team care and counselling/psychosocial support as outlined in AHCDO's roadmap for the implementation of gene therapy. While MSAC noted that these services are needed, MSAC considered that costs of these services are unlikely to have a significant impact on the total financial impact.

MSAC noted that the uptake of ED in international jurisdictions has been very low, attributed to system-level barriers, RSA monitoring requirements, the availability of current effective therapy with FIX, and patient concern with the 'one and done' nature of gene therapy that precludes further treatment lifelong. MSAC further noted that the ADAR estimated uptake of ED in Australia to be approximately **redacted** patients per year, but with potential to escalate over time.

Overall, MSAC considered that the available clinical data support the safety and effectiveness of ED in the short term, with many patients experiencing meaningful improvements during this time.

MSAC noted that there remains uncertainty regarding the magnitude and durability of benefit over current therapy in the long term. Thus, MSAC supported public funding of ED provided a price reduction of ED to $**redacted** per patient in conjunction with a comprehensive RSA contingent on the specified requirements outlined in Table 1.

Table 1 ED risk-share proposal as per MSAC advice

Proposal elements	Description
Net price	$**redacted** per ED infusion
Payment terms	Annual payments over 10 years (with outcomes-based conditions) Each payment is 10% of ED price ($**redacted** per year)
Contract type	Long-term supply contract over 10 years with provision for price/contract review
Warranty	10 year 'warranty' linked to annual payments predicated on continued individual patient response
Eligible population	Adult patients (≥18 years) with severe or moderately severe (FIX activity ≤2% of normal) congenital haemophilia B (cHMB), currently receiving stable FIX prophylactic therapy, who also meet the following criteria: • no history of FIX inhibitors • AAV5 NAb titre < 1:900 using 9-point assay as determined by AAV5 NAb assay (funded by CSL Behring (Australia) Pty Ltd) • no active infections, either acute or uncontrolled chronic • no known advanced hepatic fibrosis, or cirrhosis.
Outcomes-based agreement details	First payment at Month 7 post-infusion (consistent with timepoint for achievement of stable FIX expression in the HOPE-B study) Annual payment thereafter every 12 months unless patient has a documented treatment failure
Incomplete dosing	Patients with incomplete ED dose administration are not eligible for reimbursement
Initial response guarantee	**Initial response failure criteria:** • patient remained on continuous FIX prophylaxis or returned to continuous FIX prophylaxis for 6 months after ED infusion.
Long-term durability guarantee	**Long-term durability failure criteria**: • patient recorded 6 months of continuous FIX prophylaxis (regular FIX infusions in a prophylactic regimen according to the summary of product characteristics of the prescribed product) AND ≤5% FIX activity (considered conservatively as the minimum threshold for bleeding protection) • assessed every 12 months from Month 7 onwards and recorded either through ABDR and/or HCP form. If a value at or around 5% FIX activity is returned, a second verifying FIX test must be performed using a one-stage SynthasIL (HemosIL)-based assay in a defined national centre laboratory.
Return to prophylaxis (RTP) criteria	Patients will be excluded from treatment failure if prophylaxis is initiated for select reasons. MSAC advised that return to long-term prophylaxis criteria should be defined **redacted**. MSAC advised that clinically appropriate short-term prophylaxis, such as for perioperative use, may not necessitate cessation of payment.
Action at failure	Next payment ceases if treatment failure is proven.
Payment adjustment for assay validity issues	Payments to be nullified or reduced if the anti-AAV5 NAb assay lacks validity and misclassifies patients.

Proposal elements	Description
Conditions for cessation of payment	Payment will be ceased under any of the following circumstances: • if the patient receives any registered therapy other than FIX therapy for the treatment of haemophilia B for any length of time after receiving ED. MSAC noted that there are upcoming therapies for the treatment of haemophilia, some of which have entered the MSAC process to request for public funding (e.g. tissue factor pathway inhibitors) • if the patient develops FIX inhibitors • if the patient dies due to any cause or requires liver transplantation
Contract review provision	Price/contract review periods are to be stipulated in the contract, with consideration of updated HOPE-B and extension study data. Provision to review contract after the final analysis of effectiveness and safety data from HOPE-B at approximately 5 years post-treatment. Provision to review contract after the extension study (NCT05962398) that is following HOPE-B subjects up to 15 years post-treatment (planned study completion in 2035). Provision to review contract if substantive changes are made to the provisional TGA registration, or if new safety signals arise through clinical trial or post-marketing ED use. Price and contract review upon the emergence of alternative therapies that may replace ED.

AAV5 = adeno-associated virus type 5; ABDR = Australian Bleeding Disorders Registry; ADAR = Applicant Developed Assessment Report; FIX = Factor IX; HCP = healthcare professional; NAb = neutralising antibody; RTP = return to prophylaxis; TGA = Therapeutic Goods Administration.

4. Background

This is the second application for this technology. ED was previously considered by the Medical Services Advisory Committee (MSAC) at the August 2024 MSAC meeting, MSAC 1728 PSD. At that meeting, MSAC did not support public funding of the gene therapy for the treatment of adult patients with moderately severe or severe congenital HMB.

MSAC considered any re-application would need to provide additional longer-term clinical evidence, including evidence for the NAb test (consistent with post-marketing registration requirements), revised economic and financial analyses, a significantly reduced price, and details for a proposed risk sharing arrangement (Table 2).

Table 2 Summary of requirements for a re-application to MSAC

Component	Matter of concern	How the current assessment report addresses it
Proposed price	A significantly reduced proposed price (PSD 1728, p.7)	Addressed. The proposed price of ED (per infusion) was reduced from $**redacted** to $**redacted** (a **redacted**% price reduction). In addition, **redacted** ($**redacted** per year) over a **redacted** period in an outcomes-based risk sharing arrangement.
Clinical safety and effectiveness	Additional longer-term clinical evidence from HOPE-B study (PSD 1728, p.7)	Addressed. Additional 4-year data were provided from the HOPE-B study. Analysis at this timepoint was post hoc (no CSR was planned at 3 or 4 years). The commentary noted that 4-year follow up is not adequate to address the durability of clinical effectiveness or the longer-term risk of adverse effects from ED. A final analysis of effectiveness and safety from HOPE-B will be performed at approximately 5 years post-treatment. Thereafter, an extension study (NCT05962398) will follow HOPE-B subjects up to 15 years post-treatment (planned study completion in 2035).

Component	Matter of concern	How the current assessment report addresses it
Clinical safety and effectiveness	Evidence on FIX consumption, activity, presence/extent of FIX inhibitors after ED treatment for a minimum of 2 years follow-up (PSD 1728, p.7)	Addressed. Additional 4-year data from the HOPE-B study were provided, including FIX consumption, activity, presence of FIX inhibitors.
Test validation	Evidence on anti-AAV5 NAb assay performance, validity, reproducibility and clinically meaningful threshold (consistent with post-marketing registration requirements) (PSD 1728, p.7)	Not adequately addressed. After MSAC consideration of ADAR 1728, the FDA provided notification to CSL Behring that the post-marketing requirement 'to validate a sensitive and accurate assay for the detection of anti-AAV5 NAbs, specifically to detect anti-AAV5 NAb titres up to 1:1400 or higher' had been fulfilled. However, the only new information presented in the ADAR was related to test turnaround time and test failures (a statement from the third-party supplier) and updated data on the predictive value of the test on response to ED at 4 years. The data presented in the ADAR for the 9-point assay were insufficient to demonstrate the appropriateness of the proposed threshold.
Eligibility requirements	A codependent application for ED with anti-AAV5 NAb testing, including an updated proposed population eligibility criteria that specifies an appropriate anti-AAV5 titre threshold (as above)	Addressed. Updated eligibility criteria were proposed, incorporating additional screening criteria and an anti-AAV5 NAb titre threshold of <1:900. The proposed threshold was based on limited data (33 subjects were pre-treatment titre negative, 21 were titre positive, and only 1 subject had a pre-treatment titre above the proposed threshold). An FDA mandated study is expected to refine (or re-define) an appropriate threshold for treatment response to ED but results will not be available before October 2028.
Healthcare resource use	Evidence on all healthcare use after ED treatment for a minimum of 2 years follow-up (PSD 1728, p.7)	Partially addressed. Expected healthcare resource use was derived from the ED PI and consultations with key opinion leaders. Direct evidence on healthcare use was not available from the HOPE-B study.
Economic analysis	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 (PSD 1728, p.7)	Addressed. A revised economic evaluation was presented with health states related to natural history, a more conservative FIX activity threshold of 5%, updated durability projections, and a reduced time horizon of 15 years (previously 25 years). The model processes were supported by limited evidence and concerns remain regarding the method used to extrapolate treatment effect beyond the duration of study follow-up; however, this is addressed by the risk-share proposal.
Financial analysis	Provide additional evidence to support the estimated utilisation (PSD 1728, p.7)	Partially addressed. Estimated uptake of ED was informed by experience in other markets. This remained the largest source of uncertainty in the financial estimates. The revised financial estimates incorporated annual ED instalments and costs to other government budgets for screening, administration, monitoring and management of infusion-related immune response.
Risk-share proposal	Provide details of a risk sharing arrangement as described by ESC (PSD 1728, p.7)	Addressed. A risk-share proposal was outlined **redacted**.

AAV5 = adeno-associated virus type 5; ADAR = Applicant Developed Assessment Report; CSR = clinical study report; ESC = Evaluation Sub-Committee; FDA = U.S. Food and Drug Administration; FIX = Factor IX; MSAC = Medical Services Advisory Committee; NAb = neutralising antibody; PI = Product Information; PSD = Public Summary Document; TGA = Therapeutic Goods Administration.
Source: Derived from Table 1-1 of MSAC 1728.1 ADAR + in-line commentary.

Throughout this document, content that was unchanged from MSAC's previous 2024 consideration is shaded in blue.

5. Prerequisites to implementation of any funding advice

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

> ED® is an adeno-associated virus vector-based gene therapy indicated for treatment of adults with HMB (congenital Factor IX (FIX) deficiency), without a history of FIX inhibitors, who:
>
> - currently use FIX prophylaxis therapy, or
> - have current or historical life-threatening haemorrhage, or repeated, serious spontaneous bleeding episodes.
>
> This decision to provisionally 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 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.

6. Proposal for public funding

Under the National Blood Agreement, 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, which is administered by the NBA. Although ED 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 National Blood Agreement, as it is proposed as an alternative therapy to the use of blood products currently funded under the National Blood Agreement.

ED will be prescribed and administered in an HTC (a public hospital outpatient clinic) under the supervision of a specialist with experience in the diagnosis and management of HMB. Patients will already be familiar with and known to the HTC and will be monitored through the ABDR.

AHCDO's position is that gene therapy should be implemented via a 'Hub and Spoke' model in line with emerging international best practice. Hub and spoke sites will work in partnership to ensure continuity of care to patients receiving gene therapy. Five of the existing HTCs will be designated as expert hubs that prescribe and administer haemophilia gene therapies nationally.[5]

[5] The 5 hub sites proposed in the AHCDO Gene Therapy Roadmap (2022) are the clinical trial sites that already have the requisite infrastructure and expertise for gene therapy: Royal Brisbane & Women's Hospital (QLD); Royal Prince Alfred Hospital (NSW); The Alfred Hospital (VIC); Royal Adelaide Hospital (SA); Fiona Stanley Hospital (WA).

Other centres will become spokes, responsible for pre- and post-gene therapy care, including undertaking screening tests to assess suitability for gene therapy, conducting follow up appointments and tests after infusion, and providing or facilitating access to psychosocial support. Hub and spoke sites would share responsibility for making the decision to approve patients for gene therapy; determining post-infusion monitoring and care; and managing and reporting adverse events.

The applicant did not seek funding for the codependent diagnostic. The anti-AAV5 NAb test will be run from a single laboratory site located at Precision for Medicine (PfM), the third-party supplier of the assay, in the United States (U.S.). This single site will support testing requirements for all ED markets globally. 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.

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. However, the ADAR advised that PfM holds accreditation from the College of American Pathologists' Laboratory Accreditation Program (CAP), certification from the U.S. Clinical Laboratory Improvement Amendments (CLIA) and various International Organization for Standardization (ISO) Quality System certifications. CLIA sets federal standards for all U.S. facilities that perform testing on human specimens for health purposes and is supported by the Centers for Disease Control and Prevention (CDC), in collaboration with the Centers for Medicare & Medicaid Services (CMS) and the U.S. FDA.

Anti-AAV5 NAb testing would be ordered, and interpreted, by the treating specialist in the HTC. The expected turnaround time for a test result is 2–3 weeks.

ED 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. An average patient weighing 86 kilograms would receive 172 mL product (18 x 10 mL vials with 8 mL wastage). In ADAR 1728, the proposed price per ED infusion was $**redacted.** No rationale was provided by the applicant for this price.

ADAR 1728.1 proposed a reduced price per ED infusion of $**redacted**. A risk-share proposal was also offered by CSL Behring, **redacted**. The details of the risk-share proposal are outlined below.

Risk-share proposal

Redacted.

Table 3 Summary ED risk-share proposal proposed in the original application (ADAR 1728)

Table redacted.

The risk-share proposal in ADAR 1728.1, outlined in Table 4, was intended to address key uncertainties raised in relation to ADAR 1728, such as risk of treatment failure, patient variability in response, long-term durability, and upfront budget impact. The commentary noted that this risk-share model has the advantage that it incentivises continuous patient monitoring and aligns payments with response to treatment.

Reimbursement has been approved for ED in Canada and a number of European countries (Austria, Denmark, France, Germany, Spain, Switzerland, UK); however, details of their risk sharing agreements are not publicly available.

Table 4 ED risk-share proposal proposed in the current application (ADAR 1728.1)

Table redacted.

The commentary suggested that payments should cease on death (regardless of whether related to treatment with ED). Liver transplantation and the occurrence of treatment-related serious adverse events (SAEs) could also be considered reasonable grounds for cessation of payment.

The commentary noted that the risk-share proposal as presented in the ADAR does not address practical implementation considerations such as the methodology and responsibility for comprehensive and transparent data collection from individual patients, and centralised data management and analysis. The risk-share further lacks clarity regarding funding responsibilities for anti-AAV5 NAb testing and re-testing (if required) to determine eligibility for ED.

7. Population

The population proposed in ADAR 1728 was adults ≥18 years of age with HMB (congenital FIX 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 FIX inhibitors.

Anti-AAV5 NAb titre was not included in the population because it was not specified in the TGA indication, despite the provisional registration stating that baseline testing of pre-existing anti-AAV5 NAb titre is required.

The revised population in ADAR 1728.1 incorporated the co-dependent diagnostic – the 9-point anti-AAV5 NAb assay – and additional clinical criteria listed as contraindications in the Australian Product Information (PI) for ED.

Test (anti-AAV5 NAb assay): Adult patients (≥18 years) with severe or moderately severe (FIX activity ≤2% of normal) congenital HMB, currently receiving stable FIX prophylactic therapy, who also meet the following criteria:

- no active infections, either acute or uncontrolled chronic, and
- no known advanced hepatic fibrosis, or cirrhosis.

Intervention (ED): Adult patients (≥18 years) with severe or moderately severe (FIX activity ≤2% of normal) congenital HMB, currently receiving stable FIX prophylactic therapy, who also meet the following criteria:

- anti-AAV5 NAb titre <1:900 using 9-point anti-AAV5 NAb assay, and
- no active infections, either acute or uncontrolled chronic, and
- no known advanced hepatic fibrosis, or cirrhosis.

For consistency with the TGA indication, the commentary noted that the test and intervention populations should also include:

- no history of FIX inhibitors.

Treatment with the intervention was proposed as an alternative to current best supportive care, which is a stable prophylactic regimen of recombinant FIX concentrate. Treatment with ED 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.

8. Comparator

Patients not treated with gene therapy will continue to be treated with a prophylactic regimen of recombinant FIX concentrate, or other registered prophylactic agents. On-demand or episodic treatment with FIX is administered only at the time of a bleeding event (or event anticipated to cause bleeding). At the time of the ADAR submission, the procurement arrangements were such that Alprolix (eftrenonacog alfa/extended half-life [EHL]) and Benefix (nonacog alfa/standard half-life [SHL]) recombinant FIX clotting factor concentrates were available, along with Monofix, a plasma derived clotting factor with minimal utilisation. All treatments for HMB are currently fully funded (no patient co-payment) by all Australian governments under the National Blood Agreement.

9. Summary of public consultation input

Consultation input was welcomed from:

1728.1 – Etranacogene dezaparvovec for the treatment of Haemophilia B (CSL Behring (Australia) Pty Ltd)	No. of Inputs Received
Organisations (2)	
I am providing input on behalf of a consumer group or organisation. Consumer organisations are not-for-profit organisations representing the interests of healthcare consumers, their families and carers.	1
I am providing input on behalf of a medical, health, or other (non-consumer) organisation. For example, input on behalf of a group of clinicians, research organisation, professional college, or from an organisation that produces a similar service or technology.	1
Grand Total	**2**

The organisations that submitted input were:

- Haemophilia Foundation Australia (HFA)
- Australian Haemophilia Centre Directors' Organisation (AHCDO)

Level of support for public funding

HFA expressed support for the public funding of this application. AHCDO referred to previous input it provided for MSAC application 1728, where they expressed explicit support for the access to haemophilia gene therapy as a funded treatment option in the treatment of haemophilia.

Comments on PICO

- AHCDO suggested comparator study methodology cannot be readily applied to rare disorders, such as haemophilia, where the principal manifestation of severe haemophilia is bleeding, and thus the demonstration of no bleeding (or significant reduction) is important and clinically meaningful.
- HFA noted its lack of scientific expertise, but stated the eligibility criteria appear to be related to the population that received benefit from the therapy in clinical trials.
- HFA noted that due to the highly specialised services required, there is a risk that gene therapy will be restricted to individuals who can access it via large HTCs.

Perceived Advantages

- AHCDO noted mathematical modelling suggests a clinically meaningful response of gene therapy in HMB might last 25 years.
- AHCDO noted that for patients with congenital mild HMB, spontaneous bleeding is rarely observed, and thus the need and burden of regular prophylaxis with clotting factor concentrates (CFC) is removed. Advantages include patients being able to: travel more freely; participate in more active sport; widen their scope of vocation; and potentially provide an infused patient with a "haemophilia-free" lifestyle.
- HFA noted that clinical trial data is positive, with promising long-term and safety results.
- HFA noted its community consultation showed one of the most significant outcomes for quality of life is not needing a regular regimen of prophylaxis therapy, as well as the development of a 'haemophilia free mind'.

Perceived Disadvantages

- HFA noted the following community concerns with current gene therapies in those affected by haemophilia:
    - Uncertainty about long-term outcomes with safety and side-effects.
    - Uncertainty about how long the effect will last long-term.
    - Treatment may not work.
    - You can only have this treatment once; if it fails, you have to return to regular prophylaxis.
    - Potential need to use steroids to manage side-effects.
    - Commitments with preparation and follow-up: no alcohol, contraception, many appointments over several years, travel to attend clinic.

Support for Implementation and Issues

- AHCDO referred to an ongoing clinical trial that seeks to evaluate the efficacy and safety of Hemgenix in patients with HMB who have pre-existing immunity to adeno-associated virus (AAV) neutralising antibodies (NAb), noting results will further inform patient care.
- AHCDO noted their favour towards a "hub and spoke" approach in order to standardise and ensure equity of access for gene therapy. This approach was supported by HFA.
- AHCDO noted the need to explicitly discuss the requirement for ongoing long-term safety and efficacy monitoring with eligible patients once infused.
- HFA noted the anticipated need for a multidisciplinary HTC team who can perform a range of relevant services, including medical, nursing, laboratory, psychosocial, physiotherapy, and data management services.
- HFA expressed concerns that individuals may overlook specialist services provided at HTCs (reducing haemophilia-related joint and muscle damage management) after they receive a positive gene therapy outcome. HFA noted the need to consider and develop ways to connect and engage individuals and their carers with HTC services, particularly as individuals:
    - are likely to deskill in recognising bleeds and being able to self-treat
    - will need ongoing physiotherapy to build strength and manage existing joint and muscle damage
    - will need support in management of complications, such as decisions about and management of joint replacement surgery and other musculoskeletal services that will still be required; and psychosocial support for a range of existing issues, including managing the long-term and traumatic impact of HIV and hepatitis C

- will need support and liaison with other health services to manage invasive procedures and injury appropriately
- may need testing, advice and counselling on genetics and reproduction/family planning and a record kept of their family factor IX gene mutation.

10. Characteristics of the evidence base

Evidence for etranacogene dezaparvovec (ED)

The evidence base consisted of 3 single arm observational studies: two of etranacogene dezaparvovec (ED) (AMT-061) and one of its precursor gene therapy construct (AMT-060).

The Phase III HOPE-B study was an open-label, single arm study with a before-and-after design, designated an interrupted time series by the commentary. Eligible subjects underwent a lead-in period of 6 months during which participants received continuous FIX prophylactic therapy prior to treatment with ED. ADAR 1728 presented 36-month data from this study.

Results from the Phase I/II AMT-060-01 study (precursor gene therapy construct) and Phase IIb AMT-061-01 study were considered supportive evidence.

ADAR 1728 presented 7-year data from AMT-060-01/AMT-060-04 (after 5 years of follow up in AMT-060-01, 9 of the 10 subjects were enrolled in a 5-year extension study, AMT-060-04). Planned completion of the extension study is May 2026).

ADAR 1728 presented 5-year data from the AMT-061-01 study. After completion of this study, the 3 participants were enrolled in a 15-year extension study (CSL222_3003; NCT05962398), which is ongoing to 2035 and will also enrol participants from the Phase III HOPE-B study.

Results from the HOPE-B study were presented in ADAR 1728.1 with updated data from a 48-month post-hoc analysis. The median duration of follow-up at the 3 June 2024 cut-off was not provided.

No clinical study report (CSR) is planned for the 4-year data. A final analysis will be performed at 5 years post treatment when the study concludes (in March 2025).

No longer-term follow-up data were presented in ADAR 1728.1 for subjects who were enrolled in the 2 supportive studies. Analyses are not yet available from the 15-year extension study.

Table 5 Key features of the included evidence for etranacogene dezaparvovec (ED)

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 x 10^{13} gc/kg)	ABR 6–18 mo post-treatment Uncontaminated FIX activity FIX utilisation AEs EQ-5D-5L HAEM-A-QoL	Yes ADAR 1728: FIX activity, ABR, SAEs, EQ-5D-5L ADAR 1728.1: FIX activity, ABR, AjBR, SAEs
Phase IIb AMT-061-01 NCT03489291	3	Case series NR, MC, OL, SA Very high	Adults with HMB (severe or moderate)	etranacogene dezaparvovec (2 x 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 x 10^{12} gc/kg 2 x 10^{13} gc/kg	Frequency and incidence of AEs at 1 y, 5 y	No

ABR = annualised bleed rate; ADAR = Applicant Developed Assessment Report; AE = adverse event; AjBR = annualised joint bleed rate; 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.

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 6). No subjects were excluded from the study on the basis of pre-treatment anti-AAV5 NAb titre.

Table 6 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 ED	☒ k=1 n=54 (21 with pre-existing anti-AAV5 NAb)	High

AAV5 = adeno-associated virus type 5; k = number of studies; n = number of subjects; NA = not applicable; NAb = neutralising antibody.
Source: Table 2 of Commentary Executive Summary for MSAC 1728.

The 7-point assay used in the HOPE-B study is the clinical utility standard. The assay that will be used in clinical practice 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. The commentary noted that assay correlation was based on small sample size (n=30) and a limited number of samples at the relevant decision threshold (around 1 in 900 using the 9-point assay) and considered the evidence extremely limited.

11. Comparative safety

Etranacogene dezaparvovec (ED)

Acute peri-infusion adverse effects

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

The Australian PI for ED does not specify a pre-treatment regimen to reduce the risk of hypersensitivity reactions. However, in the event of an infusion reaction during administration, the infusion rate of 500 mL/hour (8 mL/minute) is slowed or interrupted, and a corticosteroid or antihistamine may be considered, based on clinical judgement.

Common adverse events

Up to the 4-year database extract date, 818 treatment-emergent adverse events (TEAEs) were reported in 54/54 (100%) subjects. Most TEAEs (603/818) were mild in severity. The post-treatment AEs occurring in at least 5% of subjects were mostly non-specific events suggestive of inflammatory or flu-like symptoms, except for elevated alanine aminotransferase (ALT), creatine kinase and aspartate aminotransferase (AST) enzymes (which indicate a reaction focused on the liver, consistent with the ED mechanism of action and class effects observed with other AAV-based gene therapies). More TEAEs (307/818) occurred within the first 6 months post dose than during any other 6-month post-dose time interval. AE frequency remained relatively stable across each time period from Month 13 onwards.

A total of 110 TEAEs were reported between the 3- and 4-year database extracts. The most frequently reported were arthralgia (11.1%), back pain (5.6%), depression (5.6%) and joint swelling (5.6%).

Treatment-related adverse events

At 48 months, TEAEs that were considered related to ED were reported in 39/54 subjects (98 events). Most treatment-related TEAEs (92/98) occurred within the first 3 months post dose. Between the 3- and 4-year database extracts, 3 TEAEs that were considered potentially treatment-related were reported in 3 subjects:

- mild metabolic-dysfunction associated liver disease without signs of steatohepatitis or fibrosis – redacted
- insomnia – redacted
- myelodysplastic syndrome (MDS) – redacted.

Serious adverse events

During the 6-month lead-in period of HOPE-B, 5 SAEs were reported in 4 subjects: muscle haemorrhage, gastrointestinal haemorrhage, haemophilic arthropathy, pseudoarthrosis and haemarthrosis.

At 36 months post-treatment, 22 SAEs had occurred, of which 7 were bleeds or bleed-related, and a further 2 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 subject with multiple risk factors (including a history of both hepatitis B and C and fatty liver disease).

At 48 months post-treatment, a total of 32 SAEs were reported in 20/54 (37.0%) subjects. Ten SAEs were reported between the 3- and 4-year database extracts: knee prosthesis breakage, lumbosacral radiculopathy, hypertensive urgency, hypertensive emergency, coronary artery disease, atrioventricular block, worsening of depression, right eye blindness, glossopharyngeal schwannoma and MDS. All were judged to be not related to ED by the study investigator, except for schwannoma (judged to be unlikely related) and MDS (judged to be possibly related). CSL Behring assessed the MDS case as unrelated to ED because the subject had 2 allelic variants specific to MDS.

Neoplasms

At 4 years, 16 neoplasms (including benign and malignant) were reported in 9 ED recipients. The 3 new neoplasms that emerged between the 36-month and 48-month datasets were skin papilloma (benign) and the cases of MDS and glossopharyngeal schwannoma (benign) mentioned above.

Of the 16 cumulative neoplasm events, 7 were malignant, observed in 6 subjects. Five of these neoplasms (in 4 subjects) were considered AEs qualifying for special notification (AESIs): HCC, MDS, glossopharyngeal schwannoma, and 2 basal cell carcinomas.

The patient population evaluated in HOPE-B had a high rate of prior or ongoing hepatitis C (57.4%) and hepatitis B infection (16.7%), and HIV positivity (5.6%), which are known pre-existing risk factors for cancer. This may have contributed to the neoplasm events in HOPE-B; nonetheless, 16 neoplasms over 4 years in a study population of 54 subjects is notable.[6]

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 humoral (antibody-based) response. Where reported as AEs, these events were typically managed with oral corticosteroid use.

From the first post-treatment visit (for most, this was at Week 3), and throughout the remaining study period (including through to the 48-month data point), all subjects experienced anti-AAV5 NAb titres at the upper limits of detection (>8,748). There was no relationship between these levels and treatment efficacy, however the commentary noted the very high post-treatment titres

[6] 17 neoplasms in total, counting the gastrointestinal lymphoma event recorded at 18 and 24 months, which was omitted from the 36- and 48-month data extracts for unknown reasons.

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

No new events of ALT increased, AST increased, or transaminase increased were reported between the 36- and 48-month analyses. No subjects have developed post-infusion FIX inhibitors.

Lack of efficacy

Criteria for how lack of efficacy was determined were not described in the ADAR.

Three subjects experienced confirmed lack of efficacy, or loss of response, in the HOPE-B post-treatment period to 48 months:

- redacted experienced lack of efficacy after receipt of a partial (10%) dose of ED following a hypersensitivity reaction and withdrew from the study at 24 months
- redacted had a very high pre-treatment AAV5 NAb titre (3,212.3) and reported lack of efficacy on post-treatment Day 14; this subject would not be eligible for treatment under the proposed funding indication where anti-AAV5 NAb titre is used as a criterion for access
- redacted demonstrated initial FIX expression after ED but experienced a loss of FIX expression and increased bleeding at approximately 29 months post infusion and recommenced continuous FIX prophylaxis at 30 months (pre-treatment anti-AAV5 NAb titre was 98.5).

No new cases of lack of efficacy/loss of response were reported in the period between the 3- and 4-year datasets.

AAV vector (deoxyribonucleic acid) DNA shedding

Although not an outcome specified in the PICO, AAV vector shedding was measured in semen and blood in the HOPE-B study. According to the 4-year database extract, the number of subjects who attained vector negative shedding in semen and blood was 45 (83.3%) and 47 (87.0%), respectively. The median time to attaining a vector shedding negative status was 43.7 weeks (95% confidence interval (CI) 34.1, 51.9) in semen and 52.6 weeks (95% CI 48.1, 77.9) in blood.

Conclusion regarding safety of ED

Given the HOPE-B study design, rare and common AEs will not be detectable in the clinical data. The study 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 1-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 use of ED was considered by the commentary to be inferior to standard of care for the outcomes of acute peri-infusion AEs and laboratory indicators of safety (specifically elevated liver enzymes), which were common TEAEs in the 6 months following ED administration. At 48 months, the use of ED was considered at least non-inferior to standard of care in terms of AEs. More TEAE's occurred within the first 6 months post ED administration than during any other 6-month period, with all 6-month periods (after Month 12) demonstrating a lower frequency of AE's compared to the lead-in period.

The safety profile of ED beyond 4 years is uncertain due to the small number of subjects with longer follow up in the supportive studies (3 subjects in AMT-061-01 followed up to 5 years and 10 subjects in AMT-060-01 followed up to 7 years). No longer-term follow-up data from the supportive studies were presented in the 1728.1 ADAR. The available follow-up is relatively short 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.

Anti-AAV5 NAb titre assay

Regarding direct harms, the assay is inferior compared to no testing but did not pose additional harms compared to any other serology test.

Indirect harms of the test could include patients being excluded from treatment with ED where it would be beneficial, or conversely receiving treatment with ED where it may not be effective (or where it may be less effective) with exposure to potential harms (including risk of peri-infusion AEs).

12. Comparative effectiveness

Etranacogene dezaparvovec (ED)

Bleeds and annualised bleed rate (ABR)

The aim of the primary efficacy endpoint in the HOPE-B study 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% CI for the rate ratio (RR) was 0.64, which was less than the prespecified margin of 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).

Summary statistics of bleeds and ABR are presented in Table 7. There was a statistically significant reduction in bleeds as measured by the rate ratio at all time points. The adjusted ABR for all bleeding episodes increased between the 3- and 4-year datasets but remained statistically significantly lower than the lead-in period.

Table 7 Summary of bleeding episodes in HOPE-B study to 48 months

Any bleeding episode	Lead-in period (N=54)	Month 7-18	Month 7-24	Month 7-36	Month 7-48
Any episode, n (%)	40 (74.1)	20 (37.0)	27 (50.0)	31 (57.4)	32 (59.3)
Zero episodes, n (%)	14 (25.9)	34 (63.0)	27 (50.0)	23 (42.6)	22 (40.7)
Free of continuous routine prophylaxis, n (%)	0	52 (96.3)	52 (96.3)	51 (94.4)	51 (94.4)
Unadjusted ABR[a]	4.11	1.08	0.99	0.90	0.77
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)	1.63 (0.76, 3.48)
Rate ratio (95% CI)[b] 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**	**0.39 (0.19, 0.81) p=0.0058**

ABR = annualised bleeding rate; CI = confidence interval.
Note: One-sided p-value ≤ 0.025 for post-treatment / lead-in < 1 is regarded as statistically significant.
a Unadjusted ABR is calculated as ratio of total (pooled) patient number of bleeds to total (pooled) patient time of observation (in years)
b Rate ratio is calculated as post-treatment / lead-in.
Source: Table 2-24 of MSAC 1728.1 ADAR + in-line commentary.

ABR by bleed subtype (spontaneous, traumatic, new and true, and joint), whether the bleed was FIX-treated or not, was substantially reduced compared to the lead-in period for Months 7 to 48 post dose. The reduction in ABR was statistically significant for all bleed subtypes analysed ($p \leq 0.025$), except for any FIX-treated bleeding episodes ($p = 0.0441$) and spontaneous FIX-treated bleeding episodes ($p = 0.0816$) at Months 7 to 48 post dose which saw nominal reductions.

Plots of bleeding episodes by subject were presented in the ADAR (shown below in Figure 1 – all bleeds, and Figure 2 – joint bleeds). The analysis excluded 2 non-responders (**redacted**) as they impacted the plots' interpretability. **Redacted** who had a high pre-treatment NAb titre (3212.3) would not be eligible for ED under the proposed eligibility criteria and therefore their omission from the data was considered inconsequential. **Redacted** received a partial dose of ED (due to a hypersensitivity reaction) and continued on exogenous FIX therapy. This scenario could occur in practice. **Redacted** who lost efficacy at approximately 29 months post-infusion was included in the analysis.

The commentary on ADAR 1728 identified 3 subjects (**redacted**) with at least 10 bleeds in the post-treatment period, along with either < 12% mean FIX activity or 'contaminated' FIX activity (due to exogenous FIX use) and moderate FIX consumption of at least 0.5 – 1.0 infusions per month over the 3 years. The 48-month data showed that all 3 subjects continued to have elevated FIX-treated ABRs in the post-treatment period compared to the rest of the cohort. At least 1 of these subjects (**redacted** with pre-treatment NAb titre 449.9) still appeared to be at risk of loss of efficacy at 48 months (their post-treatment ABR was not substantially reduced from the lead-in period).

As noted in the commentary on ADAR 1728, **redacted** had a very high ABR in the lead-in period that was substantially reduced in the post-treatment period, though this subject continued to experience a high number of untreated bleeds (considered by the ADAR to be more subjective and milder in nature).

Joint bleeds (haemarthrosis) are a major cause of significant morbidity and decreased quality of life in HMB patients. There was a significant reduction in joint bleeds ($p < 0.0001$) but they were not eliminated in subjects with a lower response to ED (i.e. FIX activity remaining in the mild range, Figure 2). No joint bleeds occurred in the 2 subjects with uncontaminated FIX activity < 5% at Month 48 (one of those was the subject who experienced loss of efficacy at Month 29).

Figure 1 ABR in lead-in period versus post-treatment Month 7 to Month 48 in HOPE-B study – All bleeds (responder analysis set)

Figure redacted

** If FIX activity levels at Month 48 were not feasible, the latest uncontaminated FIX levels obtained before Month 48 were used. "Uncontaminated" means that the blood sampling did not occur within 5 half-lives of exogenous FIX use.
Source: Figure 2.13 of MSAC 1728.1 ADAR + in-line commentary.

Figure 2 ABR in lead-in period versus post-treatment Month 7 to 48 in HOPE-B study – Joint bleeds (responder analysis set)

Figure redacted

** If FIX activity levels at Month 48 were not feasible, the latest uncontaminated FIX levels obtained before Month 48 were used. "Uncontaminated" means that the blood sampling did not occur within 5 half-lives of exogenous FIX use.
Source: Figure 2.15 of MSAC 1728.1 ADAR.

FIX activity levels

FIX activity levels were analysed in the HOPE-B study using 'uncontaminated' samples, where blood sampling did not occur within 5 half-lives of exogenous FIX use. Mean uncontaminated FIX activity was increased compared to baseline at Months 6, 12, 18, 24, 36, and 48 post dose ($p < 0.0001$; not adjusted for multiplicity).

The commentary noted uncontaminated FIX activity over time was biased towards subjects who responded well to ED. Poor responders who required frequent FIX replacement were more likely to have had fewer uncontaminated samples and would be underrepresented. At Month 48, the analysis excluded 7 subjects (2 had experienced lack of efficacy, 1 had lost treatment effect at 29 months, 1 had died after cardiogenic shock, 1 had a liver transplant after a diagnosis of HCC, and 2 had contaminated Month 48 samples).

At 48 months, 29.6% of subjects could be regarded as non-haemophilic (FIX activity ≥ 40%) based on FIX activity. 55.6% of subjects were in the mild HMB category (FIX activity 5% to < 40%), of which the majority (90%) were in the 12 – 40% grouping. Only 1 subject could be regarded as having moderate HMB at Month 48 (FIX activity 4.7%); no subjects could be regarded as having severe HMB (FIX activity < 1%). Additionally, 3 subjects experienced lack of efficacy (including the subject who lost treatment effect at Month 29 and returned to routine FIX prophylaxis at Month 30).

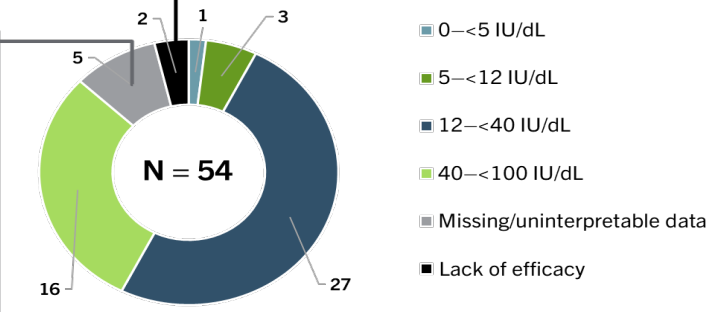
Patient categories were reasonably steady from the 18-month to 48-month time periods.

Figure 3 FIX activity level in HOPE-B subjects at 48 months

2 (3.7%) lack of efficacy
- Participant with highest NAb titre
- Participant who received ≈10% of the planned dose

5 (9,3%) missing/uninterpretable data

Reason for Missing/Uninterpretable Data	Last available FIX Activity Level*
Death at Month 15 (unrelated to treatment)	43.7 IU/dL
Liver transplant (HCC unrelated to treatment)	36.7 IU/dL
Return to FIX prophylaxis at Month 30	4.2 IU/dL
Sample contaminated (exogenous FIX use), last available result at 42 months	11.0 IU/dL
Sample contaminated (exogenous FIX use), last available result at 42 months	31.4 IU/dL



Factor IX range	N patients	Percentage %
0–<5 IU/dL	1	1,9%
5–<12 IU/dL	3	5,6%
12–<40 IU/dL	27	50,0%
40–<100 IU/dL	16	29,6%
Missing/uninterpretable data	5	9,3%
Lack of efficacy	2	3,7%

FIX = factor IX; HCC = hepatocellular carcinoma; NAb = neutralising antibody.
Based on one-stage FIX activity levels from central laboratory results. Only 'uncontaminated' samples were included in analysis; i.e. blood sampling did not occur within 5 half-lives of exogenous FIX use.
Source: Figure 2.17 of MSAC ADAR 1728.1.

FIX replacement use and prophylaxis

Post-treatment FIX replacement therapy consumption (for prophylactic use and on-demand treatment, excluding use for invasive procedures) decreased significantly from the pre-treatment lead-in period (Table 8), with a percentage reduction of at least 95% at all timepoints.

Table 8 Annualised consumption of FIX replacement therapy (IU/year) in HOPE-B study, excluding invasive procedures

Time interval	N	Mean IU/year (SD)	Mean difference (post dose – lead-in) (SD)	p-value
Lead-in period	54	257,338.8 (149,013.1)	N/A	-
Year 1 post dose	54	10,531.7 (29,870.5)	- 246,807.0 (149,280.9)	< 0.0001
Year 2 post dose	54	8,777.2 (27,208.6)	- 248,561.5 (153,996.0)	< 0.0001
Year 3 post dose	53	10,217.8 (36,097.8)	- 245,483.6 (147,850.5)	< 0.0001
Year 4 post dose	51	9,431.8 (41,959.6)	- 250,627.7 (154,102.7)	< 0.0001

CI = confidence interval; FIX = factor IX; IU = international units; N/A = not applicable; SD = standard deviation.
Post dose time interval excluded information before Day 21 post dose.
Source: Table 2.31 of MSAC ADAR 1728.1.

A plot of annualised infusion rate (AIR) comparing the lead-in period versus post-treatment period Months 7 to 48 (Figure 4) shows that subjects who experienced a lack of efficacy experienced a higher AIR compared to the responder population for whom the reduction in AIR was substantial. After ED treatment, 51/54 (94.4%) subjects discontinued and remained free of standard of care continuous FIX prophylaxis (defined as being contaminated by exogenous FIX (by the 5 half-life rule) during any contiguous 3-month period subsequent to stable FIX expression at post treatment Month 7).

Figure 4 AIR in lead-in period versus post-treatment Month 7 to 48 in HOPE-B study (infusions per year, excluding invasive procedures)

Figure redacted.

AIR = annualised infusion rate.
Source: Figure 2.19 of MSAC ADAR 1728.1.

Health-related quality of life (HRQoL)

Pre- and post-treatment EuroQol 5-dimension 5 level questionnaire (EQ-5D-5L) results are presented in Table 9. No statistically significant differences were observed between the lead-in period and any post-dose period. These results indicate that any potential HRQoL benefit from ED is not maintained over the longer term. Furthermore, questionnaires completed within 2 weeks of a bleed were not included in the analysis, which could introduce bias because subjects with recent bleeding events may have been those with lack of efficacy or frequent bleeding episodes.

Table 9 EQ-5D-5L Index Score in HOPE-B study

Analysis	Lead-in	Month 12	Month 24	Month 36	Month 48
LS mean (SE)	0.7937 (0.03241) N=50	0.8329 (0.02576) N=48	0.8388 (0.01992) N=50	0.8221 (0.02718) N=50	0.8024 (0.02552) N=47
Change from lead-in, LS mean (SE)	-	0.0392 (0.01857) N=44	0.0451 (0.02411) N=47	0.0284 (0.02740) N=46	0.0086 (0.02826) N=45
One-sided p-value (change from lead-in)	-	-	0.0198	0.0335	0.1524

EQ-5D-5L = EuroQoL-5 dimensions-5 levels; LS = least squares; SE = standard error.
A higher EQ-5D-5L score is considered favourable.
Source: Table 2.36 of MSAC ADAR 1728.1.

Changes in HAEM-A-QoL results are presented in Table 10. At 48 months, HOPE-B participants showed statistically significant reductions (indicating improvement) in the total score and in the feelings, treatment and work/school domains. The change in treatment domain may reflect a clinically meaningful reduced treatment burden of ED. At 36 and 48 months, the least squares (LS) mean reduction in the future domain (which captures concerns about disease progression, treatment burden, career prospects, family life, and overall expectations for the future) was not significantly different to the lead-in period.

Questionnaires completed within 2 weeks of a bleed were not included in the analysis; this could introduce bias because subjects with recent bleeding events may have been those with lack of efficacy or frequent bleeding episodes.

Table 10 Change from the lead-in period in HAEM-A-QoL Index Scores in HOPE-B study

Domain, statistic	Month 12	Month 24	Month 36	Month 48
Total				
LS mean (SE)	- 6.6 (0.98)	- 5.7 (1.58)	- 6.1 (1.20)	- 7.3 (1.43)
95% CI	- 8.6, - 4.6	- 8.9, - 2.6	- 8.5, - 3.7	- 10.2, - 4.4
One-sided p-value	< 0.0001	0.0003	< 0.0001	< 0.0001
Feelings				
LS mean (SE)	- 9.0 (2.02)	- 8.5 (2.17)	- 10.0 (2.51)	- 8.8 (2.89)
95% CI	- 13.0, - 4.9	- 12.8, - 4.1	- 15.1, - 5.0	- 14.6, - 3.0
One-sided p-value	< 0.0001	0.0001	0.0001	0.0018
Treatment				
LS mean (SE)	- 16.4 (2.13)	- 11.4 (2.46)	- 14.9 (2.26)	- 16.1 (2.25)
95% CI	- 20.6, - 12.1	- 16.4, - 6.5	- 19.4, - 10.3	- 20.7, - 11.6
One-sided p-value	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Work / School				
LS mean (SE)	- 5.9 (2.60)	- 3.5 (2.99)	- 6.3 (2.12)	- 7.2 (2.09)
95% CI	- 11.1, - 0.7	- 9.5, 2.5	- 10.5, - 2.0	- 11.4, - 3.0
One-sided p-value	0.0136	0.1247	0.0023	0.0005
Future				
LS mean (SE)	- 6.1 (2.14)	- 6.6 (2.15)	- 4.3 (2.56)	- 4.9 (2.45)
95% CI	- 10.4, - 1.8	- 11.0, - 2.3	- 9.5, 0.8	- 9.8, 0.0
One-sided p-value	0.0032	0.0016	0.0477	0.0251

CI = confidence interval; HAEM-A-QoL = Haemophilia Quality of Life Questionnaire for Adults; LS = least squares; SE = standard error.
A one-sided p-value of ≤ 0.025 for post dose - lead-in > 0 was statistically significant. p-values were not adjusted for multiplicity.
Source: Adapted from Table 2.35 of MSAC ADAR 1728.1.Conclusion regarding effectiveness of etranacogene dezaparvovec (ED)

The HOPE-B study showed a significant benefit over 48 months follow up in terms of bleeds, FIX activity and FIX use. A benefit in quality of life was demonstrated with a haemophilia-specific tool (HAEM-A-QoL) but no difference was observed with a generic measure of HRQoL (EQ-5D-5L). Outcomes were stable from 36 to 48 months follow up. The size of the treatment 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.

Anti-AAV5 NAb titre assay

Direct evidence

During the HOPE-B study, subjects were tested for anti-AAV5 titre at screening and then at each of the monthly visits prior to ED infusion. The pre-treatment value on the day of infusion was reported as the subject's titre. Of the 54 treated participants, 21 were positive for anti-AAV5 NAbs (titre range 9 to 3,212.3). 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 subject or due to the nature of the anti-AAV5 NAb test.

It was noted that in a few instances, pre-treatment titre increased above 1:700 (7-point assay) during the pre-treatment period and was below 1:700 on infusion day.

The HOPE-B study pre-specified a subgroup analysis reporting ABR change from baseline based on anti-AAV5 NAb titre status. The unadjusted ABR for the titre negative group at 48 months was 0.56, whereas for the titre positive group it was 1.18 (Table 11).

In the adjusted analyses, the rate ratio (i.e. adjusted ABR post treatment /adjusted ABR in the lead-in period) for the titre negative group was considerably lower than that for the titre positive group and the latter did not reach statistical significance. Excluding the subject with a very high pre-treatment titre, who would be excluded under the proposed indication, the rate ratio was significantly reduced at Month 7-18 and Month 7-24, but not for later time periods, likely driven by the subject who resumed prophylaxis at 30 months.

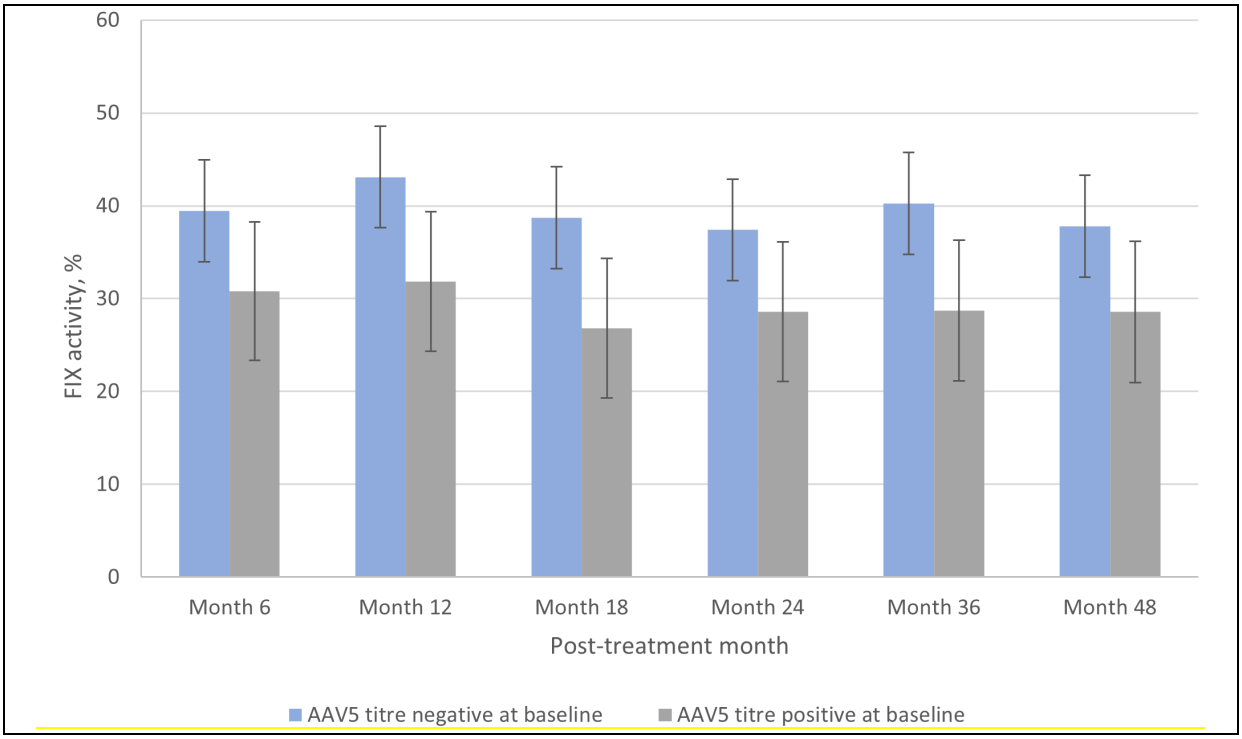
Table 11 Annualised bleed rate in anti-AAV5 titre negative versus anti-AAV5 titre positive subjects in HOPE-B study

Any bleeding episode	Lead-in period	Post treatment period (N=54)			
	(N=54)	Month 7-18	Month 7-24	Month 7-36	Month 7-48
Anti-AAV5 titre negative (n=33)					
Unadjusted ABR[a]	3.76	0.90	0.79	0.63	0.56
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)	0.57 (0.31, 1.07)
Rate ratio[b] (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**	**0.15** **(0.09, 0.25)** **p<0.0001**
Anti-AAV5 titre all positive (n=21)[c]					
Unadjusted ABR[a]	4.64	1.40	1.37	1.42	1.18
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)	26.03 (5.60, 121.01)
Rate ratio[b] (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	5.38 (1.14, 25.27) p=0.9835
Anti-AAV5 titre >LOD and <3000 (n=20)[c]					
Unadjusted ABR[a]	4.84	1.13	1.18	1.30	1.10
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)	2.81 (0.86, 9.17)
Rate ratio[b] (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	0.64 (0.19, 2.12) p=0.2292

AAV5 = adeno-associated virus type 5; ABR = annualised bleed rate; CI = confidence interval; LOD = limit of detection.
Note: Values in bold met criteria for statistical significance.
a Unadjusted ABR is calculated as ratio of total (pooled) patient number of bleeds to total (pooled) patient time of observation (in years).
b Rate ratio is adjusted ABR post-treatment / lead-in.
c Two anti-AAV5 titre positive analysis sets are shown, all titre positive (n=21) and titre <3000 (n=20), which excludes the high antibody titre subject (15-42-259). The highest titre in the <3000 analysis was 678 (7-point assay).
Source: Adapted from Table 2.37 of MSAC 1728.1 ADAR + in-line commentary.

After ED treatment, mean FIX activity increases were statistically significant at Months 6, 12, 18, 24, 36, and 48 post dose compared with lead-in in subjects with and without AAV5 NAb at baseline ($p < 0.0001$; not adjusted for multiplicity). The levels of FIX were numerically lower in the AAV5 titre positive group compared to the AAV5 titre negative group and this difference persisted throughout the post-treatment period to 4 years. The difference between subgroups was not statistically significant (Figure 5). The analysis at Month 48 excluded 7 patients, all with positive pre-treatment AAV5 NAb (range 11.1 to 3,212.3). The highest titre patient was appropriately excluded as they would not be eligible under the proposed population. The other 6 exclusions were for lack of efficacy after receiving 10% ED dose (1), loss of treatment effect at 29 months (1), death after cardiogenic shock (1), liver transplant after diagnosis of HCC (1), and contaminated Month 48 samples (2). No clinically meaningful correlation was identified between a subject's AAV5 NAb titre at baseline (up to a titre of 1:700) and their FIX activity at Month 48 post dose.

Figure 5 FIX activity, anti-AAV5 titre positive versus negative (change from baseline, LS mean % over time, with 95% CI) in HOPE-B study



AAV5 = adeno-associated virus type 5; CI = confidence interval; FIX = factor IX; LS = least squares.
Source: Commentary Figure 1 (data from Table 2.38) of MSAC 1728.1 ADAR + in-line commentary.
Note that the results presented in Figure 5 are derived from post-hoc analyses conducted during the evaluation specifically for the purposes of informing the MSAC consideration. These analyses were not part of the pre-specified statistical plan for the HOPE-B study. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the MSAC outcome and should not be used for any other purpose.

Correlation of clinical utility standard against proposed test

The assay used in the HOPE-B study – the clinical utility 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 the tests are sufficiently well correlated (adjusted R^2 value of 0.9632 across the range of titres evaluated from 30 donors, and adjusted R^2 value of 0.9939 in the reflex assay across the range of titres evaluated from 12 donors).

The linearity validation in the studies of the 9-point anti-AAV5 NAb assay with reflex testing demonstrated the maximal reporting range for testing was up to a titre of 4400 (1100 without reflex testing).

The precision and reproducibility studies for the 9-point anti-AAV5-NAb assay met the acceptance criteria for operator-to-operator, between-reader, and lot-to-lot precision for each of the four AAV5 NAb standard serum samples (panel members) with approximate titres from 110 to 900. Acceptance criteria were also met for operator-to-operator precision for the 9-point reflex assay.

The reference range of the NAb assay was established by evaluating sera from 60 apparently healthy adult male volunteers. The reference range was determined to be between 18.5 and 3487 (including the reflex test).

No additional data were provided in ADAR 1728.1 to support correlation of the 7-point and 9-point assays.

The FDA has notified the applicant that the post-marketing requirement 'to validate a sensitive and accurate assay for the detection of anti-AAV5 neutralizing antibodies, specifically to detect anti-AAV5 NAb titers up to 1:1400 or higher' has been fulfilled (May 2024). However, a second post-marketing requirement remains open – a post-market study to assess the association of ED failure and anti-AAV5 NAbs including at least 10 patients with high (1:1400 or higher) pre-treatment anti-AAV5 NAbs.

Clinical claim

The ADAR concluded that, in comparison to standard care for HMB with no gene therapy, ED had non-inferior and acceptable safety outcomes and superior efficacy outcomes including superior HRQoL.

The commentary considered that these outcomes were not all supported by the evidence and concluded the following for patients with severe to moderately severe HMB.

Safety:

- Overall, ED had non-inferior safety at 48 months follow up compared with standard of care.
    - The use of ED resulted in at least non-inferior safety for medium-term AEs (up to 48 months post-infusion)
    - The use of ED resulted in inferior safety for the outcomes of peri-infusion AEs and laboratory indicators of safety.

Effectiveness:

- The use of ED resulted in superior effectiveness compared with standard of care for annualised bleed rates, joint bleed rates, endogenous FIX activity, change in patient disease categorisation and exogenous FIX utilisation.
- There were insufficient data available to establish the effectiveness of ED compared with standard of care for the outcome of resolution of target joint bleeding.
- The use of ED resulted in non-inferior effectiveness compared with standard of care over 48 months for HRQoL outcomes. The small sample size of the key study was likely to be a limitation for establishing superiority for these outcomes.
- The use of ED in patients who were anti-AAV5 NAb positive trended towards inferior effectiveness compared to patients who were anti-AAV5 NAb negative, however in both subgroups, the use of ED resulted in superior effectiveness compared with standard of care.
- There were patients who experienced lack of efficacy and reduced efficacy. The sample size was too small for the factors contributing to this to be established.

All clinical conclusions were limited to a follow-up period of 48 months. The clinical conclusions remained stable from 36 to 48 months and no further loss of efficacy was reported over this period.

The commentary noted that ED 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 characterising the assessment of eligibility screening for ED treatment.
2. A long term (15 years) Markov model with 5 health states, 4 of which model the extent of joint damage via the Pettersson Score (PS). Transition probabilities were informed by general Australian population mortality rates adjusted by a standardised mortality ratio (SMR) in HMB patients and by outcomes reported in the HOPE-B study (FIX activity levels, annualised bleeding rates, annualised joint bleeding rates, annualised FIX consumption, and incidence of SAEs).

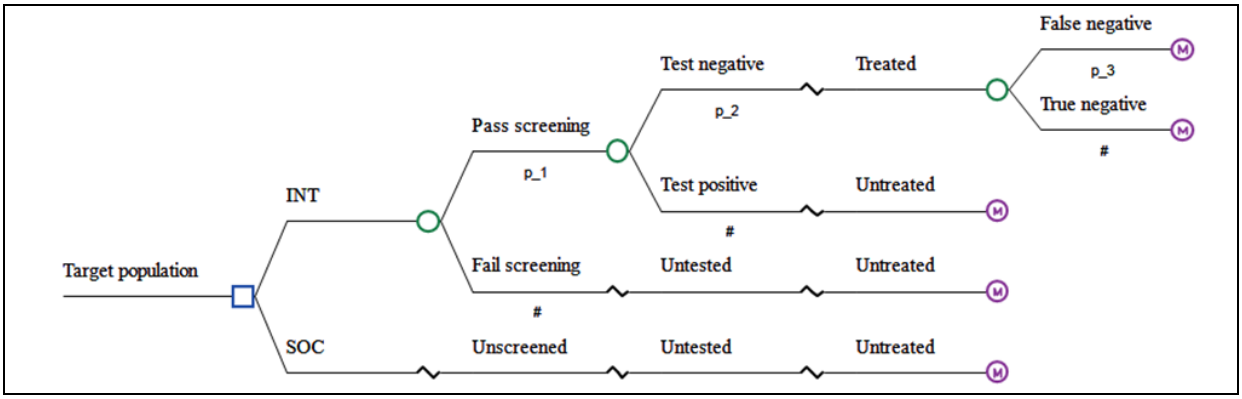
An overview of the economic model is provided in Table 12. Graphical depictions are provided in Figure 6 (initial decision tree) and Figure 7 (long term Markov model).

Table 12 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 FIX inhibitors, who are receiving regular prophylaxis using FIX concentrate
Intervention	Screening: Conventional tests for FIX inhibitors, active hepatitis, or severe liver disease Testing: Precision for Medicine (PfM) 9-point luciferase assay (anti-AAV5 NAb test) Treatment: Single IV infusion of ED at a dose of 2×10^{13} gc/kg
Comparator	Standard care (continuous prophylaxis with FIX replacement therapy); no anti-AAV5 NAb test or gene therapy
Type of analysis	Cost utility analysis
Outcomes	Quality-adjusted life years gained
Time horizon	15 years in the base case (versus 4 years in the HOPE-B study)
Methods used	Initial decision tree followed by long term 'five state' Markov state transition model Cohort expected value calculation methods
Health states	4 health states based on Pettersson Score categories: 0-4; 5-12; 13-20; 21-28 Dead
Cycle length	6 months
Transition probabilities	Decision tree: • Point prevalence of anti-AAV5 NAb > 1:900 • Probability of a false negative result using proposed assay Markov model: • General population mortality • Standardised mortality ratio for HMB • FIX concentrations above threshold (% of patients) • FIX prophylaxis proportion (% of patients) • Annualised bleeding rate (events/cycle) • Annualised FIX consumption (IU/cycle) • Number of bleeds per Pettersson Score increment • SAE incidence (events/cycle)
Discount rate	Annual rate of 5% for both costs and outcomes
Software	Microsoft Excel

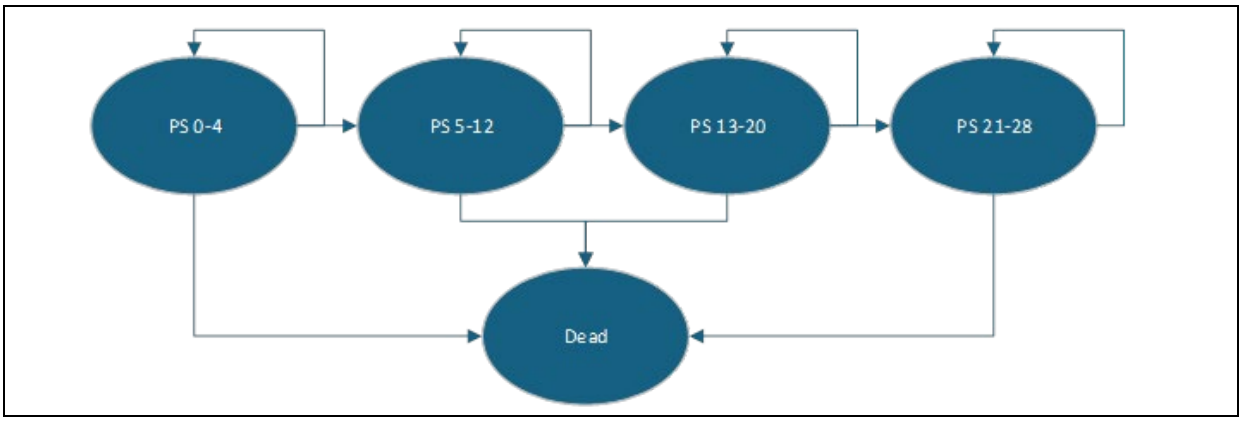
AAV NAb = adeno-associated virus type 5 neutralising antibody; FIX = factor IX; gc/kg = gene copies per kilogram; HMB = haemophilia B; IU = international units; IV = intravenous; SAE = serious adverse event.
Source: Table 3.1 of MSAC 1728.1 ADAR + in-line commentary.

Figure 6 Initial decision tree



INT = ED test-treatment intervention; SOC = standard of care.
Source: Figure 3.1 of MSAC ADAR 1728.1.

Figure 7 Long term Markov model



PS = Pettersson Score

Source: Figure 3.2 of MSAC ADAR 1728.1.

The initial decision tree identified patients who receive ED from the potentially eligible population. It had two stages, firstly screening for the presence of FIX inhibitors, active hepatitis and severe liver disease. Secondly, in those who pass screening, anti-AAV5 Nab testing where patients with a titre <1:900 progressed to treatment (Figure 6). The decision tree included false negative test results where a test wrongly indicates that the anti-AAV5 NAb titre is below the threshold of 1:900, which led to a person receiving ED who was not appropriate for treatment. In the model these false negatives are assumed to receive no benefit from ED and therefore their health outcomes are assumed to be equal to standard of care. Repeat anti-AAV5 NAb testing, if required, was not included in the decision tree nor accounted for in the costs.

The long-term Markov model included 4 health states that were associated with progression of haemophilia-related joint damage. Transition through these health states occurred following an accumulation of joint bleeds, with 12.6 joint bleeds leading patients to advance 1 PS unit and a PS score of 28 indicating a requirement for joint replacement surgery. Initial distribution across these health states was intended to reflect the different levels of arthroplasty in the starting cohort.

The Markov model was more reflective of HMB than the economic evaluation presented in ADAR 1728 but the commentary considered that development of the model was limited by the availability of reliable data to inform it. The HOPE-B study did not have sufficient power nor follow up to provide data on the natural history of HMB and the studies used to inform the model were

also small, dated and tended to be in younger populations including paediatric patients, as would be expected for a rare condition. Therefore, in addressing the oversimplification of the earlier model, the revised model necessarily introduced additional uncertainty.

Due to the high number of joint bleeds required to progress to a different health state, progression through them was slow and the health state distribution did not differ between the intervention and comparator over the model time horizon. Differences in QALYs were driven by quality-of-life decrements applied for bleeding events. The assignment of costs was influenced by people in the intervention group falling below a FIX threshold of 5% and resuming prophylactic FIX replacement therapy. Therefore, the model structure cannot be interpreted based on Figure 7 alone.

The model included additional costs associated with ED treatment (screening, testing and monitoring) though the base case assumed that routine HMB management and monitoring costs were equal for all patients, irrespective of treatment status. Staged annual payments were incorporated based on the proposed risk-share arrangement, which reduces the upfront cost burden.

Time horizon and extrapolation of trial results

MSAC did not consider the 25-year time horizon in ADAR 1728 to be reasonable and requested a reduced time horizon in a reapplication. The base case in ADAR 1728.1 applied a 'truncated' 15-year time horizon, to reflect a more conservative trade-off than proposed in the original application, between the likely lifetime duration of clinical effects of ED treatment and the currently available clinical evidence. Extrapolation of the long-term durability of FIX activity levels after ED was based on a published analysis and updated to include 48-month follow-up data from the HOPE-B study.

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 2 patients who did not respond to ED.

The extrapolation analysis was adjusted *post-hoc* to include these 2 treatment failures and the patient with loss of efficacy at 29 months.

The commentary noted that the extrapolation analysis had some important limitations. Patients requiring external FIX after treatment with ED likely had FIX activity levels contaminated 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 were not accounted for in the extrapolation analysis.

A FIX activity threshold of 5% was used to predict return to prophylaxis and comparator bleeding rates. The commentary considered this the most plausible threshold and noted its consistency with discontinuation of FIX infusions in the HOPE-B study.

Results

The results of the CUA were driven by the costs of treatment in each arm. Both treatment options are effective and therefore neither group progresses through the health states within the 15-year time horizon in the base case, limiting the influence of additional costs, or QALY loss, associated with disease progression. However, as bleeds are associated with a transitory QALY decrement, QALYs are consistently slightly higher in the intervention group at all time points.

Due to the annual staged payment, incremental costs during the initial 6-month cycles of the model are 'lumpy', however the intervention becomes consistently cost saving from around 11 years and is dominant in the 15-year base case analysis.

The stepped economic evaluation results are provided in Table 13. The trial-based results at 4 years include reducing the number of payments from 10 to 4.

Table 13 Results of the stepped economic analysis

Step	ED	Standard of care	Increment	ICER ($/QALY)
Comparative study data; trial-based Time horizon 4 years[a]				
Costs	$**redacted**	$916,759	$**redacted**	$**redacted**
QALY	2.99	2.96	0.027	
Study evidence extrapolated Time horizon 10 years				
Costs	$**redacted**	$1,959,000	$**redacted**	$**redacted**
QALY	6.39	6.33	0.059	
Study evidence extrapolated Time horizon 15 years				
Costs	$**redacted**	$2,582,233	-$**redacted**	-$**redacted**
QALY	8.43	8.35	0.077	

ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year.
a Results for the 4-year time horizon were calculated by the commentary and assumed payment over 4 equal instalments rather than 10. The ICER for the 4-year time horizon presented in the ADAR ($**redacted**/QALY) was calculated without adjustment to the number of ED payments.
Source: Commentary Table 7 of MSAC 1728.1 ADAR + in-line commentary.

Key drivers of the model were the time horizon, the presence of the outcomes-based agreement, the cost of the comparator and the event-based utility decrements (Table 14).

Table 14 Key drivers of the model

Description	Method/value	Impact Base case: -$redacted/QALY gained
Time horizon	Treatment effect continued beyond the 4-year study period for up to 15 years. Waning of FIX activity level was extrapolated from study data.	High, favours intervention Reducing the time horizon from 15 years to 4 years (with payment over 4 years) resulted in an ICER of $**redacted**.
Outcomes-based agreement	The risk-share proposal **redacted**.	High, favours intervention Without the outcomes-based agreement the ICER is increased by 36% (but remains dominant). A single upfront payment results in an ICER of $redacted and the intervention is no longer dominant over the 15-year time horizon.
Cost of the comparator	Extended half-life FIX price of $**redacted** per IU.	High, favours intervention A price reduction of 25% increased the ICER to $**redacted** and the intervention is no longer dominant over the 15-year time horizon.
Event-based utility decrements	QALY decrements decreased to -0.001 for all events (joint and non-joint bleeds, joint replacement, and SAEs)	High Joint and non-joint bleed rates differ between arms. A smaller QALY decrement leads to a smaller overall QALY difference, and the smaller denominator leads to a more negative ICER (-$**redacted**).

FIX = Factor IX; ICER = incremental cost-effectiveness ratio; IU = international unit; QALY = quality-adjusted life year; SAE = serious adverse event.
Source: Compiled for the executive summary.

Sensitivity analysis

The results of key univariate sensitivity analyses are summarised in Table 15.

The model was highly sensitive to the time horizon employed with the threshold for dominance between 11 and 12 years. The commentary considered the 10-year time horizon critical **redacted**. The high ICER of $**redacted** over a 10-year horizon is driven by the high costs for ED, the relatively high ongoing costs for FIX and the relatively small QALY difference in relation to these costs. Under the base case, the price of ED needs to be reduced to approximately $**redacted** to reach dominance in a 10-year time horizon **redacted**. The model is also sensitive to assumptions around FIX price.

Sensitivity analysis was undertaken to explore the impact of a loss of treatment effect across the entire cohort after 4 years (the duration of follow up in the HOPE-B study) and after 10 years **redacted**. Analyses assuming loss of treatment effect at 4 years counter-intuitively resulted in increased cost-utility (ICER of - **$redacted**) compared with loss of treatment effect at 10 years (ICER of $**redacted**) because the **redacted**.

The model was very sensitive to the event-based utility decrements applied for bleeds, joint bleeds, joint surgery and SAEs and removal of these decrements resulted in no difference in QALYs between intervention and comparator. Although there were no statistically significant differences in EQ-5D-5L in HOPE-B at any time point post treatment compared with the lead-in period, these were used to inform QALY differences in ADAR 1728 rather than event-based decrements.

Table 15 Key sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER
Base case	**-$redacted**	**0.077**	**-$redacted**
Time horizon: 10 years (base case: 15 years)	**$redacted**	0.059	**$redacted**
Starting age: 18 years (base case: 43 years)	-**$redacted**	0.080	-**$redacted**
AFC where FIX activity is ≤5% = 195,000 IU/year/patient (base case: 260,000 IU/year/patient)	-**$redacted**	0.077	-**$redacted**
FIX threshold <2% (base case: <5%)	-**$redacted**	0.078	-**$redacted**
Joint bleeds per PS increment 6.52 (base case: 12.6)	-**$redacted**	0.096	-**$redacted**
No event-based utility decrements (bleeds, joint bleeds, joint surgery, SAEs) (base case: -0.003 to -0.03)	-**$redacted**	0.000	NC

AFC = annualised FIX consumption; FIX = Factor IX; ICER = incremental cost-effectiveness ratio; IU = international units; NC = not calculable; PS = Pettersson Score; QALY = quality adjusted life year; SAEs = serious adverse events.
Source: Adapted from Table 3.20 of MSAC ADAR 1728 + in-line commentary.

Post-ESC additional analyses

At the June 2025 ESC meeting, ESC requested the assessment group to undertake additional analyses on what the price of ED would need to be, in order to be cost neutral (compared to the comparator) at 10 years. The assessment group conducted these analyses using:

- FIX usage data from HOPE-B study and the ADAR FIX replacement therapy prices (presented in this section)
- FIX usage data from the HOPE-B study and effective FIX replacement therapy prices (presented in the CIC section)
- FIX usage data from the 2023-2024 ABDR provided by the NBA and effective FIX replacement therapy prices (presented in the CIC section).

Cost neutral at 10 years using HOPE-B data and ADAR FIX replacement therapy prices

The ADAR base case used a price of $**redacted**/IU for standard half-life (SHL) FIX and $**redacted**/IU for extended half-life (EHL) FIX. Using the ADAR's base case inputs over a time horizon of 10 years, the ICER is $**redacted**. The price of ED needs to be reduced from $**redacted** (proposed in ADAR 1728.1) to $**redacted** to be cost neutral at 10 years.

Table 16 ED price to achieve cost neutrality at 10 years (using inputs from ADAR 1728.1 base case)

Analysis	SOC AFC (IU/yr/patient)	FIX price	Price of ED	ICER
Base case	257,339	SHL $**redacted**/IU EHL $**redacted**/IU	$**redacted**	$**redacted**
Cost neutral price for ED	257,339	SHL $**redacted**/IU EHL $**redacted**/IU	$**redacted**	cost neutral

AFC = annualised FIX consumption; EHL = extended half-life; FIX = Factor IX; ICER = incremental cost effectiveness ratio; IU = international units; SHL = standard half-life; SOC = standard of care; yr = year.
Note: Analyses assume FIX replacement therapy for prophylaxis is 85% EHL, 15% SHL.

14. Financial/budgetary impacts

WA mixed epidemiology and market-based approach was used to estimate the uptake and financial implications for the proposed introduction of ED for the treatment of HMB in Australia. The eligible patient population was estimated from ABDR data and assumed to have a stable growth rate.

The ADAR claimed the ED uptake estimates from the original application were realistic and probable and are supported by slow uptake in international markets. The ADAR reiterated that a large influx of patients electing to receive ED in the first years would be highly unlikely due to patient considerations, including their willingness or apprehension to receive innovative therapies, as well as their 'suitability' to receive gene therapy, which encompasses career and travel plans, as well as their ability to follow the post dose monitoring requirements. However, the ADAR acknowledged inherent uncertainty in the estimates and the commentary noted that uptake of ED could increase as more data on longer-term safety and efficacy of ED becomes available.

As per the updated risk-share proposal, the financial estimates assumed the total cost per ED infusion was redacted that were linked to an outcomes-based agreement. The base case conservatively assumed that no patients fail treatment, and thus the financial analysis included the full cost of ED for each patient over the 6-year projection period (noting that 6 years was insufficient to capture all payments).

The financial analysis captured costs related to screening, administration, management of infusion-related reactions (raised transaminases treated with oral corticosteroids) and long-term monitoring of liver function and FIX activity (although the calculations only accounted for 5 years, rather than the redacted). For simplicity in the financial analysis, healthcare resource use costs were all assumed to occur in the year that ED was administered.

The commentary noted that screening costs were likely underestimated because these costs were applied to patients who received ED rather than those screened for eligibility. The additional cost to the MBS for screen failures would become material if the proportion of HMB patients who are willing to receive ED is higher than anticipated in the ADAR.

Costs for multidisciplinary team meetings, counselling/psychosocial support (outlined in the AHCDO Gene Therapy Roadmap), baseline hepatic ultrasound and management of adverse events (such as hypersensitivity reactions or bleeding) were not incorporated in the financial analyses.

The financial impact of ED to the National Blood Agreement and other government health budgets is shown in Table 17. MBS costs were calculated using 100% of the schedule fee (including patient copayment). The financial estimates presented in Table 17 are slightly different from those provided in the ADAR because they incorporate the cost of a baseline liver ultrasound in all patients, assume corticosteroid use in 16.7% of patients (from HOPE-B) and correct the calculation of FIX costs.

The estimates assumed an average of 9,740 IU/year FIX replacement therapy after treatment with ED, based on 4-year data from the HOPE-B study. Costs were calculated using $redacted/IU for Alprolix (EHL) and $redacted/IU for Benefix (SHL), assuming EHL has 85% market share. The commentary noted that the total cost of FIX use after treatment with ED is underestimated because the calculations excluded FIX use during invasive procedures and during the first 21 days after ED administration when patients remain on routine FIX prophylaxis.

Table 17 Financial implications of funding ED

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Assumed uptake rate	**redacted**%	**redacted**%	**redacted**%	**redacted**%	**redacted**%	**redacted**%
Patients electing ED	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**
Cumulative patients electing ED	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**
Cost to the National Blood Agreement – ED	$**redacted**	$**redacted**	$**redacted**	$**redacted**	$**redacted**	$**redacted**
Cost to the National Blood Agreement – change in use of FIX therapy[a]	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**	-$**redacted**
Change in use of other healthcare resources[b]	$**redacted**	$**redacted**	$**redacted**	$**redacted**	$**redacted**	$**redacted**
Overall net financial impact of funding ED[c]	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**
Net financial impact to the National Blood Agreement[d]	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**
States and Territories (37%)	$**redacted**	$**redacted**	$**redacted**	$**redacted**	$**redacted**	$**redacted**
Commonwealth (63%)	$**redacted**	$**redacted**	$**redacted**	$**redacted**	$**redacted**	$**redacted**

FIX = Factor IX.
a Incorporated correction of error in calculation of FIX replacement therapy costs (the ADAR applied annual FIX consumption rather than annual FIX cost in the calculation).
b Included healthcare resource use for screening (collection of serum sample, anti-AAV5 Nab test, FIX inhibitor test, test for active infections, liver enzyme testing, baseline liver ultrasound, specialist consultation), ED administration (specialist attendance, infusion cost), management of infusion-related reactions (corticosteroid treatment in 16.7% of patients) and differential monitoring costs (specialist attendance, liver enzymes test, FIX % activity test, abdominal ultrasounds and tests for alpha-fetoprotein [in 79.7% of patients with pre-existing risk factors for hepatocellular carcinoma]). MBS and PBS costs based on Schedule fee (including patient copayment).
c ED, FIX replacement therapy and other healthcare resource use.
d ED and FIX replacement therapy only.
Source: Commentary Table 13 of MSAC 1728.1 ADAR + in-line commentary.

The risk-share proposal **redacted** significantly reduced the upfront budget impact. The ADAR claimed that ED was expected to be cost saving to the National Blood Agreement and would accumulate cost savings due to compounding cost offsets. However, these cost savings did not materialise in the 6-year projections in Table 17 (nor the 10-year projections in the financial estimate workbook).

The change in healthcare resource utilisation associated with ED was relatively small in comparison to the acquisition costs of ED and current FIX replacement therapy. Given that ED would be prescribed and administered at HTCs, healthcare resource use costs may be incurred by the public system and/or the MBS.

Table 18 shows the impact of key uncertainties in the financial estimates (assumed uptake rate and standard of care FIX consumption).

Table 18 Results of scenario analyses on the net financial implications of funding ED

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Higher uptake rate						
Assumed uptake rate	5%	10%	15%	20%	25%	30%
Patients electing ED	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**
Cumulative patients electing ED	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**
Overall net financial impact of funding ED[a]	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**
Net financial impact to the National Blood Agreement[b]	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**
Standard of care FIX consumption lower (-25%)						
Cumulative patients electing ED	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**
Overall net financial impact of funding ED[a]	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**
Net financial impact to the National Blood Agreement[b]	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**
Standard of care FIX consumption higher (+25%)						
Cumulative patients electing ED	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**	**redacted**
Overall net financial impact of funding ED[a]	-**$redacted**	-**$redacted**	-**$redacted**	-**$redacted**	-**$redacted**	-**$redacted**
Net financial impact to the National Blood Agreement[b]	-**$redacted**	-**$redacted**	-**$redacted**	-**$redacted**	-**$redacted**	-**$redacted**

FIX = Factor IX.
a ED, FIX replacement therapy and other healthcare resource use.
b ED and FIX replacement therapy only.
Source: Commentary Table 14 of MSAC 1728.1 ADAR + in-line commentary.

15. Other relevant information

Other gene therapies for haemophilia B

Clinical studies have been completed for at least 3 other gene therapies in patients with severe to moderately severe HMB (FIX activity ≤2%):

- fidanacogene elaparvovec (also known as SPK-9001, PF-06838435, Durveqtix and Beqvez), developed by Spark Therapeutics and licensed to Pfizer
- verbrinacogene setparvovec (also known as FLT180a), developed by Freeline Therapeutics (now Spur Therapeutics)
- dalnacogene ponparvovec (also known as BBM-H901), developed by Belief Biomed and being commercialised in mainland China, Hong Kong and Macau by Takeda China.

A Phase 3 study of fidanacogene elaparvovec (BENEGENE-2, NCT03861273) was the basis for regulatory approval by Health Canada in December 2023 and the FDA in April 2024. However, global development and commercialisation was discontinued by Pfizer in February 2025, citing 'soft demand from patients and their doctors'. Pfizer claimed that discontinuation was due to several reasons, including 'limited interest' in gene therapies for the bleeding disorder.

Phase 1/2 studies of verbrinacogene setparvovec (B-AMAZE, NCT03369444; B-LIEVE, NCT05164471) were terminated early and clinical development has been paused 'for business priorities'.

Other prophylactic therapies for haemophilia B

Two new prophylactic therapies administered by subcutaneous injection (prefilled pen) are registered for use in Australia for HMB (and haemophilia A [HMA]), but neither has yet received funding approval.

Concizumab (brand name Alhemo, developed by Novo Nordisk) is a humanised monoclonal antibody administered once daily. The TGA-approved indication (effective 14 January 2025) is:

> 'Alhemo is indicated where prophylaxis is required to prevent or reduce the frequency of bleeding in patients at least 12 years of age who have:
> ○ HMB (congenital FIX deficiency)
> ○ HMB (congenital FIX deficiency) with FIX inhibitors
> ○ HMA (congenital factor VIII [FVIII] deficiency)
> ○ HMA (congenital FVIII deficiency) with FVIII inhibitors.'

Marstacimab (brand name Hympavzi, developed by Pfizer) is a fully human monoclonal antibody administered once weekly. The TGA- approved indication (effective 18 February 2025) is:

> 'Hympavzi is indicated for routine prophylaxis of bleeding episodes in patients 12 years of age and older with:
> ○ severe HMA (congenital FVIII deficiency, FVIII <1%) without FVIII inhibitors
> ○ severe HMB (congenital FIX deficiency, FIX <1%) without FIX inhibitors.'

16. Committee-in-confidence information

Redacted.

17. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

Anti-AAV5 NAb testing:

- No reference standard is currently available to determine the accuracy of the anti-adeno-associated virus type 5 (anti-AAV5) neutralising antibodies (NAb) assay. The 7-point anti-AAV5 NAb assay (used in the HOPE-B study) and the 9-point anti-AAV5 NAb assay (proposed in this application) differ only by the number of dilution points. Limited data on the correlation between the 7-point and 9-point assay were reported, but data are unpublished and were not provided. Likewise, limited data on the precision and reproducibility of the 9-point assay were described but not provided. The appropriateness of the proposed 1:900 titre threshold with the 9-point assay is currently unclear. There is an evidence gap for patients with titres between 1:900 to 1:4417 on the 9-point assay (corresponding to 1:700 and 1:3212 in the 7-point assay), and such patients may be excluded inappropriately.
- Although the applicant described NAb testing as a complementary tool, its role in determining eligibility suggests functional co-dependency. Given its clinical use in selecting patients, ESC considered that a co-dependent assessment may be warranted, but the evidence presented in the ADAR does not allow such an assessment.
- ESC expressed concern that the uncertain performance of the assay could lead to misclassification. False positive results indicating titres above the 1:900 could inappropriately exclude patients from treatment. False-negative results indicating titres below the 1:900 threshold could expose patient to treatment emergent adverse events (TEAEs) without meaningful clinical gain.
- Patients with high baseline anti-AAV5 NAb titres had lower FIX activity across all timepoints compared to patients with low titres, however, the evidence does not clearly support baseline Nab titre as a reliable predictor of treatment response. There appeared to be a difference in annualised bleeding rate between NAb positive and negative subgroups, but it was not reported if this was statistically significant.

Etranacogene dezaparvovec treatment:

- MSAC previously requested longer-term clinical evidence for etranacogene dezaparvovec (ED) in Haemophilia B (HMB). The applicant has supplied data for one additional year (i.e., a total of 4 years post-treatment) in this reapplication. The additional follow-up data (i.e. from 36 months to 48 months) from the 54 patients in the HOPE-B study showed sustained efficacy, including stable annualised bleeding rates, stable endogenous FIX activity, and reduced FIX usage. However, the durability of effect beyond 4 years remains unknown. The longer-term data (5-year and 15-year extension studies) are not yet available, and the single-arm design and small sample size limit interpretation of long-term safety and effectiveness.
- The economic model may overestimate the true treatment effect due to under-representation of patients with poor or no response. While most participants achieved mild or non-haemophiliac status, some continued to bleed despite elevated FIX activity, indicating variability in treatment response.
- Some patients continued to bleed post-treatment. Subgroup differences by ancestry and liver steatosis were suggested in the forest plot for Annualised Bleed Rate (ABR) at 48 months presented in the ADAR. Possible effect modification by these patient characteristics was not explored in the ADAR, creating uncertainty as to whether the treatment is effective in all potential subgroups of the clinical population.

- ESC advised that including a ratio of annualised FIX infusion rate (AIR) (pre- vs post-treatment) alongside ABR could serve as an additional treatment response measure to aid with decision-making.

Economic issues:

- The revised economic model has a structure that includes health states related to natural history, addresses ESC's previous concerns in regarding the extrapolation and threshold for FIX % activity, and has a reduced time horizon (from 25 years to 15 years). However, the 15-year time horizon was not well justified, and the assumptions of long-term treatment durability were not well-supported. ESC advised that a 10-year horizon is preferred redacted.
- The proposed price of ED is over $redacted per patient, which ESC advised is high relative to the uncertain long-term benefits and minimal additional QALY gains. The incremental cost-effectiveness ratios (ICERs) were extremely high at 4 years ($redacted per QALY gained), reduced at 10 years ($redacted per QALY gained), and dominant (-$redacted per QALY gained) at 15 years. However, ESC noted that these ICERs are uncertain due to limited clinical inputs, outdated health state proportion data, and exclusion of non-responders from FIX activity analysis, likely overstating treatment effectiveness. The model omitted several relevant costs such as imaging, long-term monitoring and consultations which would lead to underestimated total costs.
- ESC requested the assessment group undertake additional analysis to estimate a price for ED that would be cost neutral at 10 years. Subsequently, the assessment group produced an Addendum. Using the HOPE-B study data and the ADAR FIX replacement therapy prices, the price of ED would need to be reduced from the proposed $redacted to $redacted to achieve cost neutrality at 10 years. If current FIX replacement therapy prices were used instead, the price of ED would need to be further reduced to $redacted. Incorporating both current FIX prices and adjusted annualised FIX consumption (AFC) based on unpublished ABDR 2023-24 data, the cost neutral price would need to be further reduced to $redacted.

Financial issues:

- The actual uptake of gene therapy in patients with HMB remains uncertain. As of late 2024, only redacted patients had received ED globally, with low uptake attributed to system barriers, RSA monitoring requirements, and the availability of effective therapy with FIX.

Other relevant information:

- ED has been granted provisional registration by the Therapeutic Goods Administration (TGA) and is due to be reviewed by the TGA in 2026.
- The applicant proposed a redacted% price reduction (from $redacted to $redacted), redacted.
- ESC advised that the proposed RSA presents implementation challenges and contains language open to interpretation. ESC agreed with the suggestions in the commentary on how the RSA terms could be refined and advised that any formal RSA be based on the Deed of Agreement template[7] refined by the department for the PBS over many years.
- ESC advised that the proposed redacted.
- Redacted.

[7] Australian Government Department of Health, Disability and Ageing, Attachment B – Basic De-identified Deed (example only). https://www.pbs.gov.au/industry/listing/elements/deeds-agreement/attachment-b-basic-deidentified-deed.pdf

ESC discussion

ESC noted that this re-application application from CSL Behring requested public funding through the National Blood Agreement 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 clotting factor IX (FIX).

Etranacogene dezaparvovec (ED) is a somatic gene therapy in which 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 FIX for on-demand and/or prophylaxis use after ED treatment.

ESC noted that MSAC had not supported this application at its August 2024 meeting (PSD 1728). MSAC noted the limited, low certainty clinical evidence indicated ED may be effective for some patients in the short term but considered that there was substantial inter-individual variability in the patient response to ED. MSAC also considered the clinical evidence (3-year follow-up) was insufficient to substantiate its long-term safety and effectiveness. Furthermore, MSAC considered the neutralising antibody test essential for determining patient eligibility to ED, but noted this test has not been validated. MSAC also considered that the cost effectiveness of ED compared to factor IX replacement therapy was highly uncertain due to the uncertainties in both the clinical evidence and the oversimplified economic model.

At the time of its consideration, ESC noted and welcomed input from one organisation (Australian Haemophilia Centre Directors' Organisation) received via public consultation. ESC considered it important that informed patient consent for treatment is obtained, as patients treated with ED may not be able to receive any other AAV-based gene therapies in the future. ESC noted that treatments for cHMB (gene therapies and non-gene therapies) are likely to evolve rapidly, with several such therapies on the horizon.

ESC considered that the clinical need or demand for ED compared to standard care is not clear, as FIX infusion is available as on-demand and prophylactic therapy.

ESC noted the reapplication included anti-AAV5 NAb testing as an eligibility requirement to access the treatment, as patients with high Nab titres may have a poorer response to the AAV5-based ED. While the HOPE-B study used a 7-point assay for anti-AAV5 NAb testing, the applicant has proposed to use a 9-point assay in clinical practice.

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 noted the clinical management algorithm, where patients with moderate to severe disease (based on FIX activity levels) and with no active FIX inhibitor would be offered the NAb testing. Those who are found to have a NAb titre of <1:900 on a 9-point assay are proposed to be eligible for ED.

ESC noted that the evidence provided to support the proposed anti-AAV5 NAb assay titre threshold was primarily from the HOPE-B study, supplemented by a systematic literature search. In the HOPE-B study, 33 subjects were titre-negative and 21 were titre-positive pre-treatment. Only 1 subject had a pre-treatment titre above 1:700 on the 7-point scale (corresponding to 1:900 on the 9-point scale). Although data showed numerically lower response in Nab titre-positive patients, ESC considered this insufficient to demonstrate appropriateness of the 1:900 threshold. ESC also noted that an FDA-mandated study aimed at redefining the appropriate threshold for predicting treatment response is underway, but these results will not be available until after October 2028.

ESC considered that plots of NAb titre vs bleed ratio and other outcomes would be helpful for MSAC decision-making. ESC considered that it would be informative for the applicant to report the statistical significance of the difference in treatment effect between the baseline NAb titre category subgroups to help assess this likely treatment effect modifier. Regarding the relationship between FIX activity and anti-AAV5 titre, ESC considered lower Nab titres appeared to be associated with increased FIX activity, however these results were based on a subset of patients who were most likely to respond to ED. ESC noted wide variation within the patient group, as some patients with low NAbs also had low FIX activity after treatment. ESC noted that, contrary to MSAC's view, the applicant maintains that the NAb testing is not essential and is not a co-dependent technology but rather is a complementary test that was added to the eligibility criteria.

The applicant highlighted the FDA's notification that a post-marketing requirement 'to validate a sensitive and accurate assay for the detection of anti-AAV5 neutralizing antibodies, specifically to detect anti-AAV5 NAb titres up to 1:1400 or higher' had been fulfilled. ESC agreed with the commentary that, aside from this FDA notification, the only new information provided in this reapplication includes test turnaround time, test failures and updated predictive value data for treatment response at 48 months.

ESC considered that the data to support test accuracy remain limited, with no additional evidence provided to support the validity of the assay beyond correlation between the 7- and 9-point assay versions, and no published studies comparing the 9-point and 7-point assays. The HOPE-B study used the 7-point assay, but the applicant-developed assessment report (ADAR) proposed the 9-point assay.

ESC raised concerns that a false-negative test result incorrectly indicating an anti-AAV5 titre below the threshold of 1:900 may lead to a person receiving ED who is less likely to benefit from treatment. ESC considered that there is an evidence gap for individuals with a titre between 1:900 and 1:4417 (corresponding to 1:700 and 1:3212 with the 7-point assay) in relation to the likelihood of whether a person will receive benefit from ED (and who, if treated, will be subject to a risk of treatment emergent adverse events (TEAEs)).

ESC considered that the limited evidence on analytical performance of the test appears to demonstrate a relationship between bleeding episodes and pre-treatment Nab titre depending on the baseline NAb titre from months 7 to 48 post-treatment, but this is highly uncertain due to the limited evidence, wide confidence intervals of rate ratios, and significant interpatient variability.

Regarding the evidence on safety of ED, ESC noted that the HOPE-B study design was not comparative, and the small sample size limited the ability to detect safety events in either the lead-in or post-treatment phases unless they were very common (i.e. with a cumulative 1-year incidence of at least 10%).

ESC noted that the commentary considered ED had inferior safety compared to the standard of care for acute peri-infusion AEs and laboratory safety indicators, particularly elevated liver enzymes- both of which were common TEAEs in the 6 months following ED administration. ESC further noted that at 48 months, the use of ED was considered at least non-inferior to standard of care in terms of AEs, with more TEAEs occurring within the first 6 months post-ED administration than during any other 6-month period, with all 6-month periods after month 12 demonstrating a lower frequency of AE's compared to the lead-in period. Beyond the 4 years, ESC considered that the safety of ED is uncertain due to the small number of subjects with longer follow up in the supportive studies, and no longer-term follow-up data from these studies were presented in the ADAR.

ESC noted that the clinical evidence for the effectiveness of ED was informed by 3 single-arm observational studies, however the HOPE-B study (*n* = 54 patients with severe or moderately severe cHMB treated with ED) provided the pivotal evidence. The outcomes considered from the HOPE-B study were annualised bleeding rate (ABR) 6-48 months post-treatment, uncontaminated FIX activity, FIX utilisation, AEs, and EQ-5D-5L and Haem-A-QoL scores. This application incorporated 4-year data from the HOPE-B study (compared to the previously available 3-year data); however, these extended data did not address durability of clinical effectiveness or longer-term risk of adverse effects. The final analysis of safety and efficacy of HOPE-B data is planned for 5 years post-treatment, and an extension study will collect data to 15 years post-treatment (study completion 2035). ESC considered that the longer-term effectiveness and safety of ED remain highly uncertain.

ESC noted that one of the outcomes for assessing treatment effectiveness was ABRs. The adjusted ABR was 1.63 (95% CI 0.76, 3.48) and the rate ratio was 0.39 (*P* = 0.0058, 95% CI 0.19, 0.81). Comparing pre- and post-treatment ABRs for all bleeds, ESC considered the treatment to be effective for most patients; however, 3 patients experienced ≥10 bleeds post-treatment and had <12% mean FIX activity or 'contaminated' FIX activity (due to exogenous FIX), and moderate FIX consumption (≥0.5–1.0 infusions per month), indicating continued bleeding episodes 36–48 months post-treatment. Similarly, when comparing the ABR pre- versus post-treatment for joint bleeds, ESC considered that the ED does appear to be effective for most patients, but does not prevent all bleeds, and is not effective in all patients.

ESC also noted that the subgroup analysis shown in the ADAR forest plot appears to indicate a difference in effectiveness based on patient ancestry (labelled as Race in the plot) and baseline steatosis grade, which was not addressed in the ADAR. ESC considered that it would be informative for the applicants to report the statistical significance of the difference in ABR ratios between strata for these two possible treatment effect modifiers.

Overall, ESC considered that ED had inferior safety and superior effectiveness compared to standard care, although longer term safety and effectiveness outcomes were uncertain, with data limited to 48 months' follow-up. There was some evidence that effectiveness was modified by pre-treatment NAb levels (i.e. supporting a claim of codependency), and refinement of the test threshold may increase effectiveness in a selected subgroup. Based on the FIX replacement use and prophylaxis data, ESC considered that patients expressing endogenous FIX were still receiving FIX. ESC queried if a ratio of annualised infusion rate (AIR) pre- and post-treatment could be calculated similar to ABR, which could provide an additional response measure to aid with decision-making.

ESC considered that if this application is supported, MSAC may wish to consider requiring a well-conducted registry-based cohort study, to collect robust long-term clinical outcome data to complement the HOPE-B results. ESC noted the pre-ESC response indicated that discussions were underway with stakeholders to advance this possibility.

ESC noted that the main issue affecting the economic evaluation and financial implications is the extremely high cost of ED, at more than $**redacted** per patient for one infusion ($**redacted** in the original application; $**redacted** in the reapplication).

Due to the claim of clinical superiority and non-inferior safety, ESC considered a cost-utility analysis is appropriate.

The reapplication presented a revised economic model comprising an initial decision tree followed by a long-term 5-state Markov model (4 health states based on Pettersson Score

categories [0–4, 5–12, 13–20, 21–28] and dead). The six-month cycle length of the model aligns with the HOPE-B data. ESC noted several potential issues with the model:

- The proportions of people starting in each health state were based on older data from 1997 that was not reflective of the current patient population who would be using FIX replacement therapy.
- The excess mortality was not well justified, and the survival benefit was not appropriate.
- The HOPE-B study informed the number of bleeds per Pettersson Score increment, but the patients assumed in the model do not align with the study because the HOPE-B study included patients with high and low NAb titres, and the model includes those with negative NAb only.
- The serious adverse events (SAEs) may be double counted in the model if the model already includes bleeding episodes.
- Some costs were missing, including hepatologist consultations and pre-treatment abdominal ultrasound.
- The monitoring costs were assumed to be equal in all health states, and ESC considered this unlikely.

ESC noted that the model used a 15-year time horizon extrapolated from 4 years of follow-up data. However, ESC considered the evidence supporting many of the model inputs was limited, and the applicability of these assumptions to the Australian context not justified. In addition, the model was not adequately validated.

ESC considered that the concerns raised regarding the original application remain. Specifically, the long-term durability of the treatment effect remains highly uncertain. ESC noted that the extrapolation of the long-term durability of FIX activity levels after ED was based on a published analysis and updated to include 48-month follow-up data from the HOPE-B study. Patients who required exogenous FIX after ED administration were excluded from analysis due to "contaminated" FIX levels, which ESC considered may have led to underrepresentation of patients with poorer responses, thus overstating the effectiveness of ED. ESC further considered that the variability in responses for these patients could have also been underestimated if measurements during periods of poor response were excluded.

ESC also noted that the ADAR did not include a literature search of model-based cost-effectiveness analyses for haemophilia treatments. Based on a literature search undertaken by the assessment group, ESC noted that the long-term benefits from ED treatment are highly uncertain, with all models assuming a non-waning, durable effect. Both FIX and ED are high-cost therapies, but there is considerable uncertainty regarding the claims of cost saving for ED. ESC noted an assessment from Canada (CADTH 2024) found that while ED was less costly and more effective than the comparators in the base-case analysis, ED's cost savings were potentially overestimated due to uncertainty around bleed rate assumptions over the long-term.

ESC noted that the base case incremental cost-effectiveness ratios (ICERs) were $**redacted** per quality-adjusted life year (QALY) at 4 years, $**redacted** per QALY at 10 years (extrapolated), and dominant (–$**redacted** per QALY) after 15 years (extrapolated). ESC considered that a 10-year time horizon more appropriate **redacted**. ESC noted that the sensitivity analysis showed the main drivers of the ICER were the cost of ED, the high ongoing costs for FIX, and the relatively small QALY difference. ESC noted that, when considering the FIX prices used in the base case (SHL $**redacted**/IU and EHL $**redacted**/IU), the proposed price of ED ($**redacted**) needs to be reduced to approximately:

- $**redacted** to reach dominance over a 10-year time horizon (**redacted**), assuming 10 payment instalments; or **$redacted** when taking into account current prices of the two therapies used

for routine prophylaxis- ALPROLIX and BeneFIX (a **redacted%** price reduction relative to the current proposed price of $**redacted**)

- $**redacted** to reach dominance at 4 years (the duration of follow-up in HOPE-B), assuming 4 payment instalments; or **$redacted** when taking into account current prices of the two therapies used for routine prophylaxis- ALPROLIX and BeneFIX (a **redacted%** price reduction relative to the current proposed price of $**redacted**).

ESC noted that the approximate price for ED to reach an ICER of $100,000/QALY at

- 4 years is $**redacted** (with 4 payment instalments) or a price of **$redacted** when taking into account current prices of the two therapies used for routine prophylaxis- ALPROLIX and BeneFIX

- 7 years is $**redacted** (with 7 payment instalments) or a price of **$redacted** when taking into account current prices of the two therapies used for routine prophylaxis- ALPROLIX and BeneFIX.

- 10 years is $**redacted** (with 10 payment instalments) or a price of **$redacted** when taking into account current prices of the two therapies used for routine prophylaxis- ALPROLIX and BeneFIX.

ESC acknowledged that the revised economic model structure in this application is improved and informative for understanding cost implications but remains highly uncertain due to limited long term clinical evidence and the absence of evidence of survival and quality-of-life advantage with ED.

ESC noted the resubmitted financial impact included additional costs as requested by MSAC:

- additional eligibility criteria
- additional evidence to support the estimated utilisation
- pre-treatment testing and screening and post-treatment monitoring costs, including AEs
- estimates that included the payment schedule as per the proposed RSA.

ESC noted that the net financial impact of funding ED (considering the current prices of FIX therapies) was **$redacted** in year 1 to **$redacted** in year 6. Most of these costs would be for the National Blood Agreement, with the states and territories responsible for 37% of these costs and the Australian Government responsible for the remaining 63%.

ESC compared ED with other previously considered highly specialised therapies. Voretigene neparvovec (Luxturna®) (MSAC application 1623) was supported at a cost of **$redacted** per patient. ESC noted that there was a high clinical need for this therapy as there were no alternative treatments for this condition and patients would eventually progress to blindness, and a stronger evidence base (a randomised controlled trial *(n* = 29) with 7 years follow-up) than for ED. ESC noted that the RSA for voretigene neparvovec was very detailed and included multiple requirements. ESC further noted that other high-cost therapies, such as CAR-T therapies (considered by MSAC) and nusinersen and onasemnogene abeparvovec (considered by PBAC), are all substantially less expensive than the proposed price for ED.

ESC noted other relevant significant factors, including that global uptake of ED has been low, likely due to other upcoming therapies, system barriers and the effectiveness of FIX treatment and prophylaxis. The ADAR reported that **redacted** patients had received ED and were participating in post-marketing studies in the US and France (up to November 2024). ESC noted the pre-ESC response explained that this low uptake was partly due to the operation of RSAs with individual monitoring requirements and other barriers which delay treatment. ESC also noted that

ED currently holds a provisional registration by the Therapeutic Goods Administration (TGA), with this status due to be reviewed in 2026. ESC also raised a concern regarding potential supply constraints, which may affect the ability of the sponsor to supply the treatment in Australia.

ESC noted that the funding for ED is proposed through the National Blood Agreement; redacted. ESC also noted that cost savings associated with the use of ED, due to its use as an alternative or complement to FIX, would accrue to the National Blood Agreement. However, ESC also noted that any decision to fund ED under the National Blood Agreement is a decision of all governments, facilitated through the Jurisdictional Blood Committee ahead of consideration by all health ministers.

ESC reviewed the proposed RSA. The applicant proposed a price reduction of ~redacted% (from $redacted to $redacted), with redacted. The RSA redacted.

ESC agreed with the commentary that the proposed RSA was not entirely feasible from an implementation perspective and was open to interpretation, and agreed with the specific proposals made by the commentary on how to further amend the RSA. Thus, clarification around the wording would be required. ESC considered the proposed price reduction to be inadequate and noted that the redacted were not a price reduction. ESC noted in the pre-ESC response the applicant's willingness to work with the Department on the RSA. ESC queried whether the applicant would be willing to fund the data collection process for the RSA, and, if so, whether appropriate independence and access to the results would apply. ESC requested the applicant to share treatment failure criteria from ED RSAs in other jurisdictions.

Redacted. Alternatively, ESC proposed using other outcomes from the HOPE-B study, such as pre- and post-treatment ABR or annualised bleed ratio, with a trough FIX activity of <12%.

ESC also noted the redacted.

ESC requested additional information from the applicant to address remaining clinical uncertainties:

- Using the HOPE-B data, calculate a ratio of annualised infusion rate (AIR) pre- and post-treatment (similar to ABR) based on the data from the clinical evidence on effectiveness, which could provide an additional response measure to aid with decision-making
- Provide additional evidence for effect modification in the form of the statistical significance of differences in effect on all outcomes for AAV5 Nab positive vs Nab negative, and for Nab ≥1:700 (7-point assay) vs Nab<1:700 (the proposed eligibility criterion).
- Provide individual patient data and plots for pre-treatment AAV5 Nab titre vs annualised bleed ratio for all 54 HOPE-B patients and indicate on the plot of F-IX activity vs Nab titre the patients who had a major bleed.
- Provide evidence for other possible effect modifiers such as the statistical significance of difference in effect on ABR ratio for White vs Non-white patients, for Steatosis grade ≥ 2 vs <2, and for presence/absence of joint disease at baseline in HOPE-B.
- Provide more details on the analytical performance studies, including characteristics of the people donating serum for the correlation studies, and on the 'panel' members, and data points for the reproducibility and precision studies
- Provide information on the failure criteria used for performance-based funding arrangements in other countries where available.

ESC also requested that the applicant should review the financial modelling and

- consider whether there are any ongoing monitoring costs beyond 5 years and report 10-year financial estimates (redacted) ahead of MSAC consideration of this application

including all other relevant implementation, patient counselling, consultation costs that are missing
- update the economic model to reflect any additional costs identified.

Note: As ESC raised concerns regarding the proposed price for ED, ESC requested the assessment group undertake additional analysis to estimate a price for ED that would be cost neutral at 10 years. The assessment group subsequently produced an Addendum. To achieve cost neutrality over a 10-year time horizon using the HOPE-B study data and the FIX replacement therapy prices from the ADAR base case ($**redacted**/IU for SHL and $**redacted**/IU for EHL), the price of ED would need to be reduced from the proposed $**redacted** to $**redacted**. To achieve cost neutrality over a 10-year time horizon using the HOPE-B study data and the current FIX replacement therapy prices, the cost of ED needs to be reduced to $**redacted**. Incorporating both current prices for FIX replacement therapy and adjusted annualised FIX consumption (AFC) based on unpublished ABDR 2023-24 data, the price of ED would need to be reduced even further to $**redacted** to be cost neutral at 10 years.

18. Applicant comments on MSAC's Public Summary Document

CSL welcomes MSAC's support for public funding of ED in Australia and its recognition of the therapy's clinical value, including the endorsement of innovative pay-for-performance models that support sustainable and timely access. However, CSL believes that the application of a cost-neutrality framework does not account for the transformative nature of ED, which offers the potential to eliminate lifelong, burdensome, intravenous prophylaxis through a one-time treatment. CSL notes that negotiations with the National Blood Authority will be required, as both the final pricing and risk-share arrangements are yet to be agreed. CSL remains committed to working in partnership with decision makers to bring access to Australian patients as soon as possible.

19. Further information on MSAC

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