NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B [ID3812]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B [ID3812]

Contents:

The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the NICE website.

1. **Company submission** from CSL Behring:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Haemophillia Society
   b. UKHCDO

4. **External Assessment Report** prepared by PenTAG

5. **External Assessment Report – factual accuracy check**

6. **Technical engagement response from company**

7. **Technical engagement responses and statements from experts:**
   a. Charles Percy – clinical expert, nominated by NHS England
   b. Priyanaka Raheja – clinical expert, nominated by CSL Behring
   c. Ross Bennett – patient expert, nominated by Haemophilia Society

8. **Technical engagement responses from stakeholders:**
   a. British Society for Haematology / The Royal College of Pathologists – *endorsed by Royal College of Physicians*
   b. UKHCDO
   c. Novo Nordisk

9. **External Assessment Report critique of company response to technical engagement** prepared by PenTAG

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B [ID3812]

Document B

Company evidence submission

20 January 2023

File name	Version	Contains confidential information	Date
ID3812 Etranacogene Dezaparvovec Company Evidence Submission Document [AIC]	FINAL Confidential marking revised	Yes	22 June 2023

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Abbreviations

Abbreviation	Definition
AAV5	Adeno-associated viral vector of serotype 5
ABR	Annualised bleeding rate
AE	Adverse event
AFP	Alpha-fetoprotein
AjBR	Annualised joint bleeding rate
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AsBR	Annualised spontaneous bleeding rate
ASH	American Society for Hematology
AST	Aspartate aminotransferase
BIM	Budget impact model
BNF	British National Formulary
BPI	Brief Pain Inventory
BSH	British Society for Haematology
bw	Body weight
CCC	Comprehensive Care Haemophilia Centre
CFH	Congrès Français d'Hemostase (French Haemostasis Congress)
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CPK	Creatine phosphokinase
CRP	C-reactive protein
DHSC	Department of Health and Social Care
DNA	Deoxyribonucleic acid
DSA	Deterministic sensitivity analysis
EAHAD	European Association for Haemophilia and Allied Disorders
EHL	Extended half-life
EMA	European Medicines Agency
EQ-5D-5L	EuroQol-5 dimensions-5 levels
ESS	Effective sample size

EtranaDez	Etranacogene dezaparvovec
EU	European Union
evLYG	Equal-value life years gained
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEIBA	Factor eight inhibitor bypassing agent
FIX	Factor IX
GC	Genome copy
Haem-A-QoL	Haemophilia Quality of Life Questionnaire for Adults
HAL	Haemophilia Activities List
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HERO	Haemophilia Experiences, Results and Opportunities
hFIXco-Padua	Codon optimised naturally occurring variant of human coagulation Factor IX
HIV	Human immunodeficiency virus
HJHS	Haemophilia Joint Health Score
HOPE-B	Health outcomes with Padua gene; evaluation in haemophilia B
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ICH	Intracranial haemorrhage
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-1β	Interleukin-1-beta
IL-2	Interleukin-2
IL-6	Interleukin-6
INFγ	Interferon-gamma
iPAQ	International Physical Activity Questionnaire
IPD	Individual patient-level data
IPTW	Inverse probability of treatment weighting
ITC	Indirect treatment comparison
ITI	Immune tolerance induction
IU	International unit

LLOQ	Lower limit of quantitation
LOD	Limit of detection
LS	Least square
LYG	Life years gained
MAIC	Matching-adjusted indirect comparison
MCP-1	Monocyte chemotactic protein-1
MD	Mean difference
MET	Metabolic Equivalent of Task
MIMS	Monthly Index of Medical Specialities
NAb	Neutralising antibody
NBU	Nijmegen-Bethesda Unit
PAS	Patient Access Scheme
PP	Per-protocol
PRO	Patient-reported outcome
PROBE	Patient-Reported Outcomes Burdens and Experiences
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life years
QoL	Quality of life
rAAV5	Recombinant adeno-associated viral vector of serotype 5
rFIX	Recombinant Factor IX
rFIXFc	Recombinant Factor IX Fc fusion protein (Alprolix)
rIX-FP	Recombinant Factor IX albumin fusion protein (Idelvion)
RNA	Ribonucleic acid
RR	Rate ratio
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SE	Standard error
SHL	Standard half-life
SLD	Summary-level data

SLR	Systematic literature review
SMD	Standardised mean difference
SOC	System organ class
STC	Simulated Treatment Comparison
TEAE	Treatment-emergent adverse event
TSD	Technical Support Documents
TTO	Time trade-off
UK	United Kingdom
US-ICER	Institute for Clinical and Economic Review
UKHCDO	United Kingdom Haemophilia Centres Doctor's Organisation
ULN	Upper limit of normal
US	United States
VAS	Visual analogue scale
vs	Versus
WFH	World Federation of Haemophilia
WPAI	Work Productivity and Activity Impairment Questionnaire

B.1 Decision problem, description of the technology and clinical care pathway

This submission is the first haemophilia B treatment to be appraised by NICE. Since there is no previous precedence for haemophilia B treatments undergoing NICE appraisal, there are no direct comparative methodologies from previous HTAs, as was noted at the decision problem meeting.

Please note that each main section in this submission is preceded by an executive summary with the key messages covered in the section, with the full, referenced information and data substantiating the top-level statements being provided within each section.

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication. The decision problem as per final scope is outlined in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with moderately severe* or severe haemophilia B	As per final scope	Not applicable
Intervention	Etranacogene dezaparvovec	As per final scope	Not applicable
Comparator(s)	Established clinical management (including prophylaxis and on-demand treatment)	As per final scope, comparator is mainly prophylaxis with on-demand option used in some patients	Factor IX prophylaxis is the most relevant comparator used in clinical practice. A very small cohort of patients using on-demand Factor IX treatment may be eligible for etranacogene dezaparvovec, i.e. those who are eligible for prophylaxis but continue to treat on-demand due to patient choice or clinical challenges
Outcomes	The outcome measures to be considered include: • change in factor IX levels • need for further treatment with factor IX injections • annualised bleeding rate • durability of response to treatment • complications of the disease (e.g., joint problems and joint	As per final scope	Not applicable

	surgeries) • adverse effects of treatment • health-related quality of life.		
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The use of etranacogene dezaparvovec is conditional on the presence of a specific biomarker (currently considered confidential by the company). The economic modelling should include the costs associated with diagnostic testing for biomarkers in people with	As per final scope, noting that the use of etranacogene dezaparvovec is conditional on the test result for a biomarker.	The clarification included in the previous column intends to flag that patients will require to undertake a specific biomarker test for neutralising antibodies before receiving etranacogene dezaparvovec. Clinicians will consider the use of etranacogene dezaparvovec based on the test result (no cut-off values defined). The company will provide the test free of charge, which is not routinely performed in the NHS, and therefore its costs are not included in the cost-effectiveness model. The company assumes that indirect costs associated with testing patients (e.g., staff time) will not be substantial, as testing will take place as part of routine clinic follow-up.

	haemophilia B who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.		
Subgroups to be considered	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	As per final scope	Not applicable
Special considerations including issues related to equity or equality	None in the final scope.	None in the final scope	Not applicable

*Moderately severe haemophilia does not have a standard definition but is considered here to be less than or equal to 2% of normal clotting Factor IX, as used in clinical trials for gene therapies in haemophilia B to date,[1-5] agreed by UK clinicians,[6] and as per final scope.

B.1.2 Description of the technology being evaluated

Table 2: Technology being evaluated

UK approved name and brand name	Hemgenix® (etranacogene dezaparvovec)
Mechanism of action (see Section B.1.2.1)	• Etranacogene dezaparvovec is a gene therapy product designed to introduce a copy of the human Factor IX coding DNA sequence into hepatocytes to address the root cause of the Haemophilia B disease. • Etranacogene dezaparvovec consists of a codon-optimised coding DNA sequence of the gain-of-function Padua variant of the human Factor IX (hFIXco-Padua), under control of the liver-specific LP1 promoter, encapsulated in a non-replicating recombinant adeno-associated viral vector of serotype 5 (rAAV5). • Following single intravenous infusion, etranacogene dezaparvovec preferentially targets liver cells, where the vector DNA resides almost exclusively in episomal form. After transduction, etranacogene dezaparvovec directs long-term liver-specific expression of Factor IX-Padua protein. • As a result, etranacogene dezaparvovec ameliorates the deficiency of circulating Factor IX procoagulant activity in patients with Haemophilia B.
Marketing authorisation/CE mark status	At the time of this submission, January 2023, etranacogene dezaparvovec has only been approved by the FDA in the United States.[7] Anticipated date of European Marketing Authorisation is February/March 2023 Anticipated date of Great Britain marketing authorisation is March 2023. In 2018, etranacogene dezaparvovec was granted orphan designation status for the treatment of haemophilia B by the European Commission.[8] Etranacogene dezaparvovec has been granted Breakthrough Therapy Designation by the U.S. Food and Drug Administration and access to the Priority Medicines (PRIME) regulatory initiative by the European Medicines Agency (EMA).[9,10]
Indications and any restriction(s) as described in	Proposed indication: Etranacogene dezaparvovec is indicated for the treatment of severe and

the summary of product characteristics (SmPC)	moderately severe haemophilia B (congenital Factor IX deficiency) in adult patients without a history of Factor IX inhibitors. Etranacogene dezaparvovec should only be administered to patients who have demonstrated absence of Factor IX inhibitors. In case of a positive test result for human Factor IX inhibitors, a re-test within approximately 2 weeks should be performed. If both the initial test and re-test results are positive, the patient should not receive etranacogene dezaparvovec. Etranacogene dezaparvovec is contraindicated for patients with: • hypersensitivity to the active substance or to any of the excipients • active infections, either acute or uncontrolled chronic • known advanced hepatic fibrosis or cirrhosis.
Method of administration and dosage	Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia and/or bleeding disorders. This medicinal product should be administered in a setting where personnel and equipment are immediately available to treat infusion related reactions. The recommended dose of etranacogene dezaparvovec is a single dose of 2×10^{13} GC/kg body weight (bw) corresponding to 2 mL/kg bw, administered as an intravenous infusion after dilution with sodium chloride 9 mg/mL (0.9%) solution for injection. Etranacogene dezaparvovec must not be administered as an intravenous push or bolus. The diluted product should be administered at a constant infusion rate of 500 mL/hour (8 mL/min). • In the event of an infusion reaction during administration, the infusion rate should be slowed or stopped to ensure patient tolerability. If the infusion is stopped, it may be restarted at a slower rate when the infusion reaction is resolved. • If the infusion rate needs to be reduced, or the infusion stopped and restarted, the etranacogene dezaparvovec solution should be infused within the shelf life of diluted

	etranacogene dezaparvovec, i.e. within 24 hours after the dose preparation. Etranacogene dezaparvovec can be administered only once.
Additional tests or investigations	**Pre-treatment monitoring** *Anti-AAV5 NAbs* Prior to the treatment with etranacogene dezaparvovec, patients should be assessed for the titre of pre-existing neutralising antibodies against adeno-associated viral vector serotype 5 (AAV5). *Baseline hepatic function* Prior to the treatment with etranacogene dezaparvovec, patient's liver transaminases should be evaluated and liver ultrasound and elastography performed. This includes: • Enzyme testing (alanine aminotransferase (ALT), aspartate aminotransferase (AST) alkaline phosphatase (ALP) and total bilirubin). ALT test results no later than within 3 months prior to treatment should be obtained, and ALT testing repeated at least once prior to etranacogene dezaparvovec administration to establish patient's ALT baseline. • Hepatic ultrasound and elastography assessment obtained no later than within 6 months before etranacogene dezaparvovec administration. In case of radiological liver abnormalities and/or sustained liver enzyme elevations, consideration of a consultation with a hepatologist is recommended to assess eligibility for etranacogene dezaparvovec administration. **Infusion-related reactions** Patients should be closely monitored for infusion reactions throughout the infusion period and at least for 3 hours after end of infusion. **Post-treatment monitoring** *Hepatotoxicity* After etranacogene dezaparvovec administration, transaminases should be closely monitored, e.g., once per week for at least 3 months. Follow-up monitoring of transaminases in all patients who developed liver enzyme elevations is

	recommended on a regular basis until liver enzymes return to baseline values. *Hepatic function and Factor IX monitoring* After administration, the patient's ALT and Factor IX activity levels should be monitored according to the following schedule: • First 3 months after treatment: weekly • Months 4–12 (Year 1) after treatment: every 3 months • Year 2: every 6 months for patients with Factor IX activity levels >5 IU/dL. Consider more frequent monitoring in patients with Factor IX ≤5 IU/dL and consider the stability of Factor IX levels and evidence of bleeding • After Year 2: every 12 months for patients with Factor IX activity levels >5 IU/dL. Consider more frequent monitoring in patients with Factor IX ≤5 IU/dL and consider the stability of Factor IX levels and evidence of bleeding To assist in the interpretation of ALT results, monitoring of ALT should be accompanied by monitoring of AST and creatine phosphokinase (CPK) to help rule out alternative causes for ALT elevations. In case of ALT elevations, it is further recommended to assess possible alternative causes of the ALT elevation including administration of potentially hepatotoxic medicinal products or agents, alcohol consumption, or strenuous exercise. Retesting of ALT levels within 24–48 hours and, if clinically indicated, performing additional tests to exclude alternative aetiologies should be considered. If a patient returns to prophylactic use of Factor IX concentrates/haemostatic agents for haemostatic control, consider following monitoring and management consistent with instructions for those agents. An annual health check-up should include liver function tests. *Factor IX inhibitors* Patients should be monitored through appropriate clinical observations and laboratory tests for the development of inhibitors to Factor IX after etranacogene dezaparvovec administration. *Risk of malignancy*

	It is recommended that patients with pre-existing risk factors for hepatocellular carcinoma (such as hepatic fibrosis, hepatitis C or B disease, non-alcoholic fatty liver disease) undergo regular liver ultrasound screenings and are regularly monitored for alpha-fetoprotein (AFP) elevations (e.g., annually) for at least 5 years after etranacogene dezaparvovec administration.
List price and average cost of a course of treatment	The list price of £2,600,000 per treatment for a single-dose intravenous infusion of etranacogene dezaparvovec (1×10^{13} genome copies/mL concentrate for solution for infusion) has been submitted and provisionally approved by the Department of Health and Social Care subject to Marketing Authorisation.
Patient access scheme (if applicable)	An application for a simple patient access scheme has been submitted to NHSE and is in process for advice to be issued on 27th January 2023.

Source: Hemgenix® (etranacogene dezaparvovec) SmPC, 2022.[11]

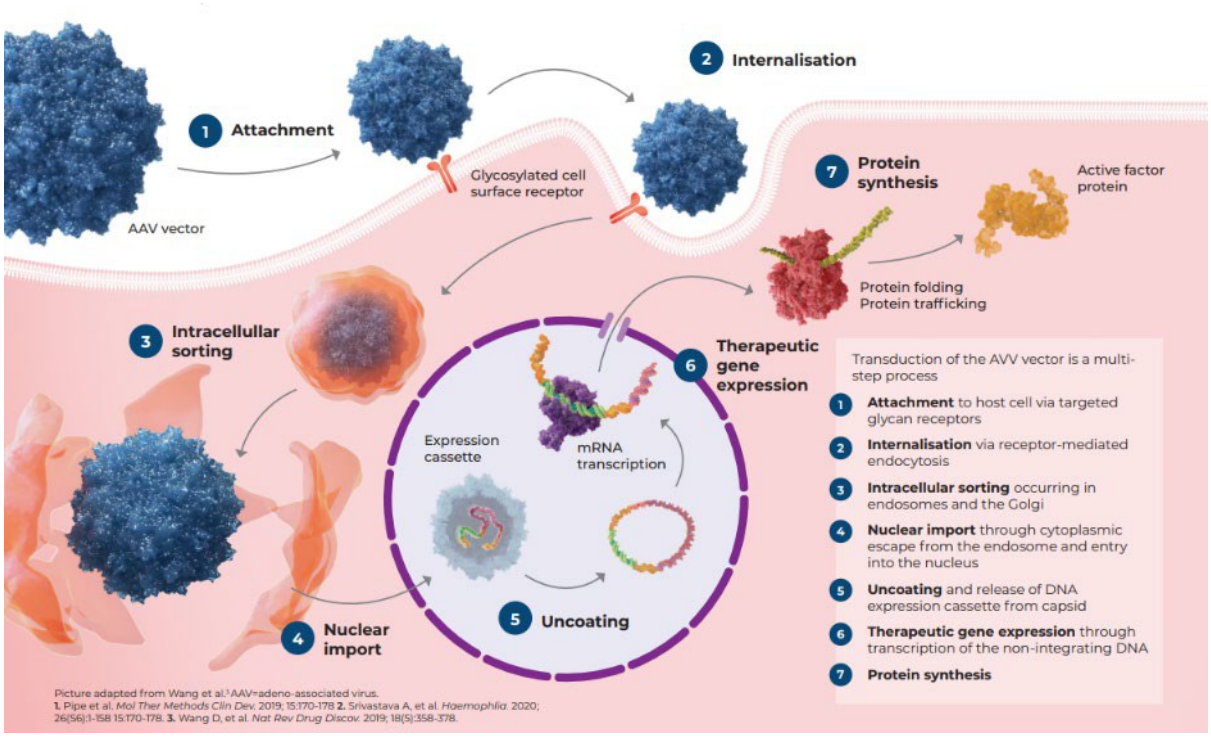
B.1.2.1 Mechanism of action and development of etranacogene dezaparvovec

Etranacogene dezaparvovec is a gene therapy product designed to introduce a copy of the human Factor IX gene into hepatocytes (liver cells) to address the lack of functional Factor IX protein expression in people with haemophilia B (see Summary of Product Characteristics [SmPC] in Appendix C). Etranacogene dezaparvovec uses the recombinant adeno-associated viral vector of serotype 5 (rAAV5) and delivers the gain-of-function hFIXco-Padua gene variant (a highly active, naturally occurring variant that generates five to 10 times greater Factor IX activity levels than the normal wild-type Factor IX gene) under the control of a liver-specific promoter (Appendix C).

As shown in Figure 1 following single intravenous infusion, etranacogene dezaparvovec preferentially targets liver cells, where the vector DNA will reside almost exclusively in episomal form (Appendix C). Subsequent to transduction, etranacogene dezaparvovec directs long-term liver-specific expression of Factor IX-Padua protein (Appendix C). As a result, etranacogene dezaparvovec ameliorates the deficiency of circulating Factor IX procoagulant activity of patients suffering from haemophilia B,

restoring the haemostatic potential, limiting haemophilia-related bleeding episodes and the need for Factor IX replacement treatment (Appendix C).

Figure 1: Schematic showing the mechanism of action of etranacogene dezaparvovec



Source: Wang et al., 2019[12]

1.2.1.1 Molecular and cellular pathways involved

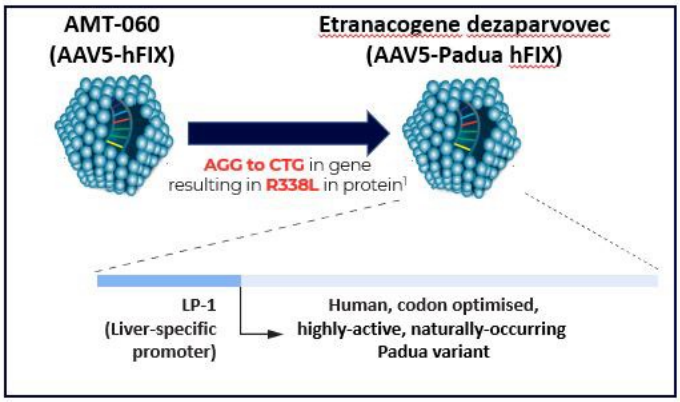
In summary, the transgene (Factor IX) expression is targeted to liver by using a protein capsid that interacts primarily with liver cells, while the transgene is expressed under the control of a liver-specific promoter meaning that the transduced Factor IX gene is activated specifically in liver cells, and not in any other cells.[13,14]

1.2.1.2 hFIX-Padua coding sequence

The transgene (Factor IX) selected for etranacogene dezaparvovec encodes a hyperactive Factor IX variant known as “Padua”.[14] Originally, development was started on AMT-060, with the same protein capsid and cassette design as etranacogene

Padua variant by only one amino acid, i.e. arginine 338 in the factor IX protein is changed to leucine (Figure 2).[15,16]

Figure 2: Etranacogene dezaparvovec capsid vs AMT-060



Source: Miesbach et al., 2022[17]

After the Phase I/II trial of AMT-060, the product was enhanced to AMT-061 (etranacogene dezaparvovec) with the "Padua" variant of the gene.[14] The Factor IX-Padua variant, which has demonstrated an eightfold increase in Factor IX-specific activity compared with the Factor IX wild-type gene,[16,18] was selected to attain a gain-of-function in Factor IX activity over the wild-type Factor IX gene. Factor Expression of this transgene in liver cells yields functional human clotting Factor IX-Padua, which is secreted into circulation.[14]

B.1.3 Health condition and position of the technology in the treatment pathway

- Haemophilia B is a rare X chromosome-linked congenital bleeding disorder characterised by a deficiency of coagulation Factor IX.
- The severity of haemophilia B generally correlates with the degree of clotting-factor deficiency and is categorised as either severe (Factor IX <1%), moderate (Factor IX 1% to 5%), or mild (Factor IX 5% to <40%).
- A total of 1200 adults in the UK live with haemophilia B, of which 242 and 271 are categorised to have severe and moderate disease, respectively.
    - Across England, it is estimated that there are 867 adults with haemophilia B; of which 31% (262) have moderately severe or severe disease (Factor IX <2%). A total of [redacted] adults with moderately severe or severe haemophilia B comprise the patient population of interest for this submission.
- People with moderately severe (Factor IX 1–2%) or severe (Factor IX <1%) haemophilia B tend to have bleeding after an injury or surgery or spontaneous bleeds, with joint bleeds (hemarthrosis) being the most common bleeding manifestation
- Haemophilia B can cause substantial functional limitations and reduced health-related quality of life (HRQoL) associated with bleeding and joint damage
- As the bleeding episodes can be fatal, the mortality rate in people with severe haemophilia is reported as 2.7 times higher than that of the general population, with up to 15 years lost in life expectancy
- The mainstay of treatment of haemophilia B consists of Factor IX replacement therapy as Factor IX prophylaxis therapy or on-demand treatment to prevent and/or manage bleeding episodes
- Current treatments do not eliminate the risk of bleeding events, and negatively impact patients' HRQoL, as measured by the Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL), since regular infusions can be burdensome, impact mental health and are associated with side-effects such as injection site reactions
- Etranacogene dezaparvovec is a single-dose gene therapy that induces stable Factor IX expression, potentially eliminating the burden associated with current need for frequent Factor IX intravenous injections

B.1.3.1 Overview of the disease

1.3.1.1 Definition

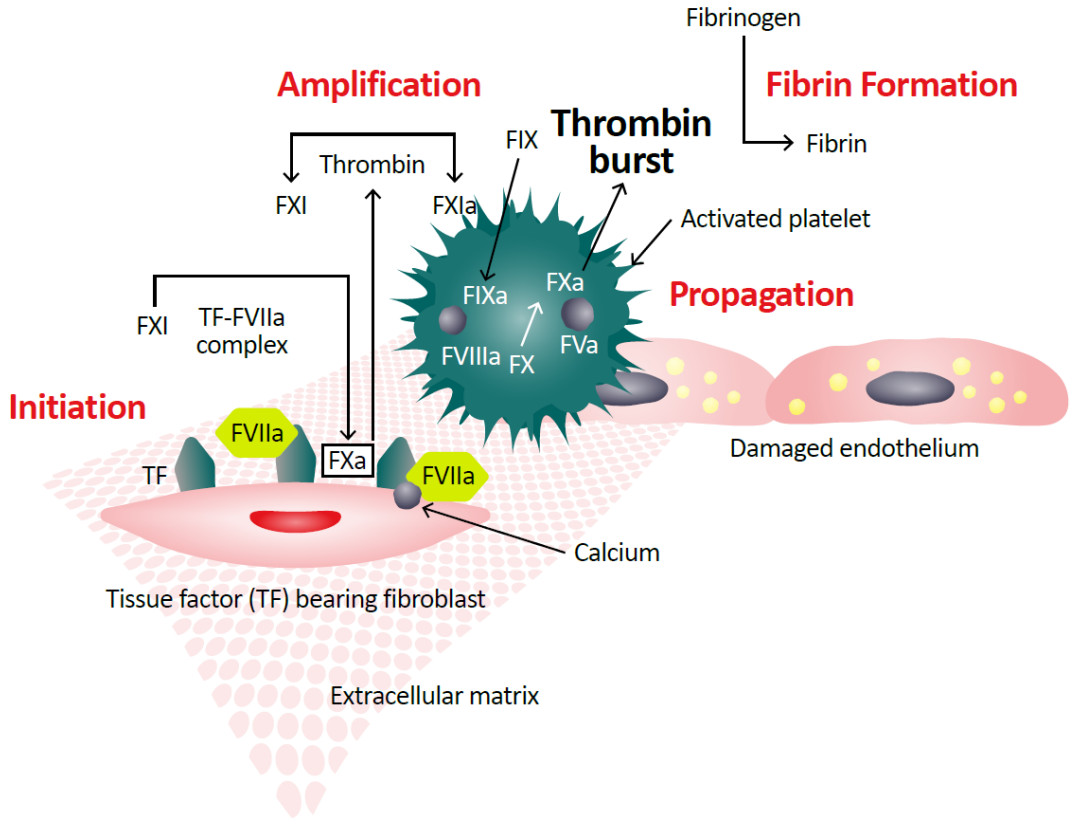
Haemophilia B is a rare, X-chromosome-linked, congenital bleeding disorder characterised by a deficiency of coagulation Factor IX. Haemophilia B predominantly affects men (who have only one X chromosome), while women are more commonly heterozygote carriers with no, mild or moderate bleeding symptoms. In rare cases, women can have haemophilia B.[19] The majority (70%) of haemophilia cases are inherited, while approximately 30% result from a spontaneous mutation.[20,21] It has been reported that up to 50% of haemophilia cases (including both haemophilia A and haemophilia B) have no previous family history, either owing to lack of male relatives or spontaneous mutation, which occurs in 40–50% of cases of severe haemophilia.[22]

1.3.1.2 Pathophysiology

Haemophilia B is caused by insufficient activity levels of coagulation Factor IX, which arises from mutations in the Factor IX gene which is located on the long arm of the X chromosome at Xq27.[23,24] Disruptions in the Factor IX gene that can cause haemophilia include point mutations, deletions, insertions, duplications, complex changes, and neutral polymorphisms.[25]

Factor IX is a serine protease that helps platelets bind together to form blood clots and stop bleeding.[26] Without Factor IX, bleeding would ensue due to the insufficient amount of Factor Xa (FXa) and thrombin (Figure 3).

Figure 3: Cell-based coagulation model



Abbreviations: F#, Factor #; TF, tissue factor
Source: Ho and Pavey, 2017[27]

1.3.1.3 Diagnosis and classification

Haemophilia B diagnosis requires a detailed clinical history including clinical examination, the use of bleeding assessment tools, laboratory testing and genetic testing. It is also important that the clinicians obtain their patients' bleeding history and family history of abnormal or unexplained bleeding to assess patterns of inheritance to assist with diagnosis.[21] In patients with clinical history suggestive of an underlying bleeding disorder, screening tests including full blood count, prothrombin time and activated partial thromboplastin time (aPTT) can be done. A prolonged aPTT and subsequently a one-stage Factor IX clotting assay showing reduced Factor IX activity levels suggest a diagnosis of haemophilia B.[28-30] Neonates with a family history of bleeding disorders will be tested routinely after birth, whereas those without a family history are diagnosed incidentally due to spontaneous bleeds.[29] A diagnosis of mild

haemophilia is frequently made later in life than that of more severe forms of the disease.[19]

The severity of haemophilia B generally correlates with the degree of the clotting-factor deficiency.[21] The normal range for Factor IX clotting activity is approximately 50–150% (5–15 international units [IU]/dL) whereas patients with plasma Factor IX levels ≤400 IU/dL can be diagnosed with haemophilia B. Thus, depending on Factor IX activity level, haemophilia B has been categorised as either severe, moderate or mild (Table 3).[21,28,31,32]

Table 3: Classification of severity for haemophilia B

Clinical severity	Factor IX clotting activity	Symptoms	Usual age at diagnosis
Severe	<1% of normal (<1 IU/dL)	• Frequent spontaneous bleeding • Excessive and/or prolonged bleeding after minor injuries, surgery, or tooth extractions	Age ≤2 years
Moderate	1–5% of normal (1–5 IU/dL)	• Seldom have spontaneous bleeding • Excessive and/or prolonged bleeding after minor injuries, surgery, or tooth extractions	Age <5–6 years
Mild	5% to <40% of normal (5–40 IU/dL)	• Rare spontaneous bleeding • Excessive and/or prolonged bleeding after major injuries, surgery, or tooth extractions	Often later in life, depending on haemostasis challenges

Abbreviation: IU/dL, international unit per decilitre
Sources: Konkle et al., 1993,[28] White et al., 2001,[31] Peerlinck and Jacquemin, 2010[32]

The age at diagnosis and the frequency of bleeds are generally related to the Factor IX level.[28] If Factor IX clotting activity is between 5% and 40% (mild haemophilia B, Table 3), patients rarely experience spontaneous bleedings but may experience excessive and/or prolonged bleeding after major injuries, surgeries, or tooth extractions. If 1% to 5% factor activity of normal is present (moderate haemophilia B, Table 3), bleeding usually presents after trauma, injury, dental work, or surgery. In moderate disease, recurrent joint bleeds may be present in up to 25% of cases, and the diagnosis usually gets delayed due to the symptoms of joint bleeds not being clear

immediately. If factor activity is less than 1% of normal (severe haemophilia B, Table 3), bleeding often presents spontaneously. Severe haemophilia usually manifests in the first few months of life, while mild or moderate haemophilia can present later in childhood or adolescence (Table 3).[33]

The residual Factor IX activity generally correlates well with clinical characteristics; however, phenotypic heterogeneity can occur among individuals with the same factor levels,[23] e.g., a proportion of severe cases display a milder phenotype and, conversely, those with mild haemophilia B may display a more severe phenotype.[34] This phenotypic heterogeneity in haemophilia B exists due to a complex relationship between the Factor IX gene mutation and polymorphisms in other genes, epigenetic influences, and environmental effects.[34,35]

1.3.1.4 Clinical features and mortality

Patients with severe haemophilia tend to have spontaneous bleeds or bleeding after an injury or surgery (Table 3).[21,36] Spontaneous bleeds, which are bleeding for no apparent or known reason, most commonly occurs in joints (haemarthrosis), but may also occur in muscles, soft tissue, skin, mucosa, the gastrointestinal system, the neck or throat, and the central nervous system (including intracranial haemorrhage).[24]

Joint bleeds (haemarthrosis)

Haemarthrosis is a condition of articular bleeding into the joint cavity and it is generally categorised into traumatic, non-traumatic (spontaneous), and post-operative haemarthrosis.[37] Joint trauma further increases the likelihood of developing haemarthrosis, especially in patients with severe haemophilia, in which more than 90% of bleeding episodes occur in joints.[38] In the Haemophilia Experiences, Results and Opportunities (HERO) online survey study, 67% of adults with haemophilia B experienced spontaneous joint bleeds.[36] In addition, chronic synovitis, a form of chronic joint disease, is another major cause of disability from bleeding.[28] With chronic synovitis, the thickened and inflamed synovium can eventually degrade the cartilage and bone within the joint.[39] Repeated joint bleeding leads to acute and chronic pain as well as risk of joint destruction and severe functional impairment secondary to the inflammatory condition that haemarthrosis triggers. In some cases, it is enough for the

patient to have a single severe bleed in a joint to cause chronic joint injury. Repeated bleeding can lead to joint replacement, which is costly for the healthcare system and causes suffering for the patient.[38,40]

The risk and severity of bleeding manifestations in haemophilia correlates with the degree of coagulation factor deficiency.[21,41] People with severe haemophilia experience spontaneous bleeding into joints or muscles, predominantly in the absence of identifiable haemostatic challenge. Moderate haemophilia (Factor IX 1–5%) is associated with prolonged bleeding with minor trauma or surgery and occasional spontaneous bleeding. In mild haemophilia (Factor IX 5–40%), spontaneous bleeding episodes are rare and severe bleeding normally occurs only in connection with trauma or surgery.[21] Haemophilia related morbidity worsen with severity, as spontaneous bleeding events are more common with severe than with mild haemophilia.[41]

HRQoL from joint damage is not only impacted in patients with severe disease. Patients with moderate haemophilia also have poor foot and ankle specific outcomes and ankle haemarthropathy, driven by chronic levels of ankle joint pain. Despite moderate haemophilia being considered less affected by haemarthrosis and haemarthropathy, patients with a bleeding or haemarthropathy phenotype are clinically similar to patients with severe haemophilia.[42]

Intracranial haemorrhage

One of the most substantial life-threatening manifestations of haemophilia B is intracranial haemorrhage (ICH), especially among people with severe haemophilia and those with Factor IX inhibitors.[28,43] The latest United Kingdom Haemophilia Centres Doctor's Organisation (UKHCDO) report states that one adult patient with severe haemophilia B was reported to suffer an ICH in 2021-2022 (out of a total of 242 patients with severe haemophilia B in the UK).[44] Among the established risk factors of ICH are: severe disease, the presence of Factor IX inhibitors (see Section B.1.3.3), young age and prior ICH.[43]

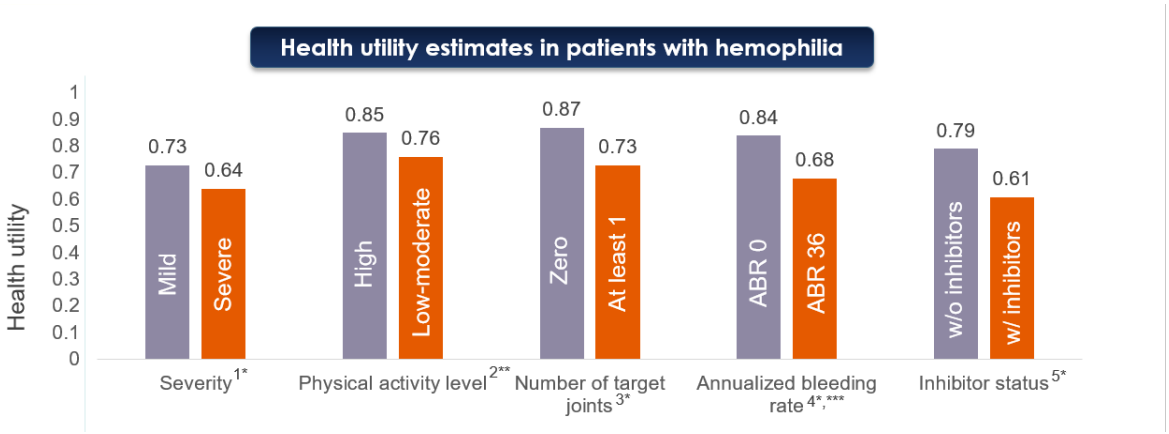
Quality of life

Haemophilia is associated with a reduced QoL due to symptoms including pain, functional impairment, anxiety and depression, while bleeding events and progression

of joint disease is associated with a reduction in work productivity and an increase in healthcare resource use.[45-49] Moreover, without adequate treatment, haemophilia B is associated with pronounced reduction in QoL and premature death.[50] Untreated disease also leads to permanent joint damage,[39] risk of serious conditions in the case of brain haemorrhage,[51] and bleeding in the gastrointestinal tract.[52]

Figure 4 demonstrates that the mean health utility score (scale from 0–1) for those with severe disease is lower (0.64 vs 0.73) compared to those with mild disease.[53-56] Similarly, a recently published multinational and observational study (B-Natural study) showed that patients with severe haemophilia B have worse QoL scores when compared to patients with mild and moderate haemophilia B.

Figure 4: Health utility estimates in people with haemophilia B



Abbreviations: Health utilities for 'severity' were derived using the TTO (Time-Trade-Off) method; for all the other categories, by EQ-5D (EuroQol five-dimension scale)
Figure legend: *Patients with both haemophilia A and B; **Patients with haemophilia B; ***Annualised bleed rate (ABR) was extrapolated based on reported monthly bleed rate
Source: Niu et al., 2014,[56] Kritikou et al., 2018,[54] Hoxer et al., 2019,[55] Camp et al., 2016[53]

Beyond the physical burden, the collective experience of living with haemophilia has substantial effects on mental well-being, particularly among young people living with the condition, within whom signs of major depressive disorder are common.[57,58]

If an injury occurs in a joint, the joint may need to be replaced, which can be a relatively demanding operation and could also lead to postoperative complications with long-

term rehabilitation and chronic pain as a result. Pain in one or more joints is a daily reality for as many as two-thirds of patients with severe haemophilia.[59,60] QoL among individuals with haemophilia is thus impaired, mainly due to pain and disability associated with haemophilic arthropathy.[21] In the CHESS study, 515 patients with haemophilia A and B responded to a QoL instrument (the EuroQoL 5-dimension [EQ-5D] questionnaire). The mean index score for patients with and without joint damage was 0.731 and 0.875 ($p<0.000$), respectively, showing that joint injuries have a significant negative impact on the patient's QoL.[61] Moreover, results from same study showed that 85% of patients with severe haemophilia B experienced chronic pain over the previous 12 months.[47]

An eastern European study demonstrated that depressive symptoms were negatively associated with all QoL domains (including mental and physical). The study also demonstrated that for patients with haemophilia B, depressive symptoms are associated with more urgent hospital visits due to haemophilia, more bleeding episodes and affected joints, as well as low self-esteem and worse QoL.[62]

Long-term impairments in mobility and functional status (as a result of recurrent bleeding episodes) can limit the participation of patients with haemophilia in daily life activities.[63-65] Studies also show that adults with haemophilia are less likely to work fulltime, and some form of activity limitation is more common among patients with haemophilia compared to the general population.[66] Lost productivity influences the financial status of patients and can lead to reduced capacity to work and a reduced ability to participate in society.[47]

The negative effects of haemophilia related complications on work productivity are shown through absenteeism from work and/or school. Patients are less likely to proceed into full-time employment and occupational disability is typically greater among patients compared with the general population.[57] In the European CHESS study, patients experienced lost wages and substantial costs related to early retirement/work stoppage.[47]

Haemophilia B also significantly impacts caregivers, who also experience loss of productivity at the workplace resulting in indirect costs including lost work time. The importance of the impact of haemophilia on patients and their families should not be overlooked, and observational studies play a key role in capturing a 'snapshot' of information about what it is like to live with a rare disease.[67] The burden on patients and their caregivers despite current treatment options is discussed in Section B.1.3.3.

Mortality

In Europe, the mortality rate of patients with severe haemophilia between 1997 and 1998 has been reported being as 2.7 times higher than that of the general population, with their life expectancy being up to 15 years shorter.[50] The median lifespan for the general population in the UK is 78 years, whereas that for people with haemophilia B (without human immunodeficiency virus [HIV]) in that study ranged from 63 years for those with severe disease to 75 years for patients with mild/moderate disease.[50] The life expectancy for patients with haemophilia was severely affected by HIV and hepatitis C virus (HCV) from contaminated blood products during the 1980s and 1990s.[68,69] Patients with haemophilia who were co-infected with HIV and HCV can exhibit a comparatively rapid progression of liver disease, with cirrhosis, hepatic failure, and hepatocellular carcinoma potential complications.[68]

A systematic literature review has found that mortality is strongly correlated with age and haemophilia severity, with haemorrhage, HIV, HCV, and hepatic disease the leading causes of death.[69] Fewer deaths were attributable to HIV after the year 2000, whilst the number attributable to haemorrhage remains unchanged,[69] and despite treatment advances in the past decades with consequent reduction in mortality, haemorrhage remains a leading cause of death in people with haemophilia.[70]

A retrospective chart review study in Italy found that the life expectancy of patients with haemophilia increased from 64.0 years to 71.2 years between 1990 and 1999 and 2000 and 2007, respectively.[71] This increase was particularly high among patients with severe haemophilia B (40.3 years between 1990 and 1999 vs 66.3 years between 2000 and 2007).[71] Although the life expectancy of people with haemophilia has

improved, premature mortality remains a challenge in severe haemophilia or in cases where treatment adherence is poor (see Section B.1.3.3).[50,71,72]

1.3.1.5 Epidemiology

Haemophilia B accounts for approximately 22% of all haemophilia cases, with an estimated prevalence at birth of 3.8/100,000 males across all severity levels and 29% of haemophilia B cases being severe.[73] According to the Annual Global Survey by the World Federation of Haemophilia (WFH) in 2020, approximately 33,000 people were living with haemophilia B around the world.[74]

The United Kingdom Haemophilia Centres Doctors' Organisation (UKHCDO) Annual Report of 2022 reported that, in the financial year of 2021/2022, there were a total of 1200 adults with congenital haemophilia B, registered and treated in the UK.[44] A total of 242 and 271 adults were categorised as having severe or moderate haemophilia B, respectively (Table 4). The vast majority of adults with severe haemophilia B were treated with Factor IX concentrate that year (n=211/242, 87%), as were the majority of those with moderate haemophilia B (n=157/271, 58%) (Table 4).

Table 4. Adults with congenital haemophilia B, registered and treated in the UK, 2021/2022

	Factor IX <1% (severe)	Factor IX 1–5% (moderate)	Factor IX >5–<40% (mild)
Total number of adults (≥18 years) in register	242	271	687
Total numbers of adults (≥18 years) treated with Factor IX concentrate this year	211	157	129

Source: UKHCDO, Annual Report 2022.[44]

For the Budget Impact Model (BIM) developed alongside this submission, the prevalence of adults with haemophilia B who are eligible for etranacogene dezaparvovec was calculated for England, and this was utilised to estimate budget impact. The total number of those eligible in England was calculated to be [redacted]; there

are a total of 867 adults with haemophilia B in England, of which 262 (31%) have moderately severe (Factor IX ≤2%) to severe haemophilia B. A further [redacted]% were excluded based on HOPE-B exclusion criteria which included having a history of Factor IX inhibitors, other coagulation disorders, pre-existing anti-AAV5 antibody titre greater than 1:700 and previous treatment with gene therapy from clinical trials, resulting in a total of [redacted] people. These calculations are described in further detail in the budget impact template.

B.1.3.2 Treatment pathway

The primary goal of haemophilia B care is to prevent bleeding, which is usually achieved by the long-term Factor IX prophylaxis treatment and/or the on-demand treatment of Factor IX at the time of a bleeding event.[21,75]

1.3.2.1 On-demand treatment

On-demand treatment is defined as the administration of Factor IX therapy at the time of a bleeding event and is not recommended for severe haemophilia B.[21] While on-demand treatment reduces the pain and debilitating impact of individual bleeds, it does not alter the bleeding profile significantly or provide effective protection from musculoskeletal damage and other complications associated with bleeding. Although on-demand treatment is associated with lower clotting factor cost, Factor IX prophylaxis therapy leads to better clinical outcomes, including annualised bleeding rate (ABR).[76]

1.3.2.2 Prophylaxis therapy

Factor IX prophylaxis therapy in haemophilia B consists of regular administration of Factor IX with the goal of maintaining haemostasis to prevent bleeding, especially joint bleeds, which may lead to arthropathy and disability.[21] Long-term Factor IX prophylaxis therapy can be further divided into three types based on when the therapy is initiated:[75,77]

- Primary Factor IX prophylaxis commences in early childhood at the latest before the second joint bleed or the age of 3 years, in the absence of

documented joint disease, with the aim that the child reaches maturity with normal joints.

- Secondary Factor IX prophylaxis commences after ≥2 joint bleeds, but before the onset of proven joint disease. It is likely that these bleeds have caused subclinical but established, irreversible joint disease. Prophylaxis aims to limit the consequence of this damage by preventing further bleeding, maximising function long-term.
- Tertiary Factor IX prophylaxis is introduced after the onset of clinically/radiologically apparent joint disease and aims to slow down progression of joint disease, reducing pain and maintaining quality of life. It cannot, however, reverse established joint disease.[75]

Guidelines from the British Society for Haematology (BSH) state that prophylaxis should be started before or immediately after the first joint bleed in a person with severe or moderate haemophilia with a baseline level 1–3 IU/dL. This will usually be at the time of ambulation, around 12 months of age and certainly before 24 months.[75] Underscoring that prophylaxis should ideally be initiated at a young age, the BSH Guidelines add that some adults who did not have prophylaxis as a child may start prophylaxis later in life to preserve musculoskeletal function (secondary/tertiary prophylaxis).[75] In a recent CSL Behring advisory board, an independent panel of eight UK clinical experts stated that they were in agreement with these guidelines.[6]

Recommendations from the BSH state that:

- All children with severe haemophilia A or haemophilia B should receive primary prophylaxis.
- Primary prophylaxis should be considered for all children with baseline factor levels of 1–3 IU/dL.
- Prophylaxis should be offered to any person with haemophilia who has sustained one or more spontaneous joint bleeds.
- Prophylaxis should be offered to a person with haemophilia who has established joint damage due to haemarthroses who experiences ongoing bleeding.

- Following initial treatment of a spontaneous intracranial haemorrhage, prophylaxis should be commenced and continued long term.[75]

Prophylaxis has conventionally been defined as the intravenous infusion of the missing clotting factor (Factor IX in haemophilia B) to convert a person with severe haemophilia to a bleeding phenotype of moderate or mild haemophilia and, ultimately, prevent bleeding.[21] Management through Factor IX prophylaxis therapy is the preferred treatment approach that can be tailored to prevent bleeding considering the patients' lifestyle. Prophylaxis results in a higher and more consistent Factor IX level for the patient, reducing the frequency of joint bleeding events and substantially reduces the frequency of arthropathy compared to on-demand treatment.[72,78] However, increasing evidence has shown that Factor IX levels associated with moderate haemophilia may still result in occasional clinical and subclinical bleeds, resulting in the gradual progression of joint disease.[21]

In Haemophilia B, prophylaxis is typically achieved by administering standard half-life (SHL) Factor IX concentrates, to increase Factor IX levels and reduce the risk of bleeding events.[21] However, owing to their short half-life, SHL products require frequent administration (2–3 times weekly), which can negatively affect patient adherence and, potentially, clinical outcomes. Novel recombinant Factor IX concentrates have been developed that have extended half-life (3- to 5-fold longer than that of SHL Factor IX concentrates), allowing for less frequent injections, thereby reducing burden on patients. Furthermore, extended half-life (EHL) Factor IX concentrates have demonstrated longer-lasting beneficial effects, as a results of sustained higher trough levels, compared with SHL products.[21]

Overall, Factor IX prophylaxis therapy reduces bleeding and its deleterious effects into joints in persons with haemophilia. This is corroborated by a multicentre randomised study that compared the ABR between two Factor IX prophylaxis therapies and an on-demand therapy among people with moderately severe or severe haemophilia B.[79] The study found that Factor IX prophylaxis therapy (given 1 to 2 times weekly by intravenous infusion) reduced ABR by 89.4% relative to on demand therapy.[80] Supporting this, the reduction in haemarthroses leads to reduced haemophilic

arthropathy, reduced disability, reduced need for orthopaedic surgery and ultimately improved quality of life.[81] Furthermore, management through prophylaxis is associated with fewer missed work and school days, improved physical health status scores, decreased pain, and higher HRQoL.[72]

1.3.2.3 Factor IX treatment in the UK

The standard treatment option for haemophilia B is replacement Factor IX therapy, which is generally classified into plasma derived and recombinant therapies.[21] Plasma-derived Factor IX replacement therapies are made from human plasma, where donors and the plasma are tested for viral infections, and the manufacturing process includes dedicated viral inactivation/reduction steps. On the other hand, recombinant products are manufactured using genetically engineered cells and recombinant technology, resulting in a theoretically lower risk of passing on infectious diseases such as HIV and hepatitis C.[21]

In the UK, and as confirmed by key consultant haematologists, haemophilia B is typically managed with recombinant Factor IX therapies. The most widely used Factor IX replacement therapies in the UK include albutrepenonacog alfa (Idelvion; recombinant Factor IX albumin fusion protein [rIX-FP]), eftrenonacog alfa (Alprolix; recombinant Factor IX Fc fusion protein [rFIXFc]), nonacog alfa (BeneFIX), and nonacog beta pegol (Refixia; N9-GP).[82]

Even though Factor IX prophylaxis is the preferred treatment approach for many patients in the UK, its effectiveness varies depending on disease severity, bleed frequency and phenotype, complications (e.g., reduced venous access, Factor IX inhibitors development), treatment regimens, including dosing, and patient adherence to treatment.[72,78]

1.3.2.4 Factor IX inhibitors

The development of inhibitors (neutralising antibodies [NAbs])* against Factor IX is a serious complication of haemophilia B treatment, and is almost exclusively seen in

*As of note, the term Factor IX inhibitor refers to the presence of a high-affinity neutralising Ig G antibody directed against Factor IX that develops in response to exogenous Factor IX exposure, usually following Factor IX replacement therapy.

patients with a severe form of haemophilia B.[21,83] Inhibitor development is rare in patients with severe haemophilia B (cumulative incidence of up to 5%) and occur most commonly in those with null variants, in which no endogenous clotting factor is produced.[21] Potential risk factors for Factor IX inhibitor development include family history, genotype, haemophilia severity, and clotting factor concentrate replacement intensity. Nevertheless, there is no known ancestral predilection to inhibitor development in haemophilia B, and it has been reported in those receiving plasma-derived and recombinant Factor IX therapies alike.[21]

The development of Factor IX inhibitors leads to loss of response to Factor IX replacement therapy and consequently results in an increased risk of serious bleeding and earlier onset of progressive arthropathy. Furthermore, additional associated risks of inhibitor development include anaphylaxis, nephrotic syndrome and higher treatment-related costs.[21,83] Managing bleeds in older patients with inhibitors is particularly challenging, since the presence of age-related comorbidities adds further complications to an already complex clinical scenario.[83]

Treatment used in patients with Factor IX inhibitors

Due to the low Factor IX inhibitor prevalence in haemophilia B, patients with Factor IX inhibitors have limited evidence-based treatment options.

The BSH has published guidelines specifically for the management of patients with haemophilia who develop inhibitors.[21] For patients with haemophilia B, the BSH recommends the following:[84]

- **Immune tolerance induction (ITI)**
    - ITI should be attempted only after careful consideration, as it has been associated in haemophilia B with poor response rates, as well as anaphylaxis and nephrotic syndrome risk.
- **Acute treatment**
    - In patients with haemophilia B and Factor IX inhibitors, bleeds should be treated within 2 hours, either at home or in hospital.

- Use of large doses of Factor IX is recommended for low-responders and factor eight inhibitor bypassing agent (FEIBA) or recombinant Factor VIIa in high responders.
- The frequency of Factor IX infusions, not the dose, should be increased in low responders with low-titre inhibitors.
- Recombinant Factor VIIa should be the treatment of choice for patients who had allergic reactions to Factor IX.
- FEIBA and recombinant Factor VIIa should be considered as treatment options for early haemarthroses.
- Non-joint bleeds should be treated with Factor IX, FEIBA or recombinant Factor VIIa, whereas tranexamic acid should be considered for mucosal bleeds, specifically.
- For bleeds unresponsive to bypassing agents, removal of the inhibitor using plasmaphaeresis and immunoadsorption together with high dose Factor IX, may be considered as sometimes successful.
- Combined recombinant Factor VIIa and FEIBA treatment should be used exclusively for life- or limb-threatening bleeds.

- **Surgery**
  - Surgery is an at-risk procedure for patients with haemophilia B and inhibitors, as no haemostatic agent can guarantee haemostasis; as such it should be carried out only after careful assessment of benefits and risks.
  - Factor IX use is recommended, provided that satisfactory plasma levels can be attained.
  - Recombinant Factor VIIa and FEIBA can be used interchangeably at the recommended licensed doses.
- **Prophylaxis**
  - Early tolerization of inhibitors is preferred, owing to the lower efficacy of bypassing agents, compared with Factor IX replacement.
  - Bypassing agents should be considered in young children after the first haemarthrosis, to reduce the risk of arthropathy.
  - Recombinant Factor VIIa should be used in patients awaiting ITI.

- Prophylaxis may be considered for older patients who experience recurrent bleeds or have progressive arthropathy.
- The frequency of the infusions, not the dose, should be increased if the initial regimen is unsuccessful, as this approach is more likely to be effective.

All Factor IX inhibitor treatment options require specialised medical expertise and all patients with inhibitors must have their treatment coordinated by a Comprehensive Care Haemophilia Centre (CCC).[84]

Limitations and unmet needs associated with the currently available treatments are further explored in Section B.1.3.3.

B.1.3.3 Limitations of current therapies

A central aspect of haemophilia care is that treatment is individualised and tailored to fit the individual patient's needs (e.g., bleeding profile, pharmacokinetics), lifestyle, and preferences. It is thus important that there are treatment options that fit all patients, which is not the case today. Even current prophylactic regimens may not eliminate all bleeds and, even when adherent, patients may experience traumatic or life-threatening bleeds, and associated increased healthcare visits resulting in substantial clinical and economic burden for patients and health systems. Despite improvements, current therapies do not adequately improve functional ability by preventing joint bleeding, nor do they address the impact on mental health.[58,85] As a result of this lifetime condition, patients experience an impact on productivity, including a reduced capacity to work and absenteeism from employment and education. This lost productivity has a financial impact on patients and their families and caregivers.[67,86] Additionally, research indicates that families and caregivers of people with haemophilia experience substantial mental, physical and social burden, as demonstrated by increased levels of anxiety, depression and bodily pain, as well as reduced social activity.[46,87]

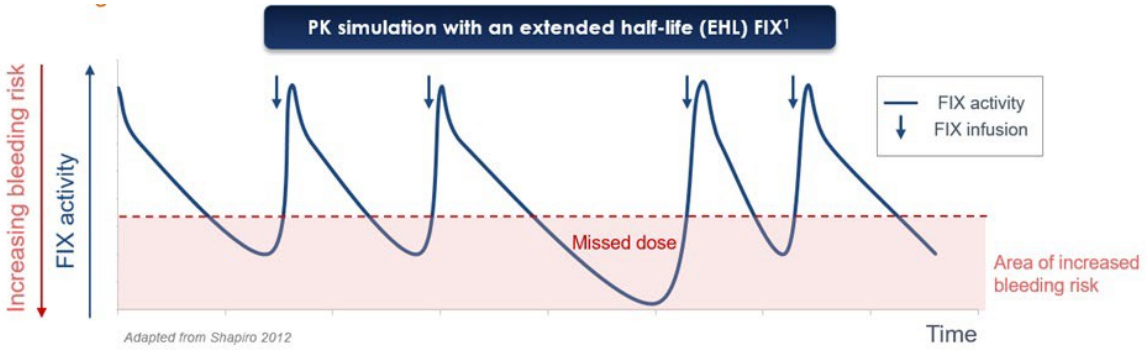
B.1.3.4 Unmet needs

Frequent IV injections are commonly used to achieve higher plasma levels of Factor IX, yet sufficient haemostatic protection may still not be reached. Despite

burdensome and time consuming IV injections with prophylaxis therapy, bleeding can lead to increased pain and other injection-related complications (such as problems with venous access, including risk of infection and blood clot formation) as well as increased healthcare costs.[79,88,89] This can lead to an increased treatment burden for the patient, relatives, and healthcare. In addition, it could have a negative impact on QoL, including limiting the patient's mobility and social interaction, which can be particularly difficult for younger and active patients.[88] In addition, frequent IV injections can affect adherence to treatment, which in turn is critical to the risk of developing arthropathy.[90] These complications are also associated with an increased need for healthcare resources and costs for medical treatments and interventions.

Moreover, standard-of-care treatment results in peaks and troughs of Factor IX activity levels with an associated suboptimal efficacy (Figure 5). Aside from subclinical microbleeds, the low trough levels in patients with haemophilia B can increase the occurrence of breakthrough joint bleeds. Therefore, novel treatments with longer duration of effects are needed to stabilise the Factor IX activity levels in the normal range.

Figure 5: Fluctuation in Factor IX activity level increases risk of breakthrough bleeding



Abbreviations: EHL, extended half-life; FIX, Factor IX; PK, pharmacokinetics
Source: Shapiro et al., 2012[80]

Despite important advances in haemophilia control with the use of Factor IX prophylaxis therapies, haemophilia management still requires sustained daily

vigilance with or without the support of caregivers.[91] Such demands can be stressful for the caregiver, not only physically, but also emotionally, psychologically, and financially.[91] Although data from the UK are not available, research conducted in the USA indicates that around 84% of caregivers' spouses/partners also experienced a negative impact on their employment.[92]

Frequent intravenous injections are associated with several complications and reduced QoL.[93] Patient-reported benefits of reduced infusion frequency and longer duration of the factor level include an increased ability to participate in physical activities and sports, better vein health, less time to schedule and administer the factor concentrate, as well as a reduced impact on daily work and school and improved emotional well-being. Extended dose intervals and reduced bleeding frequency through the maintenance of high factor levels can thus improve QoL in patients and their caregivers.[94,95]

The limitations of current treatment options and their associated burden highlight the need for less burdensome treatments that limit the longer-term complications experienced by people with haemophilia B. Despite advances in the available therapeutic approaches to prevent and treat breakthrough bleeding, notable unmet needs remain with regards to further improving clinical, humanistic, economic and societal outcomes. An independent panel of expert haematologists participating in a CSL Behring advisory board, were in agreement that a gene therapy option would be needed to free patients from routine IV injections, thus reducing the burden of treatment whilst giving patients freedom from the risk of bleeding. A new therapy is needed that can offer clinical benefits that enable patients to have higher productivity and reduced absenteeism from education and employment so that they may participate more fully in society.[67,86]

B.1.3.5 Proposed positioning of etranacogene dezaparvovec

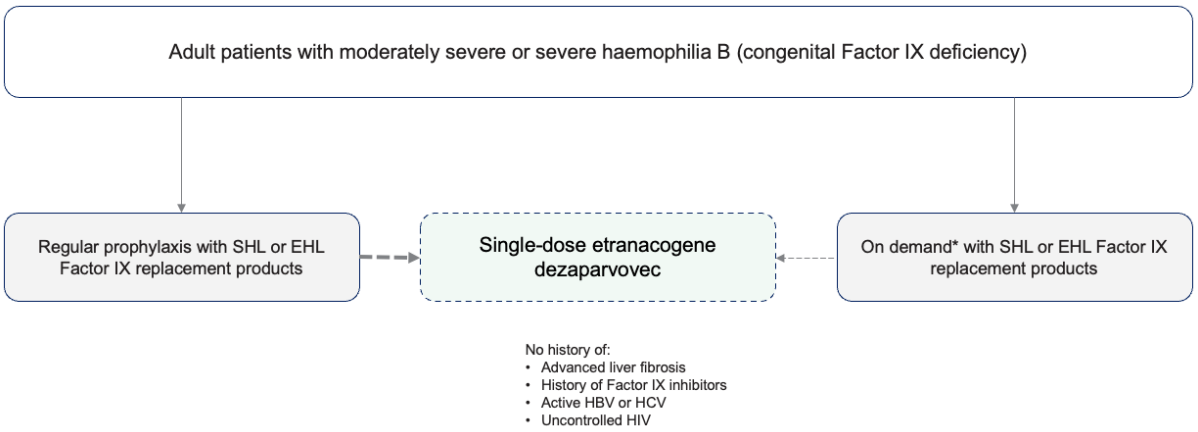
Etranacogene dezaparvovec can represent a step-change in the management of patients with moderately severe or severe haemophilia B, as a single-infusion gene therapy that induces stable Factor IX expression, potentially eliminating regular Factor IX intravenous injections as well as reducing long-term complications. A trial

participant explained why they had taken part in the etranacogene dezaparvovec study, highlighting the potential of this gene therapy in changing the lives of eligible people with haemophilia B:

> *"I've done it for the next generation. I don't want anyone to have to go through what I went through."*[96]

Figure 6 shows the current treatment pathway in England and the proposed positioning of etranacogene dezaparvovec, also considering patient choice.

Figure 6: Treatment pathway and positioning of etranacogene dezaparvovec in England



Abbreviations: EHL, extended half-life; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; SHL, standard half-life
Dotted line denotes intended positioning of etranacogene dezaparvovec, mainly displacing prophylaxis as demonstrated by the thicker, dotted line.
*Unlike prophylaxis, on-demand treatments are administered at the time of a bleed and aim to stop haemorrhages rapidly. A small number of patients opt to receive on-demand treatment despite being eligible for prophylaxis due to personal choice or clinical challenges and, in this group, etranacogene dezaparvovec could displace on-demand treatment.

B.1.4 Equality considerations

CSL Behring notes that, during the scoping consultation, consultees raised the two potential equality considerations associated with patients' HIV status and sex. Firstly, NICE should ensure its recommendations do not discriminate against people with HIV

or historical hepatitis B or C infection in accessing this treatment. Second, NICE should ensure that the evaluation does not exclude based on sex.

The pivotal Phase III trial for etranacogene dezaparvovec (HOPE-B) excludes women, people with positive HIV test at screening, not controlled with antiviral therapy (as shown by CD4 counts ≤200 µL) and active infection with hepatitis B or C virus at screening. This may present a potential equality consideration for the Committee to discuss.

B.2 Clinical effectiveness

- One Phase III, non-randomised trial with etranacogene dezaparvovec was identified as the most relevant study for this submission — HOPE-B is an ongoing multicentre, open-label, single-dose, non-inferiority trial, with a screening period, a lead-in period, a post-treatment follow-up period after product administration, and a long-term follow-up period after Factor IX-expression stabilisation, with data available up to 24 months
- Results at 24 months post-etranacogene dezaparvovec administration in 54 adult males with haemophilia B showed:

  - effective bleed control, including statistically significant reductions in the ABR (a decrease of 64%) and in the number of bleeds requiring treatment (a decrease of 73%) from Month 7–24 post-treatment, compared with Factor IX prophylaxis in the 6-month lead-in period.

  - a significant reduction (a decrease of 75%) in mean annualised spontaneous bleeding rate (AsBR) from Month 7–24 post-treatment, compared with the 6-month lead-in period with Factor IX prophylaxis therapy.

  - a significant reduction (a decrease of 80%) in the annualised joint bleeding rate (AjBR) from Month 7–24 post-treatment, compared with the 6-month lead-in period with Factor IX prophylaxis therapy.

  - eliminated the need for routine Factor IX prophylaxis therapy in nearly all (96.3%) treated patients.

  - a rapid and sustained significant increase in mean endogenous Factor IX activity level to 36.7%.

  - a significant decrease (by 96%) in mean unadjusted annualised Factor IX consumption (prophylaxis therapy plus on-demand use) at Month 24 post-dose, compared with the 6-month lead-in period with Factor IX prophylaxis therapy.

  - zero bleeds observed in [redacted]% of patients at Month 24 post-treatment.
- Patients treated with etranacogene dezaparvovec demonstrated improvements in total score and across four domains (feelings, treatment, work/school, future) of the Haem-A-QoL patient-reported outcome (PRO) measure, and in mean EQ-5D-5L VAS and EQ-5D-5L index score at 24 Months post-dose.
- Reductions in ABR were observed in most subgroups from Month 7–24 and increased Factor IX activity was demonstrated at Month 24, with no clinically meaningful correlation between baseline anti-AAV5 NAb status and long-term durability of Factor IX expression.
- Etranacogene dezaparvovec is well tolerated: no treatment-related serious adverse events have been reported; most mild or moderate treatment-related adverse events (e.g., headache, dizziness) were resolved, and only 16.7% of patients required short-term steroid use for liver enzyme elevation, which was discontinued by Week 26.

B.2.1 Identification and selection of relevant studies

The clinical evidence base for etranacogene dezaparvovec was established using a systematic literature review (SLR) of publications (abstracts, manuscripts) in literature databases (e.g., PubMed, EMBASE), trial registries, and major scientific/medical congresses. Searches were run on 18 August 2021 for the time period of 22 March 2013 to 18 August 2021. An 'update review' was then run on 17 October 2022. Publications prior to these SLRs were identified from two published SLRs that identified clinical, economic and HRQoL evidence in haemophilia B.[97,98] The earliest search date for these SLRs was 22 March 2013. The search strategy identified clinical and safety studies with available treatments for haemophilia B. Appendix D describes the process and methods used to identify and select clinical evidence relevant to the technology being appraised. Four randomised clinical trials were identified.

B.2.2 List of relevant clinical effectiveness evidence

The clinical development programme supporting etranacogene dezaparvovec includes three studies in adult patients (≥18 years) with moderately severe or severe haemophilia B (Factor IX activity ≤2% of normal). The safety and efficacy of etranacogene dezaparvovec was evaluated in two prospective, open-label, single-dose, single-arm studies, a Phase IIb study performed in the US (CT-AMT-061-01, NCT03489291)[99,100] and a pivotal Phase III multinational study performed in the US and Europe (HOPE-B, CT-AMT-061-02, NCT03569891). The pivotal Phase III HOPE-B included three sites in England: Royal London, Cambridge and Southampton, with all patients having etranacogene dezaparvovec administered at the Southampton centre.

Prior to the final development of etranacogene dezaparvovec, initial development of the gene therapy resulted in AMT-060, a gene therapy product with the same vector and cassette design as etranacogene dezaparvovec but using a wild-type Factor IX transgene (as explained in Section B.1.2.1).[101] After a Phase I/II trial of AMT-060 (CT-AMT-060-01, NCT02396342), the vector's Factor IX transgene was replaced with the gain-of-function hFIXco-Padua variant of the gene, and that product was designated AMT-061 (etranacogene dezaparvovec).[102]

Table 5 provides a summary of the Phase I/II and Phase IIb open-label, multicentre studies designed to assess the efficacy and safety of AMT-060 and etranacogene dezaparvovec (AMT-061).

Table 5: Clinical trial programme of AMT-060 and etranacogene dezaparvovec

	AMT-060		Etranacogene dezaparvovec	
Name/code	CT-AMT-060-01 NCT02396342		CT-AMT-061-01 NCT03489291	**HOPE-B,** CT-AMT-061-02 NCT03569891
Phase	Phase I/II	Extension	Phase IIb	Phase III
Design	Open label	Extension	Open label	Open label with observational lead-in period
Dose (GC/kg)	Cohort 1: 5×10^{12} Cohort 2: 2×10^{13}	–	2×10^{13}	2×10^{13}
Number of subjects	Cohort 1: 5 Cohort 2: 5	Transfer from Phase I/II	3	75 screened 67 lead-in period 54 dosed*
Planned follow-up	5 years after dosing	10 years after dosing	5 years after dosing	5 years after dosing
Analysis completed	Cohort 1: 5 years Cohort 2: 5 years	–	3 years	52 weeks
Follow-up to date	6 years†		3.5 years	
Primary objective	Adverse events over 5 years	Long-term safety over 6–10 years post-dosing	Factor IX activity at 6 weeks	Factor IX activity at 26 and 52 weeks, ABR at 52 weeks compared to lead--in

Abbreviations: ABR, annualised bleeding rate; GC, genome copy
*Partial dose (~10%) administered to one patient with hypersensitivity reaction.
†Follow-up of 6 years completed for 8 patients, with 1 patient dying of causes not related to the study treatment and 1 not consenting to follow-up.[103]
Sources: ClinicalTrials.gov. Identifier NCT02396342;[2] ClinicalTrials.gov. Identifier NCT03489291;[3] ClinicalTrials.gov. Identifier NCT03569891[1]; CT-AMT-060-01 CSR, CSL Behring; [103] CT-AMT-061-01 CSR, CSL Behring;[100] HOPEB CSR, CSL Behring.[14]

This submission focusses on the ongoing Phase III HOPE-B and its data are included in the economic model, as shown in Table 6. Indirect treatment comparisons using HOPE-B data versus that with current standard of care in England are presented in Section B.2.9.

Table 6: Clinical effectiveness evidence

Study	HOPE-B, CT-AMT-061-02, NCT03569891
Study design	Phase III, open label, single dose, single arm, multicentre (including three UK centres)
Population	Adult patients with moderately severe or severe haemophilia B with Factor IX level ≤2%
Intervention(s)	Etranacogene dezaparvovec (previously AMT-061)
Comparator(s)	Lead-in period (minimum of 26 weeks) when patients received prophylaxis
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	Not applicable
Reported outcomes specified in the decision problem*	**ABR at 7–24 Months** post-treatment and comparison of ABR between Factor IX prophylaxis therapy used in the lead-in and after administration of etranacogene dezaparvovec. Secondary endpoints: Factor IX activity levels at 6, 12, 18 and 24 Months after etranacogene dezaparvovec dosing.
All other reported outcomes*	Use of Factor IX prophylaxis therapy, AsBR, **AjBR**, Factor IX activity levels correlated to pre-existing AAV5 NAb titres, **PROs** (**EQ-5D**, iPAQ, BPI, HAL, **Haem-A-QoL**, WPAI, PROBE), **treatment-related adverse events.**

Abbreviations: AAV5, adeno-associated virus vector serotype 5; ABR, annualised bleeding rate; AjBR, annualised joint bleeding rate; AsBR, annualised spontaneous bleeding rate; BPI, Brief Pain Inventory; EQ-5D, EuroQol-5 dimensions; HAL, Haemophilia Activities List;
HOPE-B, Health Outcomes with Padua Gene, Evaluation in Haemophilia B; iPAQ, international Physical Activity Questionnaire; NAb, neutralising antibody; PROBE, Patient Reported Outcome Burdens and Experiences; PROs, patient-reported outcomes; UK, United Kingdom; WPAI, Work Productivity and Activity Impairment Questionnaire.
*Outcomes marked in bold are incorporated into the economic model.
Source: ClinicalTrials.gov. Identifier NCT03569891[1]

The available evidence from the Phase I/II and Phase IIb trials are summarised in Appendix M, although their data were not used to populate the economic model as per rationales below:

- CT-AMT-060-01 (NCT02396342): the 5-year data of this study can support the validation of the durability of the effect of etranacogene

dezaparvovec. This study was not included in the economic model, as the expression cassette within AMT-060 was a predecessor to etranacogene dezaparvovec; AMT-060 contains the coding DNA sequence of codon-optimised wild-type human Factor IX, whilst etranacogene dezaparvovec has a codon-optimised coding DNA sequence of the naturally occurring gain-of-function Padua variant of the human Factor IX (containing a single amino acid change.

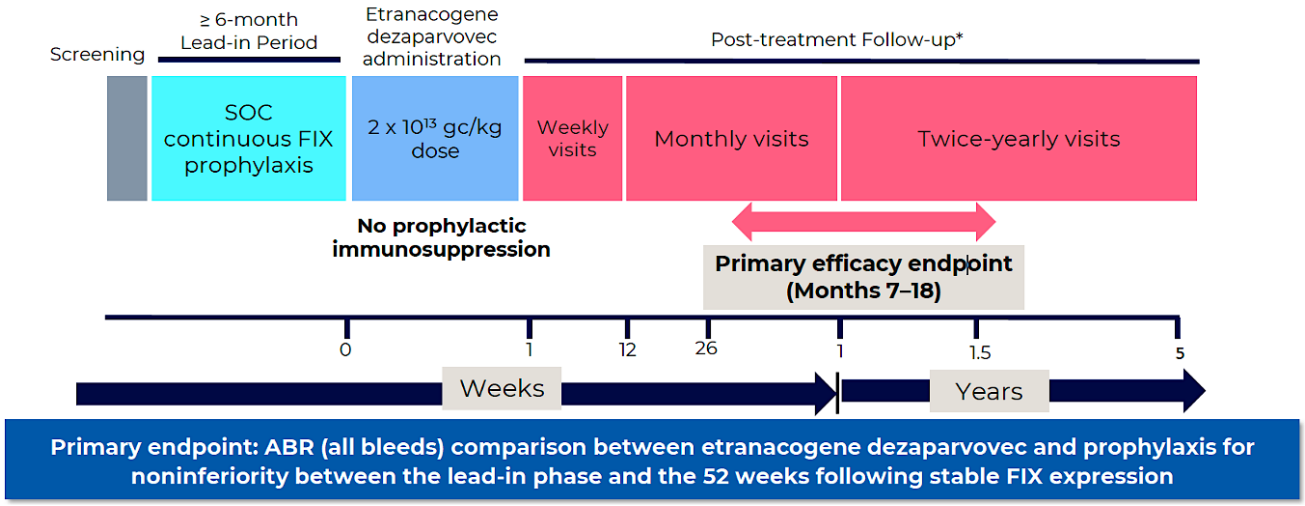
- CT-AMT-061-01 (NCT03489291): the data of this ongoing dosing-confirmation trial can support the efficacy and safety profile of single-dose etranacogene dezaparvovec, which contains the coding sequence for the Padua variant of Factor IX instead of the previously used wildtype Factor IX. This study was not included in the economic model because it only included three patients.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 HOPE--B trial methodology

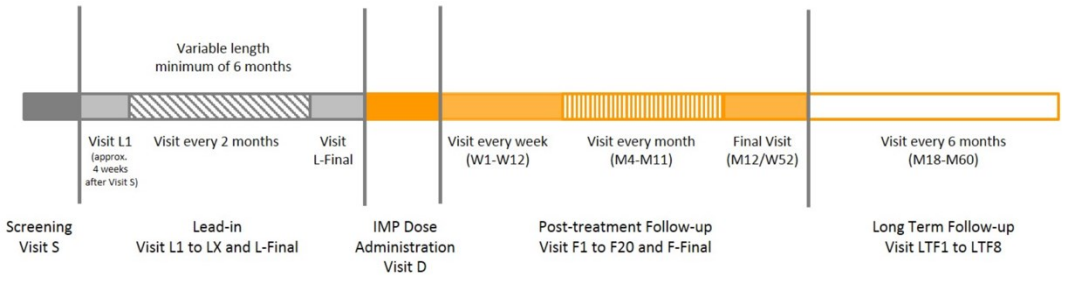
The primary clinical efficacy and safety data supporting the use of etranacogene dezaparvovec in severe or moderately severe (≤ 2% of normal circulating Factor IX levels) haemophilia B is from the pivotal HOPE-B trial (NCT03569891).[1] HOPE--B is an ongoing Phase III, open-label, single-dose, multicentre, multinational study evaluating the efficacy and safety of etranacogene dezaparvovec in adult patients with moderately severe or severe haemophilia B (Figure 7).[1] A summary of the trial methodology is shown in Table 7.

Figure 7: HOPE-B study design



Abbreviations: ABR, annualised bleeding rate; AE, adverse event; FIX, Factor IX; GC, genome copy; Q1, Quarter 1; SOC, standard of care
*At least quarterly contact (±2 weeks) between site staff and subjects to monitor occurrence of AEs. Last subject visit planned Q1 2025.
Sources: CSL Behring. Clinical trial protocol and study results. 2022 [data on file],[14] ClinicalTrials.gov. NCT03569891[1]

Table 7: Comparative summary of trial methodology

Trial number (acronym)	HOPE-B, NCT03569891, CT-AMT-061-02
Location	Multicentre; 33 sites, including 17 sites in the United States (US), 13 sites in the European Union (EU), and 3 sites in the United Kingdom (UK)
Trial design	CT-AMT-061-02 (Health Outcomes with Padua Gene; Evaluation in Hemophilia B [HOPE-B]) is an ongoing open-label, single-dose, multi-centre, multi-national trial, with a screening phase/period, a lead-in phase/period, a treatment plus a post-treatment follow-up phase/period, and a long-term follow-up phase/period.  At screening (Visit S), subjects were assessed for eligibility and were instructed in how to record bleeding episodes and use of Factor IX replacement therapy in a dedicated electronic diary. The approximately 4-week period between screening up to the start of the lead-in phase (Visit L1) was considered a training period where

	subjects became familiar with recording their use of Factor IX replacement therapy and bleeding episodes. A pre-defined wash-out period of 3 days for regular-acting Factor IX products and 10 days for extended half-life Factor IX products occurred between screening and the lead-in phase. During the lead-in phase, which lasted for a minimum of 26 weeks (i.e., ≥6 months), subjects recorded their use of Factor IX replacement therapy and bleeding episodes in their dedicated e-diary. After the lead-in phase, subjects received a single-dose of etranacogene dezaparvovec at the dosing visit (Visit D) and were followed for 1 year (i.e., post-treatment follow-up phase; 52 weeks) to evaluate efficacy and safety. One of the secondary endpoints, endogenous Factor IX activity at 26 weeks after etranacogene dezaparvovec dosing, was assessed once the last subject had achieved 26 weeks after etranacogene dezaparvovec treatment. Following the post-treatment follow-up phase, subjects continued into the long-term follow-up phase for an additional 4 years, with visits planned every half year (6 months) for evaluation of safety and efficacy parameters. During the long-term follow-up phase, subjects are instructed to document Factor IX usage and bleeding episode information in study-specific paper diaries. Due to the Coronavirus disease 2019 (COVID-19) pandemic, this trial was adapted to allow for flexibility for remote telemedicine/telehealth visits where possible. Adjustments to the visit location/method or schedule may have been made to accommodate safety concerns and restrictions experienced by individual subjects and sites.
Eligibility criteria for participants	**Inclusion criteria** Subjects could not have been enrolled in the trial before all of the following inclusion criteria were met: 1. Male 2. Age ≥18 years 3. Subjects with congenital haemophilia B with known severe or moderately severe Factor IX deficiency (⩽2% of normal circulating Factor IX) for which the subject was on continuous routine Factor IX prophylaxis* 4. >150 previous exposure days of treatment with Factor IX protein 5. Had been on stable prophylaxis for at least 2 months prior to screening 6. Had demonstrated capability to independently, accurately, and in a timely manner complete the diary during the lead-in phase as judged by the Investigator 7. Acceptance to use a condom during sexual intercourse in the period from IMP administration until AAV5 had been cleared from semen, as evidenced by the central laboratory, from negative analysis results for at least 3 consecutively collected semen samples (this criterion was applicable also for subjects who were surgically sterilised) 8. Able to provide informed consent following receipt of verbal and written information about the trial * Continuous routine prophylaxis was defined as the intent of treating with an a priori defined frequency of infusions (e.g., twice weekly, once every two weeks, etc.) as documented in the medical records.

Exclusion criteria

Subjects were excluded from the trial if any of the following exclusion criteria (including local and central laboratory test results, as specified) were met:

1. History of Factor IX inhibitors
2. Positive Factor IX inhibitor test at screening and Visit L-Final (based on local laboratory results)
3. Screening and Visit L-Final laboratory values (based on central laboratory results):
    a. ALT >2 times upper normal limit (i.e., upper limit of normal [ULN])
    b. AST >2 times ULN
    c. Total bilirubin >2 times ULN (except if caused by Gilbert disease)
    d. ALP >2 times ULN
    e. Creatinine >2 times ULN
4. Positive human immunodeficiency virus serological test at screening and Visit L-Final, not controlled with anti-viral therapy as shown by CD4+ counts ≤200/μL (based on central laboratory results)
5. Hepatitis B or C infection with the following criteria present at screening:
    a. Currently receiving antiviral therapy for this/these infection(s) and/or
    b. Positive for any of the following (based on central laboratory results):
        i. Hepatitis B surface antigen (HBsAg), except if in the opinion of the Investigator this was due to a previous hepatitis B vaccination rather than active hepatitis B infection
        ii. Hepatitis B virus (HBV) DNA
        iii. Hepatitis C virus (HCV) ribonucleic acid (RNA)
6. Known coagulation disorder other than haemophilia B
7. Thrombocytopenia, defined as a platelet count below 50 × 109/L, at screening and Visit L-Final (based on central laboratory results)
8. Known severe infection or any other significant concurrent, uncontrolled medical condition including, but not limited to, renal, hepatic, cardiovascular, hematological, gastrointestinal, endocrine, pulmonary, neurological, cerebral or psychiatric disease, alcoholism, drug dependency, or any other psychological disorder evaluated by the Investigator to interfere with adherence to the protocol procedures or with the degree of tolerance to the IMP
9. Known significant medical condition that may have significantly impacted the intended transduction of the vector and/or expression and activity of the protein including, but not limited to:
    a. Disseminated intravascular coagulation
    b. Accelerated fibrinolysis
    c. Advanced liver fibrosis (suggestive of or equal to Meta-analysis of Histological Data in Viral Hepatitis [METAVIR] Stage 3 disease; e.g., a FibroScan™ score of ≥9 kPa was considered equivalent)
10. Known history of an allergic reaction or anaphylaxis to Factor IX products
11. Known history of allergy to corticosteroids
12. Known uncontrolled allergic conditions or allergy/hypersensitivity to any component of the IMP excipients
13. Known medical condition that would require chronic administration of steroids
14. Previous gene therapy treatment

	15. Receipt of an experimental agent within 60 days prior to screening 16. Current participation or anticipated participation within one year after IMP administration in this trial in any other interventional clinical trial involving drugs or devices.
Settings and locations where the data were collected	• United States o Phoenix Children's Hospital, Arizona, o Arkansas Children's Hospital, Little Rock, Arkansas, o Los Angeles Orthopedic Hospital, California, o Children's Hospital of Los Angeles, Los Angeles, California, o University of California, Davis, Sacramento, California o University of California, San Diego o University of Colorado Denver, Aurora, Colorado, o Children's National Medical Center Hematology and Oncology, Washington, District of Columbia, o University of South Florida, Tampa, Florida o University of Michigan, Ann Arbor, Michigan o Hemophilia Center of Western New York, Buffalo, New York, o University of North Carolina, Chapel Hill, North Carolina, o Oregon Health & Science University, Portland, Oregon, o University of Tennessee Health Science Center, Memphis, Tennessee, o Vanderbilt University Medical Center, Nashville, Tennessee, o University of Texas Health Science Center & Medical School, Houston, Texas, o University of Utah, Salt Lake City, Utah, o Washington Institute for Coagulation, Seattle, Washington, o University of Washington, Seattle, Washington, • Belgium o Cliniques universitaires Saint-Luc, Bruxelles, o University Hospital Leuven, Leuven • Denmark o Righospitalet, Copenhagen • Germany o Vivantes Klinikum im Friedrichshain, Berlin, o Klinikum der Johann Wolfgang Goethe Universitat, Frankfurt am main, • Ireland o National Coagulation Centre, St James's Hospital, Dublin, • Netherlands o Amsterdam UMC, AMC, Amsterdam, o Universitair Medisch Centrum Groningen, Groningen, o Erasmus MC, Rotterdam, Netherlands o UMC Utrecht, Van Creveldkliniek, Utrecht • Sweden o Center for Thrombosis and Hemostasis Skåne University Hospital Malmö, Malmö • United Kingdom o The Cambridge Haemophilia and Thrombophilia Centre Cambridge

	University Hospitals NHS Foundation Trust, Cambridge o The Royal London Hospital (Barts Health NHS Trust), London, o University Hospital Southampton NHS Foundation Trust, Southampton
Trial drugs	Reference therapy in lead-in phase of the study (N=67) Factor IX prophylaxis therapy used during the lead-in phase, prior to treatment with etranacogene dezaparvovec Active treatment period — dose and mode of administration (N=54) Subjects were planned to receive a single intravenous infusion of 2×10^{13} GC/kg etranacogene dezaparvovec in a peripheral vein.
Permitted and disallowed concomitant medication	The following treatments were not allowed during trial participation: • Continuous routine Factor IX prophylaxis post-dose if a subject's endogenous Factor IX activity result was above 5% • Treatment in another interventional clinical trial involving drugs or devices for 1 year following treatment administration in this trial • Another gene therapy treatment • Chronic administration of steroids (oral and/or inhaled) For any known hepatotoxic medications, other alternatives were considered. The Investigator was expected to review the concomitant medications on an ongoing basis for these types of medications. Where possible, subjects were taken off any known hepatotoxic drugs before Visit D. Apart from the above listed treatments, no protocol restrictions applied with respect to concomitant medications: • Subjects were permitted to continue administration of their continuous routine Factor IX treatment on the day of dosing (after the pre-treatment assessments were completed) and continue their continuous routine Factor IX treatment in the first weeks after dosing to provide sufficient Factor IX coverage for the initial days post-treatment. During the post-treatment follow-up visits, endogenous Factor IX activity was assessed. If the endogenous Factor IX activity result was ≥5%, continuous routine Factor IX prophylaxis was discontinued, and further management was based on the Investigator's clinical judgement and subject preference. • Continuation or re-initiation of continuous routine Factor IX prophylaxis may have been considered if the endogenous Factor IX activity was between 2% and 5% in at least two consecutive laboratory measurements, based on the Investigator's clinical judgement and subject preference. If endogenous Factor IX activity was <2%, continuous routine prophylaxis must have been continued or reinstated. Additional on-demand and/or intermittent prophylactic Factor IX treatment may have been given after treatment with etranacogene dezaparvovec, if considered necessary. • Factor IX infusions were not recommended for subjects with Factor IX activity in the non-haemophilic (≥40% of normal) range especially in subjects with a confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, as increased thrombogenic risk is a known complication of COVID-19
Primary outcomes (including scoring methods and timings of assessments)	**Primary outcomes** The primary objective was to demonstrate the non-inferiority of etranacogene dezaparvovec during the 52 weeks following establishment of stable Factor IX expression (Months 6–18) post-treatment follow-up compared to standard of care continuous routine Factor IX prophylaxis during the lead-in phase, as measured by the ABR.

Secondary outcomes

The secondary objective was to demonstrate additional efficacy and safety aspects of systemic administration of etranacogene dezaparvovec, focused on the following:

- Endogenous Factor IX activity 6 months after a single etranacogene dezaparvovec treatment
- Endogenous Factor IX activity 12 months after a single etranacogene dezaparvovec treatment
- Endogenous Factor IX activity 18 months after a single etranacogene dezaparvovec treatment
- Annualised consumption of Factor IX replacement therapy
- Annualised infusion rate of Factor IX replacement therapy
- Discontinuation of previous continuous routine prophylaxis
- Trough Factor IX activity
- Prevention of bleedings (comparison for superiority)
- Prevention of spontaneous bleeding
- Prevention of joint bleeding
- Estimated ABR – during the 52 weeks following stable Factor IX expression (6–18 months) – as a function of pre-treatment anti-AAV5 antibody titres using the luciferase based NAb assay (as a "correlation" analysis)
- Correlation of pre-IMP anti-AAV5 antibody titres using the luciferase based NAb assay on Factor IX activity levels after etranacogene dezaparvovec dosing
- Occurrence and resolution of target joints
- Proportion of subjects with zero bleeding episodes during the 52 weeks following stable Factor IX expression (6–18 months) after etranacogene dezaparvovec dosing
- International Physical Activity Questionnaire (iPAQ)
- EuroQol-5 dimensions-5 levels (EQ-5D-5L) Visual Analog Scale (VAS)

Exploratory outcomes

Exploratory efficacy objectives investigated the effect of etranacogene dezaparvovec on the following:

- Factor IX protein levels during the 18 months following etranacogene dezaparvovec dosing
- Haemophilia Joint Health Score (HJHS) scores
- Other Patient Reported Outcome (PRO) questionnaires: Work Productivity and Activity Impairment Questionnaire (WPAI), Brief Pain Inventory (BPI), Hemophilia Activities List (HAL), and Hemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) during the lead-in phase (prophylaxis) and during the 12 months following etranacogene dezaparvovec dosing
- Estimated ABR over time as a function of mean Factor IX activity (as a "correlation" analysis) over the 18-month post-treatment follow-up
- Rate of traumatic bleeding events during the 52 weeks following stable Factor IX expression (6–18 months) post-treatment follow-up compared to the lead-in phase

	• Subgroup analyses will be carried out for the following endpoints:
	  o Endogenous Factor IX activity at 18 months
	  o Annualised consumption of Factor IX replacement therapy, excluding replacement for invasive procedures
	  o Annualised infusion rate of Factor IX replacement therapy
	  o ABR comparison between etranacogene dezaparvovec and Factor IX prophylaxis
	  o Comparison of the percentage of subjects with trough Factor IX activity <12% of normal between the lead-in phase and after treatment with etranacogene dezaparvovec over the 52 weeks following stable Factor IX expression (6–18 months)
	  o Proportion of subjects remaining free of previous prescribed continuous routine prophylaxis.
	• All efficacy endpoints (as exploratory endpoints) at 2, 3, 4, and 5 years after etranacogene dezaparvovec dosing
	
	Safety outcomes
	• Adverse events [Time Frame: 5 years]
	• Monitoring of adverse events
	• Changes in abdominal ultrasound
	• Formation of anti-AAV5 antibodies (total immunoglobulin M and immunoglobulin G, NAbs)
	• AAV5 capsid-specific T cell response, formation of anti-Factor IX antibodies
	• Formation of Factor IX inhibitors and recovery
	• Serum chemistry parameters
	  o serum electrolytes (sodium, potassium)
	  o creatinine
	  o creatine kinase
	  o gamma-glutamyltransferase
	  o AST
	  o ALT
	  o ALP
	  o C-reactive protein (CRP)
	  o albumin
	  o total bilirubin
	  o glucose (non-fasting)
	• Haematology parameters
	  o haemoglobin
	  o haematocrit
	  o platelet count
	  o red blood cells
	  o white blood cells with differential count
	  o CD4+ count
	• Shedding of vector DNA in blood and semen
	• Inflammatory markers
	  o interleukin-1beta (IL-1β)

	○ interleukin-2 (IL-2) ○ interleukin-6 (IL-6) ○ interferon gamma (IFNγ) ○ monocyte chemotactic protein-1 (MCP-1) ○ AST and ALT level increases and use of corticosteroids for AST/ALT increases • Alpha-fetoprotein
Other outcomes used in the economic model/ specified in the scope	N/A
Pre-planned subgroups	**Pre-planned subgroups:** • Age categories: <40 years, 40 to <60 years, ≥60 years • Race and/or ethnicity subgroups • Zero bleeding episodes vs. ≥1 bleeding episodes in lead-in period ○ Because this subgrouping was defined using information from the lead-in phase, the analysis provided descriptive statistics for only the post-treatment phase. • Presence or absence of target joints at screening • Baseline anti-AAV5 NAb titre categories: positive titre (≥limit of detection [LOD]) vs. negative titre (<LOD) • HIV-negative vs. controlled HIV positive (CD4+ count >200/μL) at baseline • History of hepatitis B or C at baseline • Baseline liver pathology, according to baseline FibroScanTM or equivalent shear wave • elastography, magnetic resonance elastography result: ○ Degree of fibrosis (≥9 kPA vs. <9 kPa) ○ Degree of steatosis (Controlled Attenuation Parameter [CAP] score ≥S2 [≥260 dB/m] vs. <S2 [<260 dB/m]) vs. missing **Reported subgroup:** Full Analysis Set (FAS) baseline NAb titre <700 (to report ABR during lead-in and post treatment period by subgroup)

Sources: 24-Month CSR, CSL Behring. Clinical trial protocol and study results. 2022 [data on file],[14] ClinicalTrials.gov. NCT03569891[1]

B.2.3.2 Overview of PRO measures used in HOPE-B

The HOPE-B trial included the following PROs:[14]

- EuroQol-5 dimensions-5 levels (EQ-5D-5L)
- International Physical Activity Questionnaire (iPAQ)
- Brief Pain Inventory (BPI)
- Haemophilia Activities List (HAL)
- Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL)
- Work Productivity and Activity Impairment Questionnaire (WPAI)
- Patient Reported Outcomes Burdens and Experiences (PROBE)

The following two endpoints were included as secondary endpoints:[14]

- iPAQ total physical activity score during the 12 months following dosing compared with the lead-in phase
- EQ-5D-5L visual analogue scale (VAS) scores during the 12 months following dosing compared with lead-in phase

All other patient-reported outcomes were included as exploratory endpoints and the PROBE study was included as an optional sub-study.

The PRO QoL questionnaires were completed by the subject after signed informed consent was obtained and then prior to the initiation of any other visit procedure at screening (Visit S), Visit L3, Visit L-Final, Visit F15 (26 weeks/6 months), and every year post-baseline. Questionnaires were completed in the same order at each visit, following the order presented in the protocol: EQ-5D-5L, iPAQ, WPAI, BPI-sf, HAL, Haem-A-QoL, and (optional) PROBE.[14]

Additionally, Haemophilia Joint Health Scores (HJHS) were assessed at screening, Visit L-Final, and every year post-baseline by a trained physician/physiotherapist/ designee.[14]

2.3.2.1 Description of the PROs and HJHS

- **EQ-5D-5L** is a standardised measure of health status that provides a simple, generic measure of health for clinical and economic appraisal. It consists of two parts:[14]

    - A descriptive profile comprising the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; respondents rate each dimension based on five levels of severity (i.e., no problems, slight problems, moderate problems, severe problems, and extreme problems).

    - A vertical VAS, on which the respondent rates their overall health from 'best imaginable health state' to 'worst imaginable health state.

- **iPAQ** is a 27-item self-reported measure of physical activity for use with adults aged 15–69 years old. The recall period is 7 days, and 5 types of physical activity are included: 1) job related 2) transportation 3) housework, house maintenance, caring for family 4) recreation, sport, and leisure time 5) time spent sitting. It was designed with the intent of finding a common way to measure physical activity in different countries. In each of the domains the number of days per week and the time per week spend in both moderate and vigorous activity are recorded. iPAQ measures the volume of activity by weighting each type of activity by its energy requirements defined in multiples of the resting metabolic rate (metabolic equivalent of task [MET]) and the total activity score will be measured in MET minutes per week.[14] Two forms of the iPAQ have been developed: a short and a long version, both of which involve 7-day recall of physical activity. The short form was used starting with Protocol Amendment 2; the long form of the iPAQ was completed by some subjects prior to this amendment.

- The **BPI** is a self-reported or interview measure that assesses severity of pain, impact of pain on daily function, location of pain, pain medication use, and amount of pain relief in the past 24 hours or the past week.[14]

- The **HAL** measures the impact of haemophilia on self-perceived functional abilities in adults. It includes 42 multiple choice questions in 7 domains: 1) lying/sitting/kneeling/standing 2) function of the legs 3) function of the arms 4) use of transportation 5) self-care 6) household tasks and 7) leisure activities and sports.[14]

- The **Haem-A-QoL** consists of 46 items comprising 10 domains: physical health, treatment, work and school, dealing with haemophilia, feelings, family planning, future, partnerships and sexuality, sports and leisure, and view of yourself. Items are rated by participants with one of five response options: never, seldom, sometimes, often, and always; although, for some items there is also a 'not applicable' option. The Total Score is based on the scores for each domain and ranges from 0 to 100, with lower scores reflective of better quality of life.[14]

- The **WPAI** measures absenteeism, presenteeism, and impairments in unpaid activity because of health problems with a 7-day recall.[14]

- The **PROBE** study collects information general health problems including presence of acute and chronic pain, use of pain medications, limitations in mobility and absence from work or school.[14] The PROBE Questionnaire is a novel, patient-developed, tool specific to haemophilia and is intended to capture clinical outcomes that are considered relevant by patients. The Short Form is the full PROBE questionnaire minus the EQ-5D-5L. The Follow-up Short Form includes select questions from the Short Form (without the EQ-5D-5L). The Short Form PROBE was completed at screening, Visit L-Final (end of the Lead-in period), and Visit LTF8 (Month 60). The PROBE Follow-up Form was completed at Visit L3 (Lead-in Month 6), Visit F15 (26 weeks/Month 6), and every year post-baseline.[14]

- The **HJHS** measures joint health, in the domain of body structure and function (i.e., impairment), of the joints most commonly affected by bleeding in haemophilia: the knees, ankles, and elbows. The total score ranges from 0 to 124, with higher scores considered unfavourable. Preferably, the same assessor consistently performed the assessment on the individual subject throughout the entire trial period.[14]

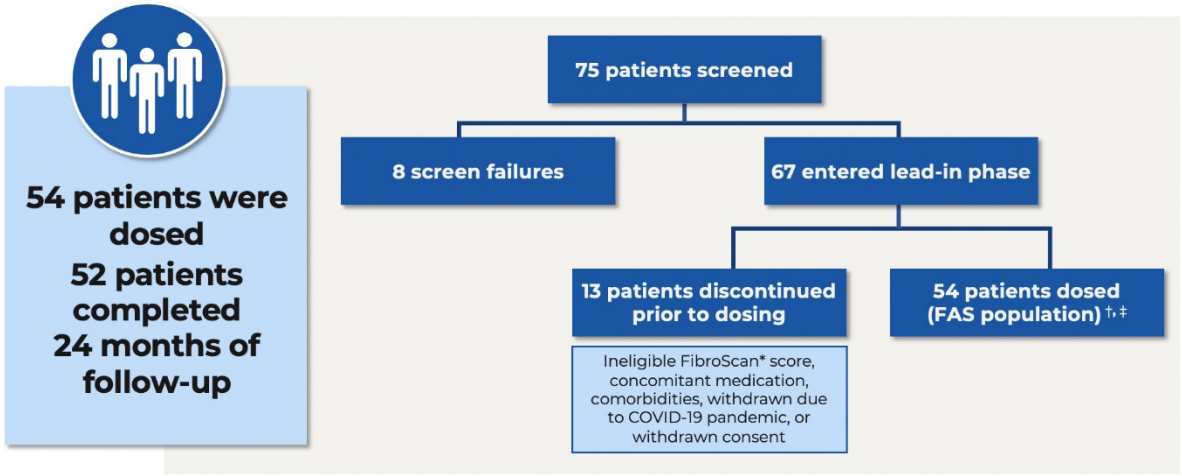
B.2.3.3 HOPE-B baseline characteristics

A total of 75 patients were screened, of whom 67 entered the lead-in phase. Of these 67 patients, 13 patients discontinued the study prior to dosing due to ineligible FibroScan® score, concomitant medication, comorbidities, the COVID-19 pandemic, or withdrawal of consent, while the remaining 54 patients constituted the Full Analysis Set (FAS) (see data set definitions in B.2.4).[14,104]

A total of 52 patients received the full dose of etranacogene dezaparvovec and completed 6, 12, 18 and 24 months of follow-up (Figure 8).[104] One subject who received full treatment died 464 days (approximately 15 months) post-treatment due to an event unrelated to etranacogene dezaparvovec (see Section 2.10.3.7 for further detail). One subject who received full treatment but remained on routine prophylaxis withdrew consent after 24 Months post-treatment (Month 24 visit not completed); this subject will be followed for long-term safety through medical record review. One subject discontinued study treatment infusion due to a TEAE of hypersensitivity after approximately 10% of the full dose of study drug was administered. This subject continued in the study for follow-up.[14]

Baseline characteristics of the FAS population are presented in Table 8. At data cut-off date for the 24-month analysis discussed in this submission, 52/54 patients treated with etranacogene dezaparvovec were still participating in the study.

Figure 8: Overview of selected patients in the HOPE-B trial



Abbreviations: FAS, Full Analysis Set; PP, Per Protocol.
*Or equivalent scan (magnetic resonance elastography, shear wave elastography).
†FAS (N=54) included subjects who enrolled, entered the lead-in period, were dosed with etranacogene dezaparvovec and provided ≥1 efficacy endpoint assessment.
‡PP population (N=53) included all subjects from the FAS who adhered to a stable and adequate prophylaxis use during the lead-in period, completed ≥18 months of efficacy assessments, and had no major protocol deviations that impacted the interpretation of efficacy.
Note: the Screen Failure Population included screened patients who never entered the lead-in period.
Adapted from; 24 Month CSR, CSL Behring. 2022 [data on file][14]

Table 8: Summary of demographic and baseline characteristics (safety population)

Patient characteristics	Full analysis set N=54[a]
Male, n (%)	54 (100.0)
Age, mean (SD, min–max), years	41.5 (15.8, 19–75)
Severity of haemophilia B at time of diagnosis, n (%)	
Severe (Factor IX <1%)	44 (81.5)
Moderately severe (Factor IX ≥1% and ≤2%)	10 (18.5)
Positive HIV status, n (%)	3 (5.6)
Prior hepatitis B infection, n (%)	9 (16.7)
Prior or ongoing hepatitis C infection, n (%)	31 (57.4)
Pre-screening Factor IX prophylaxis therapy n (%)	
Extended half-life	31 (57.4)
Standard half-life	23 (42.6)

Patient characteristics	Full analysis set N=54[a]
Detectable anti-AAV5 NAbs at baseline[a], n	
Titre ≥ limit of detection <3,000	20 (37.0)
Titre ≥3,000	1 (1.9)

Abbreviations: AAV5, adeno-associated virus vector serotype 5; HIV, human immunodeficiency virus; max, maximum; min, minimum; NAb, neutralising antibody; SD, standard deviation
[a]Baseline antibody titre was the value obtained immediately prior to dosing or the value obtained at Visit L Final in cases where the value immediately prior to dosing was missing
Source: 24 Month CSR, CSL Behring. Clinical trial protocol and study results. 2022 [data on file][14]

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

In the pivotal Phase III HOPE-B trial, the primary endpoint assessed the ABR between Month 7-18 post-treatment with etranacogene dezaparvovec compared with the 6 -month lead-in period. In this submission we also present the latest available data of 24 Months post-dose. The HOPE-B secondary endpoints included evaluations at 18 Months and 24 Months post-treatment, which are presented in this submission.

For visit-based endpoints of Months 6–18 or Months 6–24 post-treatment, the analyses used data from Month 7 to the Month 18 or Month 24 visits, respectively. For rate-based endpoints of Months 6–18 or Months 6–24 post-treatment, the analyses used data from discrete months (i.e., from Months 7–18 or Month 7–24, respectively, where Month 7 data collection started after 6 months Factor IX expression stabilisation time post-dose). Statistical analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC 27513).[14]

B.2.4.1 HOPE-B data sets

The following data sets were analysed:[14]

- The Screen Failure Population (n=8) included all subjects who were screened but never entered the lead-in phase.

- The Lead-in Discontinuers Population (n=13) included all subjects who entered the lead-in phase but discontinued from the study prior to etranacogene dezaparvovec dosing.

- The Safety Population (n=67) consisted of all subjects who were enrolled in either the Lead-in Safety Population (n=67) or the Post-treatment Safety Population (n=54). The Lead-in Safety Population consisted of all subjects who were enrolled into the lead-in phase. The Post-treatment Safety Population consisted of all subjects who received etranacogene dezaparvovec, irrespective of any protocol deviations. Period-specific safety tabulations used the period-specific safety population for the 'n' and denominator (for percentages).

- The FAS (n=54) included all subjects who were enrolled, entered the lead-in phase, were dosed with etranacogene dezaparvovec, and provided at least one efficacy endpoint assessment for any efficacy endpoint subsequent to etranacogene dezaparvovec dosing. The FAS population was the primary population for all efficacy statistical analyses.

- The Per-Protocol (PP) Population (n=53) included all subjects from the FAS population who adhered to a stable and adequate prophylaxis use during the lead-in phase, who completed at least 18 months of efficacy assessments (52 weeks after achieving stable Factor IX expression) for the 24-month (data cut) analysis, who completed at least a full year of efficacy assessments for the 12-month (data cut) analysis, or who completed at least 6 months of efficacy assessments for the 6-month (data cut) analysis, and who had no major protocol deviations that impacted the interpretation of efficacy. Definitive decisions regarding subject evaluability for the PP Population took place at the multidisciplinary evaluability meeting for the respective data cut-off. The PP Population was used for sensitivity analyses.

B.2.4.2 HOPE-B trial objectives

The primary objective in HOPE-B was to demonstrate the non-inferiority of etranacogene dezaparvovec (2×10^{13} GC/kg) during the 52 weeks following establishment of stable Factor IX expression (Months 7–18 post-treatment) compared to standard-of-care continuous routine Factor IX prophylaxis during the 6-month lead-in phase, as measured by the ABR. The secondary objective was to demonstrate additional efficacy and safety aspects of systemic administration of etranacogene dezaparvovec. A hierarchical testing method was used during analysis of primary and secondary clinical endpoints in order to retain the Type I error rate (see below).[14]

2.4.2.1 Efficacy

The primary efficacy analyses of Factor IX activity were completed using the FAS population.† Consecutively, the primary efficacy analysis of ABR for the non-inferiority assessment was completed using the PP population.‡ Factor IX activity levels are considered an appropriate surrogate endpoint for haemophilia severity. For all secondary efficacy analyses, the FAS population was used as the primary population. Exploratory analysis was based on the FAS and PP populations. Formal statistical testing was performed for the primary and secondary efficacy endpoints only.[14] All exploratory endpoints are presented using descriptive statistics, where applicable; no formal statistical testing was performed for exploratory endpoints and p-values were presented for some endpoints but were not controlled for multiplicity.[14]

2.4.2.2 Safety

All safety analyses were performed based on the safety population, which consisted of all subjects who were in either the lead-in safety population or the post-treatment safety population.[14]

†Includes patients who enrolled, entered the lead-in phase, were dosed with etranacogene dezaparvovec and provided ≥1 efficacy endpoint assessment.

‡Includes all subjects from the FAS who adhered to a stable and adequate prophylaxis use during the lead-in phase, completed assessments through the six-month visit, and had no major protocol deviations that impacted the interpretation of efficacy.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

A summary of the quality assessment for pivotal Phase III, non-randomised HOPE-B trial is presented in Table 9, and the full details of all studies included in this submission are presented in Appendix D.

HOPE-B is of high quality as it is being conducted with accepted standards of good clinical practice, and all applicable federal, state and local laws, rules, regulations, requirements and guidelines (including all foreign laws and governmental requirements as applicable) relating to the conduct of the clinical trial.

Table 9: Quality assessment of HOPE-B

HOPE-B (NCT03569891)	
Was the cohort recruited in an acceptable way?	Yes, patients were recruited following all technical requirements applicable and the trial is being conducted in accordance with current Good Clinical Practice codes
Was the exposure accurately measured to minimise bias?	Yes, exposure to this single-dose treatment was properly measured
Was the outcome accurately measured to minimise bias?	Yes, the trial was powered for non-inferiority of primary endpoint and the efficacy endpoints (where performed) were assessed using a hierarchal approach to reduce Type I error
Have the authors identified all important confounding factors?	Not applicable as not yet published
Have the authors taken account of the confounding factors in the design and/or analysis?	Not applicable as not yet published
Was the follow-up of patients complete?	No, the trial is still ongoing and final readout will be at 5 years
How precise (for example, in terms of confidence interval and p values) are the results?	The results are expressed appropriately, with p-values provided where applicable and specified in the statistical plan outlined in Section B.2.4

B.2.6 Clinical effectiveness results of the relevant studies

The efficacy and tolerability of etranacogene dezaparvovec has been demonstrated in the 7–24-Month post-dose analysis period of HOPE-B, an ongoing pivotal trial in patients with moderately severe or severe haemophilia B.

The trial's primary and secondary clinical efficacy endpoints were met, demonstrating the superiority of etranacogene dezaparvovec in reducing ABR compared with standard of care in the treatment of haemophilia B.[14]

The results of HOPE-B presented in this submission are described in the 24-Month clinical study report,[14] with the key 18-month results being presented at the 15th Annual Congress of European Association for Haemophilia and Allied Disorders (EAHAD) [17] and the 24-month data at the American Society of Hematology (ASH), [105-107] both held in 2022. A publication with the final 18-month primary end point results is expected to be published in February 2023.

B.2.6.1 ABR (Primary endpoint)

Primary HOPE-B endpoint (7–18 Months post-dose)

The primary clinical efficacy endpoint was met, demonstrating that treatment with etranacogene dezaparvovec was found to be non-inferior to standard of care routine Factor IX prophylaxis with regards to the ABR. The adjusted ABR for all bleeding episodes was reduced following etranacogene dezaparvovec treatment and stable Factor IX expression, from a rate of 4.19 (95% Confidence Interval [CI]: 3.22–5.45) for the ≥6-month lead-in period to 1.51 (95% CI: 0.81–2.82) for Months 7–18 of the post-treatment period (64% reduction [95% CI: 36%–80%; p=0.0002]) (Table 10).[14]

The adjusted ABR rate ratio for the Month 7–18 post-treatment period to 6-months lead-in period was 0.36 (95% Wald CI: 0.20–0.64). As the upper limit of the Wald CI was less than 1.8, non-inferiority can be declared vs the lead-in standard of care Factor IX prophylaxis. Moreover, additional analysis indicated that treatment with etranacogene dezaparvovec was superior to standard of care routine Factor IX prophylaxis for all bleeding episodes and Factor IX-treated bleeding episodes.[14]

Table 10. ABR (all bleeds) of ≥6-month lead-in period versus 7–18 Month post-treatment

	≥ 6-month Lead-in Period ABR		Post-treatment Period ABR	Reduction (%)	95% CI	p-value
Months 7 to 18 Post-treatment						
All bleeds (N = 54)	4.19	----→	1.51	64%	36%, 80%	0.0002
All bleeds, FIX-treated (N = 54)	3.65	----→	0.84	77%	54%, 88%	< 0.0001

Abbreviations: ABR, annualised bleed rate; CI, confidence interval; FIX, clotting Factor IX; FAS, Full Analysis Set
Source: Adapted from 24-Month CSR, CSL Behring. Clinical trial protocol and study results. 2022 [data on file][14]

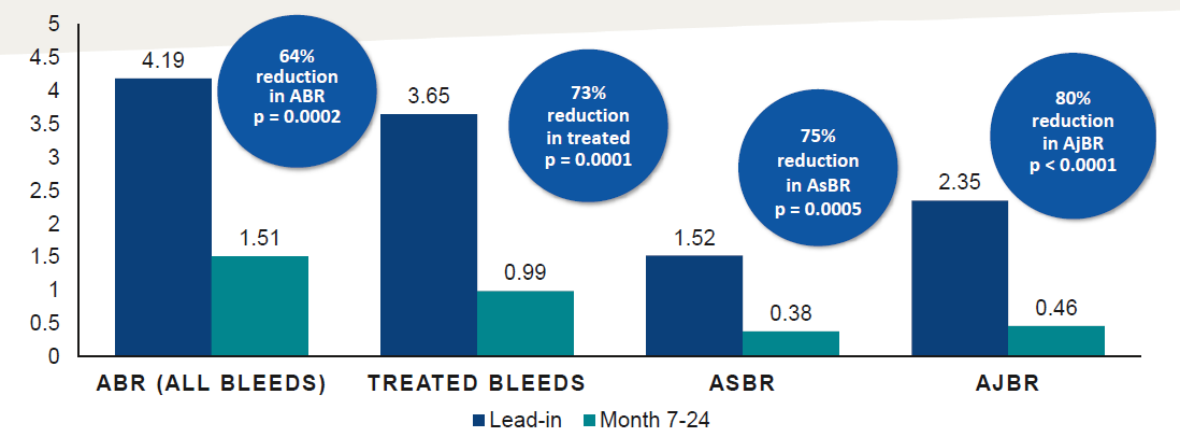
Latest HOPE--B data cut-off (7–24 Months post-dose)

In the HOPE-B trial, the adjusted ABR for all bleeding episodes after stable Factor IX expression decreased in the FAS population (n=54) from 4.19 (95% CI: 3.22–5.45) for the ≥6-month lead-in period with Factor IX prophylaxis to 1.51 (95% CI: [redacted]) after 7–24 Months post-treatment, a reduction of 64% (95% CI: 37%–79%; p=0.0002) (Figure 9, Table 11).[14]

Mean AsBR decreased by 75% (from 1.52 to 0.38; p=0.0005) from 7–24 Months compared with Factor IX prophylaxis in the ≥6-month lead-in period, while the mean AjBR decreased by 80% (from 2.35 to 0.46; p<0.0001) from 7–24 Months compared with Factor IX prophylaxis in the ≥6-month lead-in period (Figure 9, Table 11).[14]

At 7–24 Months post-treatment, etranacogene dezaparvovec demonstrated a 73% reduction (from 3.65 to 0.99; 95% CI: [redacted]%; p=0.0001) in the number of bleeds that required Factor IX-treatment, compared with Factor IX prophylaxis in the ≥6-month lead-in period. Etranacogene dezaparvovec also demonstrated a reduction of 87% in traumatic bleeds at 24 Months post-treatment compared with Factor IX prophylaxis in the ≥6-month lead-in period (from 1.74 to 0.23; p<0.0001) (Figure 9, Table 11).[14]

Figure 9: ABR comparison of the lead-in phase with the post-treatment period (7–24-month post-dose of etranacogene dezaparvovec)[a]



Abbreviations: ABR, annualised bleeding rate; AjBR, annualised joint bleeding rate; AsBR, annualised spontanous bleeding rate

[a]Adjusted ABR and comparison of ABR between the lead-in and post-treatment periods was estimated from a repeated measures generalised estimating equations negative binomial regression model accounting for the paired design of the study with an offset parameter to account for the differential collection periods. The treatment period was included as a categorical covariate.

Source: 24-Month CSR, CSL Behring. Clinical trial protocol and study results. 2022 [data on file][14]

Table 11: ABR by bleeding type (FAS)

Endpoint	≥6-month lead-in period		Months 7–24 post-treatment period					
	Unadjusted ABR [a] (mean No. of bleeds)	Adjusted ABR (95% CI) [b]	Unadjusted ABR [a]	Adjusted ABR (95% CI) [b]	Rate ratio (post-treatment /lead-in) [b]	Two sided 95% Wald CI	p-value[c]	Conclusion
All bleeding episodes (N=54)	4.11(2.5)	4.19 (3.22, 5.45)	0.99	1.51 (0.83, 2.76)	0.36	0.21, 0.63[d]	0.0002	NI met SUP met
All bleeding episodes (baseline anti-AAV5 NAb negative) (N=33)	3.76(2.3)	3.79 (2.55,5.63)	0.79	0.80 (0.39, 1.67)	0.21	0.12, 0.37	<0.0001	NI met SUP met
All bleeding episodes (baseline anti-AAV5 NAb positive) (N=21)	4.64	4.97 (3.66, 6.75)	1.37	12.59 (2.95, 53.66)	2.56	0.61, 10.66	0.0986	NI not met SUP not met
All bleeding episodes (baseline anti-AAV5 NAb titre <1:700) (N=53)	4.17(2.6)	3.89 (2.93, 5.16)	0.93	1.09 (0.67, 1.79)	0.28	0.17, 0.46[d]	<0.0001	NI met SUP met
All bleeding episodes (baseline anti-AAV5 NAb titre >1:700) (N=1)	88.71	Not reported	1,673.97	N/A	N/A	N/A	N/A	N/A
Spontaneous bleeding episodes (N=54)	1.51(0.9)	1.52 (1.01, 2.30)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NI met SUP met
Spontaneous Factor IX replacement therapy-treated bleeding episodes (N=54)	1.33(0.8)	1.34 (0.87, 2.06)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NI met SUP met
Bleeding episodes, Factor IX	3.56(2.2)	3.65 (2.82, 4.74)	0.58	0.99 (0.48, 2.03)	0.27	0.14, 0.54[d]	<0.0001	NI met SUP met

Endpoint	≥6-month lead-in period		Months 7–24 post-treatment period					
	Unadjusted ABR [a] (mean No. of bleeds)	Adjusted ABR (95% CI) [b]	Unadjusted ABR [a]	Adjusted ABR (95% CI) [b]	Rate ratio (post-treatment /lead-in) [b]	Two sided 95% Wald CI	p-value[c]	Conclusion
replacement therapy-treated (N=54)								
Joint bleeding episodes (N=54)	2.33(1.4)	2.35 (1.74, 3.16)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NI met SUP met
Joint bleeding episodes, Factor IX replacement therapy-treated (N=54)	2.11(1.3)	2.13 (1.58, 2.88)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NI met SUP met
Traumatic bleeding episodes (N=54)	2.11(1.3)	2.09 (1.42, 3.08)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NI met SUP met
Traumatic bleeding episodes, Factor IX replacement therapy-treated (N=54)	1.75(1.1)	1.74 (1.21, 2.49)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NI met SUP met
New and true bleeding episodes (N=54)	3.71(2.3)	3.83 (2.93, 5.01)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NI met SUP met
New and true bleeding episodes, Factor IX replacement therapy-treated (N=54)	3.23(2.0)	3.35 (2.57, 4.37)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NI met SUP met

Abbreviations: ABR, annualised bleeding rate; CI, confidence interval; FAS, Full Analysis Set; NAb, neutralising antibody; NI, noninferiority; SUP, superiority

[a]Unadjusted ABR was calculated as the ratio of the number of bleeding episodes to the time at risk (in years).

[b]Adjusted ABR and comparison of ABR between the Lead-in and Post-treatment Periods was estimated from a repeated measures generalised estimating equations negative binomial regression model accounting for the paired design of the study with an offset parameter to account for the differential collection periods. Treatment period was included as a categorical covariate.

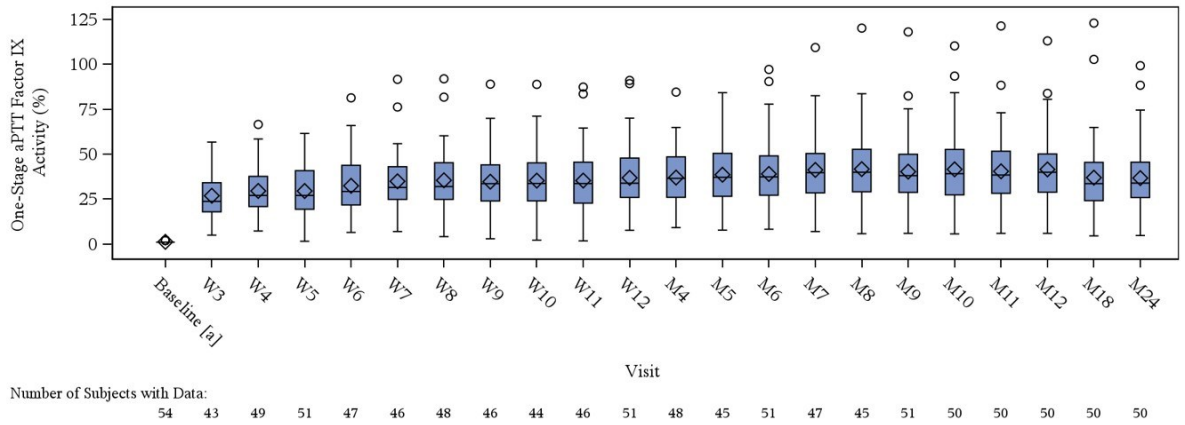
[c]One-sided p-value ≤0.025 for post-treatment / lead-in <1 was regarded as statistically significant.
[d]The upper limit of the CI of the rate ratio was compared with the noninferiority margin of 1.8. If the upper limit was <1.8, then non-inferiority was declared.
[e]p-value not adjusted for multiplicity.
Source: CSL Behring. Clinical trial protocol and study results. 2022 [data on file][14]

B.2.6.2 Factor IX activity outcomes (secondary endpoint)

At 7–24 Months post-treatment, participants continued to demonstrate durable, sustained endogenous Factor IX activity levels with a mean endogenous Factor IX activity of 36.7 IU/dL (standard deviation [SD], minimum–maximum [min–max]: ±18.96, 4.7–99.2), as measured by a one-stage aPTT-based clotting assay (Figure 10). This eliminated the need for routine Factor IX prophylaxis therapy in nearly all (96.3%) patients, potentially decreasing the burden on patients in managing disease. At 24 Months post-treatment, the increase in endogenous Factor IX activity level (least square [LS] mean value) from baseline was 34.13 IU/dL (p<0.001,

Table 12). By the end of the ≥6-month lead-in period, 43/54 (79.6%) subjects had endogenous Factor IX activity levels <12% of normal, and at Month 24 post-treatment, only 5/50 (10.0%) subjects had endogenous Factor IX activity levels <12% of normal. Moreover, there was no clinically meaningful correlation between baseline anti-AAV5 NAbs status and long-term durability of Factor IX expression (see B.2.7).[14]

Figure 10: Endogenous Factor IX activity level from baseline to Month 24 post-treatment[a]



Abbreviations: APTT, activated partial thromboplastin time; CSR, Clinical Study Report; FAS, Full Analysis Set; M, month; W, week
Data are from 'uncontaminated' central laboratory one-stage, meaning that the blood sampling did not occur within 5 half-lives of exogenous Factor IX use. Factor IX levels beginning with the Week 3 assessment were used in the analysis. Both the date and time of the exogenous Factor IX use (start) and the blood sampling were considered in determining contamination. Subjects with zero uncontaminated central laboratory post-treatment values had their post baseline values set equal to their baseline value. The lower and upper edges of the box correspond to the interquartile range, the 25th, and 75th percentile. The line at the middle of the box corresponds to the median. The whiskers (horizontal lines connected to vertical lines) show the lowest and highest observation within 1.5 times

the interquartile range of the bottom and top of the box, respectively. The diamond is the arithmetic mean. Any points outside of the whiskers are plotted individually.
[a]Baseline Factor IX was imputed based on the historical severity of subjects' haemophilia B as documented in the case report form. For subjects who had documented severe Factor IX deficiency (Factor IX plasma level <1%), the baseline Factor IX activity level was imputed as 1%. For subjects who had documented moderately severe Factor IX deficiency (Factor IX plasma level ≥1% and ≤2%), the baseline Factor IX activity level was imputed as 2%. The standard error was not provided at baseline.
Source: 24-Month CSR, CSL Behring. Clinical trial protocol and study results. 2022 [data on file][14]

Table 12: Factor IX activity (%) from uncontaminated central laboratory one-stage (aPTT-based) assay at 6, 12, 18, and 24 Months post-treatment (FAS)

		Result		Change from baseline		
Visit[a]	N	Mean (SD)	Median (min, max)	LS Mean (SE)[b]	95% CI	p-value[c]
Baseline	54	1.19 (0.39)	1.00 (1.0, 2.0)	-	-	-
Month 6	51	38.95 (18.72)	37.30 (8.2, 97.1)	36.18 (2.432)	31.41, 40.95	<0.0001
Month 12	50	41.48 (21.71)	39.90 (5.9, 113.0)	38.81 (2.442)	34.01, 43.60	<0.0001
Month 18	50	36.90 (21.40)	33.55 (4.5, 122.9)	34.31 (2.444)	29.52, 39.11	<0.0001
Month 24	50	36.66 (18.96)	33.85 (4.7, 99.2)	34.13 (2.325)	29.57, 38.69	<0.0001

Abbreviations: aPTT, activated partial thromboplastin time; CI, confidence interval; FAS, Full Analysis Set; LS, least square; max, maximum; min, minimum; SD, standard deviation; SE, standard error
[a]Data are from 'uncontaminated' central laboratory one-stage, meaning that the blood sampling did not occur within 5 half-lives of exogenous Factor IX use. Both the date and time of exogenous Factor IX replacement therapy use and blood sampling were considered in determining contamination. Factor IX levels beginning with the Week 3 assessment were used in the analysis. Patients with zero uncontaminated central laboratory post-etranacogene dezaparvovec values had their change from baseline assigned to zero for this analysis and had their post-baseline values set equal to their baseline value; however, the ratio of chromogenic to one-stage (APTT-based) assay was not imputed. Baseline Factor IX was imputed based on patients' historical haemophilia B severity documented on the Case Report Form. If the subject had documented severe Factor IX deficiency (Factor IX plasma level <1%), their baseline Factor IX activity level was imputed as 1%. If the subject had documented moderately severe Factor IX deficiency (Factor IX plasma level ≥1% and ≤2%) their baseline Factor IX activity level was imputed as 2%.
[b]LS mean from repeated measures linear mixed model with visit as a categorical covariate.
[c]One-sided p-value ≤0.025 for post-treatment > baseline was regarded as statistically significant.
Source: 24-Month CSR, CSL Behring. Clinical trial protocol and study results. 2022 [data on file][14]

B.2.6.3 Zero bleeds (secondary endpoint)

The number of subjects with zero bleeds increased from 14/54 (25.9%) subjects during the ≥6-month lead-in period to 27/54 (50.0%) subjects at 7–24 Months post-treatment. No clinically relevant correlation was found between baseline AAV5 NAb titre and rate of subjects with zero bleeds. For subjects with a negative baseline AAV5 NAb titre, the number of subjects with zero bleeding episodes increased from 11/33 (33.3%) during the lead-in period to 19/33 (57.6%) at 24 Months post-treatment. For subjects with a positive baseline AAV5 NAb titre, the number of subjects with zero bleeds increased from 3/21 (14.3%) during the lead-in period to 8/21 (38.1%) at 7–24 Months post-treatment.[14]

B.2.6.4 Annualised consumption of Factor IX replacement therapy at 7–24 Months post-treatment (secondary endpoint)

In the HOPE-B trial, etranacogene dezaparvovec demonstrated a significant reduction in Factor IX replacement therapy consumption at 24 Months post-treatment compared with the 6-month lead-in period with Factor IX prophylaxis therapy, with the mean (SD) difference in Factor IX replacement therapy consumption being –248,393 (21,050) IU/year/participant (p<0.0001) (Table 13). In subjects with a baseline NAb titre <1:700, the adjusted mean consumption of Factor IX replacement therapy decreased by [redacted] IU/year for the Month 7–24 post-treatment period (p<[redacted]). Between Month 19–24 post-treatment, the number of subjects using Factor IX replacement therapy decreased from [redacted]% (n=[redacted]) to [redacted]% (n=[redacted]) (Table 14) compared with the ≥6-month lead-in period with Factor IX prophylaxis therapy. The mean number of infusions of Factor IX replacement therapy per subject decreased from 44.1 infusions/year during the ≥6-month lead in period, to 2.54 infusions/year for the Month 7–24 post-treatment period (95% CI: 0.98–6.59, rate ratio: 0.04, p<0.0001).[14]

Table 13: Annualised use of Factor IX replacement therapy excluding invasive procedures (FAS)

All patients (N=54)	≥6-month lead-in period	Post-treatment period			
		Month 0–6	Month 7–12	Month 13–18	Month 19–24
Annualised exogenous Factor IX replacement therapy Consumption (IU/year), n	54 (100%)	54 (100%)	54 (100%)	54 (100%)	53 (98.1)
Unadjusted mean (SD)	257,339 (149,013)	12,913 (37,093)	8,399 (29,721)	8,487 (28,770)	9,751 (29,140)
Summary statistics	**≥6-month lead-in period**	**Post-treatment period**			
		Month 0–6	Month 7–18	Month 7–24	Month 0–24
Post-treatment period – lead-in period differences					
Unadjusted mean (SD)	-	-244,426 (143,457)	-248,825 (155,066)	-248,393 (154,686)	-247,579 (151,592)
Adjusted mean (SE)	-	-244,426 (19,522)	-248,825 (21,102)	-248,825 (21,102)	–
95% CI	-	-283,582, -205,270	-291,150, -206,500	-290,614, -206,172	–
p-value[b]	-	<0.0001	<0.0001	<0.0001	–

Abbreviations: CI, confidence interval; IU, international units; SD, standard deviation; SE, standard error
[a]Two patients remained on prophylaxis (one patient received a partial infusion, one patient Factor IX expression remained <2%).
[b]P-values were calculated using a paired t-test comparing post-treatment and lead-in periods. One-sided p-value ≤0.025 for post-treatment – lead-in <0 was regarded as statistically significant.
Source: CSL Behring. Clinical trial protocol and study results. 2022 [data on file][14]

Table 14: Annualised use of Factor IX replacement therapy excluding invasive procedures (FAS), infusions/year

Summary statistics	≥6-month lead-in period	Post-treatment period			
		Month 0–6	Month 7–12	Month 13–18	Month 19–24
Number of subjects using Factor IX replacement therapy, n (%)	54 (100.0)	14 (25.9)	10 (18.5)	11 (20.4)	13 (24.5)
Number of infusions of Factor IX replacement therapy, n	2380	85	70	64	42
Mean (per subject)	44.1	1.6	1.3	1.2	0.8
Number of person-years observed for usage of Factor IX replacement therapy	33.12	24.10	26.91	26.12	25.85

Summary statistics	≥6-month lead-in period	Post-treatment period			
		Month 0–6	Month 7–18	Year 7–24	Month 0–24
Cumulative number of Infusions of Factor IX replacement therapy	2,380	85	134	176	155
Cumulative number of person-years observed for Factor IX usage	33.12	24.10	53.03	79.18	51.01
Unadjusted annualised infusion rate[a]	71.87	3.53	2.53	2.22	3.04
Adjusted annualised infusion rate[b]					
Adjusted Rate (95% CI)[b]	72.49c (63.52, 82.71)	–	2.53 (0.92, 6.96)	2.54 (0.98, 6.59)	3.04 (1.14, 8.12)
Rate ratio (post-treatment/ lead-in)[b]	–	–	0.03	0.04	0.04
Two-sided 95% Wald CI	–	–	0.01, 0.10	0.01, 0.09	0.02, 0.11
p-value[d]	–	–	<0.0001	<0.0001	<0.0001

Abbreviations: CI, confidence interval; FAS, Full Analysis Set
[a]Unadjusted use was calculated as the ratio of the number of infusions of Factor IX to the time of observation (in years). Usage related to invasive procedures was not included.
[b]Adjusted use and comparison of use between lead-in and post-treatment periods was estimated from a repeated measures generalised estimating equations negative binomial regression model accounting for the paired design of the study with an offset parameter to account for the differential collection periods. Treatment period was included as a categorical covariate.
[c]For comparison with post treatment Month 7 to 18.
[d]One-sided p-value ≤0.025 for post treatment/lead in <1 was regarded as statistically significant.
Source: CSL Behring. Clinical trial protocol and study results. 2022 [data on file][14]

B.2.6.5 Durability of etranacogene dezaparvovec activity over Month 7–24 after administration (secondary endpoint)

The durability of etranacogene dezaparvovec was observed over the period of 7–24 Months post-treatment, during which patients (n=50) continued to demonstrate sustained increases in Factor IX activity post-infusion with a mean Factor IX activity level of 36.7% (±19.0) of normal and effective bleed control (Figure 10,

Table 12). The study will follow patients up to 5 years post-administration of etranacogene dezaparvovec to further evaluate its long-term efficacy and safety.[14]

2.6.5.1 Durability predictions

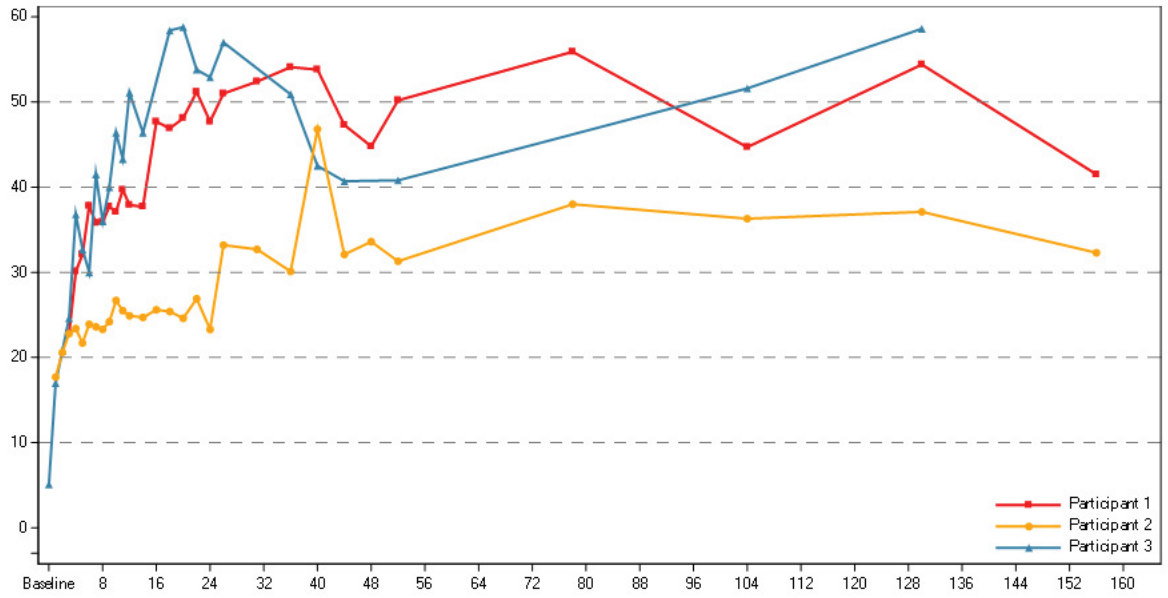
It is reasonable to believe that etranacogene dezaparvovec has a long-term therapeutic effect. This based on the following facts: rAAV based gene therapy is predominantly non-integrating and consequently the persistence of therapeutic effect after treatment is dependent on the formation and maintenance of circular episomes in non-dividing cells. Since episomes are likely to be lost during mitosis, the cell turnover may affect the durability of transgene expression in the target tissue.[108] Studies prove that the effects of rAAV-based gene therapy can be maintained over long periods of time; the most recently published follow-up of the earliest successful haemophilia B gene therapy trial, demonstrated stable therapeutic expression of Factor IX over a period of 8 years without late toxicities. The rAAV-based vector used, similarly to etranacogene dezaparvovec, contained a codon-optimised Factor IX gene, under control of a liver specific promoter.[109] During a presentation at the Congrès Français d'Hemostase (CFH) in 2021, Dr Nathwani stated that the dose-dependent, multiyear increase in Factor IX was sustained in an rAAV-based trial, with the longest follow-up being up to 10 years (oral presentation, recording available upon request due to file size).

Clearly, existing data for liver-directed rAAV therapies show a durability far in excess of the commonly reported lifespan for human hepatocytes, indicating that either the lifespan of some transduced cells is longer than expected, or that episomes are maintained through some other unknown mechanism. The episome may, by chance

segregate with one of the daughter nuclei and be maintained there until the next cell division. Alternatively, because many hepatocytes are either polyploid or multinucleated, they may undergo multiple modes of cell division during development or regeneration.[110] Thus, a multinucleated cell carrying an rAAV episome in one nucleus could divide without entry into S phase and pass the episome to a daughter cell more efficiently. Similarly, hepatocytes can undergo S phase without entry into M phase, potentially allowing the episome to remain associated with the nucleus, meaning that the durability of therapeutic effect would not be limited to one lifespan.[108]

Recent updates trials with etranacogene dezaparvovec have shown continued stable Factor IX expression over 3 years in the Phase IIb trial (Figure 11) and 2 years in the Phase III trial (Figure 10), as well as 5 years in the Phase I AMT-060 trial.[99,105,107]

Figure 11: One-stage aPTT Factor IX activity (%) for the three patients in the Phase IIb study

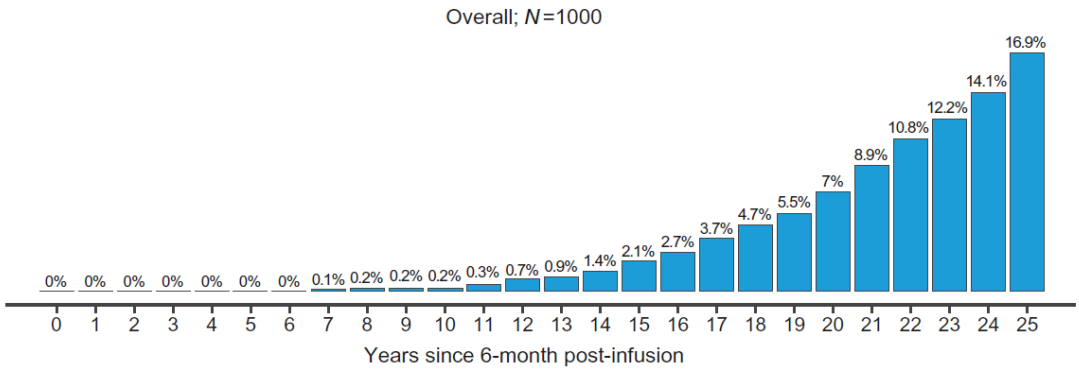


Time after etranacogene dezaparvovec administration shown on x-axis (weeks).
Source: von Drygalski et al., 2022[99]

With available data from the Phase IIb and Phase III etranacogene dezaparvovec studies, the likelihood for study patients to retain therapeutic levels of factor expression after etranacogene dezaparvovec infusion can be statistically analysed, and the chance for a patient to remain off prophylaxis over time predicted. In a recent

publication,[111] Bayesian and Frequentist linear mixed models were used to predict Factor IX activity levels for up to 25.5 years at an individual and population level. Both models predicted that no more than 6/55 (10.91%) observed participants would have Factor IX activity levels less than 2%, up to 25.5 years post-infusion (Figure 12), suggesting that more than 80% of patients would remain free from prophylactic Factor IX replacement products 25.5 years post-infusion. Moreover, an additional analyses from the same model has estimated that [redacted]% of patients treated with etranacogene dezaparvovec will have Factor IX levels >2% and >5% after a median of [redacted] and [redacted] years post-treatment, respectively.[112] Though these long-term Factor IX durability predictions are based on statistical methods and results in vivo may differ, it is reasonable to assume that most treated patients will experience long-term etranacogene dezaparvovec therapeutic benefit. The credibility of this prediction of durability has been validated by eight key haematologists from England in a recent advisory board.[6]

Figure 12: Bayesian statistical model prediction of the overall cumulative percentage of treated patients, who over time will return to Factor IX activity levels less than 2%



Based on using currently available data from the Phase IIb and Phase III etranacogene dezaparvovec studies.
Source: Shah et al., 2022[111]

B.2.6.6 PRO analyses and results (exploratory outcomes)

For all PRO endpoints, except the optional PROBE sub-study, the post treatment values during the 24-Month post-treatment period were compared with the ≥6-month lead-in period using a repeated measures linear mixed model to determine whether there was a statistically significant improvement after etranacogene dezaparvovec was administered. The analysis of the optional PROBE sub-study was based on the FAS population for the set of subjects participating in the respective sub-study. Any subject with at least one assessment of the sub-study endpoint was considered to be participating in the respective sub-study.[14]

Measured PROs are described in Section 2.3.2.1. The repeated measures linear mixed models controlled for the effect of period, visit and period by visit interaction. A one-sided p-value of ≤0.025 for the post-treatment — lead-in period was regarded as statistically significant. Since these are all exploratory endpoints, no adjustment was made to control for multiplicity. Those endpoints that achieved significance, are in bold in the tables below. Results are presented for the FAS population at 24 months (Table 15), which were consistent with those for the modified intention-to-treat approach.[14]

Table 15: PRO Haem-A-QoL treatment domain score comparison between treatment periods (FAS; N=54)

Domain (overall: lead-in period vs 7–24 Months post-treatment period)	Lead-in period, LS mean (SE)[a]	7–24 Months post-treatment period, LS mean (SE)[a]	Difference between treatment period, mean (SE)[a]	One-sided p-value[b]
Haem-A-QoL, total	**26.20**	**20.0**	**−6.20 (1.19)**	**<0.0001**
Work/school	**17.31**	**12.07**	**−5.24 (2.19)**	**0.0102**
Feelings	**20.32**	**11.22**	**−9.10 (1.96)**	**<0.0001**
Treatment	**25.78**	**11.54**	**−14.24 (2.10)**	**<0.0001**
Future	**31.20**	**24.63**	**−6.57 (1.83)**	**0.0004**
Physical health	[redacted]	[redacted]	[redacted]	[redacted]
Family planning	[redacted]	[redacted]	[redacted]	[redacted]
Dealing with haemophilia	[redacted]	[redacted]	[redacted]	[redacted]
Sport and leisure	[redacted]	[redacted]	[redacted]	[redacted]

Domain (overall: lead-in period vs 7–24 Months post-treatment period)	Lead-in period, LS mean (SE)[a]	7–24 Months post-treatment period, LS mean (SE)[a]	Difference between treatment period, mean (SE)[a]	One-sided p-value[b]
View of yourself	[redacted]	[redacted]	[redacted]	[redacted]
Partnerships and sexuality	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-5L				
Score	[redacted]	[redacted]	**0.0439 (0.019)**	**0.010**
VAS	[redacted]	[redacted]	**2.800 (11.400)**	**0.024**
WPAI				
Absenteeism	[redacted]	[redacted]	[redacted]	[redacted]
Presenteeism	[redacted]	[redacted]	[redacted]	[redacted]
Work Productivity Loss	[redacted]	[redacted]	[redacted]	[redacted]
Activity Impairment	[redacted]	[redacted]	[redacted]	[redacted]
BPI, FAS				
Pain intensity	[redacted]	[redacted]	[redacted]	[redacted]
Pain interference	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BPI, Brief Pain Inventory; CSR, Clinical Study Report; FAS, full analysis set; Haem-A-QoL, Haemophilia Specific Quality of Life Index; LS, least square; SE, standard error; VAS, visual analogue scale; WPAI, Work Productivity and Activity Impairment

[a]LS mean from repeated measures linear mixed model with period (lead-in or post-treatment), Visit (A or B), and period-by-visit interaction as categorical covariates. Subject was modelled as a random effect.

[b]The overall p-value for the Lead-in Period vs post-treatment first year was based on a contrast across Visits A and B, with equal weight. A one-sided p-value ≤0.025 for post-treatment, lead-in of <0 was regarded as statistically significant.

Note: Questionnaires completed within 2 weeks of a bleed were not included in the analysis or descriptive summaries. A higher score indicated a lower quality of life. Score ranged from 0 to 100.

Source: 24 Month CSR, CSL Behring (Data on file)[14]

2.6.6.1 EQ-5D-5L

There was a statistically significant improvement in Months 7–24 post-treatment compared to the lead-in period (Table 15).

At 12 Months post-treatment, there was a numerical improvement in mean EQ-5D index scores compared to the lead-in period, but it was not statistically significant at the p=0.025 threshold.[14] The LS mean difference (SE) was 0.0310 (0.01903; 95%

CI: -0.0067, 0.0686; p-value: 0.0530 [not adjusted for multiplicity]). There was a statistically significant improvement in the second year following treatment compared to the lead-in period (Post-treatment Month 12-24 vs. lead-in), with an LS mean difference (SE) of [redacted] ([redacted]; 95% CI: [redacted], [redacted]; p value [redacted] [not adjusted for multiplicity]).[14] Improvements in EQ-5D-5L scores may not have occurred at the 7–12 Month post-treatment period due to the relatively intensive follow-up period in the first year post-treatment, which may have impacted patients' self-reporting on improvement.[14]

The improvement in the EQ-5D index scores at 24-Month post-treatment was primarily the result of improvements in pain and discomfort, and over time, fewer subjects were reporting severe or extreme pain/discomfort. At the post-treatment period baseline, [redacted]% of subjects reported no pain/discomfort, and [redacted]%, [redacted]%, [redacted]%, and [redacted]% of subjects reported slight, moderate, severe, or extreme pain/discomfort, respectively. By Month 24 post-treatment, [redacted]%, [redacted]%, and [redacted]% of subjects reported no, slight, or moderate pain/discomfort, respectively; no subjects reported severe or extreme pain/discomfort. The majority of subjects had no problems with self-care, usual activities, or anxiety/depression based on the EQ-5D-5L categorical responses. Slight to no problems in mobility were noted in most subjects.[14]

2.6.6.2 Haem-A-QoL

Significant model-based mean differences in scores and the percentage improvement compared with the lead-in period were observed in the Total Score and the domains regarding 'Work/School', 'Feelings', 'Treatment' and 'Future' at 24 Months post-treatment (Table 15). 'Treatment' reflects how burdened patients are by their haemophilia treatments. 'Feelings' reflects current emotions associated with having haemophilia. 'Future' reflects concerns about how haemophilia will affect their life plans. 'Work/School' reflects how well patients think they perform these responsibilities. Results were not significant for the six remaining Haem-A-QoL domains.[113]

At 12 Months post-treatment, significant model-based mean differences in scores were noted compared with the lead-in period for the Total Score (LS mean difference

-5.50; p<0.0001). These improvements were primarily due to improvements in the domains “Treatment” (LS mean difference -14.88; p<0.0001), “Feelings” (LS mean difference -9.42; p<0.0001), “Future” (LS mean difference -5.02; p=0.0023), and “Work/School” (LS mean difference -4.99; p=0.0036). This indicates that these improvements in QoL may be maintained over time.[14]

2.6.6.3 HJHS

Based on the repeated measures linear mixed models, there were small but statistically significant improvements in each of the first two years post-treatment compared to the lead-in period. Mean (SD) HJHS at screening, at the end of the lead-in period, and following 12 and 24 months of treatment with etranacogene dezaparvovec was 20.8 (17.1), 21.2 (16.9), 19.5 (16.8) and [redacted] ([redacted]), respectively. Based on the repeated measures linear mixed models, there were small but statistically significant improvements in each of the first two years post-treatment compared to the lead-in period (Table 28). The LS mean difference (SE) in the first 12 months was -1.7 (0.79; 95% CI: -3.3, -0.1; p-value 0.0196) and between 12–24 months was [redacted] ([redacted]; 95% CI: [redacted]; p-value [redacted]; p-values not adjusted for multiplicity).[14]

2.6.6.4 WPAI

During the 7–24 Months post-treatment, there were no significant differences in LS mean absenteeism, presenteeism, work productivity loss, or activity impairment compared to the lead-in period (Table 15).[14]

2.6.6.5 BPI

The numerical differences in the mean pain interference and pain intensity scores were not statistically significant in the lead-in period compared to Month 7–24 post-treatment (Table 15).[14]

2.6.6.6 HAL

Based on the repeated measures linear mixed model, there were no differences in mean HAL scores between the 6-month lead-in and first- and second-year treatment periods. The LS mean difference (SE) in the first year post-treatment was 1.16 (1.287;

95% CI: -1.38, 3.71; p-value 0.1843 [not adjusted for multiplicity]) and the LS mean difference (SE) in the second year post-treatment was [redacted] ([redacted]; 95% CI: [redacted]; p-value [redacted] [not adjusted for multiplicity]).[14]

2.6.6.7 PROBE

A total of [redacted] ([redacted]%) subjects enrolled in the PROBE sub-study.[14] The mean (SD) PROBE summary scores were similar between screening (0.778 [0.161]) and the end of the 6-month lead-in period (0.787 [0.166]).[14] The mean (SD) PROBE summary score was 0.811 (0.168) at Month 12 and [redacted] ([redacted]) at Month 24 post-treatment.[14] The mean PROBE scores for males and females without bleeding disorders were reported as 0.909 and 0.869 respectively.[114] While there still appears to be a decrement in scores compared to subjects with no bleeding disorders, the mean scores in subjects treated with etranacogene dezaparvovec were higher in the post-treatment period compared to the lead-in period.[14] More research is needed in the future to ascertain what constitutes a clinically meaningful change in PROBE scores with a therapeutic intervention.

2.6.6.8 Limitations of PROs

A number of different scores have been described to evaluate QoL. For haemophilia patients, some measurement tools are non-specific, such as EQ–5D, while others have been developed specifically for patients with haemophilia, such as Haem-A-QoL. Despite the fact that many outcome measures are now available, the optimal way to evaluate daily functioning and QoL is not well defined and patients with haemophilia often report good or excellent QoL while observers characterise the patients' daily struggles much less favourably (the disability paradox).[115,116] As a result, disease burden is often underestimated and treatment effects under-valuated when using currently available PRO tools in haemophilia patients.[116]

B.2.7 Subgroup analysis

Subgroup analyses were carried out for the following subgroups in the HOPE-B trial:

- Age categories: <40 years, 40 to <60 years, ≥60 years
- Race and/or ethnicity subgroups

- Zero bleeding episodes vs ≥1 bleeding episodes in lead-in period
  - Because this subgrouping was defined using information from the lead-in phase, the analysis provided descriptive statistics for only the post-treatment phase.
- Presence or absence of target joints at screening
- Baseline anti-AAV5 NAb titre categories: positive titre (≥limit of detection [LOD]) vs negative titre (<LOD)
- HIV-negative vs controlled HIV positive (CD4+ count >200/µL) at baseline
- History of hepatitis B or C at baseline
- Baseline liver pathology, according to baseline FibroScan™ or equivalent shear wave elastography, magnetic resonance elastography result:
  - Degree of fibrosis (≥9 kPA vs <9 kPa)
  - Degree of steatosis (Controlled Attenuation Parameter [CAP] score ≥S2 [≥260 dB/m] vs <S2 [<260 dB/m]) vs missing

Figure 13 shows the ABR during lead-in and post-treatment period by subgroup for FAS with baseline NAb titre >700, as described above. The subgroup analyses show that etranacogene dezaparvovec provides clinical benefit over the lead-in phase in almost all subgroups (n=[redacted]), with the only two inconclusive subgroups being the age category of ≥60 years and baseline stenosis grade of ≥2 (Figure 13).[14] The inconclusiveness of these subgroup analyses is potentially associated with the small sample size of these subgroups.

Importantly, this subgroup analysis shows that the ABR primary endpoint was met in both subjects with or without pre-existing anti-AAV5 NAbs at baseline, demonstrating an improved haemostatic protection compared with the standard of care Factor IX prophylaxis therapy (Figure 13).[14]

Figure 13: ABR during lead-in and post-treatment period by subgroup (FAS baseline NAb titre <700)

Abbreviations: ABR, annualised bleeding rate; CI, confidence interval; FAS, Full Analysis Set; HIV, human immunodeficiency virus; NAb, neutralising antibody; S2, moderate steatosis
[a]Ratio is the ABR ratio of Months 7–24 post-treatment vs lead-in adjusted ABR and comparison of ABR between lead-in and post-treatment period is estimated from a repeated measures generalised estimating equations negative binomial regression model accounting for the paired design of the study with an offset parameter to account for the differential collection periods. Treatment period is included as a categorical covariate.
[b]Two-Sided 95% Wald CI is compared to the noninferiority margin of 1.8. If the upper limit was less than 1.8, then noninferiority was declared.
[c]One-sided P-value ≤0.025 for post-treatment / lead-in <1 was regarded as statistically significant.
Source: CSL Behring. Clinical trial protocol and study results. 2022 [data on file][14]

To further explore the efficacy of the treatment in patients with AAV5 NAbs, the Factor IX activity was measured during the post-treatment period in patients with and without pre-existing NAbs (Table 16). As shown in Table 16 (and

Table 12), both groups showed a significant increase in endogenous Factor IX activity (p<[redacted]) at Month 7–24 post-treatment compared with the 6-month lead-in period.

Table 16: Factor IX activity (%) from uncontaminated central laboratory one-stage (aPTT-based) assay at 6, 12, 18, and 24 Months post-treatment for subjects with and without pre-existing NAbs to AAV5 (FAS)

		Result		Change from Baseline		
Visit[a]	N	Mean (SD)	Median (min;max)	LS Mean (SE)[b]	95% CI	p-value[c]
Pre-existing anti-AAV5 NAbs						
Baseline[c]	21	1.24 (0.44)	1.0(1.0, 2.0)			
6 Months Post-treatment	18	35.91 (19.02)	35.60 (8.2, 90.4)	30.79 (3.827)	23.26, 38.32	<0.0001
12 Months Post-treatment	18	35.54 (17.84)	39.95 (8.5, 73.6)	[redacted]	[redacted]	[redacted]
18 Months Post-treatment	17	31.14 (13.75)	32.00 (10.3, 57.9)	26.83 (3.854)	19.24, 34.41	<0.0001
24 Months Post-treatment	17	32.98 (18.51)	33.50 (9.1, 88.3)	28.35 (3.928)	20.62, 36.08	<0.0001
Without pre-existing Anti-AAV5 NAbs						
Baseline[c]	33	1.15 (0.36)	1.00 (1.0, 2.0)			
6 Months Post-treatment	33	40.61 (18.64)	37.30 (8.4, 97.1)	39.46 (3.172)	33.23, 45.69	<0.0001
12 Months Post-treatment	32	44.82 (23.21)	38.65 (5.9, 113.0)	[redacted]	[redacted]	[redacted]
18 Months Post-treatment	33	39.87 (24.08)	35.00 (4.5, 122.9)	38.72 (3.172)	32.49, 44.95	<0.0001
24 Months Post-treatment	33	38.55 (19.19)	35.40 (4.7, 99.2)	37.40 (2.933)	31.64, 43.16	<0.0001

Abbreviations: AAV5, adeno associated virus serotype 5; aPTT, activated partial thromboplastin time; CI, confidence interval; CSR, Clinical Study Report; FAS, Full Analysis Set; LS, least square; max, maximum; min, minimum; NAb, neutralising antibody; SD, standard deviation; SE, standard error

Uncontaminated data were used; blood samples did not occur within 5 half-lives of exogenous Factor IX replacement therapy use. Both the date and time of the exogenous Factor IX replacement therapy use (start) and the blood sampling were considered in determining contamination. Factor IX

levels beginning with the Week 3 assessment were used in the analysis. Subjects with zero uncontaminated central laboratory post etranacogene dezaparvovec values had their change from baseline assigned to zero for this analysis and had their post baseline values set equal to their baseline value. 'With antibodies' was defined as having a titre of > limit of detection. 'Without antibodies' was defined as having a titre of ≤ limit of detection. Baseline antibody titre was the most recently collected n on missing antibody titre prior to dosing.
[a]LS Mean from repeated measures linear mixed model with visit as a categorical covariate.
[b]One sided p value ≤0.025 for post treatment > baseline was regarded as statistically significant.
[c]Baseline Factor IX was imputed based on subject's historical haemophilia B severity documented on the Case Report Form. If the subject had documented severe Factor IX deficiency (Factor IX plasma level <1%), their baseline Factor IX activity level was imputed as 1%. If the subject had documented moderately severe Factor IX deficiency (Factor IX plasma level ≥1% and ≤2%), their baseline Factor IX activity level was imputed as 2%.
Source: CSL Behring. Clinical trial protocol and study results. 2022 [data on file][14]

Moreover, although the linear regression indicated a trend to lower mean Factor IX activity in subjects with pre-existing AAV5 NAbs, no clinically meaningful correlation between an individual's titre of pre-existing anti-AAV5 NAbs with their Factor IX activity at 24 Months post-treatment was identified up to a NAb titre of 3212.3 (Pearson coefficient: -0.36; Spearman coefficient: -0.29; R2: 0.129; Figure 14).

Figure 14: Correlation of Factor IX activity levels with pre-dose anti-AAV5 NAb titres

Abbreviations: AAV5, adeno-associated virus serotype 5; aPTT, activated partial thromboplastin time; CI, confidence interval; FAS, Full Analysis Set; LOD, limit of detection; NAb, neutralising antibody; rp, Pearson product-moment correlation coefficient; rs, Spearman correlation coefficient
Source: CSL Behring. Clinical trial protocol and study results. 2022 [data on file][14]

B.2.8 Meta-analysis

As there is only one relevant study (HOPE-B) at the time of submission, a meta-analysis could not be conducted.

B.2.9 Indirect and mixed treatment comparisons

In the absence of head-to-head evidence, indirect treatment comparisons (ITCs) have been conducted to determine the comparative efficacy of etranacogene dezaparvovec to currently available prophylactic treatments for moderately severe or severe haemophilia B, including extended half-life products as Idelvion (albutrepenonacog alfa), Alprolix (eftrenonacog alfa), Refixia (nonacog beta pegol) and BeneFIX (nonacog alfa).[117] The ITCs included results from HOPE--B and other data sources identified in a SLR by Davis et al. 2019,[118] which has been updated for this submission (see Appendix D). The SLRs identified four pivotal Phase III comparator trials, namely PROLONG-9FP,[119] B-LONG,[120] Paradigm™ 2,[121] and NCT00093171,[122] as key sources of efficacy data for Idelvion, Alprolix, Refixia, and BeneFIX, respectively (Table 17). The main ITC report is provided in the reference pack of this submission,[117] alongside its addendum presenting the comparisons versus BeneFIX (the rationale for this approach is provided in Section B.2.9.1).[123]

Table 17: Summary of the single-arm trials used to carry out the ITCs

Trial name	Treatment	Data cut-off	Post-treatment follow-up (months)	Analysis dataset	N
HOPE-B	etranacogene dezaparvovec	24-month data cut	Approximately 18 months[b] (Months 7 to 24)	ITC analysis set	51
PROLONG-9FP	Idelvion	Final data as reported by Santagostino et al., 2016[119]	Approximately 19 months[c]	Efficacy population	40
B-LONG	Alprolix	Final data as reported by Powell et al., 2013[120]	Approximately 12 months[d]	Efficacy analysis restricted to patients who received a prophylaxis regimen prior to study entry[e]	32
				Efficacy analysis[e]	61
Paradigm™ 2	Refixia	Final data as reported by	Approximately 12 months[f]	Prophylaxis 40 IU/kg group from full analysis set	29

Trial name	Treatment	Data cut-off	Post-treatment follow-up (months)	Analysis dataset	N
		Collins et al., 2014[121]		Prophylaxis 40 IU/kg group from full analysis set restricted to patients who received a prophylaxis regimen prior to study entry	17
NCT00093171	BeneFIX	Final data as reported by Lambert et al., 2007[122]	Approximately 6 months	Efficacy population (prophylaxis regimen)	17

Abbreviations: ITC, indirect treatment comparison; IU, international unit; rIX-FP, recombinant Factor IX albumin fusion protein (Idelvion)
[a]Data cutoffs with the most complete data availability were included.
[b]The median follow-up time in HOPE-B 24-month data-cut is approximately 1.485 years.
[c]Active treatment period for the evaluation of safety and efficacy was extended up to 27 months to allow subjects to receive continuous treatment with rIX-FP until enrolment in the subsequent extension study.[119] Median follow-up time was approximately 1.6 years.
[d]The follow-up time in B-LONG was reported as 52 (±1) weeks of treatment.[120]
[e]For B-LONG, the primary analysis population comparison consisted of patients who had received prior prophylaxis in the baseline population of group 1 in B-LONG (N=33 patients, of which N=32 had outcome data), and the secondary population comparison included the entire efficacy analysis population for group 1 in B-LONG trial (N=63 patients, of which N=61 had outcome data).
[f]The follow-up time in Paradigm™ 2 was reported as 52 (±2) weeks of treatment.[121]
Source: Eversana ITC report 2022[117]

B.2.9.1 Overall approach and summary of feasibility assessments

An ITC feasibility assessment determined the best sources of data to support ITCs of etranacogene dezaparvovec and comparators, these being the following Phase III pivotal trials: HOPE-B for etranacogene dezaparvovec, PROLONG-9FP for Idelvion, B-LONG for Alprolix, Paradigm™ 2 for Refixia, and NCT00093171 for BeneFIX.[117] Because all three of the Phase III trials provide only single-arm data with no common comparators, a network meta-analysis was not feasible. The indirect comparison of etranacogene dezaparvovec and recombinant Factor IX products therefore depended on pairwise, unanchored ITC methods using the best available data (i.e. individual patient-level data [IPD] versus summary-level data [SLD]) per comparison (Figure 15).

Figure 15: Summary of feasibility of ITC analyses

Comparison	ABR	AsBR	AjBR	% 0 ABR	% 0 AsBR	% 0 AjBR	FIX consumption	EQ-5D	Haem-A-QoL
EtranaDez (IPD) vs. IDELVION (IPD)	IPTW adjusting for key factors	IPTW adjusting for key factors	IPTW adjusting for key factors	IPTW adjusting for key factors	IPTW adjusting for key factors	IPTW adjusting for key factors	IPTW adjusting for key factors	Not possible due to lack of comparator data	Not possible due to lack of comparator data
EtranaDez (IPD) vs. Alprolix (SLD)	MAIC adjusting for key factors	MAIC adjusting for key factors	MAIC adjusting for key factors	MAIC adjusting for key factors	MAIC adjusting for key factors	MAIC adjusting for key factors	MAIC adjusting for key factors	Not possible due to lack of comparator data	MAIC adjusting for key factors
EtranaDez (IPD) vs. Refixia (SLD)	MAIC adjusting for key factors	MAIC adjusting for key factors	Not possible due to lack of comparator data	MAIC adjusting for key factors	Not possible due to lack of comparator data	Not possible due to lack of comparator data	Not possible due to lack of comparator data	MAIC adjusting for key factors	MAIC adjusting for key factors
EtranaDez (IPD) vs. BeneFIX (SLD)	MAIC adjusting for age and prior EHL/SHL only	MAIC adjusting for age and prior EHL/SHL only	Not possible due to lack of comparator data	MAIC adjusting for age and prior EHL/SHL only	Not possible due to lack of comparator data	Not possible due to lack of comparator data	Not possible due to lack of comparator data	Not possible due to lack of comparator data	Not possible due to lack of comparator data

Colour Code
Feasible
Feasible but not recommended due to especially poor robustness
Infeasible

Abbreviations: ABR, annualised bleeding rate; AjBR, annualised joint bleeding rate; AsBR, annualised spontaneous bleeding rate; EQ-5D, EuroQol-5 dimensions-5 levels; EtranaDez, etranacogene dezaparvovec; FIX, Factor IX; Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults; IPD, individual patient-level data; IPTW, inverse probability of treatment weighting; SLD, summary-level data
Source: Adapted from Eversana ITC report 2022[117]

Differences in trial designs and patient populations between HOPE-B and the pivotal Phase III comparator trials PROLONG-9FP, B-LONG, and Paradigm™ 2 were identified, suggesting that population-adjustment ITC methods leveraging IPD from HOPE-B and PROLONG-9FP would be a feasible and robust approach to mitigating bias while comparing etranacogene dezaparvovec with Idelvion, Alprolix, or Refixia. Given the limited sample sizes among trials relative to the number of potentially prognostic or effect-modifying factors, it is expected that only a small number of factors may be included in adjustments. Nevertheless, an improvement upon unmatched and unadjusted (naïve) comparisons can and should be made. Selected ITC methods are described in Section B.2.9.2.

The identified limitations in reporting in the key BeneFIX trial NCT00093171 lead to the conclusion that an ITC would be feasible but severely limited in comparison with other analyses. This is on the basis that the NCT00093171 trial did not report patient baseline characteristics for the population of interest, reported very limited baseline characteristics when they were reported, and did not provide an adequate description

of outcome definitions to ensure comparability between HOPE-B and NCT00093171. Given these limitations, a comparison between etranacogene dezaparvovec and BeneFIX is provided in an addendum of the main report.[123]

B.2.9.2 Methodology of the indirect treatment comparisons

A panel of two methodological experts was assembled to provide expertise and guidance regarding ITC methodology and analytical approaches comparing HOPE-B using IPD to comparator trials using IPD or SLD. Given that HOPE-B is a single-arm trial and comparator trials provide single-arm data, a network meta-analysis between treatments of interest is not possible. Thus, the ITC methods deemed appropriate to consider for this analysis were population-adjustment methods. Indirect comparisons of etranacogene dezaparvovec (HOPE-B) with Idelvion (PROLONG-9FP) were performed using inverse probability of treatment weighting (IPTW) methods,[124,125] while indirect comparisons of etranacogene dezaparvovec (HOPE-B) with Alprolix (B--LONG) and etranacogene dezaparvovec (HOPE--B) with Refixia (Paradigm™ 2) were performed using unanchored matching-adjusted indirect comparison (MAIC).[126]

Propensity-score based methods were favoured over outcome regression-based approaches due to more severe limitations encountered with the latter, related to modelling rare event count outcomes with small sample sizes (e.g., lack of model convergence). Importantly, simulated treatment comparisons (STCs) of count type outcomes would require simulation-based approaches to overcome aggregation bias in the relative treatment effects.[127,128] This approach would require very strong assumptions regarding the multivariate correlation between baseline covariates and time at risk (e.g., through a copula)[129] to adequately simulate the data and estimate relative treatment effects.

The statistical methods behind the chosen propensity-score based population-adjustment approaches and specifications of primary and sensitivity analyses follow the NICE guidance and Technical Support Documents (TSD) approach.[130,131]

B.2.9.3 Efficacy outcomes for base-case analysis

A total of nine efficacy outcomes were assessed in this analysis, ABR, AsBR, AjBR, % 0 ABR, % 0 AsBR, % 0 AjBR, annualised Factor IX consumption, EQ-5D, and Haem-A-QoL, with the full results and summaries available in the ITC report.[117] In this submission, we have reported on the efficacy outcomes used to inform the model, namely ABR, AjBR and the PROs EQ-5D and Haem-A-QoL, where available. AsBR was reported where available for completeness. Please see Section B.3.3 for further information on the structure and approach of the economic model.

Due to reporting limitations from the comparator trials, a change from baseline analysis was not possible for most bleeding outcomes. Therefore, absolute comparisons of bleeding outcomes were pursued, adjusting for prior ABR where possible. In contrast, a change-from-baseline analysis was favoured for the PRO endpoints over using an absolute measure and adjusting for baseline. This was because the comparator trials did not report post-treatment adjusted values for these endpoints.

2.9.3.1 Etranacogene dezaparvovec versus Idelvion

The IPTW analyses for etranacogene dezaparvovec versus Idelvion targeted the population of haemophilia B patients who had received prior prophylaxis Factor IX products. Outcomes assessed included bleeding rates (ABR, AsBR, and AjBR), percent of patients with zero bleeding events (% 0 ABR, % 0 AsBR, % 0 AjBR) and annualised Factor IX consumption.

Efficacy outcomes with etranacogene dezaparvovec, as observed in the HOPE-B trial, were compared with those from patients treated with Idelvion, as observed in the PROLONG-9FP trial. This study used an IPTW method in which patients from PROLONG-9FP were weighted to be more similar to those from HOPE-B to more fairly estimate the relative efficacy between products. As the multivariable IPTW informed the economic model, its ABR, AsBR and AjBR outcomes are described here. Outcomes, summaries and conclusions of all other ITCs, as well as those of the primary analysis, are described in the provided ITC report.[117]

2.9.3.1.1 ABR

Overall, the results of the IPTW showed statistically significantly lower ABR for etranacogene dezaparvovec versus Idelvion. The unmatched and unadjusted (naïve) ABR was lower for etranacogene dezaparvovec ([redacted]; n=[redacted]) than for Idelvion ([redacted]; n=[redacted]) (Figure 5.1). This corresponded to a statistically significant RR in favour of etranacogene dezaparvovec (RR: [redacted]; 95% CI: [redacted], [redacted]; P<[redacted]). Similarly, when patients in group 1 of PROLONG-9FP were matched to patients from HOPE-B for age, ALT threshold, and AST threshold, the RR remained significant (RR: [redacted]; 95% CI: [redacted], [redacted]; P<[redacted]). Furthermore, when additionally, univariably adjusting for each of the ranked clinical factors listed in Figure 16, etranacogene dezaparvovec continued to have a favourable ABR in comparison to Idelvion. In the multivariable IPTW analyses where factors were adjusted for sequentially (i.e., adjusting for one additional variable at a time in order of ranked importance), adjustments were made for severity of haemophilia B, prior ABR, and age. A favourable ABR for etranacogene dezaparvovec ([redacted]; n=[redacted]) in comparison to Idelvion ([redacted]; effective sample size [ESS]=[redacted]) was also reported (RR: 0.19; 95% CI: 0.09, 0.41; P<[redacted]) (Figure 17). Given that the patients from group 1 of PROLONG-9FP may have had, on average, less severe baseline disease characteristics (based on the top two ranked factors for ABR) compared to those from HOPE-B, it aligns with clinical expectations that the relative treatment effect for etranacogene dezaparvovec versus Idelvion is more favourable for etranacogene dezaparvovec after matching and adjusting with IPTW than before (naïve comparison).

Figure 16: Etranacogene dezaparvovec versus Idelvion – naïve and univariable IPTWs for ABR, matching on age, ALT threshold, AST threshold

Abbreviations: ABR, annualised bleeding rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; EHL, extended half-life; ESS, effective sample size; FIX, factor IX; HIV, human immunodeficiency virus; IPTW, inverse probability of treatment weighting; RR, rate ratio; SMD, standardised mean difference; SHL, standard half-life.
Note: Prior FIX product class refers to EHL versus SHL products; The vertical reference line represents RR=1.
Source: Eversana ITC report 2022[117]

Figure 17: Etranacogene dezaparvovec versus Idelvion - sequential and multivariable IPTWs for ABR, adjusted for prior ABR, severity of haemophilia B, and age, in that order, after matching on age, ALT threshold, and AST threshold

Abbreviations: ABR, annualised bleeding rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; ESS, effective sample size; IPTW, inverse probability of treatment weighting; RR, rate ratio; SMD, standardised mean difference.
Source: Eversana ITC report 2022[117]

2.9.3.1.2 AsBR

Overall, the results of the IPTW showed statistically significantly lower AsBR for etranacogene dezaparvovec versus Idelvion. The unmatched and unadjusted (naïve) AsBR was lower for etranacogene dezaparvovec ([redacted]; n=[redacted]) than for Idelvion ([redacted]; n=[redacted]) (Figure 18). This corresponded to a statistically significant RR in favour of etranacogene dezaparvovec (RR: [redacted]; 95% CI: [redacted]; P<[redacted]). Similarly, when patients in group 1 of PROLONG-9FP were matched to patients from HOPE-B for age, ALT threshold, and AST threshold, the RR remained significant (RR: [redacted]; 95% CI: [redacted]; P<[redacted]). Furthermore, when additionally, univariably adjusting for each of the ranked clinical factors listed in Figure 18, etranacogene dezaparvovec continued to have a statistically significantly lower AsBR in comparison to Idelvion. In the multivariable IPTW analyses where factors were adjusted for sequentially after matching (i.e. adjusting for one additional variable at a time in order of ranked importance), adjustments were made for severity of haemophilia B, prior ABR, and age. A favourable AsBR for etranacogene dezaparvovec ([redacted]; n=[redacted]) in comparison to Idelvion ([redacted]; ESS=[redacted]) was also reported (RR: 0.08; 95% CI:0.03, 0.23; P<[redacted]) (Figure 19). Given that the patients from group 1 of PROLONG-9FP may have had, on average, less severe baseline disease characteristics (based on the top two ranked factors for ABR) compared to those from HOPE-B, it aligns with clinical expectations that the relative treatment effect for etranacogene dezaparvovec versus Idelvion is more favourable for etranacogene dezaparvovec after matching and adjusting with IPTW than before (naïve comparison).

Figure 18: Etranacogene dezaparvovec versus Idelvion – naïve and univariable IPTWs for AsBR, matching on age, ALT threshold, AST threshold

Abbreviations: AsBR, annualised spontaneous bleeding rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; EHL, extended half-life; ESS, effective sample size; FIX, factor IX; HIV, human immunodeficiency virus; IPTW, inverse probability of treatment weighting; RR, rate ratio; SMD, standardised mean difference; SHL, standard half-life.
Note: Prior FIX product class refers to EHL versus SHL products; The vertical reference line represents RR = 1.
Source: Eversana ITC report 2022[117]

Figure 19: Etranacogene dezaparvovec versus Idelvion – sequential and multivariable IPTWs for AsBR, adjusted for prior ABR, severity of haemophilia B, and age, in that order, after matching on age, ALT threshold, and AST threshold

Abbreviations: AsBR, annualised spontaneous bleeding rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; ESS, effective sample size; IPTW, inverse probability of treatment weighting; RR, rate ratio; SMD, standardised mean difference.
Note: The vertical reference line represents RR = 1.
Source: Eversana ITC report 2022[117]

2.9.3.1.3 AjBR

Overall, the results of the IPTW showed statistically significantly lower AjBR for etranacogene dezaparvovec versus Idelvion. The unmatched and unadjusted (naïve) AjBR was lower for etranacogene dezaparvovec ([redacted]; n=[redacted]) than for Idelvion ([redacted]; n=[redacted]) (Figure 20). This corresponded to a statistically significant RR in favour of etranacogene dezaparvovec (RR: [redacted]; 95% CI: [redacted]; P<[redacted]). Similarly, when patients in group 1 of PROLONG-9FP were matched to patients from HOPE-B for age, ALT threshold, and AST threshold, the RR remained significant (RR: [redacted]; 95% CI: [redacted]; P<[redacted]). Furthermore, when additionally, univariably adjusting for each of the ranked clinical factors listed in Figure 20, etranacogene dezaparvovec continued to have a statistically significantly lower AjBR in comparison to Idelvion. In the multivariable IPTW analyses where factors were adjusted for sequentially (i.e., adjusting for one additional variable at a time in order of ranked importance), adjustments were made for severity of haemophilia B, prior ABR, and age. A favourable AjBR for etranacogene dezaparvovec ([redacted]; n=[redacted]) in comparison to Idelvion ([redacted]; ESS=[redacted]) was also reported (RR: 0.09; 95% CI: 0.03, 0.25; P<[redacted]) (Figure 21). Given that the patients from group 1 of PROLONG-9FP may have had, on average, less severe baseline disease characteristics (based on the top two ranked factors for ABR) compared to those from HOPE-B, it aligns with clinical expectations that the relative treatment effect for etranacogene dezaparvovec versus Idelvion is more favourable for etranacogene dezaparvovec after matching and adjusting with IPTW than before (naïve comparison).

Figure 20: Etranacogene dezaparvovec versus Idelvion – naïve and univariable IPTWs for AjBR, matching on age, ALT threshold, AST threshold

Abbreviations: AjBR, annualised joint bleeding rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; EHL, extended half-life; ESS, effective sample size; FIX, factor IX; HIV, human immunodeficiency virus; IPTW, inverse probability of treatment weighting; RR, rate ratio; SMD, standardised mean difference; SHL, standard half-life.
Note: Prior FIX product class refers to EHL versus SHL products; The vertical reference line represents RR = 1.
Source: Eversana ITC report 2022[117]

Figure 21: Etranacogene dezaparvovec versus Idelvion – sequential and multivariable IPTWs for AjBR, adjusted for prior ABR, severity of haemophilia B, and age, in that order, after matching on age, ALT threshold, and AST threshold

Abbreviations: AjBR, annualised joint bleeding rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; ESS, effective sample size; IPTW, inverse probability of treatment weighting; RR, rate ratio; SMD, standardised mean difference.
Note: The vertical reference line represents RR = 1.
Source: Eversana ITC report 2022[117]

2.9.3.2 Etranacogene dezaparvovec versus Alprolix

Matching-adjusted indirect comparisons for etranacogene dezaparvovec versus Alprolix were split by B-LONG trial population. The primary analysis compared HOPE-B to the subgroup of patients from group 1 of B-LONG, who received pre-study prophylaxis and assessed ABR and Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) total score change from baseline. The secondary analysis compared HOPE-B to the full population from group 1 of B-LONG and assessed ABR, AsBR, AjBR, % 0 ABR, % 0 AsBR%, 0 AjBR, total annualised Factor IX consumption (excluding surgical Factor IX consumption), and Haem-A-QoL total score change from baseline. As the secondary analysis informed the economic model, its ABR, AsBR, AjBR and Haem-A-QoL outcomes are described here. Outcomes, summaries and conclusions of all other ITCs, as well as those of the primary analysis, are described in the provided ITC report.[117]

2.9.3.2.1 ABR

Overall, the results of the MAIC showed statistically significantly lower ABR for etranacogene dezaparvovec versus Alprolix. The unmatched and unadjusted (naïve) ABR was lower for etranacogene dezaparvovec ([redacted]; n=[redacted]) than for Alprolix ([redacted]; n=[redacted]) (Figure 22). This corresponded to a statistically significant RR in favour of etranacogene dezaparvovec (RR: [redacted]; 95% CI: [redacted]; p<[redacted]). Furthermore, when additionally, univariably adjusting for each of the ranked clinical factors listed in Figure 22, etranacogene dezaparvovec continued to have a favourable ABR in comparison to Alprolix. In the multivariable MAIC analyses where factors were adjusted for sequentially (i.e. adjusting for one additional variable at a time in order of ranked importance), adjustments were made for severity of haemophilia B, age, and BMI. A favourable ABR for etranacogene dezaparvovec ([redacted]; ESS=[redacted]) in comparison to Alprolix ([redacted]; n=[redacted]) was also reported (RR: 0.19; 95% CI: 0.08, 0.44; p=[redacted]) (Figure 23).

Figure 22. Etranacogene dezaparvovec versus Alprolix secondary analysis for ABR – naïve results and univariable MAICs

Note: The vertical reference line represents RR=1.
Abbreviations: ABR, annualised bleeding rate; BMI, body mass index; CI, confidence interval; ESS, effective sample size; HIV, human immunodeficiency virus; MAIC, matching-adjusted indirect comparison; RR, rate ratio; SMD, standardised mean difference.
Source: Eversana ITC report 2022[117]

Figure 23. Etranacogene dezaparvovec versus Alprolix secondary analysis for ABR – sequential and multivariable MAICs adjusted for severity of haemophilia B, age, and BMI, in that order

Note: The vertical reference line represents RR=1.
Abbreviations: ABR, annualised bleeding rate; BMI, body mass index; CI, confidence interval; ESS, effective sample size; MAIC, matching-adjusted indirect comparison; RR, rate ratio; SMD, standardised mean difference.
Source: Eversana ITC report 2022[117]

2.9.3.2.2 AsBR

Overall, the results of the MAIC showed statistically significantly lower AsBR for etranacogene dezaparvovec versus Alprolix. The unmatched and unadjusted (naïve) AsBR was lower for etranacogene dezaparvovec ([redacted]; n=[redacted]) than for Alprolix ([redacted]; n=[redacted]) (Figure 24). This corresponded to a statistically significant RR in favour of etranacogene dezaparvovec (RR: [redacted]; 95% CI: [redacted]; P<[redacted]). Furthermore, when additionally, univariably adjusting for each of the ranked clinical factors listed in Figure 24, etranacogene dezaparvovec continued to have a statistically significant and favorable RR in comparison to Alprolix. In the multivariable MAIC analyses where factors were adjusted for sequentially (i.e. adjusting for one additional variable at a time in order of ranked importance), adjustments were made for severity of haemophilia B, age, and BMI. A favourable AsBR for etranacogene dezaparvovec ([redacted]; ESS=[redacted]) in comparison to Alprolix ([redacted]; n=[redacted]) was also reported (RR: 0.13; 95% CI: 0.03, 0.59; p=[redacted]) (Figure 25).

Figure 24. Etranacogene dezaparvovec versus Alprolix secondary analysis for AsBR – naïve results univariable MAICs

[redacted]

Note: The vertical reference line represents RR=1.
Abbreviations: AsBR, annualised spontaneous bleeding rate; BMI, body mass index; CI, confidence interval; ESS, effective sample size; HIV, human immunodeficiency virus; MAIC, matching-adjusted indirect comparison; RR, rate ratio; SMD, standardised mean difference.
Source: Eversana ITC report 2022[117]

Figure 25. Etranacogene dezaparvovec versus Alprolix secondary analysis for AsBR – sequential and multivariable MAICs adjusted for severity of haemophilia B, age, and BMI, in that order

Note: The vertical reference line represents RR=1.
Abbreviations: AsBR, annualised spontaneous bleeding rate; BMI, body mass index; CI, confidence interval; ESS, effective sample size; MAIC, matching-adjusted indirect comparison; RR, rate ratio; SMD, standardised mean difference.
Source: Eversana ITC report 2022[117]

2.9.3.2.3 AjBR

Overall, the results of the MAIC showed statistically significantly lower AjBR for etranacogene dezaparvovec versus Alprolix. The unmatched and unadjusted (naïve) AjBR was lower for etranacogene dezaparvovec ([redacted]; n=[redacted]) than for Alprolix ([redacted]; n=[redacted]) (Figure 26). This corresponded to a statistically significant RR in favour of etranacogene dezaparvovec (RR: [redacted]; 95% CI: [redacted]; p≤[redacted]). Furthermore, when additionally, univariably adjusting for each of the ranked clinical factors listed in Figure 26, etranacogene dezaparvovec continued to have a statistically significant and favourable RR in comparison to Alprolix. In the multivariable MAIC analyses where factors were adjusted for sequentially (i.e. adjusting for one additional variable at a time in order of ranked importance), adjustments were made for severity of haemophilia B, age, and BMI. A favourable AjBR for etranacogene dezaparvovec ([redacted]; ESS=[redacted]) in comparison to Alprolix ([redacted]; n=[redacted]) was also reported (RR: 0.15; 95% CI: 0.03, 0.65; p=[redacted]) (Figure 27).

Figure 26. Etranacogene dezaparvovec versus Alprolix secondary analysis for AjBR – naïve results and univariable MAICs

Note: The vertical reference line represents RR=1.
Abbreviations: AjBR, annualised joint bleeding rate; BMI, body mass index; CI, confidence interval; ESS, effective sample size; HIV, human immunodeficiency virus; MAIC, matching-adjusted indirect comparison; RR, rate ratio; SMD, standardised mean difference.
Source: Eversana ITC report 2022[117]

Figure 27. Etranacogene dezaparvovec versus Alprolix secondary analysis for AjBR – sequential and multivariable MAICs adjusted for severity of haemophilia B, age, and BMI, in that order

Note: The vertical reference line represents RR=1.
Abbreviations: AjBR, annualised joint bleeding rate; BMI, body mass index; CI, confidence interval; ESS, effective sample size; MAIC, matching-adjusted indirect comparison; RR, rate ratio; SMD, standardised mean difference.
Source: Eversana ITC report 2022[117]

2.9.3.2.4 Haem-A-QoL

Overall, the results of the MAIC showed a favourable Haem-A-QoL total score change from baseline for etranacogene dezaparvovec versus Alprolix, but no statistically

significant differences were detected. The unmatched and unadjusted (naïve) mean Haem-A-QoL total score change from baseline was lower for etranacogene dezaparvovec ([redacted]; n=[redacted]) than for Alprolix ([redacted]; n=[redacted]) (Figure 28). This corresponded to a difference in means (MD) in favour of etranacogene dezaparvovec (MD: [redacted]; 95% CI: [redacted]; P=[redacted]), however this result was not statistically significant. Furthermore, when additionally, univariably adjusting for each of the ranked clinical factors listed in Figure 28, etranacogene dezaparvovec continued to have a favourable, yet not statistically significant, Haem-A-QoL total score change from baseline in comparison to Alprolix. In the multivariable MAIC analyses where factors were adjusted for sequentially (i.e. adjusting for one additional variable at a time in order of ranked importance), adjustments were made for severity of haemophilia B, age, and BMI. A favourable Haem-A-QoL total score change from baseline for etranacogene dezaparvovec ([redacted]; ESS=[redacted]) in comparison to Alprolix ([redacted]; n=[redacted]) was reported (MD: [redacted]; 95% CI: [redacted], [redacted]; p=[redacted]), however these results were not statistically significant (Figure 29).

Figure 28. Etranacogene dezaparvovec versus Alprolix secondary analysis for Haem-A-QoL change from baseline - naïve results and univariable MAICs

Note: The vertical reference line represents MD=0.
Abbreviations: BMI, body mass index; CI, confidence interval; ESS, effective sample size; HIV, human immunodeficiency virus; MAIC, matching-adjusted indirect comparison; MD, mean difference; SMD, standardixed mean difference.
Source: Eversana ITC report 2022[117]

Figure 29. Etranacogene dezaparvovec versus Alprolix secondary analysis for Haem-A-QoL change from baseline – sequential and multivariable MAICs adjusted for severity of haemophilia B, age, and BMI, in that order

Note: The vertical reference line represents MD=0.
Abbreviations: BMI, body mass index; CI, confidence interval; ESS, effective sample size; MAIC, matching-adjusted indirect comparison; MD, mean difference; SMD, standardised mean difference.
Source: Eversana ITC report 2022[117]

2.9.3.3 Etranacogene dezaparvovec versus Refixia

Matching-adjusted indirect comparisons for etranacogene dezaparvovec versus Refixia were split by Paradigm™ 2 trial population. The primary analysis compared HOPE-B to the subgroup of patients from the 40 IU/kg weekly prophylaxis group of Paradigm™ 2 who received pre-study prophylaxis and assessed ABR. The secondary analysis compared HOPE-B to the full population from the 40 IU/kg weekly prophylaxis group of Paradigm™ 2 and assessed ABR, AsBR, % 0 ABR, EuroQol-5 Dimension (EQ-5D) utility score change from baseline, and Haem-A-QoL total score change from baseline. As the secondary analysis informed the economic model, its ABR, AsBR, EQ-5D and Haem-A-QoL outcomes are described here. Outcomes, summaries and conclusions of all other ITCs, as well as those of the primary analysis, are described in the provided ITC report.[117]

2.9.3.3.1 ABR

Overall, the results of the MAIC showed statistically significantly lower ABR for etranacogene dezaparvovec versus Refixia. The unmatched and unadjusted (naïve) ABR was lower for etranacogene dezaparvovec ([redacted]; n=[redacted]) than for Refixia ([redacted]; n=[redacted]) (Figure 30). This corresponded to a statistically significant RR in favour of etranacogene dezaparvovec (RR: [redacted]; 95% CI: [redacted]; p<[redacted]). Furthermore, when additionally, univariably adjusting for each of the ranked clinical

factors listed in Figure 30, etranacogene dezaparvovec continued to have a favourable ABR in comparison to Refixia. In the multivariable MAIC analyses where factors were adjusted for sequentially (i.e. adjusting for one additional variable at a time in order of ranked importance), adjustments were made for severity of haemophilia B and age. A favourable ABR for etranacogene dezaparvovec ([redacted]; ESS=[redacted]) in comparison to Refixia ([redacted]; n=[redacted]) was also reported (RR: 0.30; 95% CI: 0.10, 0.94; p=[redacted]) (Figure 31).

Figure 30. Etranacogene dezaparvovec versus Refixia secondary analysis for ABR – naïve results and univariable MAICs

Note: Prior FIX product class refers to EHL versus SHL products; The vertical reference line represents RR=1.
Abbreviations: ABR, annualised bleeding rate; BMI, body mass index; CI, confidence interval; EHL, extended half-life; ESS, effective sample size; FIX, Factor IX; HIV, human immunodeficiency virus; MAIC, matching-adjusted indirect comparison; RR, rate ratio; SMD, standardised mean difference; SHL, standard half-life.
Source: Eversana ITC report 2022[117]

Figure 31. Etranacogene dezaparvovec versus Refixia secondary analysis for ABR – sequential and multivariable MAICs adjusted for severity of haemophilia B and age, in that order

Note: The vertical reference line represents RR=1.
Abbreviations: ABR, annualised bleeding rate; CI, confidence interval; ESS, effective sample size; MAIC, matching-adjusted indirect comparison; RR, rate ratio; SMD, standardised mean difference.
Source: Eversana ITC report 2022[117]

2.9.3.3.2 AsBR

Overall, the results of the MAIC showed statistically significantly lower AsBR for etranacogene dezaparvovec versus Refixia. The unmatched and unadjusted (naïve) AsBR was lower for etranacogene dezaparvovec ([redacted]; n=[redacted]) than for Refixia ([redacted]; n=[redacted]) (Figure 32). This corresponded to a statistically significant RR in favour of etranacogene dezaparvovec (RR: [redacted]; 95% CI: [redacted]; p<[redacted]). Furthermore, when additionally, univariably adjusting for each of the ranked clinical factors listed in Figure 32, etranacogene dezaparvovec continued to have a favourable RR in comparison to Refixia. In the multivariable MAIC analyses where factors were adjusted for sequentially (i.e. adjusting for one additional variable at a time in order of ranked importance), adjustments were made for severity of haemophilia B and age. A statistically significant and favourable AsBR for etranacogene dezaparvovec ([redacted]; ESS=[redacted]) in comparison to Refixia ([redacted]; n=[redacted]) was also reported (RR: 0.13; 95% CI: 0.03, 0.57; p=[redacted] (Figure 33).

Figure 32. Etranacogene dezaparvovec versus Refixia secondary analysis for AsBR – naïve results and univariable MAICs

Note: Prior Factor IX product class refers to EHL versus SHL products; The vertical reference line represents RR=1.
Abbreviations: AsBR, annualised spontaneous bleeding rate; BMI, body mass index; CI, confidence interval; EHL, extended half-life; ESS, effective sample size; FIX, Factor IX; HIV, human immunodeficiency virus; MAIC, matching-adjusted indirect comparison; RR, rate ratio; SMD, standardised mean difference; SHL, standard half-life.
Source: Eversana ITC report 2022[117]

Figure 33. Etranacogene dezaparvovec versus Refixia secondary analysis for AsBR – sequential and multivariable MAICs adjusted for severity of haemophilia B and age, in that order

Note: The vertical reference line represents RR=1.
Abbreviations: AsBR, annualised spontaneous bleeding rate; CI, confidence interval; ESS, effective sample size; MAIC, matching-adjusted indirect comparison; RR, rate ratio; SMD, standardised mean difference.
Source: Eversana ITC report 2022[117]

2.9.3.3.3 EQ-5D

Overall, the results of the MAIC showed a higher mean EQ-5D utility score change from baseline for etranacogene dezaparvovec versus Refixia. The unmatched and unadjusted (naïve) mean EQ-5D utility score change from baseline was higher for etranacogene dezaparvovec ([redacted]; n=[redacted]) than for Refixia ([redacted]; n=[redacted]) (Figure 34). This corresponded to a difference in means (MD) in favour of etranacogene dezaparvovec (MD: [redacted]; 95% CI: [redacted]; p=[redacted]), however these results were not statistically significant. Furthermore, when additionally, univariably adjusting for each of the ranked clinical factors listed in Figure 34, etranacogene dezaparvovec continued to have a favourable, yet not statistically significant, higher mean EQ-5D utility score change from baseline change from baseline in comparison to Refixia except when adjusting for prior presence of target joints. In the multivariable MAIC analyses where factors were adjusted for sequentially (i.e. adjusting for one additional variable at a time in order of ranked importance), adjustments were made for severity of haemophilia B and age. A favourable mean EQ-5D utility score change from baseline for etranacogene dezaparvovec ([redacted]; ESS=[redacted]) in comparison to Refixia ([redacted]; n=[redacted]) was estimated (MD: [redacted]; 95% CI: [redacted]; p=[redacted]), and again these results were not statistically significant (Figure 35).

Figure 34. Etranacogene dezaparvovec versus Refixia secondary analysis for EQ-5D utility score, change from baseline – naïve results and univariable MAICs

Note: Prior FIX product class refers to EHL versus SHL products; The vertical reference line represents MD=0.
Abbreviations: BMI, body mass index; CI, confidence interval; EHL, extended half-life; ESS, effective sample size; FIX, Factor IX; HIV, human immunodeficiency virus; MAIC, matching-adjusted indirect comparison; OR, odds ratio; SMD, standardised mean difference; SHL, standard half-life.
Source: Eversana ITC report 2022[117]

Figure 35. Etranacogene dezaparvovec versus Refixia secondary analysis for EQ-5D utility score, change from baseline – sequential and multivariable MAICs adjusted for severity of haemophilia B and age, in that order

Note: The vertical reference line represents MD=0.
Abbreviations: CI, confidence interval; ESS, effective sample size; MAIC, matching-adjusted indirect comparison; MD, mean difference; SMD, standardised mean difference.
Source: Eversana ITC report 2022[117]

2.9.3.3.4 Haem-A-QoL

The unmatched and unadjusted (naïve) mean Haem-A-QoL total score change from baseline was higher for etranacogene dezaparvovec ([redacted]; n=[redacted]) than for Refixia [redacted]; n=[redacted]) (Figure 36). This corresponded to a difference in means (MD) in favour of Refixia (MD: [redacted]; 95% CI: [redacted]; p=[redacted]), however these results were not statistically significant. Furthermore, when additionally, univariably adjusting for each of the ranked clinical factors listed in Figure 36, Refixia continued to have a favourable (except when adjusting for BMI, weight, race and HIV status), yet not statistically significant, mean Haem-A-QoL total score change from baseline in comparison to etranacogene dezaparvovec. In the multivariable MAIC analyses where factors were adjusted for sequentially (i.e., adjusting for one additional variable at a time in order of ranked importance), adjustments were made for severity of haemophilia B and age. A favourable mean Haem-A-QoL total score change from baseline for etranacogene dezaparvovec ([redacted]; ESS=[redacted]) in comparison to Refixia ([redacted]; n=[redacted]) was reported (MD: [redacted]; 95% CI: [redacted]; p=[redacted]), and again these results were not statistically significant (Figure 37).

Figure 36. Etranacogene dezaparvovec versus Refixia secondary analysis for Haem-A-QoL total score, change from baseline – naïve results and univariable MAICs

Note: Prior FIX product class refers to EHL versus SHL products; The vertical reference line represents MD=0.
Abbreviations: BMI, body mass index; CI, confidence interval; EHL, extended half-life; ESS, effective sample size; FIX, Factor IX; HIV, human immunodeficiency virus; MAIC, matching-adjusted indirect comparison; OR, odds ratio; SMD, standardised mean difference; SHL, standard half-life.
Source: Eversana ITC report 2022[117]

Figure 37. Etranacogene dezaparvovec versus Refixia secondary analysis for Haem-A-QoL total score, change from baseline – sequential and multivariable MAICs adjusted for severity of haemophilia B and age, in that order

Note: The vertical reference line represents MD=0.
Abbreviations: CI, confidence interval; ESS, effective sample size; MAIC, matching-adjusted indirect comparison; MD, mean difference; SMD, standardised mean difference.
Source: Eversana ITC report 2022[117]

2.9.3.4 Etranacogene dezaparvovec versus BeneFIX

This analysis of indirectly comparing etranacogene dezaparvovec to BeneFIX was performed through two sources of evidence: population-adjustment ITCs (MAICs) and a HOPE-B pre-post analysis restricted to patients on BeneFIX during the lead-in periods.

The MAICs leveraged the best available data from pivotal Phase III trials HOPE-B for etranacogene dezaparvovec and NCT00093171 for BeneFIX to adjust for the most important prognostic or treatment effect modifying factors as was feasible. As the MAICs were not used to inform the economic model, they will not be reported in this submission but they are available in full in the provided ITC report addendum.[123] A total of three efficacy outcomes were assessed in this MAIC analysis (ABR, AsBR and % 0 ABR) which found etranacogene dezaparvovec was to be statistically superior to BeneFIX for ABR outcomes.[123] Additionally, the MAIC found that etranacogene dezaparvovec was favoured without statistical significance for AsBR and % 0 ABR.[123]

Additionally, a HOPE-B pre-post analysis was conducted, restricted to the 19 patients from HOPE-B who were on BeneFIX at lead-in. The analysis was based on the 24-month data-cut only, focusing on bleeding rate outcomes only (ABR, AsBR, and AjBR) due to limited data reported for NCT0093171. This analysis was done by comparing outcomes from the 6-month lead-in phase of the HOPE-B trial to those during the 7–24 Months post-treatment period. The analysis was performed equivalently to that for the primary endpoint analysis of HOPE-B, using the exact statistical methods, but just restricted to those patients who were on BeneFIX at lead-in.

In contrast to the uncertainty around outcome definition alignment between HOPE-B and NCT0093171 behind the ITC analyses, outcome definitions within the pre-post analysis with HOPE-B are guaranteed to be the same when comparing etranacogene dezaparvovec (post-treatment) to BeneFIX (from lead-in). Overall, given the limitations, and the fact that a similar number of patients were available in the pre-post analysis ([redacted] patients) as in the key clinical trial ([redacted] patients), which was not true for any of the other therapies, the pre-post analysis based on the subgroup of patients from HOPE-B trial that received BeneFIX during the lead-in period is likely a preferable

source of comparative efficacy and was used to inform the economic model (Section B.3).The results for the pre-post analysis are reported here.

2.9.3.4.1 ABR

The results of the pre-post comparison showed a favourable and statistically significant ABR for etranacogene dezaparvovec for sensitivity analysis 6 definition (new-and-true and treated bleeds only; the same as the chosen base case for ITCs) of counting bleeds (RR: [redacted]; 95% CI: [redacted]; p<[redacted]) and primary endpoint definition (any bleeds; the same as the sensitivity analysis for ITCs) of counting bleeds (RR: [redacted]; 95% CI: [redacted]; p<[redacted]) (Table 18).

Table 18. Etranacogene dezaparvovec versus BeneFIX –results from HOPE-B pre-post analysis restricted to patients on BeneFIX at lead-in, ABR

Analysis	N (%)	Estimate (RR)	Estimate 95% CI	Estimate p-value
Sensitivity analysis 6	[redacted]	[redacted]	[redacted]	[redacted]
Primary endpoint definition				

Abbreviations: ABR, annualised bleeding rate; RR, rate ratio; CI, confidence interval
Source: Eversana ITC report addendum 2022[123]

2.9.3.4.2 AsBR

The results of the pre-post comparison showed a favourable and statistically significant AsBR for etranacogene dezaparvovec with the primary endpoint definition from HOPE-B trial (RR: [redacted]; 95% CI: [redacted]; p<[redacted]) (Table 19).

Table 19. Etranacogene dezaparvovec versus BeneFIX – results from HOPE-B pre-post analysis restricted to patients on BeneFIX at lead-in, AsBR

Analysis	N (%)	Estimate (RR)	Estimate 95% CI	Estimate p-value
Primary endpoint definition	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AsBR, annualised spontaneous bleeding rate; RR, rate ratio; CI, confidence interval
Source: Eversana ITC report addendum 2022[123]

2.9.3.4.3 AjBR

The results of the pre-post comparison showed a favourable and statistically significant AjBR for etranacogene dezaparvovec with primary endpoint definition from HOPE-B trial (RR: [redacted]; 95% CI: [redacted]; P < [redacted]) (Table 20).

Table 20. Etranacogene dezaparvovec versus BeneFIX – results from HOPE-B pre-post analysis restricted to patients on BeneFIX at lead-in, AjBR

Analysis	N (%)	Estimate (RR)	Estimate 95% CI	Estimate p-value
Primary endpoint definition	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AjBR, annualised joint bleeding rate; RR, rate ratio; CI, confidence interval
Source: Eversana ITC report addendum 2022[123]

B.2.9.4 Conclusion of ITCs

Overall, after matching and adjusting for a few important clinical factors and treatment-effect modifiers available, etranacogene dezaparvovec had a statistically significantly lower ABR, AsBR, and AjBR compared to Idelvion and Alprolix; and a statistically significantly lower ABR and AsBR compared to Refixia (Refixia trial did not report on AjBR). No statistically significant differences in Haem-A-QoL total score change from baseline and EQ-5D utility score change from baseline were found between etranacogene dezaparvovec and Alprolix or Refixia based on available data. Moreover, the pre-post analysis of etranacogene dezaparvovec versus BeneFIX found that etranacogene dezaparvovec was statistically significantly superior to BeneFIX for ABR, AsBR and AjBR.

Overall, these analyses suggest that patients who receive etranacogene dezaparvovec have fewer bleeds than patients on replacement Factor IX therapy, regardless of which specific type of replacement Factor IX therapy is utilised. Based on these study findings, keeping in mind the limitations of unanchored, non-randomised design with small sample sizes, etranacogene dezaparvovec could confer a large benefit over comparators for patients with moderately severe or severe haemophilia B.

Unanchored, small-sample size indirect comparisons are broadly considered a weaker form of evidence than direct comparisons involving blinded or randomised trial designs [131]. Comparison of ITC results to those from other study designs is therefore important. The relative treatment effects from these ITCs were aligned with the those from the published, 1 year analysis between lead-in and post-treatment designed within HOPE-B [132]. Though patients in the lead-in period for HOPE-B were taking different Factor IX products for prophylaxis, and the published HOPE-B analysis used the first year of the post-treatment period for etranacogene dezaparvovec (which included the first 6 months post-treatment), the concordance between results and conclusions from the published pre-post HOPE-B analysis and those from these ITCs strengthens the evidence base comparing etranacogene dezaparvovec to Factor IX replacement therapies. Please refer to the full ITC report (provided in the reference pack of this submission) for the full discussion of strengths and limitations of the analysis.[117,123]

B.2.10 Adverse reactions

- Etranacogene dezaparvovec was well-tolerated. There were no treatment-related serious adverse events (SAEs).
- One subject discontinued study drug infusion due to an event of hypersensitivity.
- Throughout the HOPE-B study, one death was reported and assessed as not treatment-related
- Transaminase elevations occurred; however, all occurrences were resolved and Factor IX activity was preserved in the mild or non-haemophilic range.
- The treatment-emergent AE (TEAE) and SAE profile was comparable between subjects who were positive or negative for baseline anti-AAV5 NAbs, with infusion-related reactions more prevalent in those who were positive.
- There were 557 TEAEs in 54 (100.0%) subjects during the 24-month post-treatment period, of which 93 events in 38/54 (70.4%) subjects were treatment-related. The majority ([redacted] events) of treatment-related TEAEs were mild or moderate in severity and the most common were ALT increased (16.7%), headache (14.8%), and influenza-like illness (13.0%).
- There were 7 TEAEs of special notification related to IMP administration, including infusion-related reactions, or hypersensitivity. Infusion-related reactions were more prevalent in subjects with pre-existing anti-AAV5 NAbs at baseline compared to those without.
- A total of [redacted] SAEs were experienced by [redacted] subjects, [redacted] of which occurred in the 24-month post-treatment period. The [redacted] other SAEs occurred before treatment. Of the [redacted] SAEs in the post-treatment period, [redacted] were mild or moderate in severity and [redacted] were severe, and all were assessed as not treatment-related.
- One subject (1/54 [1.9%]) was positive for anti-Factor IX antibodies at baseline and throughout the study up to Month 6. Factor IX inhibitor levels were <LOD for all subjects.
- Overall, 21/54 (38.9%) subjects had pre-existing NAbs against AAV5 at baseline. All subjects developed a humoral immune response to AAV5 within 3 weeks of treatment and anti-AAV5 NAb titres [redacted] through to Month 24 post-treatment.
- Levels of inflammatory markers were generally unaffected by treatment with etranacogene dezaparvovec. Initial elevations were noted with IL-2 and IFNγ levels, however this was followed with a return to pre-treatment levels.

B.2.10.1 Extent of exposure

Of the 54 subjects enrolled to receive etranacogene dezaparvovec, 53 subjects received a single full dose of 2×10^{13} GC/kg.[14] One subject received a reduced dose (approximately 10% of the expected dose) before treatment was withdrawn due to a TEAE of hypersensitivity that occurred during infusion. Subjects have been followed for at least 2 years post-treatment; [redacted] have reached the Month 30 visit with [redacted] also reaching the Month 36 visit.[14]

B.2.10.2 Brief overview of adverse events

During the 24-Month post-treatment period, all 54 treated subjects experienced a TEAE, for a total of 557 TEAEs (Table 21).[14] One subject experienced an event of cardiogenic shock preceded by a bacterial urinary tract infection that resulted in death in the post-treatment period; this event was assessed as not treatment-related. One TEAE of hypersensitivity led to premature treatment infusion discontinuation. The majority (424/557 events) of TEAEs during the post-treatment period were assessed as mild (Table 21). Treatment-related TEAEs were experienced by 38/54 (70.4%) subjects (93 events). There were 12/54 (22.2%) subjects with 19 TEAEs of special notification reported in the post-treatment period; all reported in the first 18 Months post-treatment. Serious AEs were experienced by 14/54 (25.9%) subjects for a total of 17 SAEs (increase of [redacted] SAEs between the 18- and 24-Month post-treatment analyses; there were no SAEs considered treatment-related.[14]

During the ≥6-month lead-in period, during which subjects were treated with routine prophylaxis treatments, 42/67 (62.7%) subjects experienced 103 AEs and [redacted] ([redacted]%) subjects experienced [redacted] SAEs (Table 21).[14] The majority of AEs (78/103 AEs) were assessed as mild in severity. The lead-in period was completed by 54 subjects and 37/54 (68.5%) subjects in this group experienced 87 of the AEs during the lead-in period ([redacted] of which were mild). Of the [redacted] subjects with SAEs, [redacted] subjects completed the lead-in period. There were no subjects who experienced an AE of special notification or who discontinued prematurely due to an AE during the lead-in period, and there were no deaths.[14]

Table 21. Overview of adverse events (Safety Population)

	Lead-in period (including lead-in discontinuers) (n=67)		Lead-in period (excluding lead-in discontinuers) (n=54)		Post-treatment period (n=54)	
	n (%)	Number of events	n (%)	Number of events	n (%)	Number of events
At least one AE	42 (62.7)	103	37 (68.5)	87	54 (100.0)	557
Mild AE	[redacted]	78	[redacted]	[redacted]	54 (100.0)	424
Moderate AE	[redacted]	[redacted]	[redacted]	[redacted]	37 (68.5)	115
Severe AE	[redacted]	[redacted]	[redacted]	[redacted]	11 (20.4)	18
AEs related to study treatment	[redacted]		[redacted]		38 (70.4)	93
AEs of special notification	0		0		12 (22.2)	19
AEs leading to premature treatment discontinuation	0		0		1 (1.9)	1
Serious AEs	[redacted]	[redacted]	[redacted]	[redacted]	14 (25.9)	17
Serious AEs related to study treatment	0		0		0	
Deaths – all causes	0		0		1 (1.9)	1

Abbreviations: AE, adverse event; n, number.
Source: 24-Month CSR, CSL Behring.[14]

B.2.10.3 Analysis of adverse events

A summary of AEs with an incidence of ≥5% in any population is presented in Table 22 by System Organ Class (SOC) and preferred term.[14]

During the post-treatment period, all 54 treated subjects experienced a TEAE, for a total of 557 TEAEs (Table 22).[14] The SOCs with the highest incidence of reported TEAEs were infections and infestations ([redacted]%), musculoskeletal and connective tissue disorders ([redacted]%), general disorders and administration site conditions ([redacted]%), gastrointestinal disorders ([redacted]%), and injury, poisoning and procedural complications ([redacted], Table 22). The most commonly reported TEAEs were arthralgia (35.2%), headache (29.6%), nasopharyngitis (27.8%), fatigue (25.9%), and ALT increased (20.4%). There were 6/54 subjects who experienced 11 TEAEs in the neoplasms benign, malignant and unspecified (incl. cysts and polyps) SOC, which

were all assessed to be non-treatment related. TEAEs in neoplasm SOCs included adenoma benign, basal cell carcinoma, benign breast neoplasm, colon adenoma, gastrointestinal lymphoma, gastrointestinal neoplasm, hepatocellular carcinoma (HCC), meningioma, pancreatic neuroendocrine tumour, prostate cancer, and skin papilloma. The TEAEs of basal cell carcinoma, HCC, and prostate cancer were TEAEs of special notification and will be further discussed in Section 2.10.3.5.[14]

During the ≥6-month lead-in period, [redacted] ([redacted]%) subjects experienced at least 1 AE while on routine prophylaxis therapy (Table 22).[14] The SOCs with the highest incidence of reported AEs were infections and infestations ([redacted]%); musculoskeletal and connective tissue disorders ([redacted]%); respiratory, thoracic, and mediastinal disorders and gastrointestinal disorders ([redacted]% each). The most commonly reported AE was nasopharyngitis ([redacted]%; Table 22).[14]

Table 22. Overall summary of AEs with incidence of ≥5% by System Organ Class and preferred term (Safety Population)

System Organ Class Preferred Term	Lead-in Period (Including Lead-in Discontinuers) (n=67)		Lead-in Period (Excluding Lead-in Discontinuers) (n=54)		Post-treatment Period (n=54)	
	n (%)	# of events	n (%)	# of events	n (%)	# of events
At least 1 AE	[redacted]	[redacted]	37 (68.5)	87	54 (100.0)	557
Infections and Infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	8 (14.8)	8	15 (27.8)	[redacted]
COVID-19	[redacted]		[redacted]		10 (18.5)	10
Cystitis	[redacted]	[redacted]	2 (3.7)	2	3 (5.6)	4
Influenza	[redacted]		[redacted]		3 (5.6)	3
Upper Respiratory Tract Infection	[redacted]	[redacted]	2 (3.7)	2	3 (5.6)	3
Musculoskeletal and Connective Tissue Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	4 (7.4)	4	19 (35.2)	34
Back Pain	[redacted]	[redacted]	[redacted]	[redacted]	9 (16.7)	12
Pain in Extremity	[redacted]	[redacted]	[redacted]	[redacted]	9 (16.7)	10
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]	4 (7.4)	4

Arthritis	[redacted]	[redacted]	[redacted]	[redacted]	3 (5.6)	3
Musculoskeletal Chest Pain	[redacted]	[redacted]	[redacted]	[redacted]	3 (5.6)	3
General Disorders and Administration Site Conditions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	14 (25.9)	17
Influenza-like Illness	[redacted]	[redacted]	[redacted]	[redacted]	7 (13.0)	12
Malaise	[redacted]	[redacted]	[redacted]	[redacted]	5 (9.3)	7
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	4 (7.4)	5
Chest Pain	[redacted]	[redacted]	[redacted]	[redacted]	4 (7.4)	4
Pain	[redacted]	[redacted]	1 (1.9)	1	4 (7.4)	4
Chills	[redacted]	[redacted]	[redacted]	[redacted]	3 (5.6)	3
Gastrointestinal Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Toothache	[redacted]	[redacted]	2 (3.7)	2	7 (13.0)	11
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	6 (11.1)	6
Nausea	[redacted]	[redacted]	2 (3.7)	2	6 (11.1)	6
Haemorrhoids	[redacted]	[redacted]	[redacted]	[redacted]	4 (7.4)	4
Abdominal Pain Upper	[redacted]	[redacted]	[redacted]	[redacted]	3 (5.6)	4
Injury, Poisoning, and Procedural Complications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ligament Sprain	[redacted]	[redacted]	[redacted]	[redacted]	5 (9.3)	5
Limb Injury	[redacted]	[redacted]	[redacted]	[redacted]	3 (5.6)	4
Contusion	[redacted]	[redacted]	[redacted]	[redacted]	3 (5.6)	3
Infusion Related Reaction	[redacted]	[redacted]	[redacted]	[redacted]	3 (5.6)	3
Investigations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alanine Aminotransferase Increased	[redacted]	[redacted]	[redacted]	[redacted]	11 (20.4)	12
Blood Creatinine Phosphokinase Increased	[redacted]	[redacted]	[redacted]	[redacted]	8 (14.8)	11
Aspartate Aminotransferase Increased	[redacted]	[redacted]	[redacted]	[redacted]	8 (14.8)	9
C-Reactive Protein Increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous System Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	16 (29.6)	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, Thoracic, and Mediastinal Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oropharyngeal Pain	[redacted]	[redacted]	2 (3.7)	2	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]	6 (11.1)	6
Rhinorrhoea	[redacted]	[redacted]	[redacted]	[redacted]	4 (7.4)	4

Vascular Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	6 (11.1)	6
Metabolism and Nutrition Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vitamin D Deficiency	[redacted]	[redacted]	[redacted]	[redacted]	3 (5.6)	3
Blood and Lymphatic System Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	4 (7.4)	4
Iron Deficiency Anaemia	[redacted]	[redacted]	2 (3.7)	2	3 (5.6)	3
Hepatobiliary Disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hepatic Steatosis	[redacted]	[redacted]	[redacted]	[redacted]	4 (7.4)	4

Abbreviations: AE, adverse event; n, number.
Source: 24-Month CSR, CSL Behring.[14]

2.10.3.1 Anti-AAV5 NAb positive and negative subgroups

The incidence and distribution of TEAEs by SOC in the baseline anti-AAV5 NAb positive and negative subgroups were comparable.[14]

For subjects who were positive for baseline anti-AAV5 NAb (n=21), there were a total of [redacted] TEAEs reported. The SOCs with the highest incidence of reported TEAEs were infections and infestations ([redacted]%), musculoskeletal and connective tissue disorders ([redacted]%), gastrointestinal disorders ([redacted]%), general disorders and administration conditions ([redacted]%), investigations ([redacted]%), and injury, poisoning and procedural complications ([redacted]%). A total of 4/21 ([redacted]%) subjects experienced [redacted] TEAEs in the neoplasms benign, malignant and unspecified (incl. cysts and polyps) SOC, none of which were treatment-related.[14]

For subjects who were negative for baseline anti-AAV5 NAb (n=33), there were a total of [redacted] TEAEs reported. The SOCs with the highest incidence of reported TEAEs were infections and infestations ([redacted]%), musculoskeletal and connective tissue disorders ([redacted]%), general disorders and administration conditions ([redacted]%), nervous system disorders ([redacted]%), and injury, poisoning and procedural complaints ([redacted]%). A total of [redacted] ([redacted]%) subjects experienced 5 TEAEs in the neoplasms benign, malignant and unspecified (incl. cysts and polyps) SOC, none of which were treatment-related.[14]

2.10.3.2 Relationship to study treatment

The majority of TEAEs (464 of 557 events in the post-treatment period) were assessed as not treatment-related to etranacogene dezaparvovec, with a total of 93 TEAEs in 28/54 (70.4%) subjects assessed as treatment-related (Table 21).[14]

The SOCs with the highest incidence of treatment-related TEAEs were general disorders and administration site conditions ([redacted]% of subjects; [redacted] TEAEs), investigations ([redacted]% of subjects; [redacted] TEAEs), and nervous system disorders ([redacted]% of subjects; [redacted] TEAEs).[14]

The most commonly reported treatment-related TEAEs were ALT increased (16.7%), headache (14.8%), and influenza-like illness (13.0%).[14] The majority of treatment-related TEAEs ([redacted] events) were mild or moderate in severity; [redacted] treatment-related TEAEs reported in [redacted] (ALT increased and AST increased) were severe. The treatment-related TEAE distribution by SOC in the subjects with baseline anti-

AAV5 NAb-positive subgroup was similar to the overall post-treatment Safety Population.[14]

[redacted] ([redacted]%) of [redacted] subjects with elevated transaminases at dosing experienced [redacted] TEAEs that were assessed as treatment-related.[14] A total of [redacted] events of influenza-like illness were experienced by [redacted] ([redacted]%) subjects, and infusion related reaction, abdominal discomfort, ALT increased, and night sweats were reported in [redacted] ([redacted]%) subject each.[14]

2.10.3.3 By severity

During the post-treatment period, the majority ([redacted] events) of TEAEs were mild or moderate in severity (Table 21). Severe TEAEs were reported in [redacted]% of subjects in the post-treatment period and TEAEs with highest severity of mild and moderate TEAEs were reported in [redacted]% and [redacted]% of subjects, respectively (Table 23). [redacted] severe TEAEs of ALT and AST increased that were assessed as treatment-related; the events resolved following treatment with prednisone. All other severe TEAEs were not treatment-related.[14]

Table 23. TEAEs by highest severity (Safety Population)

n (%)	Lead-in Period (Including Lead-in Discontinuers) (n=[redacted])	Lead-in Period (Excluding Lead-in Discontinuers) (n=[redacted])	Post-treatment Period (n=54)
Any Severity	[redacted]	[redacted]	54 (100.0)
Mild	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	11 (20.4)

Only the highest severity was counted for multiple occurrences of the same adverse event in 1 individual.

Source: 24-Month CSR, CSL Behring.[14]

2.10.3.4 Other serious AEs

During the post-treatment period, [redacted] ([redacted]%) subjects experienced a total of [redacted] SAEs (Table 21).[14] Of the [redacted] SAEs during the post-treatment period, [redacted] were mild or moderate in severity and [redacted] were considered severe. [redacted] ([redacted]; [redacted]%) subjects in the baseline anti-AAV5 NAb positive subgroup (n=21) experienced a total of [redacted] SAEs, including an event of HCC in the neoplasms benign, malignant and unspecified (incl. cysts and polyps) SOC. [redacted] ([redacted]; [redacted]%) subjects in the baseline anti-AAV5 NAb negative subgroup (n=[redacted]) experienced a total of [redacted] SAEs.[14]

No SAEs were assessed as treatment-related at the time of the data cut-off. It should be noted that SAEs of transient ischaemic attack and HCC were initially reported to be treatment-related but upon further investigation, it was determined that both of these events were unlikely treatment-related and their causality was updated in the database prior to the data cut-off.[14]

2.10.3.5 TEAE of special notification

Overall, 12/54 (22.2%) subjects experienced 19 TEAEs of special notification (Table 21). The majority of TEAEs of special notification were mild or moderate in severity (18/19 events) and considered treatment-related (14/19 events).[14]

There were [redacted] subjects with TEAEs of special notification related to etranacogene dezaparvovec administration (i.e., infusion reactions). [redacted] of the [redacted] subjects with infusion reactions required a dose interruption; treatment was started at a slower

infusion rate following administration of antihistamines. Additionally, there was a subject with a TEAE of special notification related to hypersensitivity reactions (and not classified as a TEAE of special notification related to IMP administration). The hypersensitivity reaction occurred during administration and resulted in a discontinuation of treatment and receipt of a partial dose (approximately 10%) in 1 subject. Five of these 7 subjects were positive for anti-AAV5 NAbs at baseline.[14]

There were [redacted] subjects with TEAES of special notification related to the development of any new/recurrent cancer. New and recurrent cancers included TEAEs of HCC (onset 365 days post-treatment), prostate cancer (onset: 350 days post-treatment), and basal cell carcinoma (onset: 550 days post-treatment), which were all assessed as not-treatment-related.[14]

Additionally, TEAEs of special notification related to unexpected reactions, mandatory concomitant medication, and product failure were reported in [redacted], [redacted], and [redacted], respectively. There were no subjects with TEAEs of special notification related to suspected or confirmed treatment-related opportunistic infections or related to medical devices.[14]

2.10.3.6 TEAEs associated transaminase elevations

There were 11/54 (20.4%) subjects with [redacted] TEAEs of ALT increased, [redacted] ([redacted]%) subjects with [redacted] TEAEs of AST increased, and [redacted] ([redacted]%) [redacted] with [redacted] TEAE of transaminases increased.[14] Of these, [redacted] TEAEs were associated with an ALT elevation >2×baseline, and 5 TEAEs were associated with an AST elevation >2×baseline. The majority of the TEAEs associated with elevations >2×baseline were treatment-related TEAEs except for [redacted] of ALT increased and [redacted] of AST increased experienced in [redacted].[14]

Most TEAEs associated with transaminase elevations were mild or moderate in severity; 1 subject had TEAEs of elevations in AST and ALT that were reported as severe. A total of 9/54 (16.7%) subjects overall received steroids as treatment for liver enzyme elevations, including prednisone, prednisolone, and methylprednisolone. All subjects discontinued steroid use prior to Week 26; the mean (SD) duration of corticosteroid use for elevated transaminases was 79.8 (26.6) days and ranged from

51 to 130 days. All TEAEs of elevated transaminases were non-serious and have resolved.[14]

In relation to treatment of transaminase elevations, AEs of special notification of insomnia and lymphocyte count decreased were reported. Insomnia occurred 2 days after initiation of prednisolone in one subject for a TEAE of ALT increased. Prednisolone was tapered following resolution of the transaminase elevation and the TEAE of insomnia resolved 6 days later. Lymphocyte count decreased occurred 3 days after initiation of prednisolone in another subject for a TEAE of ALT increased and resolved during prednisolone tapering.[14]

2.10.3.7 Deaths

There was one death reported in the study post-treatment; one subject experienced a fatal event of cardiogenic shock, preceded by a bacterial urinary tract infection, 464 days (approximately 15 months) post-treatment. This event which was assessed as not treatment-related.[14]

2.10.3.8 Laboratory values

2.10.3.8.1 Anti-Factor IX antibodies

The majority ([redacted] [redacted%]) of subjects tested negative for anti-Factor IX antibodies prior to dosing (at the baseline assessment) and at Month 24 post-treatment ([redacted] [redacted%] subjects). [redacted] tested positive prior to dosing and periodically during the study post-treatment to Month 6; [redacted] Factor IX activity level of [redacted]% at Month 6, [redacted]% at both Month 12 and Month 18, and [redacted]% at Month 24 post-treatment.[14]

2.10.3.8.2 Factor IX inhibitors

Levels of Factor IX inhibitors were below the limit of detection (LOD) (Nijmegen-Bethesda units [NBU]/mL=0.415) for all (54/54 [100.0%]) subjects prior to dosing (at the baseline assessment) and remained so through to Month 24 post-treatment.[14] Importantly, etranacogene dezaparvovec did not result in the development of Factor IX inhibitors during the HOPE-B study, corroborating results from the Phase I/II study with ATM-60 and the Phase IIb study with etranacogene dezaparvovec.[14]

2.10.3.8.3 AAV5 Antibodies

Levels of anti-AAV5 NAbs were <LOD (titre=7) for 33/54 (61.1%) subjects prior to dosing (at the baseline assessment) and ≥LOD for 21/54 (38.9%) subjects (median titre: 56.9 [range: 9–3212]). One subject had a titre >3000, and pre-dose titres ranged between [redacted] when [redacted] was removed from the analysis.[14] Levels of immunoglobulin G (IgG) anti-AAV5 antibodies were <LOD (titre=50) for the majority ([redacted] [redacted%]) of subjects prior to dosing (at the baseline assessment) and ≥LOD for [redacted] ([redacted%]) subjects (median titre: [redacted] [range: [redacted]]). By Week 3 post-treatment, levels of IgG anti-AAV5 antibodies were ≥LOD for [redacted] ([redacted] [redacted%]) subjects (median titre: [redacted] [range: [redacted]]) and remained elevated through to Month 24 post-treatment.[14]

Levels of IgM anti-AAV5 antibodies were <LOD (titre=50) for the majority ([redacted] [redacted%]) of subjects prior to dosing (at the baseline assessment) and ≥LOD for [redacted]. By Week 3 post-treatment, levels of IgM anti-AAV5 antibodies were ≥LOD for the majority ([redacted] [redacted%]) of subjects (median titre: [redacted] [range: [redacted]]). The proportion of subjects with detectable levels of IgM anti-AAV5 antibodies continuously declined from Week 3 to Month 12. At Month 12, [redacted] ([redacted%]) subjects had levels ≥LOD (median titre: [redacted] [range: [redacted]]), and at Month 24, [redacted] ([redacted%]) subjects had levels ≥LOD (median titre: [redacted] [range: [redacted]]).[14]

2.10.3.8.4 AAV5 capsid-specific T-cell response

AAV5 capsid-specific T-cell responses were assessed during the first year of post-treatment follow-up. The majority ([redacted] [redacted%]) of subjects with interpretable results did not have specific AAV5 capsid T-cell response prior to dosing (at the baseline assessment). The number of subjects who developed a specific AAV5 capsid T-cell response varied during the study, reaching the highest number at Week 6 post-treatment ([redacted] [redacted%] subjects). There were missing data due to issues related to insufficient number of cells and nonconformance in the analysis, Overall, [redacted] subjects had at least one visit with a specific T-cell response. Uncontaminated Factor IX activity ranged between [redacted] and [redacted]% of normal for visits where subjects also had a specific T-cell response. Specific T-cell responses concurrent with TEAEs

of ALT and/or AST increased were noted for [redacted] subjects and concurrent with corticosteroid treatment in [redacted] subjects. Review of specific AAV5 capsid T-cell responses did not identify a correlation with other clinically relevant findings.[14]

2.10.3.8.5 DNA shedding

Temporary shedding of etranacogene dezaparvovec vector DNA may occur in blood and semen of patients receiving etranacogene dezaparvovec. Due to the non-replicating nature of the shed vector DNA fragments, the risk of an adverse effect to human health upon accidental exposure and the environmental risks are considered negligible. The occurrence of vector genomes shedding was examined during the HOPE-B trial, in which a subject was considered to no longer be shedding vector DNA if they had a negative laboratory result for 3 or more consecutive timepoints.[14]

Clearance of vector DNA from semen, indicating the absence of shedding, was confirmed in [redacted] ([redacted]%) subjects in the post-treatment period. The earliest that subjects were considered to no longer be shedding vector DNA from semen was 6 weeks post-treatment ([redacted]% of subjects [95% CI: [redacted]]. Median time to absence of shedding was [redacted] weeks (95% CI: [redacted], NE). The proportion of subjects testing negative [redacted] until Week 80, at which time [redacted]% of subjects (95% CI: [redacted]) reached absence of shedding from semen; the proportion was the same at Week 96 (Month 24). Additionally, the majority ([redacted]) of subjects had a negative test result (i.e., result <LOD) at their most recent testing.[14]

Clearance of vector DNA from blood was confirmed in [redacted] ([redacted]%) subjects in the post-treatment period. The earliest that subjects were considered to no longer be shedding vector DNA from blood was 17 weeks post-treatment ([redacted]% of subjects [95% CI: [redacted]]. Median time to absence of shedding was 52.3 weeks (95% CI: [redacted], NE). The proportion of subjects testing negative increased at a continuous rate until Week 78, at which time [redacted]% of subjects (95% CI: [redacted]) reached absence of shedding from blood; the proportion was the same at Week 96 (Month 24); additionally, the majority ([redacted]) of subjects had a negative test result (i.e., result <LOD) at their most recent testing.[14]

2.10.3.8.6 Inflammatory Markers

Inflammatory markers including IL-1β, IL-2, IL-6, IFNγ, and MCP-1 were assessed during the first year of post-treatment follow-up.[14]

Levels of IL-1β, IL-6, and MCP-1 were generally unaffected by etranacogene dezaparvovec treatment, while initial elevations were noted with IL-2 and IFNγ levels following treatment, though this was followed by a return to pre-treatment levels.[14]

- Levels of IL-1β were <LLOQ (0.60 ng/L) for [redacted] prior to dosing (at the baseline assessment) and at all post-treatment visits through Month 11. At Month 12, [redacted] IL-1β levels ≥LLOQ with [redacted] ng/L.[14]
- Prior to dosing, levels of IL-6 were <LLOQ ([redacted] ng/L) for [redacted] ([redacted]%) subjects, and ≥LLOQ for [redacted] ([redacted]%) of subjects with a mean (SD) value of [redacted] ([redacted]) ng/L (range: [redacted] to [redacted] ng/L). The proportion of subjects who were < or ≥LLOQ was fairly consistent in the post-treatment period for IL-6.[14]
- Levels of MCP-1 were ≥LLOQ (1.68 ng/L) for [redacted] prior to dosing (at the baseline assessment) with a mean (SD) value of [redacted] ([redacted]) ng/L (range: [redacted] to [redacted] ng/L). In the post-treatment period, levels of MCP-1 were also ≥LLOQ for all subjects. At Month 12, mean (SD) MCP-1 was [redacted] ([redacted]) ng/L (range: [redacted] to [redacted] ng/L).[14]
- Levels of IL-2 were <LLOQ (0.72 ng/L) for the majority ([redacted] [[redacted]%]) of subjects prior to dosing (at the baseline assessment) and [redacted] levels ≥LLOQ with a value of [redacted] ng/L. At Week 1 post-treatment, [redacted] ([redacted]%) subjects had IL-2 levels ≥LLOQ, with a mean (SD) value of [redacted] ([redacted]) ng/L (range: [redacted] to [redacted] ng/L). The proportion of subjects with IL-2 levels ≥LLOQ decreased to [redacted] to [redacted] subjects between Week 2 and Week 12. From Month 4 on, IL-2 levels were <LLOQ for [redacted].[14]
- Levels of IFNγ were ≥LLOQ ([redacted] ng/L) for the majority ([redacted] [[redacted]%]) of subjects prior to dosing (at the baseline assessment) with a mean (SD) value of [redacted] ([redacted]) ng/L (range: [redacted] to [redacted] ng/L). At Week 1 post-treatment, [redacted] ([redacted] [[redacted]%]) had IFNγ levels ≥LLOQ. The proportion of subjects with IFNγ levels ≥LLOQ decreased from Week 2 to Week 8, and the

number of subjects with levels ≥LLOQ ranged between [redacted] and [redacted] subjects from Month 4 to Month 12. At Month 12, [redacted] ([redacted]%) subjects had IFNγ levels ≥LLOQ, with a mean (SD) value of [redacted] ([redacted]) ng/L (range: [redacted] to [redacted] ng/L).[14]

B.2.11 Ongoing studies

The HOPE-B trial is still ongoing, and the next readout will be at 36 months for which follow up visits will be completed by May 2023, with the analysed and validated data available 3-6 months later. A publication is also expected for the 5-year data from the Phase I/II study (currently under review). Additionally, an interim data readout of CT-AMT-060-01 at 6 years post-treatment is expected in Q2 2023; however, these new data will not be made publicly available or would impact this submission. Next data read outs that will be made publicly available will be at 7 years post-treatment.

B.2.12 Interpretation of clinical effectiveness and safety evidence

2.12.1.1 Summary and discussion of the available evidence to support etranacogene dezaparvovec

Etranacogene dezaparvovec has the potential to be a first-in-class gene therapy for patients with moderately severe or severe haemophilia B. The ongoing pivotal HOPE-B trial, which includes UK centres, provides direct comparative evidence of etranacogene dezaparvovec versus the baseline status of patients on prophylaxis, which is the current standard of care in England.[14] The trial was designed to include several distinct phases to test non-inferiority of etranacogene dezaparvovec versus routine Factor IX prophylaxis, and the trial's primary and secondary endpoints were met, demonstrating the efficacy and safety of etranacogene dezaparvovec as well as its durability of sustaining higher Factor IX activity levels over 24 Months.[14]

Evidence from HOPE-B

Results from the Phase III HOPE-B study indicated that etranacogene dezaparvovec is a highly effective treatment option for patients with moderately severe or severe haemophilia B, with improvements in QoL suggesting its potential to reduce the treatment burden of regular infusions associated with prophylaxis. At 24-Months

post-treatment, compared to the 6-month lead-in phase with routine Factor IX prophylaxis, a single dose of etranacogene dezaparvovec:[14]

- significantly reduced ABR, AsBR and AjBR by 64%, 75%, and 80%, respectively, leading to a decrease of 73% in the number of bleeds requiring treatment
- provided a rapid and sustained increase in mean endogenous Factor IX activity level to 36.7% (SD 19.0) of normal levels (36.7 IU/dL), eliminating the need for routine Factor IX prophylaxis therapy in nearly all (96%) patients, potentially decreasing the burden on patients in their disease management
- is effective in increasing endogenous Factor IX activity, with no clinically meaningful correlation between baseline anti-AAV5 NAbs status and long-term durability of Factor IX expression
- demonstrated improvements in the total Haem-A-QoL PRO score and across four of its domains (feelings, treatment, work/school, future), as well as in the mean EQ-5D-5L VAS and EQ-5D-5L index scores — improvements on non-haemophilia-specific measures (iPAQ, PROBE, WPAI) were not significant due to the limited number of patients in the study
- demonstrated a well-tolerated safety profile, with the majority of treatment-related adverse events (n=[redacted]) being mild and well-tolerated and no treatment-related serious adverse events or deaths reported
- did not lead to the development of inhibitors to Factor IX

Due to an enrolled patient population, which eight UK clinical experts agreed would cover more than 90% of the eligible patient population in the UK,[6] the findings from HOPE-B are generalisable to real-world patients with moderately severe or severe haemophilia B in the UK. The demonstrated improvements in HRQoL and bleed rates indicate that etranacogene dezaparvovec can provide substantial benefits to patients with moderately severe or severe haemophilia B in the UK, compared with the current standard of care. Additionally, the decreased necessity of Factor IX prophylaxis indicates that a single dose of etranacogene dezaparvovec can reduce the treatment burden of regular intravenous infusions associated with Factor IX prophylaxis therapy, which may ultimately contribute to the observed improvement in the performance in

work and (higher) education and may provide people with haemophilia B with a sense of optimism for the future. Moreover, patients treated with etranacogene dezaparvovec are not likely to develop Factor IX inhibitors, potentially avoiding these additional complications and costs.[14,133] The clinical data strongly support the use of etranacogene dezaparvovec in patients with moderately severe or severe haemophilia B in the UK.

Durability of treatment

After a single dose of etranacogene dezaparvovec, patients enrolled in the HOPE-B trial continued to demonstrate sustained improvements 7–24 Months post-treatment, with a mean Factor IX activity level of 36.7% of normal and effective bleed control.[14] The HOPE-B study will continue to follow patients up to 5 years post-treatment, to further evaluate its long-term efficacy and safety. The five years of sustained efficacy achieved by AMT-060 (Appendix M) further reinforces the durability evidence of etranacogene dezaparvovec, since the two therapies share the same capsid and cassette design. The main distinction between the two therapies is a different variant of the Factor IX transgene (single amino acid change); while AMT-060 contains the wildtype Factor IX gene, etranacogene dezaparvovec encodes the naturally occurring Padua variant of human coagulation Factor IX and shows a gain-of-function of 6- to 9-fold, displaying a higher Factor IX activity with similar Factor IX protein expression compared to AMT-060.

To predict the long-term durability of etranacogene dezaparvovec, Bayesian and Frequentist linear mixed models were used on the outcomes of the Phase IIb and Phase III of etranacogene dezaparvovec studies.[111] These models predicted that no more than 10.91% of observed participants would have Factor IX activity levels of <2% up to 25.5 years post-treatment.[111] Additionally, the Bayesian model-based prediction of future participants suggest that, at 25.5 years post-treatment, >80% would be free from prophylactic Factor IX replacement products. Moreover, an update to the model has estimated that [redacted]% of patients treated with etranacogene dezaparvovec will have Factor IX levels >2% and >5% after a median of [redacted] and [redacted] years post-treatment, respectively.[112] These statistical modelling results show promising longevity results for patients in the HOPE-B trial, which are generalisable to real-world patients with

moderately severe or severe haemophilia B in the UK. Together, these results suggest that etranacogene dezaparvovec could provide major benefit to patients in the UK by strongly decreasing the need for long-term burdensome prophylactic Factor IX treatment.[111]

Other long-term studies with rAAV based vectors show that the effects of rAAV-based gene therapy can be maintained over long periods of time; the most recently published follow-up of the earliest successful haemophilia B gene therapy trial, demonstrated stable therapeutic expression of Factor IX over a period of 8 years without late toxicities. The rAAV-based vector used, similarly to etranacogene dezaparvovec, contained a codon-optimised Factor IX gene, under control of a liver specific promoter.[109] During a presentation at the CFH 2021 congress, Dr Nathwani stated that the dose-dependent, multiyear increase in Factor IX was sustained in an rAAV-based trial, with the longest follow-up being up to 10 years (oral presentation, recording available upon request due to file size). This further supports the durability seen by etranacogene dezaparvovec in the HOPE-B trial and suggests that the single-dose gene therapy may provide long-term benefits to patients in the UK.

Quality of life

The HOPE-B trial demonstrated improvements in HRQoL, likely resulting from a decrease in burdensome prophylactic treatment, less bodily (joint) pain and improved overall freedom. The potential benefit that etranacogene dezaparvovec could provide patients is further highlighted by a recently published qualitative interview study in patients with haemophilia A and B.[96] This study has highlighted the importance and benefits of treating haemophilia with gene therapy, as well as concerns surrounding immunosuppression due to transaminitis.

In HOPE-B, all instances of elevated transaminases were non-serious and resolved via reactive corticosteroid treatment, with the patients who received steroids (n=9/54) being able to discontinue steroid use within 6 months post-treatment (mean (SD) duration: 79.8 (26.6) days, range: 51–130 days).[14] Moreover, despite the transaminase elevations, Factor IX activity was preserved in the mild or non-haemophilic range.[14] The substantial patient burden associated with the use of corticosteroids to treat transaminase elevation in patients receiving gene therapy for

haemophilia, as highlighted by the qualitative interview study and patient testimonials, indicates that the ability to limit corticosteroid use while maintaining Factor IX activity is key in improving patient QoL.[96]

Despite the challenges associated with corticosteroid treatment, the majority of those interviewed in the qualitative study (patients, n=[redacted]; family members, n=[redacted]) described gene therapy as life changing.[96]

> *"It's unbelievably life-changing. Life-changing." [ExiF08]*[96]

> *"I can do most of the physical actions that I couldn't do before. I can work in the garden, I can easily carry heavy bags from the grocery shop... And I don't have to worry that my elbows or my shoulder joint or anything like that will just give me a bleed. So, it's a peace of mind." [Exi15]*[96]

For others (n=[redacted]) their improvement was down to ease of travel (not have to take large volumes of factor with them and navigate customs with needles and syringes) or the ability to participate in sports in ways not previously open to them.[96]

> *"I play golf twice a weekend, I carried a bag five and a half miles, swung a golf club, and I never had a single problem. I'd get back and be completely fine. I wouldn't even dream of doing that when I had haemophilia." [Exi06]*[96]

This highlights the substantial benefit that the single-dose etranacogene dezaparvovec can give to patients with moderately severe or severe haemophilia B in the UK, compared to the current standard of care.

Evidence from indirect comparisons

To further investigate the potential role of etranacogene dezaparvovec in clinical practice in the UK, ITCs were performed on four approved prophylactic Factor IX replacement therapies for the treatment of moderately severe or severe haemophilia B: Idelvion (albutrepenonacog alfa), Alprolix (eftrenonacog alfa), Refixia (nonacog beta pegol) and BeneFIX (nonacog alfa).[117,123]

The ITCs showed that etranacogene dezaparvovec had a statistically significantly lower ABR, AsBR, and AjBR compared to Idelvion and Alprolix, and a statistically

significantly lower ABR and AsBR compared to Refixia. Moreover, the pre-post analysis with BeneFIX found that etranacogene dezaparvovec was statistically significantly superior to BeneFIX for ABR, AsBR and AjBR.[123] No statistically significant difference in Haem-A-QoL or EQ-5D scores change from baseline were found between etranacogene dezaparvovec and the available data of Factor IX replacement therapies (Alprolix and Refixia). This suggests that patients who receive etranacogene dezaparvovec have fewer bleeds than patients on replacement Factor IX therapy, with no negative impact on their HRQoL, regardless of which specific type of replacement Factor IX therapy is utilised.[117,123]

The improved ABRs compared to the standard of care is expected to result in a decrease in mortality, morbidity and disability, as well as decreased costs and improved QoL. Overall, etranacogene dezaparvovec could confer a large benefit over comparators for patients with moderately severe or severe haemophilia B.[117]

2.12.1.2 Limitations and strengths of the evidence base

The limitations of the available evidence include a small patient population, lack of randomisation and relatively short follow-up period. As with any rare condition, the low prevalence of moderately severe or severe haemophilia B resulted in a small sample size, particularly as the trial included only adults with Factor IX levels of <2%. Nevertheless, HOPE-B included over 50 patients (largest phase III clinical trial number to date in haemophilia B), being powered for non-inferiority testing of its primary endpoint. Moreover, single-arm trials are standard in this disease area, and randomisation would be a substantial challenge due to the treatments being of different modalities (Factor IX replacement therapy versus inserting a gene to produce Factor IX). The approach of including two investigative phases (lead-in phase and post-treatment phase) can be considered appropriate to provide comparative data (primary endpoint only) despite not following randomisation, which could not be feasible for a gene therapy. Regarding follow-up period, the primary and secondary endpoints reached statistical significance at 18 and 24 months, demonstrating the maturity of the evidence. Further data readouts are expected to be available as patients are followed by up to 5 years in HOPE-B. Moreover, statistical modelling of

the outcomes of the HOPE-B trial and results from other Factor IX-rAAV-based trials support the predicted long-term durability of etranacogene dezaparvovec.

B.3 Cost effectiveness

Summary of the de novo cost-effectiveness model

- A de novo cost-utility model was developed for the economic evaluation of etranacogene dezaparvovec for patients with moderately severe and severe haemophilia B.
- A markov model based on bleeding events and data from the pivotal HOPE-B trial was used to evaluate the cost-effectiveness of etranacogene dezaparvovec compared with Factor IX prophylaxis therapy (Alprolix, BeneFIX, Idelvion and Refixia). The model was comprised of four health states: no bleeds, non-joint bleeds, joint bleeds, and death.
- The analysis was conducted from an NHS/PSS perspective, with a lifetime time horizon and costs and outcomes were discounted at 3.5% per annum.
- Efficacy data for etranacogene dezaparvovec and the relevant comparators were derived from the HOPE-B trial and the ITC report, respectively.
- The utility values for etranacogene dezaparvovec and its relevant comparators were derived from the HOPE-B trial while the disutility applied for bleeding events were obtained from published literature.
- Resource use and costs included in the model were taken from appropriate published sources including the British National Formulary (BNF), National Schedule for NHS (2020/2021), Monthly Index of Medical Specialities (MIMS).
- Feedback from eight UK clinical experts was sought to validate assumptions and inputs in the model.

Base case cost-effectiveness results

- In base case analyses etranacogene dezaparvovec was cost-effective compared to all the comparators considered in the decision problem.

Sensitivity analyses

- Probabilistic sensitivity analyses (PSA) and deterministic sensitivity analyses (DSA) were conducted to assess uncertainty in the economic analysis and demonstrate that the base case cost-effectiveness results were robust to an extensive number of scenario analyses.
- The DSA results identified a number of key influential parameters such as annual bleed rate, additional treatment cost and disease monitoring cost.
- Scenario analyses were conducted to address sources of uncertainty in the model such as durability, utility values, time horizon and societal costs.

B.3.1 Published cost-effectiveness studies

- In appendix G, describe and compare the methods and results of any published cost-effectiveness analyses available for the technology and/or the comparator technologies (relevant to the technology evaluation).
- See section 3.1 of the user guide for full details of the information required in appendix G.

Three sets of SLRs have been run:

- Two published SLRs that identified clinical, economic and HRQoL evidence in haemophilia B had been conducted. The earliest search date for these SLRs was the 22 March 2013. SLRs were performed to find additional papers since the original search.
- Searches were run on 18 August 2021 for the time period to 22 March 2013 (clinical) and 1 January 2016 (economic evaluations, 'costs and resource use' and quality of life) to 18 August 2021 – described as the 'original review'.
- An 'update review' was then run on 17 October 2022 for the time period 18 August 2021 to 17 October 2022

In the original review (searched for clinical, economic, cost and resource use and HRQoL evidence simultaneously) the database searches retrieved 2,218 references, of which 154 were duplicates, leaving 2,064 unique references for first pass screening. Of the 827 full texts assessed at second pass, 378 were included, including 25 identified through grey literature, and 247 were extracted overall. Overall, three RCTs, 172 non-RCTs, five cost-effectiveness studies, four budget impact studies, 17 HRQoL studies and 46 cost and resource use studies met the selection criteria following the first and second pass of the clinical studies review and were extracted.

In the updated review the database searches (searched for economic, cost and resource use and HRQoL evidence simultaneously, clinical separately) retrieved 203 references, of which 15 were duplicates. For the economic evaluations and cost and resource use review, of the 188 titles and abstracts screened with the eligibility criteria,

94 references did not meet the criteria. Hence, full texts of the remaining 94 references were retrieved and reviewed based on the eligibility criteria, after which 25 publications were included, including 14 identified through grey literature searches. Of the 25 publications, three were economic evaluations.

Details of the eight cost-effectiveness publications on seven studies included are summarised in Table 24.

Table 24: Summary list of published cost-effectiveness studies

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Liu et al. (China, Dollars) On demand vs prophylactic FIX treatment	2020	CEA Markov model Time horizon: 17 years	Paediatric patients with haemophilia B without inhibitors	On demand vs prophylactic FIX treatment QALY gain: 2.04	On demand vs prophylactic FIX treatment Incremental cost: NR	ICER of $14,236.25 compared with on-demand treatment arm
Liu et al. (China, Dollars) On demand vs prophylactic FIX treatment	2019	CEA Markov model Time horizon: 16 years	Paediatric patients with haemophilia B without inhibitors	On demand vs prophylactic FIX treatment QALY gain: 1.62	On demand vs prophylactic FIX treatment Incremental cost: $13,943	ICER of $8,611.26 compared with on-demand treatment arm
Bolous et al. (US, USD) AAV-FIX Padua gene therapy On-demand FIX replacement therapy Primary FIX prophylaxis	2021	Microsimulation Markov model: Three health states: “Alive”, “Alive with Joint Damage” and “Dead”. Time horizon: Lifetime	500,000 simulated cohort of male patients with severe haemophilia B	NR	NR	NR

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Iannazzo et al. (Italy, Euros)	2016	CEA Markov model Time horizon: Lifetime	Previously treated patients with severe haemophilia B	Extended half-life recombinant FIX-Fc fusion protein (rFIXFc) prophylaxis vs standard prophylaxis NR	NR	NR
Polack et al. (France, Euros) On demand vs prophylaxis FIX	2015	Multi-variate regression models Time horizon: 1 year	41 patients with moderate haemophilia B and 114 patients with severe haemophilia B, N=155	NR	NR	Cost per haemorrhage event prevented with prophylaxis to have an ICER of €22,605.4

<table>
<tr>
<td>Bolous et al. 2022</td>
<td>2022</td>
<td>Microsimulation Markov model. Local clinical approaches and micro-costing data were collected from eight treatment centres, in the six low- and middle-income countries; the price of gene therapy was assumed to be $2,000,000/dose

Time horizon: Lifetime</td>
<td>Patients with severe haemophilia A or B, including those with factor inhibitors and AAV antibodies (no further details provided).</td>
<td colspan="3">The incremental cost effectiveness ratio (ICER) was above $100,000/QALY (a high-income country threshold) in all cases except Lima (Peru), where gene therapy was dominant compared with standard dose prophylaxis.
<table>
<tr><td colspan="4">FFP</td></tr>
<tr><td><u>Davo City, Philippines</u>
FFP:
Costs: $108,607
QALY: 9.41
Cost/QALY: $11,542
Gene ICER: $129,164
FFP + Gene therapy
Costs: $830,631
QALYs: 15.00
Cost/QALY: $55,375</td><td><u>Manila, Philippines</u>
FFP:
Costs: $179,415
QALY: 9.41
Cost/QALY: $19,066
Gene ICER: $126,065
FFP + Gene therapy
Costs: $884,121
QALYs: 15.00
Cost/QALY: $58,941</td><td><u>Ho Chi Minh City, Vietnam</u>
FFP:
Costs: $204,552
QALY: 9.58
Cost/QALY: $21,352
Gene ICER: $120,061
FFP + Gene therapy
Costs: $894,905
QALYs: 15.33
Cost/QALY: $58,376</td><td></td></tr>
<tr><td colspan="4">Low dose on demand:</td></tr>
<tr><td><u>Hanoi, Vietnam</u>
Low dose on demand:
Costs: $657,122
QALY: 11.25
Cost/QALY: $58,411
Gene ICER: $223,714
FFP + Gene therapy
Costs: $1,249,965
QALYs: 13.90
Cost/QALY: $89,926</td><td><u>Kathmandu, Nepal</u>
Low dose on demand:
Costs: $356,959
QALY: 10.97
Cost/QALY: $32,540
Gene ICER: $248,797
FFP + Gene therapy
Costs: $991,391
QALYs: 13.52
Cost/QALY: $73,328</td><td></td><td></td></tr>
<tr><td colspan="4">Low dose prophylaxis:</td></tr>
<tr><td><u>Hanoi, Vietnam</u>
Low dose prophylaxis:
Costs: $1,299,648
QALY: 16.21
Cost/QALY: $80,176
Gene ICER: $171,929
FFP + Gene therapy
Costs: $1,440,630
QALYs: 17.03
Cost/QALY: $84,594</td><td><u>Kathmandu, Nepal</u>
Low dose prophylaxis:
Costs: $758,005
QALY: 15.86
Cost/QALY: $47,794
Gene ICER: $256,289
FFP + Gene therapy
Costs: $986,102
QALYs: 16.75
Cost/QALY: $58,872</td><td><u>Colombo, Sri Lanka</u>
Low dose prophylaxis:
Costs: $1,157,213
QALY: 16.74
Cost/QALY: $69,129
Gene ICER: $194,068
FFP + Gene therapy
Costs: $1,349,340
QALYs: 17.73
Cost/QALY: $76,105</td><td><u>Bangkok, Thailand</u>
Low dose prophylaxis:
Costs: $523,719
QALY: 16.6
Cost/QALY: $31,549
Gene ICER: $334,921
FFP + Gene therapy
Costs: $831,846
QALYs: 17.52
Cost/QALY: $47,480</td></tr>
<tr><td colspan="4">Standard dose on demand:</td></tr>
<tr><td><u>Colombo, Sri Lanka</u>
Standard dose on demand:
Costs: $1,205,044
QALY: 11.61
Cost/QALY: $103,794
Gene ICER: $143,935
FFP + Gene therapy
Costs: $1,600,865
QALYs: 14.36
Cost/QALY: $111,481</td><td><u>Bangkok, Thailand</u>
Standard dose on demand:
Costs: $741,529
QALY: 11.52
Cost/QALY: $64,369
Gene ICER: $211,983
FFP + Gene therapy
Costs: $ 1,313,882
QALYs: 14.22
Cost/QALY: $92,397</td><td><u>Lima, Peru</u>
Standard dose on demand:
Costs: $1,419,361
QALY: 11.39
Cost/QALY: $124,615
Gene ICER: $116,175
FFP + Gene therapy
Costs: $1,731,873
QALYs: 14.08
Cost/QALY: $123,002</td><td></td></tr>
<tr><td colspan="4">Standard dose prophylaxis:</td></tr>
<tr><td><u>Lima, Peru</u>
Standard dose prophylaxis:
Costs: $2,379,083
QALY: 19.88
Cost/QALY: $119,672
Gene ICER: Dominant
FFP + Gene therapy
Costs: $2,352,711
QALYs: 20.22
Cost/QALY: $116,36</td><td></td><td></td><td></td></tr>
</table>
</td>
</tr>
<tr>
<td>Pochopien et al 2022</td>
<td>2022</td>
<td>Markov model comparing lifetime costs and health outcomes between rFIXFc</td>
<td>• Adolescent and adult (≥12 years) males with severe (≤2 IU/dL)</td>
<td>Compared with on-demand rFIX, prophylaxis with rFIXFc was associated with greater number of QALYs (15.936 versus 11.943)</td>
<td>Compared with on-demand rFIX, prophylaxis with rFIXFc was associated with lower total costs (€5,308,625 vs. €6,564,510)</td>
<td>ICER (cost/QALY gained): Dominant
ICER (cost/bleed avoided): Dominant</td>
</tr>
</table>

<table>
<tr><th>Study</th><th>Year</th><th>Summary of model</th><th>Patient population (average age in years)</th><th>QALYs (intervention, comparator)</th><th>Costs (currency) (intervention, comparator)</th><th>ICER (per QALY gained)</th></tr>
<tr><td></td><td></td><td>prophylaxis and rFIX on demand.
Three pre-defined health states, ‘No bleeds’, ‘Any bleeds’ and ‘Death’,
Time horizon: lifelong, 67 years.</td><td>haemophilia B without inhibitors.
• Base case age, years 33.6, low value: 31.0, high value: 36.1 (SD: 14.69)</td><td></td><td></td><td></td></tr>
<tr><td>US-ICER Gene Therapy 2022</td><td>2021</td><td>The structures of the models were based around the Pettersson score (PS). Bleed rates (taken from the HOPE-B trial) determined transition rates across PS, and were key in projecting costs, and utilities in the model.

The models used 6-month cycles.

Costs and effects were discounted using a rate of 3%.

Time horizon: lifelong</td><td>Haemophilia B without inhibitors who are eligible for prophylactic treatment.

All patients are assumed to be male, and patient weight and background mortality will be based on US male population averages.</td><td>Base-Case
<table><tr><th>Treatment</th><th>QALYs</th><th>Life Years</th><th>evLYs</th></tr><tr><td>Etranacogene Dezaparvovec</td><td>17.98</td><td>27.13</td><td>17.98</td></tr><tr><td>Factor IX</td><td>17.31</td><td>27.13</td><td>17.31</td></tr></table>evLYG: equal value life years gained, QALY: quality-adjusted life year
*These are based on a placeholder cost for etranacogene</td><td>Base-Case
<table><tr><th>Treatment</th><th>Drug Cost</th><th>Total Cost</th></tr><tr><td>Etranacogene Dezaparvovec</td><td>$7,494,000 *</td><td>$8,447,000</td></tr><tr><td>Factor IX</td><td>$14,029,000</td><td>$15,809,000</td></tr></table>evLYG: equal value life years gained, QALY: quality-adjusted life year
*These are based on a placeholder cost for etranacogene</td><td>Cost per QALY gained: Dominant
Cost per Life Year gained: Undefined
Cost per evLY gained: Dominant
Cost per bleed averted: Dominant</td></tr>
</table>

Study	Year	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
				dezaparvovec of $2,500,000.	dezaparvovec of $2,500,000.	

Abbreviations: QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; NR, not reported; AAV, adeno-associated virus; FIX, Factor IX; pdFIX, Plasma derived factor IX; rFIX, Recombinant factor IX; rFIXFc, recombinant factor IX fusion protein

B.3.2 Economic analysis

The identified cost-effectiveness studies presented in Appendix G differ with respect to the modelling methodology, populations, the outcomes considered, and the geographies evaluated. The one consistent element across the studies is the consideration of bleeds, be it joint or any type of bleed. Some of the studies also attempt to evaluate the effect of haemophilia B on joints, and the associated long-term effect, such as joint replacement surgeries. Nevertheless, the attempts to model joint damage are based on a number of assumptions as, due to the long-term nature of joint damage, the clinical data to prove the effectiveness of genetic treatments in their prevention is lacking.

A de-novo health economic analysis was conducted. The cost-effectiveness SLR did not identify a published cost-effectiveness analysis in a UK setting but cost effectiveness studies conducted in other countries have informed the new modelling structure for etranacogene dezaparvovec. Patient experience of bleeds formed the core of the model mechanics, and due to the data limitations, the benefit of preventing joint damage and associated joint replacement surgeries was excluded. As etranacogene dezaparvovec has been shown to reduce AjBR compared to prophylactic Factor IX replacement therapy in the ITC (Section B.2.9), it is expected that patients would receive additional benefit by the reduction of joint damage which has not been captured in the economic model. Therefore, the decision to not include the occurrence of, or costs associated with, joint damage in the model is a conservative assumption.

B.3.2.1 Patient population

The patient population included in the economic model reflects that of the population in the etranacogene dezaparvovec pivotal phase III trial: HOPE-B, Table 25 summarises the eligibility criteria in the HOPE-B trial.[14] The key inclusion criteria for the trial were: male, ≥18 years of age, congenital haemophilia B with known severe or moderately severe Factor IX deficiency (≤2% of normal), currently on continuous routine Factor IX prophylaxis with >150 previous exposure days of treatment and on stable prophylaxis for at least 2 months prior to screening. The population

demographics used in the economic model included the mean age and body weight of the 54 patients dosed in the trial.

Table 25: Summary of eligibility characteristics for the cost-effectiveness model based on the HOPE-B eligibility criteria

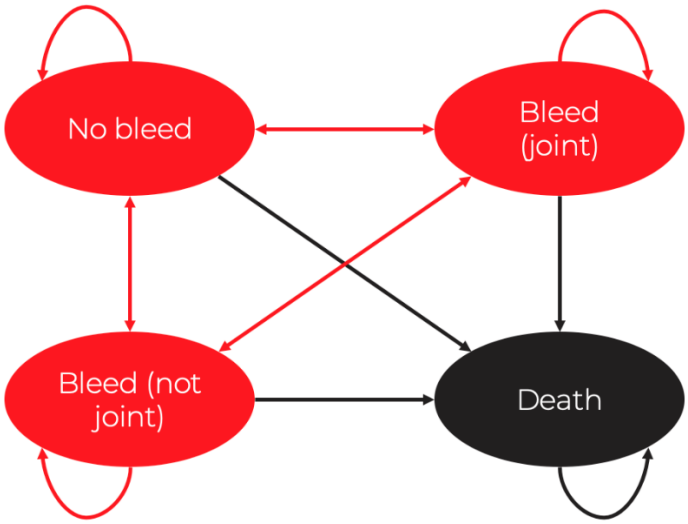
Category	Definition
Age	• 18 years and older
Gender	• Male only
Disease severity	• Subjects with known severe (Factor IX activity levels <1%) or moderately severe (Factor IX activity levels = 1–2%) congenital haemophilia B for which the subject is on continuous routine Factor IX prophylaxis*.
Treatment history	• >150 previous exposure days of treatment with Factor IX protein • Have been on stable Factor IX prophylaxis for at least 2 months prior to screening
Exclusion criteria (See Section B.2.3.1 for extensive list)	• History of Factor IX inhibitors • Positive Factor IX inhibitor test at screening and final visit during the lead-in period

*Continuous routine prophylaxis is defined as the intent of treating with a prior defined frequency of infusions (e.g., twice weekly, once every two weeks, etc.) as documents in the medical records.

B.3.2.2 Model structure

The model structure was developed using Microsoft® Excel. The economic model follows a Markov model structure and is based on bleeding events. The four Markov states consist of patients experiencing no bleeds, non-joint bleeds, joint bleeds or death in any cycle. In the economic model, all patients begin in the no-bleed state and either receive treatment with etranacogene dezaparvovec or Factor IX prophylaxis. The transition modelled in all cycles are death, non-joint bleed or joint bleed. This process is repeated over the time horizon of 59 years (3077 weeks), until the cohort of the 1000 patients reaches an age of 100 years.

Figure 38: Markov model structure



Note: Health states are categorised by treatment response. Arrows represent permissible transitions between states while loops represent no transition. Death is possible from any health state.

The Markov model structure was used because of its proven versatility.[134] A Markov model contains Markov states, which encapsulates the aforementioned states that patients with haemophilia B can reasonably find themselves experiencing at any cycle. The cycle length has been chosen to be seven days, in line with the comparators' dose administration of once or twice a week, and the fact that patients could ostensibly experience multiple events of a significant importance such as bleeds, in a single cycle if the cycle length were to be extended. Transitions amongst the Markov states are described wholistically with Markov transitional probability matrices in Section B.3.3.3, which give the exact probability that transfer patients between the states. The Markov trace offers a mathematical and graphical representation of the progression of the cohort across the cycles which the patients have experienced. The decision problem can be examined through the comparison of the aggregated Markov trace of the intervention against the Markov traces of the comparators. Lastly, the Markov structure offers a framework to capture the durable clinical effects of a gene therapy such as etranacogene dezaparvovec over the patients' lifespan.

Furthermore, the SLR identified four cost-effectiveness studies of which three utilised a Markov structure (Liu et al. 2019, Bolous et al. 2021 and Iannazzo et al. 2016).[135-137] Bolous et al. (2021) is the only to have defined their health states of:[136]

- “Alive”,
- “Alive with joint damage” and
- “Dead”.

Patients may experience minor or major bleeds in the former two health states of the Bolous et al. (2021) model according to their definitions of minor or major, whereas non-joint and joint bleeds are separately defined states in the structure of the model, which provides greater sensitivity in capturing bleeding events.[136]

Table 26: Features of the economic analysis

Factor	**Chosen values**	Justification
Perspective	NHS and PSS (base-case)	In line with the NICE health technology evaluations manual [138]
Time horizon	Lifetime	As the intervention is a gene therapy, lifetime horizon is necessary,
Discount Rates	3.5% for costs and effects	In line with the NICE health technology evaluations manual [138]
Source of utilities	HOPE-B trial[14], US-ICER (2022)[139]	Best available utility data for haemophilia B patients, sourced through the SLR and verified by clinical experts[6]
Source of costs	NHS cost reference 2019/20[140]	In line with the NICE health technology evaluations manual [138]

Abbreviations: HOPE-B, Health Outcomes with Padua Gene, Evaluation in Haemophilia B; US-ICER, Institute for Clinical and Economic Review; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal Social Services

B.3.2.3 Intervention technology and comparators

The intervention considered in the cost-effectiveness analysis was etranacogene dezaparvovec, as described in Section B.1.2. In alignment with the NICE final scope, data from the phase III HOPE-B trial supporting this submission and the SmPC for etranacogene dezaparvovec were used. [14,133] The model included the recommended single dose of 2×10^{13} genome copies/kg body weight corresponding to 2 mL/kg body weight, administered as an intravenous infusion after dilution of the required dose with sodium chloride 9 mg/mL (0.9%) solution for injection.

The current treatment options for haemophilia B in England and Wales are categorised as 'on demand' and 'prophylactic' Factor IX replacement therapy.[6]

Patients who receive 'on-demand' therapy only were not included within the CEM as the HOPE-B trial enrolled patients had been on stable Factor IX prophylaxis therapy for at least two months before screening, and then received at least 6 months of treatment with prophylaxis (the lead-in period) before etranacogene dezaparvovec administration.[14]

Therefore, the key comparators and will be compared individually in the economic model are:

- Alprolix
- BeneFIX
- Idelvion
- Refixia

Table 27: Features of comparator treatments

Comparator name	Licensed dose (IU/kg) and dosing frequency
Alprolix (eftrenonacog alfa)	• 50 IU/kg once weekly • 100 IU/kg every 10 days (well-controlled patients can be treated every 14 days or longer)[141]
BeneFIX (nonacog alfa)	• 40 IU/kg every 3–4 days[142]
Idelvion (albutrepenonacog alfa)	• 35–50 IU/kg once weekly • 75 IU/kg every 10–14 days[143]
Refixia (nonacog beta pegol)	• 40 IU/kg once weekly[144]

Abbreviations: IU/kg, international unit per kilogram

B.3.3 Clinical parameters and variables

B.3.3.1 Annualised bleeding rates and annualised joint bleeding rates

Table 28 reports the ABRs and AjBRs rate ratios that have been used to calculate the ABRs and AjBRs which are used in the economic model and serve as the basis of the transitional probabilities. The choice of the ABR and AjBR rate ratios was based off the feasibility and quality in the reduction of bias between the comparisons of the rates

whose analyses are outlined in Figure 15 in Section B.2.9.1. The ABRs (AjBRs) in Table 28 were calculated as the ABR (AjBR) rate ratio of the comparator of interest relative to etranacogene dezaparvovec, divided by the ABR (AjBR) of etranacogene dezaparvovec. This methodology has several benefits, firstly, the ABR (AjBR) rate ratios reported from the ITC are augmented to mitigate the differences in characteristics between the various studies from which the bleed rates data originates from[117,123]. Secondly, the division by ABR (AjBR) rates of etranacogene dezaparvovec restores a consistency in-line with the HOPE-B population serviced in the decision problem and economic model, which also provides a robust ABR (AjBR) rates for the comparators.

Table 28: Annual bleed rates and annual joint bleed rates calculated from the ITC report

Comparator	ABR rate ratio (RR), relative to Etranacogene dezaparvovec	AjBR rate ratio (RR), relative to Etranacogene dezaparvovec	ABR	AjBR
Etranacogene dezaparvovec	[redacted]	[redacted]	[redacted]	[redacted]
Alprolix	[redacted]	[redacted]	[redacted]	[redacted]
BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]
Idelvion	[redacted]	[redacted]	[redacted]	[redacted]
Refixia	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ABR, annualised bleeding rate; AjBR, annualised joint bleeding rate; RR, rate ratio
Note: a= refers to a multivariable MAIC comparison between the comparator mentioned and etranacogene dezaparvovec. b= refers to the pre-post analysis comparison between BeneFIX and Etranacogene dezaparvovec. c= refers to a multivariable IPTW comparison between Idelvion and Etranacogene dezaparvovec. *AjBR rate ratios of Refixia relative to Etranacogene dezaparvovec are not available (see Section B.2.9.1) where the ABR rate ratio serve as an approximation. Values are accurate to two decimal places.

B.3.3.2 Durability of etranacogene dezaparvovec

Section B.2.6.5 outlines the clinical details and evidence behind the long-term longevity of etranacogene dezaparvovec. The economic model follows the extrapolation by Shah et al. 2022 for the long-term durability of etranacogene dezaparvovec.[111,112] Bayesian model-based predictions indicate that more than 80% of patients will not need Factor IX prophylaxis treatments at 25.5 years, with the median value reaching 42 years. The inputs for the underlying exponential model, of a 2% durability threshold has been agreed by key consultant haematologists from

across England as being ‘credible and reasonable’ because, patients are typically considered for prophylaxis in England if they have baseline Factor IX levels of 2% or less.[6] This consensus supports the base case durability for the economic model.

The bleed rates and therefore the associated transitional probabilities, utilities, and costs for etranacogene dezaparvovec patients who require Factor IX prophylaxis at any point are dictated by the weighted market shares of the comparators.

B.3.3.3 Transitional probabilities

The transitional probabilities for the intervention and the comparators are outlined in Table 29. The likelihood of a patient entering a Markov state in a cycle is a logical realisation of the instantaneous probability over the cycle, calculated using Equation 1. In this formula, P is the transitional probability of interest, e is the Euler’s number, r is the rate of the specific bleed events (Section B.3.3.1) according to the Markov state of interest, and t is the time horizon of interest relative to the time horizon over which the rates are expressed over (weekly cycles).

Equation 1: Formula for conversion of per-cycle probabilities

$$p = 1 - e^{-\frac{r}{t}}$$

Source: Jones et al. 2017[145]

The r value for calculating the probability of a joint bleed is the AjBR for the comparator of interest. The r value for calculating the probability of a non-joint bleed is difference between the ABR and AjBR for the comparator of interest. The probability of entering the no bleed state is unity minus the probability of non-joint bleed and joint bleed states.

Values for etranacogene dezaparvovec at a specific cycle are augmented by the mean durability of etranacogene dezaparvovec at that specific cycle. For example, at the median durability of 42 years, half of the make-up of transitional probabilities are subject to r values from etranacogene dezaparvovec bleed rates, and the other half of transitional probabilities are subject to r values from the comparator that the intervention is being compared against.

No deaths attributed to etranacogene dezaparvovec were recorded in the HOPE-B trial over a 24-month period as outlined in Section 2.10.3.7. Haemophilia B patients are expected to live largely normal lives and as such the transition to the death state occurs according to general population statistics provided by Office for National Statistics UK 2021 national life tables, applied appropriately to each cycle according to the age of the cohort at the said cycle.[146]

Table 29: Transitional probabilities matrix of the intervention and comparators per cycle

Comparator	Probability of no-bleed	Probability of non-joint bleed	Probability of joint bleed	Probability of death
Etranacogene dezaparvovec *	[redacted]%	[redacted]%	[redacted]%	GPS
Alprolix	96.18%	1.99%	1.82%	GPS
BeneFIX	92.12%	6.31%	1.57%	GPS
Idelvion	96.27%	0.69%	3.04%	GPS
Refixia	97.61%	1.51%	0.88%	GPS

Abbreviations: GPS, General population statistics.
Note: *Etranacogene dezaparvovec values in each cycle are augment by the durability of etranacogene dezaparvovec in that cycle, this table shows initial transitional probabilities with no etranacogene dezaparvovec patients requiring further Factor IX prophylaxis. Values are accurate to two decimal places

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

The HOPE-B trial collected the outcomes of the EQ-5D-5L descriptive system of health-related QoL per patient, as noted in Section 2.6.6.1 specifically. The HOPE-B trial collected other PROs but they have not been used in the economic model.[14] The data included in the model is the EQ-5D-5L aggregated scores from the 24-month cut-off point mapped to EQ-5D-3L see Section B.3.4.2.

The disutility value corresponding to non-joint and joint bleeds were taken from the United States Institute for Clinical and Economic Review (US-ICER) 2022 gene therapy for haemophilia B evidence report.[139] The disutilities are taken from research of non-joint and joint bleeds with evidence originating from haemophilia A health-related quality of life studies as an approximate of the respective disutility that haemophilia B patients ostensibly experience, particularly as this body of work

especially focuses in eliciting utilities with respect to bleeding events. These studies include research by Neufeld et al. 2012, Mazza et al. 2016 and Fischer et al. 2016.[147]

B.3.4.2 Mapping

As per the reference case, the use of Delvin et al. 2018 utility set for the EQ-5D-5L for use in England is not recommended.[148] The utility values associated with the outcomes reported by the patients in their EQ-5D-5L scores, are the cross-walked utility values associated with the mapping function that Van Hout et al. 2012 developed for reporting EQ-5D-5L scores in terms of utilities consistent with the EQ-5D-3L data.[149]

B.3.4.3 Health-related quality-of-life studies

An updated SLR was conducted on 17 October 2022 to identify studies reporting on the HRQoL of patients with haemophilia B. Full details of the methodology and results of included studies for both the original and updated SLR are presented in Appendix H.

B.3.4.4 Adverse reactions

Decrements in utility for AEs associated with treatment with etranacogene dezaparvovec and comparators were captured in the model via the application of disutility values and estimated AE duration, where necessary. The disutility associated with AEs were sourced from published literature, as described in Table 30 and Table 31.

As noted in Table 22 the likelihood of a grade 3 and above AEs that occur in ≥ 5% of patients from the HOPE-B trial were incorporated into the model as they incur substantial costs to the healthcare system. The model also incorporated the 3-week lead-in period for etranacogene dezaparvovec following administration wherein patients could still receive Factor IX replacement therapy treatment. Therefore, the total weekly probability for each AE was calculated as a sum of both the etranacogene dezaparvovec probability and an average Factor IX replacement therapy probability, which was weighted by Factor IX market shares and time to steady state.

The comparators' probability of the adverse events was available only for the BeneFIX. As the Factor IX prophylaxis treatments offer similar safety profile, it was assumed that other comparators have the same probability of AEs as BeneFIX. The influence of the AEs, and therefore of this assumption, was investigated in the section B.3.10.2, and has shown to have negligible impact on the results.

Table 30: Etranacogene dezaparvovec disutility due to adverse events

Adverse event	Disutility	Source	Total Annual AE duration (days)	Weekly AE probability
ALT increased	0.05	NICE TA561[150]	7.00	0.15%
Headache	0.03	Sullivan et al 2011[151]	7.00	0.13%
Influenza like illness	0.08	NICE TA533[152]	7.00	0.12%
AST increased	0.05	NICE TA561[150]	7.00	0.09%
Fatigue	0.05	Hagiwara et al 2018[153]	7.00	0.07%
Blood creatine phosphokinase increased	0.05	NICE TA561[150]	7.00	0.07%
Nausea	0.06	Hagiwara et al 2018[153]	7.00	0.07%
Dizziness	0.02	Matza et al 2019[154]	7.00	0.07%
Infusion-related reactions	0.20	NICE TA561[150]	7.00	0.05%
Arthralgia	0.01	Hagiwara et al 2018[153]	7.00	0.05%
Infection	0.22	Matza et al 2019[154]	7.00	0.00%
Body pain*	0.12	Hagiwara et al 2018[153]	7.00	0.00%

Abbreviations: AE, Adverse event; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; NICE, National Institute for Health and Care Excellence. Note: * Body pain refers to the acute or chronic joint pain experienced by patients with haemophilia B

.

Table 31: Comparators disutility due to adverse events

	Disutility	Source	Total AE duration (days)	Weekly AE probability
ALT increased	0.05	NICE TA561[150]	7.00	0%
Headache	0.03	Sullivan et al 2011[151]	7.00	0.33%
Influenza like illness	0.08	NICE TA533[152]	7.00	0%
AST increased	0.05	NICE TA561[150]	7.00	0%
Fatigue	0.05	Hagiwara et al 2018[153]	7.00	0%
Blood creatine phosphokinase increased	0.05	NICE TA561[150]	7.00	0%
Nausea	0.06	Hagiwara et al 2018[153]	7.00	0%
Dizziness	0.02	Matza et al 2019[154]	7.00	0%
Infusion-related reactions	0.20	NICE TA561[150]	7.00	0%
Arthralgia	0.01	Hagiwara et al 2018[153]	7.00	0%
Infection	0.22	Matza et al 2019[154]	7.00	0.17%
Body pain	0.12	Hagiwara et al 2018[153]	7.00	0.17%

Abbreviations: AE, Adverse event; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; NICE, National Institute for Health and Care Excellence. Note: * Body pain refers to the acute or chronic joint pain experienced by patients with haemophilia B

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

The utilities applied in the economic model are those that originate from the clinical trial of HOPE-B, mentioned in Section B.3.4.1.[14] The utility values for etranacogene dezaparvovec are post-treatment 24-month and for the comparators they are the final lead-in utility values.

Table 32 summaries the utility values applied in the economic model. The comparators final lead-in utility values have a ~[redacted] disutility compared to etranacogene dezaparvovec post-treatment 24-month utility values. Clinical experts validated the ~[redacted] disutility applied to Factor IX prophylaxis treatment, describing it as

'conservative and a minimum, but reasonable'.[6] This disutility refers to patients living a precautionary life, as they fear bleeding events and lack of freedom to enjoy usual activities, as described in the dimensions of EQ-5D.

The HRQoL disutility values for bleed events utilised in the economic model are taken from the US-ICER 2022 gene therapy for haemophilia B evidence report mentioned in Section B.3.4.1.[139] The disutility from bleeds is not intrinsically part of the health states themselves. Rather, they are treated like 'adverse' events associated with the relevant health states, for the following reasons. Firstly, the cycle length is a week whereas clinical experts have identified that non-joint (joint) bleeds last two (four) days. Secondly, it allows the disutility of the bleed to be time independent of the Factor IX prophylaxis treatment.

The disutilities in Table 30 are the scaled disutilities applied in the model in line with the appropriate durations of the bleeds, accurate to two decimal places. Clinical experts have confirmed that the average duration of a non-joint bleed is two days, and four days for a joint bleed.[6] The gross utility of a non-joint bleed is -0.16, and -0.28 for a joint bleed.[139]

Table 32: Summary of utility values for cost-effectiveness analysis

Health state	Utility values for etranacogene dezaparvovec: (SE)	Utility values for comparators (SE)	95% CI Etranacogene dezaparvovec	95% CI comparators	Reference in submission (section)	Justification
No bleeds	[redacted]	[redacted]	[redacted]	[redacted]	B.2.6.6.2	HOPE-B[14]
Non-joint bleed	[redacted]	[redacted]	[redacted]	[redacted]	B.2.6.6.2	HOPE-B[14]
Joint bleed	[redacted]	[redacted]	[redacted]	[redacted]	B.2.6.6.2	HOPE-B[14]
Death	0	0	-	-	B.2.6.6.2	HOPE-B[14]
Adverse reactions		Adverse reaction Table 30 and Table 31 in section B.3.4.4				
Disutility of non-joint bleed per cycle	0.05 (-)	0.05 (-)	-	-	B.3.4.1	US-ICER (2022)[139]
Disutility of joint bleed per cycle	0.16 (-)	0.16 (-)	-	-	B.3.4.1	US-ICER (2022)[139]

Abbreviations: HOPE-B, Health Outcomes with Padua Gene, Evaluation in Haemophilia B; US-ICER, United States Institute for Clinical and Economic Review

B.3.5 Cost and healthcare resource use identification, measurement and valuation

In appendix I describe how relevant cost and healthcare resource data were identified.

An SLR was conducted to identify relevant cost or resource use studies for incorporation in the model. The searches were run on the 18th August 2021 and updated on 17th October 2022. Full details of the SLR search strategy, study selection process and results are presented in Appendix H.

The following cost categories were included in the model:

- Drug acquisition costs
- Administration costs
- Follow-up costs for etranacogene dezaparvovec
- Monitoring costs
- Bleed-related management costs
- Adverse event costs

The economic analysis was conducted from an NHS and PSS perspective and therefore included only costs that would be incurred by the NHS and PSS. Cost inputs were based on British National Formulary (BNF), Department of Health and Social Care (DHSC), Monthly Index of Medical Specialities (MIMS), National Schedule for NHS (2020/2021), and Personal Social Services Research Unit (PSSRU).[140,155-158]

B.3.5.1 Intervention and comparators' costs and resource use

3.5.1.1 Etranacogene dezaparvovec drug acquisition and administration cost

The drug acquisition costs for etranacogene dezaparvovec a one-time, intravenous infusion gene therapy is detailed in Table 33 below. Administration of etranacogene dezaparvovec was applied as a one-off cost in cycle 1. The included administration costs detailed in Table 34 were:

- Initial screening cost (FibroScan)
- Blood test (x2)
- Abdominal ultrasound
- Steroids and/or diphenhydramine
- Wound management products (gauze, plaster)

Table 33: Etranacogene dezaparvovec drug acquisition cost

Drug	Description	Pack unit size (quantity)	Treatment dose	Treatment cost (List price)
etranacogene dezaparvovec	intravenous infusion	1	2×10^{13} GC/kg bw	£2,600,000

Abbreviations: GC, genome copies; kg, kilogram; bw, body weight

Table 34: Etranacogene dezaparvovec administration cost

Resource	Resource use per year	Cost per resource	Source
Initial screening cost (FibroScan)	1.00	£225.00	NICE[159]
Blood test	2.00	£3.78	NICE Reference[140]
Abdominal ultrasound	1.00	£396.47	NICE Reference[140]
Steroids and/or diphenhydramine	1.00	£6.50	BNF[160]
Wound management products	1.00	£0.02	Assumption[6]
Total		£635.55	

Abbreviations: BNF, British National Formulary; NICE, National Institute for Health and Care Excellence

3.5.1.2 Comparators drug acquisition and administration cost

Please refer to the Appendix K for the information on the comparators drug and administration cost.

3.5.1.3 Etranacogene dezaparvovec follow-up costs

Follow-up costs for etranacogene dezaparvovec, as described in Table 35, were applied in the CE model with a varied rate in first year of treatment versus subsequent years:

In year 1:

- Weekly follow-up sessions from week 1 to 12 – collection of vital signs at all visits are assumed to be with a nurse at the hospital, liver function tests performed twice every week.
- Monthly follow-up sessions from month 4 to 12 - vital signs at all visits are assumed to be with a nurse at the hospital

In year 2-5:

- Long-term follow-up for 5 years to include once annual abdominal ultrasound and annual Haemophilia Joint Health Score assessment with a nurse at month 12.

Table 35: Follow-up costs for etranacogene dezaparvovec

Intervention	Unit costs (£)	Annual resource use	Total cost per year (2020/21)	Source
Etranacogene dezaparvovec Year 1	Nurse visit 2019/20: £38 Inflated to 2020/21: £39.17	18[6]	£ 795.86	PSSRU[158]
	Liver function test 2019/20: £3.67 Inflated to 2020/21: £3.78	24[6]		
Etranacogene dezaparvovec (Year 2-5)	Abdominal ultrasound (NHS code NZ21Z Haemophilia service) 2019/20: £384.62 Inflated to 2020/21: £396.47	1[6]	£ 396.47	NHS Reference cost[140]

Abbreviations: NHS, National Health Service; PSSRU, Personal Social Services Research Unit; SoC, Standard of care.

The model also included costs for subsequent treatment for patients whose Factor IX level has fallen below 2% on etranacogene dezaparvovec, as seen in Table 36.

Table 36: Etranacogene dezaparvovec subsequent therapy costs for patients whose Factor IX level has fallen below 2%

	Treatment cost per year (£)	Admin cost per year (£)
Alprolix	[redacted]	[redacted]
BeneFIX		
Idelvion		
Refixia		

Note: The cost of treatment and administration for comparators is outlined in Appendix K.

B.3.5.2 Health-state unit costs and resource use

Health-states are associated with health-state dependant costs and resource use. There are no additional costs incurred in health state 1: no bleeds, and in health state 4: death. Health state 2: non-joint bleeds, and health state 3: joint bleeds, incur additional costs associated with the on-demand treatment of non-joint and joint bleeds, comprising of disease management costs, cost of on-demand Factor IX use associated with each bleed, and the administrative cost per administration of on-demand Factor IX treatments.

Table 37 depicts the resource use per non-joint and joint bleed events, the unit cost (£) per one unit of resource, and the total cost per year (£) of the overall disease management costs. Table 38 depicts the treatment cost per dose of Factor IX for every bleed (£) outlined in Table 38, furthermore, it presents the results of Table 39 of administrative cost that are incurred per bleed for the particular comparator. Overall, it serves to outline the costs that patients in health state 2: non-joint, and health state 3: joint bleed, incur when the respective bleed occurs. *Note: Administration cost per bleed does not include home delivery cost as it will be administered in a clinical setting.

Table 39 summarises the health-state dependant costs per health-state by comparators. These health-state dependant costs and resource use follow recommended clinical practice for the outlined health states as per section 1.3.2.1.

The unit costs of the resources used specifically in the health-states mentioned were sourced from the National Schedule of NHS Costs 2019/2020, PSSRU 2021 and the resource uses were advised by UK clinical experts.[6,140,158]

Table 37: Disease management and event-related costs

Resource	Unit cost (£)	Resource use per bleed event[48]	Total cost per bleed (£)[48]
Haematologist visit	324.97	0.97	315.22
Orthopaedist visit	125.67	0.97	121.90
Accident and emergency visit	380.11	0.18	68.42
Inpatient hospital stay	3,081.01	0.29	878.09
Total (£)	-	-	1,383.64

Source: O'Hara et al., 2018.[48]

Table 38: Cost per bleed for the intervention and comparators – with administrative costs per bleed

Treatment	Treatment cost per dose of Factor IX for every bleed (£)	Administrative cost (£)*
Alprolix	5,616.60	0
BeneFIX	2,066.91	0
Idelvion	7,336.68	0
Refixia	8,247.89	1.26

*Note: Administration cost per bleed does not include home delivery cost as it will be administered in a clinical setting.

Table 39: Healthcare resource use per cycle per health-state

Health state	Items	Values				Reference in submission (section)
Health state 1: No bleeds	Total	£0				Section 1.3.2.1
Health state 2: non-joint bleeds	Disease/ bleed management costs per cycle[a]	Ap.	Bf.	Id.	Rf.	Table 3.5.2.4
		£26.54	£26.54	£26.54	£26.54	
	Cost of Factor IX treatment per non-joint bleed	Ap.	Bf.	Id.	Rf.	Table 3.5.2.2
		£5,616.60	£2,066.91	£7,336.68	£8,247.89	
	Administrative costs per bleed for non-joint bleed	Ap.	Bf.	Id.	Rf.	Table 3.5.2.2
		£10.62	£4.41	£10.79	£11.56	

	Total[b] cost of health state 2 by comparator	Ap.	Bf.	Id.	Rf.		
		£5,653.76	£2,097.86	£7,374.01	£8,285.99		
Health state 3: joint bleeds	Disease/ bleed management costs per cycle	Ap.	Bf.	Id.	Rf.		Table 3.5.2.4
		£26.54	£26.54	£26.54	£26.54		
	Cost of Factor IX treatment per joint bleed	Ap.	Bf.	Id.	Rf.		Table 3.5.2.2
		£5,616.60	£2,066.91	£7,336.68	£8,247.89		
	Administrative costs per bleed for joint bleed	Ap.	Bf.	Id.	Rf.		Table 3.5.2.2
		£10.62	£4.41	£10.79	£11.56		
	Total[c] cost of health state 3 by comparator	Ap.	Bf.	Id.	Rf.		
		£5,653.76	£2,097.86	£7,374.01	£8,285.99		
Health state 4: death	Total	£0					Section 1.3.2.1

Abbreviations: Ed, etranacogene dezaparvovec; Ap, Alprolix; Bf, BeneFIX; Id, Idelvion; Rf, Refixia
[a]disease/bleed management costs per cycle are calculated as disease management cost per year divided by weeks in a year.
[b]total cost of health state 2 by comparator are given as a sum of disease management cost per cycle, cost of Factor IX prophylaxis per non-joint bleed and administrative cost per dose for non-joint bleed.
[c]total cost of health state 3 by comparator are given as a sum of disease management cost per cycle, cost of Factor IX prophylaxis per joint bleed and administrative cost per dose for joint bleed.

B.3.5.3 Adverse reaction unit costs and resource use

As per Section B.2.10, etranacogene dezaparvovec has acceptable safety standards and is well tolerated. Section B.3.4.4 details the role of adverse events in the economic model. Table 40 outlines the adverse events and their respective probabilities that have occurred in the HOPE-B trial which have been included in the economic model.[14] The probabilities have been scaled to represent weekly probabilities to ensure consistency considering the cycle length applied for the Markov states, although they themselves are not inherently linked to any Markov state. There is no data on the adverse events that may occur when undergoing Factor IX prophylaxis from the Alprolix, Idelvion and Refixia comparators, therefore BeneFIX has been used to represent all Factor IX products, as in Table 40.

The unit costs of the resources associated with these adverse events were sourced from the National Schedule of NHS Costs 2019/2020, PSSRU 2021.[6,140,158]

Table 40: Adverse event unit costs

Adverse Event [AE]	Total AE dur-ation days	Unit cost (£)	AE probability per week (Intervention)	AE probability per week (Comparators)	AE expected cost (Intervention)	AE expected cost (Comparators)
ALT increased	7	606.64	0.15%	0%	£0.90	£0
Headache	7	0.13	0.13%	0.33%	£0.00	£0.00
Influenza like illness	7	7.71	0.12%	0%	£0.01	£0
AST increased	7	0	0.09%	0%	£0	£0
Fatigue	7	0	0.07%	0%	£0	£0
Blood creatine phosphor-kinase increased	7	0	0.07%	0%	£0	£0
Nausea	7	0.85	0.07%	0%	£0.00	£0
Dizziness	7	1.36	0.07%	0%	£0.00	£0
Infusion related reactions	7	6.50	0.05%	0%	£0.00	£0
Arthralgia	7	0.13	0.05%	0%	£0.00	£0
Infection	7	1,635.46	0%	0.17%	£0	£2.79
Body pain	7	187.24	0%	0.17%	£0	£0.32
Total	-	-	-	-	£0.91	£3.11

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase

B.3.5.4 Miscellaneous unit costs and resource use

Disease monitoring costs fall under the miscellaneous unit costs and resource use because they are independent of the intervention/comparators, health-states, and adverse events. Disease monitoring costs are incurred by all haemophilia B patients. UK clinical experts were consulted to ensure the resource use per year in Table 41 comprehensively covers the care required by haemophilia B patients who are eligible for etranacogene dezaparvovec.[6]

Table 41: Disease monitoring costs

Resource	Unit costs (£)	Resource use per year	Total cost per year (£)
Joint scans	396.47	0.5	198.23
Haematologist visit	324.97	6	1,949.84
Orthopaedist visit	125.67	1.5	188.51
Psychologist/psychiatrist visit	185.38	6	1,112.27
Physiotherapist	62.57	12	750.83
Abdominal ultrasound	397.47	1	397.47
Dental check-up	197	2	394
Nurse visit	39.17	18	705.07
Lab screening	42.95	2	85.91
Total	-	-	5,781.13

The unit costs of the resources used were sourced from the National Schedule of NHS Costs 2019/2020, PSSRU 2021.Unit costs and resource use per year were validated by UK clinical experts.[6,140,158]

3.5.4.1 Societal costs

Etranacogene dezaparvovec reduces non-joint and joint bleed rates relative to the comparators as outlined in Section B.2.9. The current practice recommends that each bleed event is treated with a Factor IX product, which leads to a negative impact on the ability to work during the duration of each bleed. Thereby, the treatment of haemophilia B patients with etranacogene dezaparvovec offers societal benefits relative to the comparators in terms of the value to society, which stem from the costs of productive workdays forgone. This section serves as an outline of the societal costs used in the scenario analysis in section B.3.10.3.

UK clinical experts have specified that on average the duration of a non-joint bleed is two days and four days for a joint bleed. The modelling of societal costs entails estimating the effect of the workdays missed by full and part-time labourers who may suffer such bleeds. Full-time workers are assumed to work Monday-Friday 8-hour shifts, and part-time workers are assumed to work Monday-Tuesday 8-hour shifts. The choice of these workdays should not be contentious since bleeding events are treated as independent of the weekday. For pragmatic purposes, bleeds occur at 06:00 so that two whole (four whole) workdays are missed with non-joint (joint) bleeds. No workdays are lost if the bleeds last over the weekend days which are treated as non-working days. Table 42 shows the average workdays lost, which will indicate societal costs as these will be augmented by average wages and average employment type figures for the cohort's age at the particular cycle in the model.

Table 42. Estimates of the workdays lost due to bleeding events

	Full-time (non-joint bleeds)	**Full-time (joint bleeds)**	**Part-time (non-joint bleeds)**	**Part-time (joint bleeds)**
Average workdays per week	5	5	2	2
Average workdays lost due to bleed per week	1.43	2.86	0.57	1.28
Percentage of the workdays lost per week	28.57%	57.14%	28.57%	64.29%

Table is accurate to two decimal places

B.3.6 Severity

The model assumes that Haemophilia B patients experience no excess mortality, this technology does not meet the criteria for the severity modifier.

B.3.7 Uncertainty

Etranacogene dezaparvovec is a genetic treatment, which is expected to have a lifelong effect, therefore long-term durability is the crucial input in the analysis. Statistical modelling was employed as the best available data to support the long-term

durability, which has been validated by KOL opinion. The associated incremental QALYs as well as the cost savings are determined by the durability of the treatment, it was further evaluated in the scenario analysis in section B.3.10.3.

B.3.8 Summary of base-case analysis inputs and assumptions

B.3.8.1 Summary of base-case analysis inputs

Table 43 provides a comprehensive list of all the variables used in the economic model.

Table 43: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Cohort size	1000	-	B.3.2.2
Baseline age	41.5 (Table 8)	-	B.2.3.3
Number of cycles	3077	-	B.3.2.2
Percentage of males	100% (Table 8)	-	B.2.3.3
Average weight (kg)	85.1 (Table 8)	-	B.2.3.3
Discount rate-effects	3.5%	-	Reference case
Discount rate-costs	3.5%	-	Reference case
Intervention list price	£2,600,000.00 (Table 33)	-	B.3.5.1.1
Intervention administration cost	£635.55 (Table 34)	SD, 127.11	B.3.5.1
Intervention follow-up costs – year 1	£795.86 (Table 38)	SD, 159.136	B.3.5.3
Intervention follow-up costs – years 2-5	£396.47 (Table 38)	SD, 79.294	B.3.5.3
Intervention monitoring costs, per year	£5,781.13 (Table 44)	SD, 1156.226	B.3.5.4
Intervention non-joint bleed related management costs per cycle	£2,097.86 (Table 42)	SD, 419.772	B.3.5.2
Intervention joint bleed related management costs per cycle	£2,097.86 (Table 42)	SD, 419.772	B.3.5.2
Intervention expected adverse events unit cost total per cycle	£0.91 (Table 43)	SD, 0.182	B.3.5.3

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Alprolix pack list price	£600.00 (Table 35)	-	B.3.5.1.2
Alprolix weighted annual doses	50.61 (Table 36)	-	B.3.5.1.2
Alprolix administration cost per cycle	£537.36 (Table 37)	SD, 107.472	B.3.5.1.2
Alprolix monitoring costs, per year	£5,781.13 (Table 44)	SD, 1156.226	B.3.5.4
Alprolix non-joint bleed related management costs per cycle	£5,653.76 (Table 42)	SD, 1130.752	B.3.5.2
Alprolix joint bleed related management costs per cycle	£5,653.76 (Table 42)	SD, 1130.752	B.3.5.2
Alprolix expected adverse events unit cost total per cycle	£0	-	B.3.5.3
BeneFIX pack list price	£151.80 (Table 35)	-	B.3.5.1.2
Benefix weighted annual doses	121.75 (Table 36)	-	B.3.5.1.2
BeneFIX administration cost per year	£537.36 (Table 37)	SD, 107.472	B.3.5.1.2
BeneFIX monitoring costs, per year	£5,781.13 (Table 44)	SD, 1156.226	B.3.5.4
BeneFIX non-joint bleed related management costs per cycle	£2,097.86 (Table 42)	SD, 419.772	B.3.5.2
BeneFIX joint bleed related management costs per cycle	£2,097.86 (Table 42)	SD, 419.772	B.3.5.2
BeneFIX expected adverse events unit cost total per cycle	£0.78 (Table 43)	SD, 0.156	B.3.5.3
Idelvion pack list price	£522.50 (Table 35)	-	B.3.5.1.2
Idelvion weighted annual doses	49.8 (Table 36)	-	B.3.5.1.2
Idelvion administration cost per year	£537.36 (Table 37)	SD, 107.472	B.3.5.1.2
Idelvion monitoring costs, per year	£5,781.13 (Table 44)	SD, 1156.226	B.3.5.4

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Idelvion non-joint bleed related management costs per cycle	£7,374.01 (Table 42)	SD, 1474.802	B.3.5.2
Idelvion joint bleed related management costs per cycle	£7,374.01 (Table 42)	SD, 1474.802	B.3.5.2
Idelvion expected adverse events unit cost total per cycle	£0	-	B.3.5.3
Refixia pack list price	£1221.50 (Table 35)	-	B.3.5.1.2
Refixia weighted annual doses	52.18 (Table 36)	-	B.3.5.1.2
Refixia administration cost	£603.11 (Table 37)	SD, 120.622	B.3.5.1.2
Refixia monitoring costs, per year	£5,781.13 (Table 44)	SD, 1156.226	B.3.5.4
Refixia non-joint bleed related management costs per cycle	£8,285.99 (Table 42)	SD, 1657.198	B.3.5.2
Refixia joint bleed related management costs per cycle	£8,285.99 (Table 42)	SD, 1657.198	B.3.5.2
Refixia expected adverse events unit cost total per cycle	£0	-	B.3.5.3
Percentage of workdays lost – Full-time non-joint bleed	28.57% (Table 45)	-	B.3.5.4.1
Percentage of workdays lost – Full-time joint bleed	57.14% (Table 45)	-	B.3.5.4.1
Percentage of workdays lost – part time non-joint bleeds	28.57% (Table 45)	-	B.3.5.4.1
Percentage of workdays lost – part time joint bleed	64.29% (Table 45)	-	B.3.5.4.1
Average full-time salary in England and Wales (£) per annum	£38,131.00 (Table 45)	-	B.3.5.4.1
Average part-time salary in England	£13,549.00 (Table 45)	-	B.3.5.4.1

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
and Wales (£) per annum			
Intervention health state 1 – utility	[redacted] (Table 32)	S.E, [redacted]	B.3.4.5
Intervention health state 2 - utility	[redacted] (Table 32)	S.E, [redacted]	B.3.4.5
Intervention health state 3 - utility	[redacted] (Table 32)	S.E, [redacted]	B.3.4.5
Intervention health state 4 - utility	0 (Table 32)	-	B.3.4.5
Alprolix health state 1 - utility	[redacted] (Table 32)	S.E, [redacted]	B.3.4.5
Alprolix health state 2 - utility	[redacted] (Table 32)	S.E, [redacted]	B.3.4.5
Alprolix health state 3 - utility	[redacted] (Table 32)	S.E, [redacted]	B.3.4.5
Alprolix health state 4 - utility	0 (Table 32)	-	B.3.4.5
BeneFIX health state 1 - utility	[redacted] (Table 32)	S.E, [redacted]	B.3.4.5
BeneFIX health state 2 - utility	[redacted] (Table 32)	S.E, [redacted]	B.3.4.5
BeneFIX health state 3 - utility	[redacted] (Table 32)	S.E, [redacted]	B.3.4.5
BeneFIX health state 4 - utility	0 (Table 32)	-	B.3.4.5
Idelvion health state 1 - utility	[redacted] (Table 32)	S.E, [redacted]	B.3.4.5
Idelvion health state 2 - utility	[redacted] (Table 32)	S.E, [redacted]	B.3.4.5
Idelvion health state 3 - utility	[redacted] (Table 32)	S.E, [redacted]	B.3.4.5
Idelvion health state 4 - utility	0 (Table 32)	-	B.3.4.5
Refixia health state 1 - utility	[redacted] (Table 32)	S.E, [redacted]	B.3.4.5
Refixia health state 2 - utility	[redacted] (Table 32)	S.E, [redacted]	B.3.4.5
Refixia health state 3 - utility	[redacted] (Table 32)	S.E, [redacted]	B.3.4.5
Refixia health state 4 - utility	0 (Table 32)	-	B.3.4.5
Intervention non-joint bleed disutility	0.05 (Table 32)	SD, 0.01	B.3.4.5
Intervention joint bleed disutility	0.16 (Table 32)	SD, 0.032	B.3.4.5

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Alprolix non-joint bleed disutility	0.05 (Table 32)	SD, 0.01	B.3.4.5
Alprolix joint bleed disutility	0.16 (Table 32)	SD, 0.032	B.3.4.5
BeneFIX non-joint bleed disutility	0.05 (Table 32)	SD, 0.01	B.3.4.5
BeneFIX joint bleed disutility	0.16 (Table 32)	SD, 0.032	B.3.4.5
Idelvion non-joint bleed disutility	0.05 (Table 32)	SD, 0.01	B.3.4.5
Idelvion joint bleed disutility	0.16 (Table 32)	SD, 0.032	B.3.4.5
Refixia non-joint bleed disutility	0.05 (Table 32)	SD, 0.01	B.3.4.5
Refixia joint bleed disutility	0.16 (Table 32)	SD, 0.032	B.3.4.5
Disutility for ALT increased	0.05 (Table 32)	SD, 0.01	B.3.4.4
Disutility for headache	0.03 (Table 32)	SD, 0.006	B.3.4.4
Disutility for influenza like illness	0.08 (Table 32)	SD, 0.016	B.3.4.4
Disutility for AST increased	0.05 (Table 32)	SD, 0.01	B.3.4.4
Disutility for fatigue	0.049 (Table 32)	SD, 0.098	B.3.4.4
Disutility for blood creatine phosphokinase increased	0.05 (Table 32)	SD, 0.01	B.3.4.4
Disutility for nausea	0.062 (Table 32)	SD, 0.0124	B.3.4.4
Disutility for dizziness	0.02 (Table 32)	SD, 0.004	B.3.4.4
Disutility for infusion-related reactions	0.20 (Table 32)	SD, 0.05	B.3.4.4
Disutility for arthralgia	0.013 (Table 32)	SD, 0.0026	B.3.4.4
Disutility for infection	0.22 (Table 32)	SD, 0.044	B.3.4.4
Disutility for body pain	0.123 (Table 32)	SD, 0.024	B.3.4.4
Per cycle intervention probability of ALT increased	0.15% (Table 30)	SD, 0.00	B.3.4.4
Per cycle intervention	0.13% (Table 30)	SD, 0.00	B.3.4.4

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
probability of headache			
Per cycle intervention probability of influenza like illness	0.12% (Table 30)	SD, 0.00	B.3.4.4
Per cycle intervention probability of AST increased	0.09% (Table 30)	SD, 0.00	B.3.4.4
Per cycle intervention probability of fatigue	0.07% (Table 30)	SD, 0.00	B.3.4.4
Per cycle intervention probability of blood creatine phosphokinase increased	0.07% (Table 30)	SD, 0.00	B.3.4.4
Per cycle intervention probability of nausea	0.07% (Table 30)	SD, 0.00	B.3.4.4
Per cycle intervention probability of dizziness	0.07% (Table 30)	SD, 0.00	B.3.4.4
Per cycle intervention probability of infusion-related reactions	0.05% (Table 30)	SD, 0.00	B.3.4.4
Per cycle intervention probability of arthralgia	0.05% (Table 30)	SD, 0.00	B.3.4.4
Per cycle intervention probability of infection	0.00% (Table 30)	-	B.3.4.4
Per cycle intervention probability of body pain	0.00% (Table 30)	SD, 0.00	B.3.4.4
Per cycle comparator probability of ALT increased	0% (Table 31)	-	B.3.4.4

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Per cycle comparator probability of headache	0.33% (Table 31)	SD, 0.066	B.3.4.4
Per cycle comparator probability of influenza like illness	0.00% (Table 31)	-	B.3.4.4
Per cycle comparator probability of AST increased	0.00% (Table 31)	-	B.3.4.4
Per cycle comparator probability of fatigue	0.00% (Table 31)	-	B.3.4.4
Per cycle comparator probability of blood creatine phosphokinase increased	0.00% (Table 31)	-	B.3.4.4
Per cycle comparator probability of nausea	0.00% (Table 31)	-	B.3.4.4
Per cycle comparator probability of dizziness	0.00% (Table 31)	-	B.3.4.4
Per cycle comparator probability of infusion-related reactions	0.00% (Table 31)	-	B.3.4.4
Per cycle comparator probability of arthralgia	0.171% (Table 31)	SD, 0.00	B.3.4.4
Per cycle comparator probability of infection	0.173% (Table 31)	SD, 0.00	B.3.4.4
Per cycle comparator probability of body pain	0.173% (Table 31)	SD, 0.00	B.3.4.4
Intervention ABR	[redacted] (Table 28)	SD, [redacted]	B.3.3.1
Intervention AjBR	[redacted] (Table 28)	SD, [redacted]	B.3.3.1

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Alprolix ABR	[redacted] (Table 28)	SD, [redacted]	B.3.3.1
Alprolix AjBR	[redacted] (Table 28)	SD, [redacted]	B.3.3.1
BeneFIX ABR	[redacted] (Table 28)	SD, [redacted]	B.3.3.1
BeneFIX AjBR	[redacted] (Table 28)	SD, [redacted]	B.3.3.1
Idelvion ABR	[redacted] (Table 28)	SD, [redacted]	B.3.3.1
Idelvion AjBR	[redacted] (Table 28)	SD, [redacted]	B.3.3.1
Refixia ABR	[redacted] (Table 28)	SD, [redacted]	B.3.3.1
Refixia AjBR	[redacted] (Table 28)	SD, [redacted]	B.3.3.1
Probability of no-bleed - Intervention	[redacted]% (Table 29)	Transitional probability uncertainty is dependent on the uncertainty surrounding the appropriate bleed rates	B.3.3.3
Probability of non-joint bleed - Intervention	[redacted] % (Table 29)		B.3.3.3
Probability of joint bleed - Intervention	[redacted]% (Table 29)		B.3.3.3
Probability of no-bleed – Alprolix	96.18% (Table 29)		B.3.3.3
Probability of non-joint bleed - Alprolix	1.99% (Table 29)		B.3.3.3
Probability of joint bleed - Alprolix	1.82% (Table 29)		B.3.3.3
Probability of no-bleed - BeneFIX	92.12% (Table 29)		B.3.3.3
Probability of non-joint bleed - BeneFIX	6.31% (Table 29)		B.3.3.3
Probability of joint bleed - BeneFIX	1.57% (Table 29)		B.3.3.3
Probability of no-bleed - Idelvion	96.27% (Table 29)		B.3.3.3
Probability of non-joint bleed - Idelvion	0.69% (Table 29)		B.3.3.3
Probability of joint bleed - Idelvion	3.04% (Table 29)		B.3.3.3
Probability of no-bleed - Refixia	97.61% (Table 29)		B.3.3.3
Probability of non-joint bleed - Refixia	1.51% (Table 29)		B.3.3.3
Probability of joint bleed - Refixia	0.88 % (Table 29)		B.3.3.3
Probability of death at age 41	0.00% (Table 29)	-	B.3.3.3
Probability of death at age 42	0.00% (Table 29)	-	B.3.3.3

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Probability of death at age 43	0.00% (Table 29)	-	B.3.3.3
Probability of death at age 44	0.00% (Table 29)	-	B.3.3.3
Probability of death at age 45	0.00%(Table 29)	-	B.3.3.3
Probability of death at age 46	0.00%(Table 29)	-	B.3.3.3
Probability of death at age 47	0.01%(Table 29)	-	B.3.3.3
Probability of death at age 48	0.01%(Table 29)	-	B.3.3.3
Probability of death at age 49	0.01%(Table 29)	-	B.3.3.3
Probability of death at age 50	0.01%(Table 29)	-	B.3.3.3
Probability of death at age 51	0.01%(Table 29)	-	B.3.3.3
Probability of death at age 52	0.01%(Table 29)	-	B.3.3.3
Probability of death at age 53	0.01%(Table 29)	-	B.3.3.3
Probability of death at age 54	0.01%(Table 29)	-	B.3.3.3
Probability of death at age 55	0.01%(Table 29)	-	B.3.3.3
Probability of death at age 56	0.01%(Table 29)	-	B.3.3.3
Probability of death at age 57	0.01%(Table 29)		B.3.3.3
Probability of death at age 58	0.01%(Table 29)	-	B.3.3.3
Probability of death at age 59	0.01%(Table 29)	-	B.3.3.3
Probability of death at age 60	0.01%(Table 29)	-	B.3.3.3
Probability of death at age 61	0.02%(Table 29)	-	B.3.3.3
Probability of death at age 62	0.02%(Table 29)	-	B.3.3.3
Probability of death at age 63	0.02%(Table 29)	-	B.3.3.3
Probability of death at age 64	0.02%(Table 29)	-	B.3.3.3
Probability of death at age 65	0.02%(Table 29)	-	B.3.3.3

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Probability of death at age 66	0.03%(Table 29)	-	B.3.3.3
Probability of death at age 67	0.03%(Table 29)	-	B.3.3.3
Probability of death at age 68	0.03%(Table 29)	-	B.3.3.3
Probability of death at age 69	0.03%(Table 29)	-	B.3.3.3
Probability of death at age 70	0.04%(Table 29)	-	B.3.3.3
Probability of death at age 71	0.04%(Table 29)	-	B.3.3.3
Probability of death at age 72	0.04%(Table 29)	-	B.3.3.3
Probability of death at age 73	0.05%(Table 29)	-	B.3.3.3
Probability of death at age 74	0.05%(Table 29)	-	B.3.3.3
Probability of death at age 75	0.06%(Table 29)	-	B.3.3.3
Probability of death at age 76	0.07%(Table 29)	-	B.3.3.3
Probability of death at age 77	0.08%(Table 29)	-	B.3.3.3
Probability of death at age 78	0.09%(Table 29)	-	B.3.3.3
Probability of death at age 79	0.09%(Table 29)	-	B.3.3.3
Probability of death at age 80	0.11%(Table 29)	-	B.3.3.3
Probability of death at age 81	0.12%(Table 29)	-	B.3.3.3
Probability of death at age 82	0.13%(Table 29)	-	B.3.3.3
Probability of death at age 83	0.15%(Table 29)	-	B.3.3.3
Probability of death at age 84	0.17%(Table 29)	-	B.3.3.3
Probability of death at age 85	0.19%(Table 29)	-	B.3.3.3
Probability of death at age 86	0.21%(Table 29)	-	B.3.3.3
Probability of death at age 87	0.23%(Table 29)	-	B.3.3.3
Probability of death at age 88	0.26%(Table 29)	-	B.3.3.3

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Probability of death at age 89	0.29%(Table 29)	-	B.3.3.3
Probability of death at age 90	0.31%(Table 29)	-	B.3.3.3
Probability of death at age 91	0.35%(Table 29)	-	B.3.3.3
Probability of death at age 92	0.38%(Table 29)	-	B.3.3.3
Probability of death at age 93	0.43%(Table 29)	-	B.3.3.3
Probability of death at age 94	0.47%(Table 29)	-	B.3.3.3
Probability of death at age 95	0.51%(Table 29)	-	B.3.3.3
Probability of death at age 96	0.56%(Table 29)	-	B.3.3.3
Probability of death at age 97	0.6%(Table 29)	-	B.3.3.3
Probability of death at age 98	0.64%(Table 29)	-	B.3.3.3
Probability of death at age 99	0.71%(Table 29)	-	B.3.3.3
Probability of death at age 100	0.75%(Table 29)	-	B.3.3.3
Proportion of patients free of prophylaxis, year 1	100%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 2	100%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 3	100%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 4	100%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 5	100%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 6	100%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 7	99.9%	-	B.3.3.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Proportion of patients free of prophylaxis, year 8	99.8%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 9	99.8%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 10	99.8%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 11	99.7%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 12	99.3%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 13	99.1%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 14	98.6%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 15	97.9%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 16	97.3%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 17	96.3%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 18	95.3%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 19	94.5%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 20	93%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 21	91.1%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 22	89.2%	-	B.3.3.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Proportion of patients free of prophylaxis, year 23	87.8%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 24	85.9%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 25	83.1%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 26	80.9%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 27	79%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 28	77%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 29	73.6%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 30	71.8%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 31	69.2%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 32	66.8%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 33	64%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 34	62%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 35	60.1%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 36	57.9%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 37	55.3%	-	B.3.3.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Proportion of patients free of prophylaxis, year 38	53.3%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 39	51.3%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 40	49.2%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 41	48%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 42	46.1%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 43	44.5%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 44	42.1%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 45	40.4%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 46	38.9%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 47	37.7%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 48	36.5%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 49	35.3%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 50	33.9%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 51	32.2%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 52	31%	-	B.3.3.2

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Proportion of patients free of prophylaxis, year 53	30.3%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 54	28.2%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 55	26.8%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 56	24.9%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 57	23.5%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 58	23.4%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 59	22.6%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 60	21.5%	-	B.3.3.2
Proportion of patients free of prophylaxis, year 61 and beyond	0%	-	B.3.3.2

B.3.8.2 Assumptions

Table 44: Assumptions underpinning the base-case of the economic model

Assumption	Justification	Reference in submission	Addressed in scenario analysis
The population of the HOPE-B trial is representative of the haemophilia B patients in England and Wales	Patients from the UK with haemophilia B were included in the HOPE-B trial.[14]	Section B.2.3.1	Not addressed in a scenario analysis

Assumption	Justification	Reference in submission	Addressed in scenario analysis
Non-joint and joint bleeds disutility last two and four days respectively, with their related utilities being scaled accordingly	Clinicians consulted at an advisory board reached an agreement on the length of time a non-joint and joint bleed disutility should be applied in the model.[6]	Section B.3.4.5	Not addressed in a scenario analysis
If Factor IX activity levels <2% post infusion, prophylaxis treatment will be needed as per Shah et al. (2022) validation	Published literature and clinical expert opinion.[111,6,112]	Section B.3.3.2	An alternative assumption is included as a scenario analysis see 3.10.3.1
In the event of a bleed, a patient will receive an additional dose of Factor IX treatment from the appropriate comparator	Published literature and clinical expert opinion.[14,6]	Section B.2.6.4	Not addressed in a scenario analysis
Mortality follows values parallel to the general population	clinical expert opinion[6]	Section B.3.3.3	Not addressed in a scenario analysis
Pairwise comparison between the intervention and a comparator assume full market share weighting for the given comparator	Concise pairwise results that only assess one comparator at a time	Section B.3.9.1	Not addressed in a scenario analysis
No wastage assumed for the dosing of the intervention and comparators.	The intervention is a single dose treatment. The comparators are either on-demand or prophylaxis treatments and are administered in the hospital or at home. Consistent uptake of the comparators and schedule of home deliveries ought to make administrations at home efficient.	Section B.3.5.2	Not addressed in a scenario analysis

B.3.9 Base-case results

B.3.9.1 Base-case incremental cost-effectiveness analysis results

The base-case results of the modelled inputs considered in sections B.3.2 to B.3.8 as well as the relevant assumptions are presented in the following section.

Etranacogene dezaparvovec was found to be cost-effective compared to all the comparators considered in the decision problem. Etranacogene dezaparvovec dominates all comparators for all positive willingness-to-pay values, as it offers more total QALYs at a lower total cost (£). Table 45 shows the pairwise comparisons against all the comparators, where etranacogene dezaparvovec results for a particular pair being a function of the comparator compared in that pair. For example, in the first pairwise comparison against BeneFIX, BeneFIX is assumed to hold a 100% market share such that all etranacogene dezaparvovec patients whose clinical durability wares off or require an on-demand Factor IX treatment will receive BeneFIX dosing for those needs. The same logic is applied for all other pairwise comparisons. Given etranacogene dezaparvovec is dominating in all pairwise comparisons, mathematically it will be dominating in any concave combinations of the comparators market share allocations.

These results of etranacogene dezaparvovec economic dominance are consistent with the clinical outcomes used in the economic model. For example, etranacogene dezaparvovec's clinical effectiveness to reduce non-joint and joint bleeds relative to the comparators mean cost savings from less on-demand treatments and other bleed-related resources, and QALY gains from disutility of bleeds forgone.

Disaggregated cost and QALY values are found in Appendix J.

Table 45: Pairwise base-case incremental cost-effectiveness results at list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Etranacogene dezaparvovec (BeneFIX)	[redacted]	21.356	[redacted]	-	-	-	-	-
BeneFIX	[redacted]	21.356	[redacted]	[redacted]	0	1.506	Dominating	Dominating
Etranacogene dezaparvovec (Alprolix)	[redacted]	21.356	[redacted]	-	-	-	-	-
Alprolix	[redacted]	21.356	[redacted]	[redacted]	0	1.477	Dominating	Dominating
Etranacogene dezaparvovec (Idelvion)	[redacted]	21.356	[redacted]	-	-	-	-	-
Idelvion	[redacted]	21.356	[redacted]	[redacted]	0	1.502	Dominating	Dominating
Etranacogene dezaparvovec (Refixia)	[redacted]	21.356	[redacted]	-	-		-	-
Refixia	[redacted]	21.356	[redacted]	[redacted]	0	1.443	Dominating	Dominating

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

A simple patient access scheme application is in process and Table 46 presents the PAS augmented pairwise incremental cost-effectiveness results, where the list price of etranacogene dezaparvovec is adjusted for the PAS discount rate. The cost effectiveness and dominance of the intervention is further reinforced relative to the base-case, and the clinical consistencies of the base-case results are still valid.

Table 46 : PAS augmented pairwise incremental cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER increment (£/QALY)
Etranacogene dezaparvovec (BeneFIX)	[redacted]	21.356	[redacted]	-	-	-	-	-
BeneFIX	[redacted]	21.356	[redacted]	[redacted]	0	[redacted]	[redacted]	[redacted]
Etranacogene dezaparvovec (Alprolix)	[redacted]	21.356	[redacted]	-	-	-	-	-
Alprolix	[redacted]	21.356	[redacted]	[redacted]	0	[redacted]	[redacted]	[redacted]
Etranacogene dezaparvovec (Idelvion)	[redacted]	21.356	[redacted]	-	-	-	-	-
Idelvion	[redacted]	21.356	[redacted]	[redacted]	0	[redacted]	[redacted]	[redacted]
Etranacogene dezaparvovec (Refixia)	[redacted]	21.356	[redacted]	-	-		-	-
Refixia	[redacted]	21.356	[redacted]	[redacted]	0	[redacted]	[redacted]	[redacted]

B.3.10 Exploring uncertainty

Deterministic, probabilistic and scenario sensitivity analyses were undertaken to assess the uncertainty of the estimated cost-effectiveness for the base case.

B.3.10.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was undertaken to characterise the uncertainty surrounding the various variables in the economic model in a simultaneous manner. Table 47 details which distribution and distribution specific priors were assigned to each variable. Notably, HOPE-B trial population statistics, list prices, dosing regimens, durability and mortality figures remain at their deterministic means. All those variables have no uncertainty associated with them, apart from the durability of the intervention which is examined as a scenario analysis in section 3.10.3.1.

Table 47 : Variables included in probabilistic sensitivity analysis

Variable	Mean	Variance type and value	Distribution	Alpha	Beta
Intervention administration cost	£635.55	SD, 127.11	Gamma	127	25
Intervention follow-up costs – year 1	£795.86	SD, 159.136	Gamma	25	31.83
Intervention follow-up costs – years 2-5	£396.47	SD, 79.294	Gamma	25	15.86
Intervention monitoring costs, per year	£5,781.13	SD, 1156.226	Gamma	25	231.25
Intervention non-joint bleed related management costs per cycle	£2,097.86	SD, 419.772	Gamma	25	83.91
Intervention joint bleed related management costs per cycle	£2,097.86	SD,419.772	Gamma	25	83.91
Intervention expected adverse events unit cost total per cycle	£0.91	SD, 0.182	Gamma	25	0.03
Alprolix administration cost per cycle	£537.36	SD, 107.472	Gamma	25	21.49
Alprolix monitoring costs, per year	£5,781.13	SD, 1156.226	Gamma	25	231.25
Alprolix non-joint bleed related management costs per cycle	£5,653.76	SD, 1130.752	Gamma	25	226.15
Alprolix joint bleed related management costs per cycle	£5,653.76	SD, 1130.752	Gamma	25	226.15
BeneFIX administration cost per year	£537.36	SD, 107.472	Gamma	25	21.49
BeneFIX monitoring costs, per year	£5,781.13	SD, 1156.226	Gamma	25	231.25

Variable	Mean	Variance type and value	Distribution	Alpha	Beta
BeneFIX non-joint bleed related management costs per cycle	£2,097.86	SD, 419.772	Gamma	25	83.91
BeneFIX joint bleed related management costs per cycle	£2,097.86	SD, 419.772	Gamma	25	83.91
BeneFIX expected adverse events unit cost total per cycle	£0.78	SD, 0.156	Gamma	25	0.03
Idelvion administration cost per year	£537.36	SD, 107.472	Gamma	25	21.49
Idelvion monitoring costs, per year	£5,781.13	SD, 1156.226	Gamma	25	231.25
Idelvion non-joint bleed related management costs per cycle	£7,374.01	SD, 1474.802	Gamma	25	294.96
Idelvion joint bleed related management costs per cycle	£7,374.01	SD, 1474.802	Gamma	25	294.96
Refixia administration cost	£603.11	SD, 120.622	Gamma	25	24.12
Refixia monitoring costs, per year	£5,781.13	SD, 1156.226	Gamma	25	231.25
Refixia non-joint bleed related management costs per cycle	£8,285.99	SD, 1657.198	Gamma	25	331.44
Refixia joint bleed related management costs per cycle	£8,285.99	SD, 1657.198	Gamma	25	331.45
Intervention health state 1 – utility	[redacted]	S.E, [redacted]	Beta	282.21	49.65
Intervention health state 2 - utility	[redacted]	S.E, [redacted]	Beta	282.21	49.65

Variable	Mean	Variance type and value	Distribution	Alpha	Beta
Intervention health state 3 - utility	[redacted]	S.E, [redacted]	Beta	282.21	49.65
Alprolix health state 1 - utility	[redacted]	S.E, [redacted]	Beta	74.86	20.72
Alprolix health state 2 - utility	[redacted]	S.E, [redacted]	Beta	74.86	20.72
Alprolix health state 3 - utility	[redacted]	S.E, [redacted]	Beta	74.86	20.72
BeneFIX health state 1 - utility	[redacted]	S.E, [redacted]	Beta	74.86	20.72
BeneFIX health state 2 - utility	[redacted]	S.E, [redacted]	Beta	74.86	20.72
BeneFIX health state 3 - utility	[redacted]	S.E, [redacted]	Beta	74.86	20.72
Idelvion health state 1 - utility	[redacted]	S.E, [redacted]	Beta	74.86	20.72
Idelvion health state 2 - utility	[redacted]	S.E, [redacted]	Beta	74.86	20.72
Idelvion health state 3 - utility	[redacted]	S.E, [redacted]	Beta	74.86	20.72
Refixia health state 1 - utility	[redacted]	S.E, [redacted]	Beta	74.86	20.72
Refixia health state 2 - utility	[redacted]	S.E, [redacted]	Beta	74.86	20.72
Refixia health state 3 - utility	[redacted]	S.E, [redacted]	Beta	74.86	20.72
Non-joint bleed disutility	0.05	SD, 0.01	Beta	23.81	497.06
Joint bleed disutility	0.16	SD, 0.32	Beta	20.84	109.41
Intervention ABR	[redacted]	SD, [redacted]	Gamma	7	0.05
Intervention AjBR	[redacted]	SD, [redacted]	Gamma	56	0.00
Alprolix ABR	[redacted]	SD, [redacted]	Gamma	96	0.02
Alprolix AjBR	[redacted]	SD, [redacted]	Gamma	3839	0.00
BeneFIX ABR	[redacted]	SD, [redacted]	Gamma	18	0.23
BeneFIX AjBR	[redacted]	SD, [redacted]	Gamma	270	0.00
Idelvion ABR	[redacted]	SD, [redacted]	Gamma	60	0.03
Idelvion AjBR	[redacted]	SD, [redacted]	Gamma	1130	0.00
Refixia ABR	[redacted]	SD, [redacted]	Gamma	92	0.01
Refixia AjBR	[redacted]	SD, [redacted]	Gamma	811	0.00
Disutility for ALT increased	0.05	SD, 0.01	Beta	23.7	450.3
Disutility for headache	0.03	SD, 0.006	Beta	24.22	783.11

Variable	Mean	Variance type and value	Distribution	Alpha	Beta
Disutility for influenza like illness	0.08	SD, 0.016	Beta	22.92	263.58
Disutility for AST increased	0.05	SD, 0.01	Beta	23.7	450.3
Disutility for fatigue	0.049	SD, 0.098	Beta	23.73	460.8
Disutility for blood creatine phosphokinase increased	0.05	SD, 0.01	Beta	23.7	450.3
Disutility for nausea	0.062	SD, 0.0124	Beta	23.39	353.84
Disutility for dizziness	0.02	SD, 0.004	Beta	24.48	1199.52
Disutility for infusion-related reactions	0.20	SD, 0.05	Beta	19.8	79.2
Disutility for arthralgia	0.013	SD, 0.0026	Beta	24.66	1872.41
Disutility for infection	0.22	SD, 0.044	Beta	19.28	68.36
Disutility for body pain	0.123	SD, 0.024	Beta	21.8	155.45
Per cycle intervention probability of ALT increased	0.15%	SD, 0.00	Beta	24.96	16817.28
Per cycle intervention probability of headache	0.13%	SD, 0.00	Beta	24.97	18824.93
Per cycle intervention probability of influenza like illness	0.12%	SD, 0.00	Beta	24.97	21267.33
Per cycle intervention probability of AST increased	0.09%	SD, 0.00	Beta	24.98	29252.97
Per cycle intervention probability of fatigue	0.07%	SD, 0.00	Beta	24.98	36454.24
Per cycle intervention probability of	0.07%	SD, 0.00	Beta	24.98	36454.24

Variable	Mean	Variance type and value	Distribution	Alpha	Beta
blood creatine phosphokinase increased					
Per cycle intervention probability of nausea	0.07%	SD, 0.00	Beta	24.98	36454.24
Per cycle intervention probability of dizziness	0.07%	SD, 0.00	Beta	24.98	36454.24
Per cycle intervention probability of infusion-related reactions	0.05%	SD, 0.00	Beta	24.99	47781.75
Per cycle intervention probability of arthralgia	0.05%	SD, 0.00	Beta	24.99	47781.75
Per cycle comparator probability of headache	0.33%	SD, 0.00	Beta	24.91	7459.42
Per cycle comparator probability of arthralgia	0.171%	SD, 0.00	Beta	24.96	14428.46
Per cycle comparator probability of infection	0.173%	SD, 0.00	Beta	24.96	14584.18
Per cycle comparator probability of body pain	0.173%	SD, 0.00	Beta	24.96	14584.18

The PSA results are presented in Table 48 with etranacogene dezaparvovec as a function of Refixia, with the displayed values being the averages taken over the number of iterations. This analysis was chosen because Refixia is identified as the comparator with the highest cost in section B.3.9.1, which means the intervention has the highest cost as a function of Refixia compared to functions of other comparators. Thereby, these PSA results can be interpreted as a conservative (least favourable)

simulation and characterisation of the uncertainty surrounding the base case results. 10,000 simulations were run to obtain the least biased estimated as per the law of large numbers, subject to computing limitations. Figure 39 presents a sample of the first 100 out of the 10,000 iterations of results on an incremental cost-effectiveness plane, with etranacogene dezaparvovec oriented at the origin. **Error! Reference source not found.** presents the cost-effectiveness acceptability curve which displays the probability of a technology being cost-effective at various willingness to pay thresholds. The cost-effectiveness acceptability curve is the outer frontier of the cost-effectiveness acceptability curve, which is entirely populated by etranacogene dezaparvovec for all willingness to pay thresholds.

Table 48: Averages from PSA of incremental cost-effectiveness results at list price

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)	Probability of cost-effectiveness (£30,000/ QALY)
Etranacogene dezaparvovec (Refixia)	[redacted]				-	-	96.84%
BeneFIX	[redacted]				Dominating	Dominating	2.33%
Alprolix	[redacted]				Dominating	Dominating	0.79%
Idelvion	[redacted]				Dominating	Dominating	0.04%
Refixia	[redacted]				Dominating	Dominating	0%

Note: Total life years gained is omitted from this table as they do not vary from Table 3.9.1, since general population mortality is treated as certain.

Table 48 provides consistent conclusions with Table 45 of the pairwise incremental cost-effectiveness results, particularly when analysed as a function of Refixia, etranacogene dezaparvovec dominates all comparators considerably when considering the conservative pricing approach.

Table 49: Averages from PSA of incremental cost-effectiveness results with PAS

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)	Probability of cost-effectiveness (£30,000/ QALY)
Etranacogene dezaparvovec (Refixia)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: Total life years gained is omitted from this table as they do not vary from Table 3.9.1, since general population mortality is treated as certain.

Table 49 provides the results of the PSA analysis for the PAS price of etranacogene dezaparvovec and corresponds to Figure and Figure the respective cost-effectiveness acceptability curve and incremental cost-effectiveness plane. The probability of cost-effectiveness at the £30,000 willingness to pay threshold increased relative to the list price simulations.

Figure 39: Incremental cost-effectiveness plane at list price

Figure 40: Cost-effectiveness acceptability curve at list price

Figure 41: Incremental cost effectiveness plane with PAS

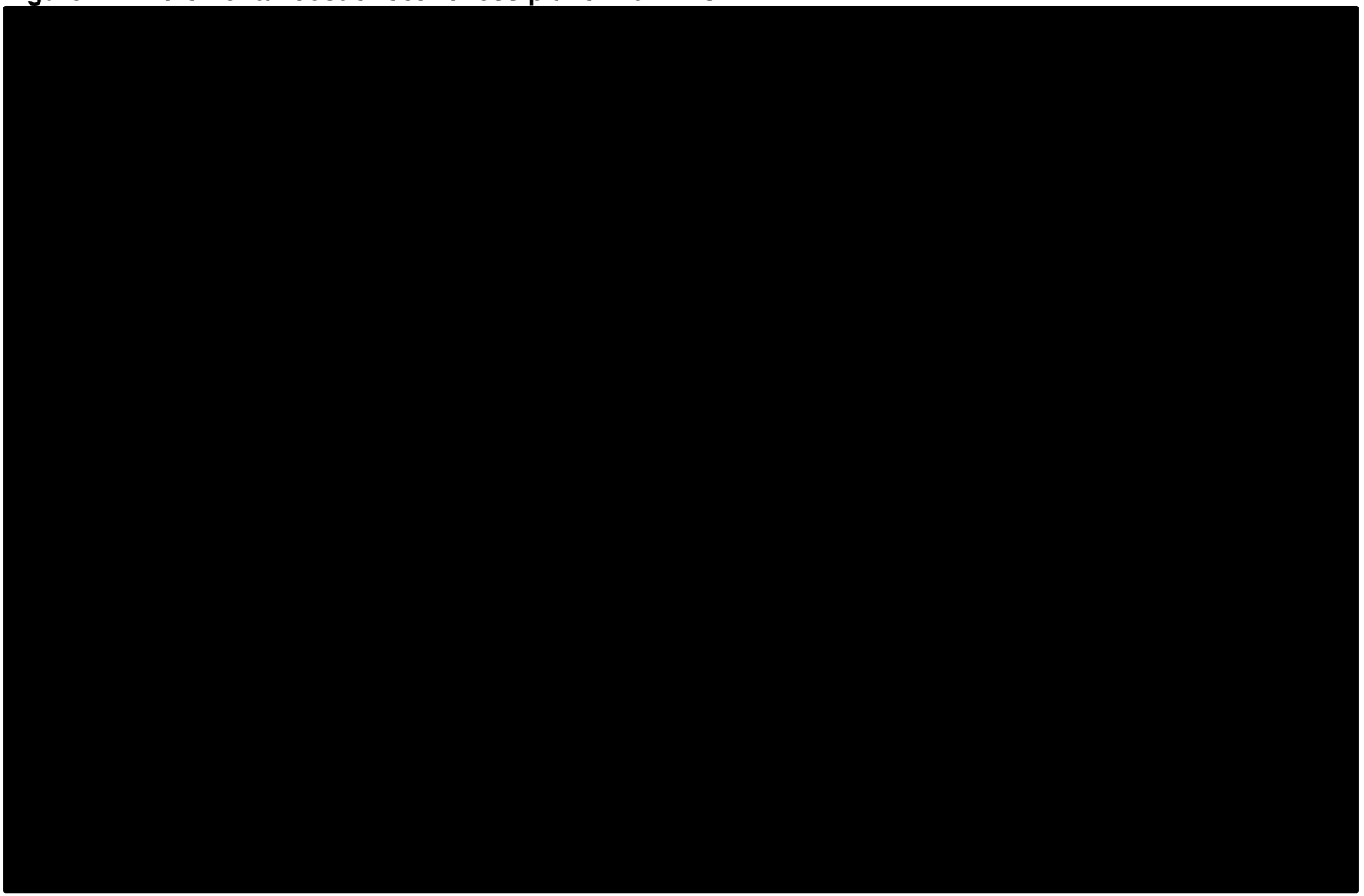


Figure 42: Cost-effectiveness acceptability curve with PAS

B.3.10.2 Deterministic sensitivity analysis

Deterministic sensitivity analysis has been conducted versus all 4 comparators and the associated tornado plots using etranacogene dezaparvovec list prices are presented on Figure 43, Figure 44, Figure 45 and Figure 46, and using PAS price on figures Figure 47, Figure 48, Figure 49 and

Figure 50. Due to the intervention being dominant, negative ICERs would need to be presented on the tornado plots, which could obscure the understanding of the results. To avoid that, a net monetary benefit was used as a metric to evaluate the importance of individual variables in the model. A willingness to pay threshold of £30,000 was applied to QALYs for the purpose of calculating monetary benefits.

Figure 43 Tornado diagram versus BeneFIX, list price

Figure 44 Tornado diagram versus Alprolix, list price

Figure 45 Tornado diagram versus Idelvion, list price

Figure 46 Tornado diagram versus Refixia, list price

Figure 47 Tornado diagram versus BeneFIX, PAS price

Figure 48 Tornado diagram versus Alprolix, PAS price

Figure 49 Tornado diagram versus Idelvion, PAS price

Figure 50 Tornado diagram versus Refixia, PAS price

As indicated by the tornado plots, none of the individual variables affect the net monetary benefit substantially to change the cost-effectiveness conclusions presented in section B.3.9.1. The more complex variables, which have substantial effect on the results are presented in the following section.

B.3.10.3 Scenario analysis

The analysis included several alternative scenarios to account for uncertainties in the modelling. Table 50: Summary of scenario analysis summarises the results of the scenario analysis, comparing etranacogene dezaparvovec to BeneFIX with and without PAS. Ultimately, BeneFIX was selected as it was the most competitive comparator in the base case analysis with respects to total costs.

Table 50: Summary of scenario analysis

Scenarios	Base case input	ICER (Without PAS)		ICER (With PAS)	Description
Durability of etranacogene dezaparvovec					
Scenario 1: 100% life-time durability	2% threshold extrapolation of Shah et al. (2022)[111,112]	Dominating		[redacted]	This scenario assumes 100% life-time durability over the modelled 60-year lifespan
Scenario 2: 5% threshold extrapolation of Shah et al. (2022)[111,112]		Dominating		[redacted]	This scenario utilises 5% threshold extrapolation of Shah et al. 2022 instead of 2% as incorporated in the base case analysis[111,112]
Scenario 3: 100% durability for 5 years		£656,728		[redacted]	This scenario assumes perfect durability over the observed 5-year time horizon based on observed clinical data (Appendix M), followed by the linear loss of durability to 0% over the next 5 years. This scenario can be seen as very pessimistic, as it assumes that the benefits of etranacogene dezaparvovec would wane straight after the longest available empirical evidence would indicate, contrary to the experts' opinion and statistical modelling.[111,6,112]

Scenario 4: 100% durability for 24 months		£1,126,027		[redacted]	This scenario assumes perfect durability over the observed 24-month from the HOPE-B trial[14], followed by the linear loss of durability to 0% over the following 5 years. This is an extremally pessimistic scenario, which assumes that the efficacy would wane straight after the duration of the pivotal Phase III study, contrary to experts' opinion and statistical modelling.[111,6,112]
Alternative health state utility value (HSUVs)					
Scenario 5: Intervention and comparator have the same HSUV (Etranacogene dezaparvovec vs BeneFIX)	Etranacogene dezaparvovec HSUV: [redacted] FIX Prophylaxis treatment HSUV: [redacted]	Dominating		[redacted]	This scenario assumes that etranacogene dezaparvovec has the same HSUV as its comparator instead of a ~[redacted] difference as depicted in the base-case
Time horizon					
Scenario 6: 5-year time horizon	Lifetime - 60 years	£4,361,352		[redacted]	This scenario assumes a shorter time horizon of 5 years
Scenario 7: 10-year time horizon		£591,829		[redacted]	This scenario assumes a shorter time horizon of 10 years
Scenario 8: 20-year time horizon		Dominating		[redacted]	This scenario assumes a shorter time horizon of 20 years
Societal Costs					
Scenario 9: Societal cost	Not included	Dominating		[redacted]	This scenario considers the societal costs of estimating the impact of workdays missed by both full-time and part-time workers who experience bleeding events.

3.10.3.1 Scenario analysis - Durability of etranacogene dezaparvovec

Considering the uncertainty around the durability of etranacogene dezaparvovec, four scenarios have been generated, all compared against BeneFIX. Scenario 1 considers 100% life-time durability over the assumed patients 60-year lifespan. Scenario 2 is an alternative to the base case analysis based on Shah et al. 2022, which extrapolates that [redacted]% of patients will have Factor IX activity levels below [redacted]% by year [redacted], and thus will require Factor IX prophylaxis treatment.[111,112] Scenario 3 assumes perfect durability over the observed 5-year time horizon based on phase II clinical data (Appendix M).

Scenario 4 assumes perfect durability over the observed 24-month time horizon of the stage 3 HOPE-B trial.[14] Scenarios 3 and 4 have a five-year waning-off period at a rate of 20% each year. The baseline in Table 51 is the less expensive of the scenario considered and baseline BeneFIX which itself is not affected by these scenarios. This serves to provide a common anchor to the comparisons.

Table 51: Durability scenario analysis at list price

Scenario/Comparator	Total costs (£)	Incremental Costs (£)	Total QALYs	Incremental QALYs	ICER versus baseline (£/QALY)
Scenario 1: 100% life-time durability - etranacogene dezaparvovec	[redacted]	[redacted]	[redacted]	[redacted]	-
BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
Scenario 2: 5% threshold extrapolation of Shah et al. (2022) - etranacogene dezaparvovec	[redacted]	[redacted]	[redacted]	[redacted]	-
BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	Dominating
BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	-
Scenario 3: 100% durability for 5 years - etranacogene dezaparvovec	[redacted]	[redacted]	[redacted]	[redacted]	656,728
BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	-
Scenario 4: 100% durability for 24 months - etranacogene dezaparvovec	[redacted]	[redacted]	[redacted]	[redacted]	1,126,027

Table 51 is consistent with the idea that etranacogene dezaparvovec is a gene therapy, where durability over reasonably expected time horizons provides large cost savings relative to prophylaxis treatments and QALY gains. Table 52 provides the above analysis evaluated at the applied PAS discount.

Table 52: Durability scenario analysis with PAS

Scenario/Comparator *	Total costs (£)	Incremental Costs (£)	Total QALYs	Incremental QALYs	ICER versus baseline (£/QALY)
Scenario 1: 100% life-time durability - etranacogene dezaparvovec	[redacted]	-	[redacted]	-	-
BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: 5% threshold extrapolation of Shah et al. (2022) - etranacogene dezaparvovec	[redacted]	-	[redacted]	-	-
BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BeneFIX	[redacted]	-	-	-	-
Scenario 3: 100% durability for 5 years - etranacogene dezaparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BeneFIX	[redacted]	-	[redacted]	-	-
Scenario 4: 100% durability for 24 months - etranacogene dezaparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* The baseline for each scenario is the technology that is less expensive.

3.10.3.2 Scenario analysis – Alternative health state utility value

The difference in HSUV for etranacogene dezaparvovec and the Factor IX prophylaxis treatment comparators were based on based on HOPE-trial and validation from clinical experts (section B.3.4.5.) and are therefore subject to a degree of uncertainty. To address this, a scenario is modelled whereby both etranacogene dezaparvovec and all the comparators have the same health state utility value. Therefore, the total utility difference from etranacogene dezaparvovec compared to the comparators will result

from the disutilities that occur from a bleed event and other adverse event. This scenario is highly conservative given the EQ-5D-5L results from the HOPE-B trial, section 2.6.6.1.

Table 53 provides the results of the pairwise incremental cost-effectiveness analysis for alternative HSUVs scenario, and Table 54 provides the same analysis but for PAS augmented values.

Table 53: Pairwise health-state utility incremental cost-effectiveness results at list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Etranacogene dezaparvovec (BeneFIX)	[redacted]	21.356	[redacted]	[redacted]	-	[redacted]	-	-
BeneFIX	[redacted]	21.356	[redacted]	[redacted]	0	[redacted]		Dominating
Etranacogene dezaparvovec (Alprolix)	[redacted]	21.356	[redacted]	[redacted]	-	[redacted]	-	-
Alprolix	[redacted]	21.356	[redacted]	[redacted]	0	[redacted]		Dominating
Etranacogene dezaparvovec (Idelvion)	[redacted]	21.356	[redacted]	[redacted]	-	[redacted]	-	-
Idelvion	[redacted]	21.356	[redacted]	[redacted]	0	[redacted]		Dominating
Etranacogene dezaparvovec (Refixia)	[redacted]	21.356	[redacted]	[redacted]	-	[redacted]	-	-
Refixia	[redacted]	21.356	[redacted]	[redacted]	0	[redacted]		Dominating

Table 54: Pairwise augmented health-state utility incremental cost-effectiveness results with PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Etranacogene dezaparvovec (BeneFIX)	[redacted]	21.356	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]

BeneFIX	[redacted]	21.356	[redacted]	[redacted]	0	[redacted]	[redacted]
Etranacogene dezaparvovec (Alprolix)	[redacted]	21.356	[redacted]	[redacted]	-	[redacted]	[redacted]
Alprolix	[redacted]	21.356	[redacted]	[redacted]	0	[redacted]	[redacted]
Etranacogene dezaparvovec (Idelvion)	[redacted]	21.356	[redacted]	[redacted]	-	[redacted]	[redacted]
Idelvion	[redacted]	21.356	[redacted]	[redacted]	0	[redacted]	[redacted]
Etranacogene dezaparvovec (Refixia)	[redacted]	21.356	[redacted]	[redacted]	-	[redacted]	[redacted]
Refixia	[redacted]	21.356	[redacted]	[redacted]	0	[redacted]	[redacted]

Etranacogene dezaparvovec offers the same cost savings as per the respective base case and PAS augmented pairwise comparisons and yields positively marginal QALY increments over the comparators. These QALY gains are derived from forgone disutility of bleeding events, since etranacogene dezaparvovec significantly reduces bleeding events. This scenario still lends the intervention to dominate the comparators.

3.10.3.3 Time horizon

This section provides a structural examination to the changes that occur given various time horizon duration for the decision problem. The three scenarios presented in Table 55 are the pairwise incremental cost-effectiveness results for time horizons of 5,10 and 20 years, compared to BeneFIX (the least expensive comparator).

Table 55 : Time horizon incremental cost-effectiveness results

Scenario/Technology*	Total costs (£)	Total Life years	Total QALYs	Incremental Costs	Incremental QALYs	ICER versus baseline (£/QALY)
BeneFIX – 5 years	[redacted]	[redacted]	[redacted]		[redacted]	-
Etranacogene dezaparvovec (BeneFIX) – 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	4,361,352
BeneFIX – 10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
Etranacogene dezaparvovec (BeneFIX) – 10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	591,829
Etranacogene dezaparvovec (BeneFIX) – 20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-
BeneFIX – 20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominating

*The baseline for each scenario is the technology that is less expensive.

Table 56 provides the same analysis as Table 55, but for PAS augmented values.

Table 56 : PAS augmented time horizon incremental cost-effectiveness results

Scenario/Technology*	Total costs (£)	Total Life years	Total QALYs	Incremental Costs	Incremental QALYs	ICER versus baseline (£/QALY)
BeneFIX – 5 years	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
etranacogene dezaparvovec (BeneFIX) – 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
etranacogene dezaparvovec (BeneFIX) – 10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BeneFIX – 10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
etranacogene dezaparvovec (BeneFIX) – 20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BeneFIX – 20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: BeneFIX was selected as it was the most cost-effective comparator in the base case analysis

3.10.3.4 Societal Costs

The results of this sections are the result of the societal costs workings outlined in section 3.5.4.1. Table 57 presents the societal cost augmented pairwise incremental cost-effectiveness results.

Table 57: Societal cost augmented incremental cost-effectiveness results at list price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Etranacogene dezaparvovec (BeneFIX)	[redacted]	21.356	[redacted]	[redacted]	-	[redacted]	-	-
BeneFIX	[redacted]	21.356	[redacted]	[redacted]	0	[redacted]	Dominating	Dominating
Etranacogene dezaparvovec (Alprolix)	[redacted]	21.356	[redacted]	[redacted]	-	[redacted]	-	-

Alprolix	[redacted]	21.356	[redacted]	[redacted]	0	[redacted]	Dominating	Dominating
Etranacogene dezaparvovec (Idelvion)	[redacted]	21.356	[redacted]	[redacted]	-	[redacted]	-	-
Idelvion	[redacted]	21.356	[redacted]	[redacted]	0	[redacted]	Dominating	Dominating
Etranacogene dezaparvovec (Refixia)	[redacted]	21.356	[redacted]	[redacted]	-		-	-
Refixia	[redacted]	21.356	[redacted]	[redacted]	0	[redacted]	Dominating	Dominating

Table 58 provides the same analysis as Table 57, but for PAS augmented results.

Table 58: PAS and societal cost augmented incremental cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incrementa (£/QALY)
Etranacogene dezaparvovec (BeneFIX)	[redacted]	21.356	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
BeneFIX	[redacted]	21.356	[redacted]	[redacted]	0	[redacted]	[redacted]	[redacted]
Etranacogene dezaparvovec (Alprolix)	[redacted]	21.356	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
Alprolix	[redacted]	21.356	[redacted]	[redacted]	0	[redacted]	[redacted]	[redacted]
Etranacogene dezaparvovec (Idelvion)	[redacted]	21.356	[redacted]	[redacted]	-	[redacted]	[redacted]	[redacted]
Idelvion	[redacted]	21.356	[redacted]	[redacted]	0	[redacted]	[redacted]	[redacted]
Etranacogene dezaparvovec (Refixia)	[redacted]	21.356	[redacted]	[redacted]	-		[redacted]	[redacted]
Refixia	[redacted]	21.356	[redacted]	[redacted]	0	[redacted]	[redacted]	[redacted]

Given that etranacogene dezaparvovec provides the greatest reduction in bleeding events, it thereby offers the least societal costs in terms of the costs of absenteeism

relative to the comparators. The societal perspective reinforces the economic dominance of the intervention.

B.3.11 Subgroup analysis

No subgroups are applied for within the population of patients with moderately severe or severe haemophilia B.

B.3.12 Benefits not captured in the QALY calculation

The model does not take into account the benefits from avoiding long-term joint damage. As outlined in section B.3.2.2, long term joint damage is expected to be reduced for patients who received etranacogene dezaparvovec, as it reduces AjBR, and joint bleeds are associated with joint damage.[6] However, in the face of the lack of a long-term studies which would provide sufficient clinical evidence to allow to quantifiably model the effect of etranacogene dezaparvovec on the joint damage, the decision was made to not include this effect. As outlined in section B.3.2.2, this modelling simplification is a conservative assumption, as etranacogene dezaparvovec would save more cost and QALYs if that effect would have been considered.

The second assumption is no effect of haemophilia B on the mortality of patients. Although patients receiving currently available prophylaxis factor IX treatments have life expectancy similar to the general population, there is some evidence of haemophilia affecting patients' mortality.[70] By lowering ABR, etranacogene dezaparvovec might lower patients' mortality, which would lead to higher QALY benefit. However, as the effect of etranacogene dezaparvovec on mortality has not been proven, it was not included in the cost-effectiveness model. This is another conservative modelling decision, which results in an underestimation of the value of etranacogene dezaparvovec.

B.3.13 Validation

B.3.13.1 Validation of cost-effectiveness analysis

The model structure and its key inputs have been validated by clinical experts.[6] The model has been reviewed by an external pharmaceutical agency and judged as fit for purpose, with minor amendments, which were introduced into the current version.

B.3.14 Interpretation and conclusions of economic evidence

Haemophilia B is characterised by bleeding episodes, which are currently being treated by a range of prophylaxis Factor IX treatments. The first benefit which etranacogene dezaparvovec brings, is the reduction in the ABR and AjBR, beyond the currently available treatments.[139]

Furthermore, an additional benefit of etranacogene dezaparvovec is the improvement of the quality of life stemming from allowing patients to live their lives without the fear of bleeds and the burden of repetitive administration of factor IX prophylaxis infusions, which has been suggested by the HOPE-B study and confirmed by the clinical experts.[14,6]

Finally, the third benefit of etranacogene dezaparvovec, and the largest one from the perspective of a cost-effectiveness analysis, is the cost savings to the NHS and PSS. By replacing years of factor IX treatments with a single infusion, etranacogene dezaparvovec not only brings benefits to patients, but also reduces the long-term cost to the NHS and PSS. Combining these benefits, etranacogene dezaparvovec both at the list and at the PAS discount, dominates the available comparators.

The qualitative conclusions of the cost-effectiveness model are sensitive to only one variable in the model, which is the durability of the effect of etranacogene dezaparvovec. Durability of the effect of an intervention is a common driver of cost-effectiveness outcomes, but as a genetic therapy, etranacogene dezaparvovec is expected to have decades long, potentially lifelong effect on patients, which makes this input particularly important in this analysis. Nevertheless, the data to scientifically confirm the durability of the etranacogene dezaparvovec effect is not yet available,

hence other sources, such as statistical modelling and expert opinions, need to be utilised to inform this crucial input in the cost-effectiveness analysis. The uncertainty around this input was investigated in section B.3.10.3, but the best currently available evidence was utilised in the creation of the base-case results, which resulted in etranacogene dezaparvovec dominating the comparators, leading to the conclusion that it is cost-effective at the willingness to pay threshold of £30,000.

B.4 References

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B.5 Appendices

Appendices are provided in separate documents.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B [ID3812]

Summary of Information for Patients (SIP)

January 2023

File name	Version	Contains confidential information	Date
ID3812 Etranacogene Dezaparvovec Company Evidence Submission SIP	FINAL	Yes, CIC	20 January 2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Etranacogene dezaparvovec 1 x 10^{13} genome copies/mL concentrate for solution for infusion Hemgenix®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

People with haemophilia B are born with an altered form of a gene needed to make Factor IX, an essential protein required for blood to clot and stop any bleeding. People with haemophilia B have insufficient levels of Factor IX and are prone to internal or external bleeding episodes. Etranacogene dezaparvovec is used for the [redacted].

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Etranacogene dezaparvovec is being assessed by regulatory authorities, including the Medicines and Healthcare products Regulatory Agency (MHRA). The expected approval date is included in Document B, Section B.1.2, Table 2.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

The relevant patient organisation for England is The Haemophilia Society. The nature of CSL Behring's relationship can be categorised into grants and contracted services with appropriate written agreements in place. Grants are reactive and unrestricted; given for the purpose of

supporting patient education, improve patient care or advocacy with no consequent obligation on the receiving organisation. Contracted services are proactive requests by the company to the patient organisation; to consult or get patient perspective on the development of company activity. Both payments are publicly disclosed annually on our company website and can also be accessed via Disclosure UK; details for the previous 3 years are provided below. Of note; data for the preceding year are compiled in March, verified and final data published in June.

- 2021 - The Haemophilia Society: Grant £35,000
- 2020 - The Haemophilia Society: Grant £35,000 & Consultancy £1000
- 2019 - The Haemophilia Society: Grant £35,000 & Consultancy £4700

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Haemophilia B is a rare, lifelong bleeding disorder that mainly affects men and, in the majority (70%) of cases, is inherited. (1, 2). Haemophilia B is characterised by a deficiency of a protein required for blood-clotting called Factor IX, which arises from mutations in the Factor IX gene (3, 4), making this a target for therapeutic approaches in haemophilia B. Depending on the level of Factor IX activity, haemophilia B can be classified as mild (>5% to <40% of normal), moderate (1–5% of normal) or severe (<1% of normal) (5). This submission focusses on **moderately severe or severe haemophilia B** (Factor IX activity levels of ≤2% of normal).

People with severe haemophilia B tend to have spontaneous bleeds or prolonged bleeding after an injury or surgery (2, 6). Spontaneous bleeds, which are bleeding for no apparent or known reason, most commonly occurs in joints (referred to as haemarthrosis), but may also occur in muscles, soft tissue, skin, lining of cavities (e.g. mouth, nose) , the gastrointestinal (digestive) system, the neck or throat, and the brain or spinal cord (4).

It is estimated that 867 adults across England live with haemophilia B. Those that have severe or moderately severe disease are treated with Factor IX, usually on a regular basis to prevent bleeding (prophylaxis) or rarely as a response following bleeds (on-demand therapy) and comprise the patient population of interest for this submission.

The impact of haemophilia B and its treatments on patients and their carers is substantial, with reduced quality of life arising from pain, functional impairment, anxiety and depression, a reduction in work productivity, and an increase in healthcare resource use (7-11).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

The diagnosis of haemophilia B requires a detailed clinical history including clinical examination, the use of bleeding assessment tools, laboratory testing and genetic testing. It is also important that the clinicians obtain their patients' bleeding history and family history of abnormal or unexplained bleeding to assess patterns of inheritance to assist with diagnosis (2). In patients with clinical history suggestive of an underlying bleeding disorder, specific screening tests can be done. Newborns with a family history of bleeding disorders will be tested routinely after birth, whereas those without a family history are diagnosed incidentally due to spontaneous bleeds (12). A diagnosis of mild haemophilia is frequently made later in life than that of more severe forms of the disease (13). A blood test to measure the neutralising antibody (NAb) to the adeno-associated viral vector serotype 5 (AAV5) within the gene therapy will be required to determine patients' suitability for haemophilia B gene therapy (14).

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

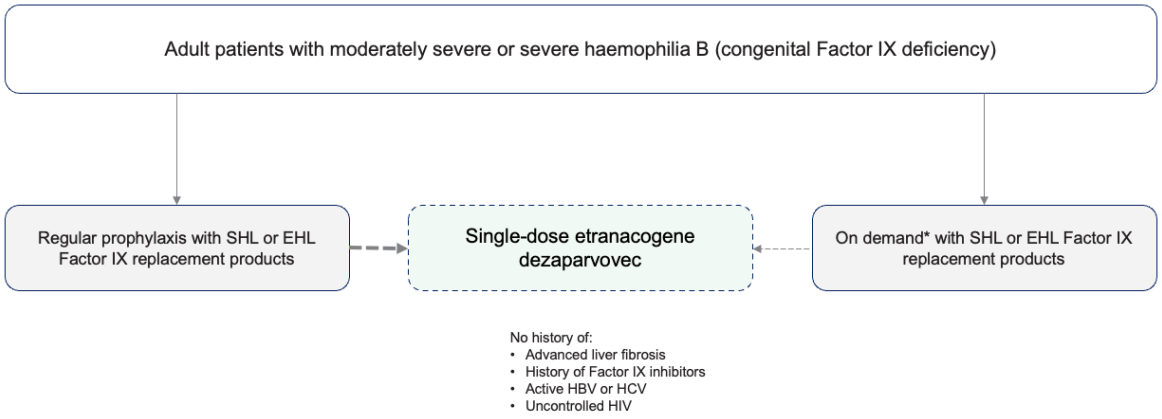
The primary goal of haemophilia B care is to prevent bleeding, which is usually achieved by the long-term Factor IX prophylaxis treatment and/or the on-demand treatment (2, 15). Management through prophylaxis is the preferred treatment approach that can be tailored to prevent bleeding taking into consideration the patients' lifestyle and needs. Compared with the on-demand approach, prophylaxis leads to better clinical outcomes, including lower annualised bleeding rate (16).

The current standard of care for treating haemophilia B in England is Factor IX replacement therapy, which is mainly used on a prophylactic (preventative) basis through frequent intravenous injections (2). Unfortunately, patients can still experience bleeds despite burdensome and time-consuming intravenous injections with prophylaxis therapy. The need for frequent injections can lead to increased pain and other injection-related complications. Frequent bleeds into single or multiple joints has a negative impact on quality of life by restricting daily activities and social interaction(17, 18).

A group of key consultant haematologists in England agreed that gene therapy as an option for eligible patients with haemophilia B can potentially free patients from routine intravenous injections, reducing the burden of treatment whilst giving patients freedom from the risk of bleeding. A new therapy could provide patients with clinical benefits that enable them to have higher productivity and reduced absenteeism from employment and education, and manage their daily lives with fewer restrictions (19, 20).

Figure *1* shows the current treatment pathway in England and the proposed positioning of etranacogene dezaparvovec.

Figure 1: Treatment pathway and positioning of etranacogene dezaparvovec in England



Abbreviations: EHL, extended half-life; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; SHL, standard half-life

Dotted line denotes intended positioning of etranacogene dezaparvovec, mainly displacing prophylaxis as demonstrated by the thicker, dotted line.

*Unlike prophylaxis, on-demand treatments are administered at the time of a bleed and aim to stop haemorrhages rapidly. A small number of patients opt to receive on-demand treatment despite being eligible for prophylaxis due to personal choice or clinical challenges and, in this group, etranacogene dezaparvovec could displace on-demand treatment.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Haemophilia is associated with a reduced quality of life due to symptoms including pain, functional impairment, anxiety and depression, while bleeding events and progression of joint disease is associated with a reduction in work productivity and an increase in healthcare resource use (7, 11, 19-21). Moreover, without adequate treatment, haemophilia can result in bleeding within joints that can lead to chronic joint disease and pain. On rare occasions bleeding in the head and sometimes in the brain can occur, which can cause long term problems such as seizures

and paralysis. Death can occur if the bleeding cannot be stopped or if it occurs in a vital organ such as the brain (22).

The burden of severe haemophilia for the patient's daily life and the economic burden for society have been widely reported with several studies reporting impaired quality of life. In the CHESS European Study (20), 515 patients with haemophilia A and B responded to a Quality-of-life instrument (EuroQoL 5-dimension [EQ-5D] questionnaire). The mean health utility score (scale from 0–1, where 0 equals death and 1 equals perfect health) for patients with joint damage was significantly lower (0.731) than people without (0.875) ($p<0.000$), demonstrating that joint injuries have a significant negative impact on the patient's quality of life (20). Similarly, disease severity has been linked to worse quality of life, with one study demonstrating a lower mean health utility score for those with severe disease compared to those with mild disease (0.64 vs 0.73), a finding confirmed by the recent multinational observational B-Natural study, which showed that patients with severe haemophilia B have worse quality-of-life scores when compared to patients with mild and moderate haemophilia B (7).

Long-term impairments in functional status because of recurrent bleeding episodes can limit the participation of patients with haemophilia in daily life activities such as sport, work and sexual activity (23-25). The CHESS US/CHESS US+ population study showed that approximately 9% of patients with haemophilia B experienced a bleed-related hospitalisation during the 12-month study period, and 85% of patients had experienced chronic pain (19), which may make patients reluctant to participate in daily activities. Studies also show that adults with haemophilia are less likely to work full time, and some form of activity limitation is more common among patients with haemophilia compared to the general population (26). Lost productivity influences the financial status of patients and can lead to reduced capacity to work and a reduced ability to participate in society (19).

The experience of living with haemophilia has substantial effects on mental wellbeing. People with haemophilia with higher anxiety and depression symptoms were more likely to have had, in the previous year, more urgent hospital visits due to haemophilia, more bleeding episodes, more affected joints and pain, as well as worst levels of perceived functionality and quality of life (27). Among young people living with the condition, signs of major depressive disorder are common (28, 29). The real-life experiences of 141 young adults in the US (aged 18–34 years) with haemophilia were collected through patient initial interview and 2-year follow-up surveys (28). Young US adults with haemophilia experienced significant health and social burdens: more liver disease, joint damage, joint pain, and unemployment as well as lower high-school graduation rates compared to age-matched counterparts in the general US population, and nearly half were overweight or obese (28).

In the Exigency Study (30), 16 patients with haemophilia A or B (both types have similar impact) were interviewed about their experiences of gene therapy. Patients reported a desire to receive gene therapy to help both themselves, but also to save future generations from the same experiences: "I don't want anyone to have to go through what I went through", reported one participant(30). Parents of children with haemophilia B experience feelings such as guilt, loss of self-esteem, and sadness that could potentially lead to isolation, over-protectiveness of the child, and heightened sensitivity about lost opportunities compared with the child's peers (31). Experience of healthcare may not be pleasant, hospital attendances may be stressful, and access to services may be unsatisfactory. The ever-present risk of a bleeding episode means that haemophilia can never be forgotten or ignored. The importance of the impact of haemophilia on patients and their families should not be overlooked, and observational studies play a key role in capturing a 'snapshot' of information about what it is like to live with a rare disease (20).

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment? Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities. If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.
Etranacogene dezaparvovec is a gene therapy product that contains the active substance etranacogene dezaparvovec. A gene therapy product works by delivering a gene into the body to correct a genetic defect, in this case the Factor IX gene. The active substance in etranacogene dezaparvovec is based on a virus that does not cause disease in humans. This virus has been modified so that it cannot spread in the body but can deliver a copy of the Factor IX gene into the liver cells. This allows the liver to produce the Factor IX protein and raise the levels of working Factor IX in the blood. This helps the blood to clot more normally and prevents or reduces bleeding episodes.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines? • Yes / No If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together. If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects. **If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.**
No, etranacogene dezaparvovec is intended to be used alone as a single dose.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
Etranacogene dezaparvovec will be given in a hospital setting under direction of a doctor experienced and trained in the treatment of haemophilia B. Etranacogene dezaparvovec will be

given **only once** by a single slow infusion (drip) into a vein. The infusion will usually take 1 to 2 hours to be completed. The correct dose will be worked out based on the patient's body weight.

Discontinuation of exogenous Factor IX treatment

It may take several weeks before improved bleeding control becomes apparent after etranacogene dezaparvovec infusion, and patients may need to continue their replacement therapy with exogenous Factor IX during the initial weeks after etranacogene dezaparvovec infusion. The patient's blood will be monitored for the Factor IX activity levels regularly, i.e. weekly for at least first 3 months, and at regular intervals thereafter. Using this, the doctor will decide if and when patients should receive, reduce, or stop their replacement Factor IX therapy.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The safety and efficacy of etranacogene dezaparvovec is being evaluated in two prospective, open-label, single-dose, single-arm studies:

- a Phase IIb study performed in the US (CT-AMT-061-01, NCT03489291) (32)
- a pivotal Phase III multinational study of 54 patients performed in the US and Europe (HOPE-B, CT-AMT-061-02, NCT03569891)

The pivotal Phase III HOPE-B includes three sites in England: Royal London, Cambridge and Southampton, with all patients in England having had etranacogene dezaparvovec administered at the Southampton centre (33). Preliminary results of the HOPE-B trial (currently up to 2 years after treatment) have not yet been published but are described in Section B2.6 of Document B of the Company Submission. The study will collect data for up to 5 years after treatment.

Recently, results of the Phase IIb study have been published, reporting on the safety and efficacy up to 3 years after treatment in 3 patients. Further data is still being collected for up to 5-years after treatment (32).

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

The efficacy of etranacogene dezaparvovec was demonstrated in the Phase IIb and Phase III (HOPE-B) trials mentioned in Document B, Section B.2.2 and Section 3d above. To compare the efficacy of etranacogene dezaparvovec to currently used treatments, these treatments would

ideally be compared in a head-to-head study. As these were not available, indirect treatment comparisons have been conducted, using clinical trial data available from the key Phase III trials for etranacogene dezaparvovec and its main comparators.

Indirect treatment comparisons determined the comparative efficacy of etranacogene dezaparvovec to currently available prophylactic treatments for moderately severe or severe haemophilia B available in England, including the extended half-life products Idelvion (albutrepenonacog alfa), Alprolix (eftrenonacog alfa), Refixia (nonacog beta pegol) and the standard half-life product BeneFIX (nonacog alfa) (34). These indirect treatment comparisons are performed by comparing the main results (annualised bleeding rates, annualised joint bleeding rates, annualised spontaneous bleeding rates and any available quality of life measurements) of the Phase III HOPE-B trial studying etranacogene dezaparvovec, to the main Phase III trials of the main comparators described above. The four pivotal Phase III comparator trials included PROLONG-9FP (35), B-LONG (36), Paradigm™ 2 (37), and NCT00093171 (38), as key sources of efficacy data for Idelvion, Alprolix, Refixia, and BeneFIX, respectively.

Results of the indirect treatment comparisons
Overall, after matching and adjusting for the individual trial protocols and measurements, etranacogene dezaparvovec had a statistically significantly lower annualised bleeding rate, annualised spontaneous bleeding rate and annualised joint bleeding rate compared to Idelvion, Alprolix and BeneFIX; and a statistically significantly lower annualised bleeding rate and annualised spontaneous bleeding compared to Refixia (Refixia trial did not report on the annualised joint bleeding rates, so no conclusion could be drawn for that outcome). The outcomes of the quality-of-life measurements are described in Section 3f below.

Overall, these analyses suggest that patients who receive etranacogene dezaparvovec have fewer bleeds than patients on replacement Factor IX therapy, regardless of which specific type of replacement Factor IX therapy is utilised. Based on these study findings, keeping in mind the limitations of unanchored (meaning that the evidence of the trials is not connected to each other due to a lack of common comparators), non-randomised design with small sample sizes, etranacogene dezaparvovec could confer a large benefit over comparators for patients with moderately severe or severe haemophilia B.

Limitations
Indirect comparisons that are unanchored and have a small sample size are broadly considered a weaker form of evidence than direct comparisons involving blinded or randomised trial designs (39). Comparison of these results to those from other study designs is therefore important. The relative treatment effects from these indirect treatment comparisons were aligned with the those from the published, 1-year analysis that compares the lead-in period of HOPE-B, during which patients used routine prophylaxis treatments, to the post-treatment phase of the HOPE-B trial (40). The concordance between results and conclusions from the published HOPE-B analysis and those from these indirect treatment comparisons strengthens the evidence base comparing etranacogene dezaparvovec to Factor IX replacement therapies.

Outcomes of particular importance for patients
All outcomes described here are of importance to patients, the annualised bleeding rates describe the estimation of the number of bleeding events a patient experiences per year. Similarly, the annualised joint and spontaneous bleeding rates are estimations of how many joint or spontaneous bleeds patients may experience. Spontaneous bleeds and joint bleeds can severely impact a patient's life and quality of life due to the potential of causing disability.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Phase III HOPE-B trial

In the pivotal Phase III HOPE-B trial, several quality-of-life instruments were used, including:

- **5-level EuroQoL-5-dimension (EQ-5D-5L):** a standardised measure of health status that provides a simple, generic measure of health for clinical and economic appraisal (33).
- **International Physical Activity Questionnaire (iPAQ):** a self-reported measure of physical activity for adults aged 15–69 years old (33).
- **Brief Pain Inventory (BPI):** a self-reported or interview measure that assesses severity of pain, impact of pain on daily function, location of pain, pain medication use, and amount of pain relief in the past 24 hours or the past week (33).
- **Work Productivity and Activity Impairment questionnaire (WPAI):** measures absenteeism, presenteeism, and impairments in unpaid activity because of health problems with a 7-day recall (33).

Additionally, HOPE-B reported on several measurement tools that were developed specifically for patients with haemophilia, namely:

- **Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL):** self-reported measure of 10 domains related to quality of life of haemophilia patients: physical health, treatment, work and school, dealing with haemophilia, feelings, family planning, future, partnerships and sexuality, sports and leisure, and view of yourself (33).
- **Haemophilia Activities List (HAL):** self-reported measure on the self-perceived functional abilities in adults with haemophilia over seven domains: 1) lying/sitting/kneeling/standing 2) function of the legs 3) function of the arms 4) use of transportation 5) self-care 6) household tasks and 7) leisure activities and sports (33).
- **Patient Reported Outcomes Burdens and Experiences (PROBE):** The PROBE Questionnaire is a novel, patient-developed, tool specific to haemophilia and is intended to capture clinical outcomes that are considered relevant by patients, including general health problems such as the presence of acute and chronic pain, use of pain medications, limitations in mobility and absence from work or school (33). The optional PROBE study was only performed on participants who volunteered to participate in the PROBE questionnaire sub-study. The objective of this sub-study was to provide data complementary to the compendium of established PRO tools regarding the impact of gene therapy on patient-relevant outcomes and Quality of life over time (33).

Since these measurements are developed specifically to measure quality of life in patients with haemophilia, these are thought to capture haemophilia-specific aspects more accurately.

Two years after treatment with etranacogene dezaparvovec, patients enrolled in the HOPE-B trial showed statistically significant improvements in:

- the total score of **Haem-A-QoL**
- four of the **Haem-A-QoL** domains ('work/school', 'feelings', 'treatment' and 'future')
- **EQ-5D-5L** scores, which was primarily the result of improvements in pain and discomfort; over time, fewer subjects were reporting severe or extreme pain/discomfort (33).

No significant differences on the quality of life were reported for the other measurement tools for data reported at 2 years. Monitoring is ongoing up to 5 years (33). Please see Document B, Section B.2.6.6 for the full results.

Indirect treatment comparison (ITC)

When comparing the impact of etranacogene dezaparvovec on patient's quality of life (as measured during the HOPE-B trial) with that of the current standard of care (data was available for Alprolix and Refixia), no statistically significant changes in quality of life were reported (33). This suggests that etranacogene dezaparvovec decreases the annualised bleeding rate of patients with haemophilia (Section 3h) with no negative impact on their quality of life. Please see Document B, Section B.2.9.3 for the full results.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

The following side effects were observed in clinical studies with etranacogene dezaparvovec.

Very Common (may occur with more than 1 in 10 patients)

- Headache
- Increased levels of liver enzymes in the blood (Alanine aminotransferase increased)
- Increased levels of liver enzymes in the blood (Aspartate aminotransferase increased)
- Flu-like illness (Influenza-like illness)
- Increased levels of C-reactive protein, a marker of inflammation
- Infusion related reaction (allergic reactions (hypersensitivity), infusion site reaction, dizziness, eye itching (pruritus), reddening of the skin (flushing), upper tummy (abdominal) pain, itchy rash (urticaria), chest discomfort, and fever)

Common (may occur with up to 1 in 10 patients)

- Dizziness
- Feeling sick (Nausea)
- Tiredness (Fatigue)
- Feeling generally unwell (Malaise)
- Increased blood levels of bilirubin, a yellow breakdown substance of the red blood cells
- Increased blood levels of creatine phosphokinase, an enzyme (protein) found mainly in the heart, brain and skeletal muscle

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Reduced need for burdensome prophylactic treatments

Etranacogene dezaparvovec, as a single-infusion gene therapy that induces stable Factor IX expression, can potentially eliminate regular Factor IX intravenous injections as well as reduce long-term complications. Preliminary results from HOPE-B corroborate this, indicating that 2 years after treatment, nearly all patients are free from these regular Factor IX replacement injections (see Section B2), which may ultimately contribute to the observed improvement in the performance in work and (higher) education and may provide people with haemophilia B with a sense of optimism for the future.

Reduced bleed rates compared to current standard of care, without impact on quality of life

In order to compare the efficacy of etranacogene dezaparvovec with the efficacy of the current standard of care in England, so-called 'indirect treatment comparisons' were performed on the results from the HOPE-B trial and the trials performed on the most-used prophylaxis therapies in England. These comparisons showed that etranacogene dezaparvovec led to a lower annualised bleeding rate than replacement Factor IX therapy, with no negative impact on their quality of life, regardless of which specific type of replacement Factor IX therapy is utilised (34, 41).

The lower annualised bleeding rate with etranacogene dezaparvovec compared with standard of care is expected to result in a decrease in morbidity and disability, as well as decreased costs and improved quality of life. Overall, etranacogene dezaparvovec could confer a large benefit over comparators for patients with moderately severe or severe haemophilia B (34).

Improved joint health and reduced progression of joint disease

Based on a statistical modelling approach (called repeated measures linear mixed models), there were small but statistically significant improvements in joint health in each of the first 2 years post-treatment with etranacogene dezaparvovec compared to the lead-in period when patients received standard of care prophylaxis (33).

Improved health-related quality-of-life scores

Significant improvements were noted in the HOPE-B trial in quality-of-life measures, such as the Haem-A-QoL, and the EQ-5D-5L questionnaires. In the Haem-A-QoL questionnaire, significant improvements were noted in the 'Work/School', 'Feelings', 'Treatment' and 'Future' at 24 Months posttreatment. Treatment' reflects how burdened patients are by their haemophilia treatments. 'Feelings' reflects current emotions associated with having haemophilia. 'Future' reflects concerns about how haemophilia will affect their life plans. 'Work/School' reflects how well patients think they perform these responsibilities. In the EQ-5D-5L questionnaire there was a significant improvement in quality of life at Months 7–24 post-treatment, as over time, fewer patients reporting severe or extreme pain/discomfort.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

The benefits of etranacogene dezaparvovec in the eligible population have shown to outweigh its risks. Nevertheless, as with any treatment, some potential disadvantages should be considered.

Transaminase elevations and immunosuppressive treatment

Successful gene therapy requires the safe and effective delivery of a functioning gene, which allows for the expression of the protein at levels that help to improve the disease and its symptoms (42). After receiving the gene therapy, a patient may develop an immune response against the treatment. This is the body's attempt to fight off what they perceive to be a 'foreign invader'. The patient's immune response to the treatment can affect the efficacy and durability of the treatment (42).

The management of the immune response is crucial for both the long-term expression of the transgene and for limiting the short-term toxicity in the tissues targeted for gene transfer. Intravenous administration of a gene therapy where the target organ is the liver may lead to an immune response which clinically presents as the elevation of liver enzymes called transaminases, which is also called transaminitis. Many gene therapy studies have therefore included the use of immunosuppression, either preventatively or reactively, with the aim of fighting off the immune response (42). In the HOPE-B trial immunosuppression (steroids to treat liver enzyme elevations, including prednisone, prednisolone, and methylprednisolone) was required in 16.7% of patients for an average of 79.8 days. All patients stopped usage prior to Week 26, and all adverse events relating to elevated transaminases were non-serious and resolved (42).

This highlights the importance of developing a new therapy that can maintain Factor IX activity while limiting the use of immunosuppressants. Document B, Section B.2.3.10.6 describes the number of patients receiving immunosuppressants after etranacogene dezaparvovec treatment and for how long they received this treatment.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

How the model reflects the condition

- The health economic model has a structure of a Markov model, which is a well-accepted structure for representing real-world patients' experiences. The model evaluates patients weekly, and assesses if they had a non-joint bleed or a joint bleed, the two key outcomes for patients with Haemophilia B. It takes into account the variations of these bleeds associated with the different therapies available on the market, as well as hypothetical changes in the efficacy of treatments over time.

Modelling how much a treatment extends life

- There is no scientific evidence that etranacogene dezaparvovec extends life, as patients on already available prophylaxis Factor IX treatment have life expectancy similar to the general population.
- The Annual Bleed rates, the Annual Joint Bleed Rates and Health Related Quality of Life results from HOPE-B trial were utilised in the health economic model (33). The full duration of the trial (24 months) was used in the model, but as etranacogene dezaparvovec is a genetic therapy, it is expected to have a long-term beneficial effect on patients, extending years above currently available clinical trials data. The results from the HOPE-B were therefore extrapolated using statistical modelling to up to 60 years, with the results of the extrapolation being consulted and approved by clinicians.

Modelling how much a treatment improves quality of life

- Etranacogene dezaparvovec is improving quality of life via two routes. The first route, is by lowering the number of bleeds that people can expect over their lifetime, as shown in HOPE-B trial. The second route, which stems beyond the disutility of bleeds themselves, is by allowing people to live lives without the fear of a bleed and without repetitive intravenous infusions, as shown by the improved Health Related Quality of Life in HOPE-B study.
- EQ-5D measurements was used to evaluate quality of life, which are considered to capture the wholistic impact on people's quality of life.

Modelling how the costs of treatment differ with the new treatment

- Etranacogene dezaparvovec leads to an additional cost for the health service at its initiation when it is administered. This initial cost is then offset by the savings associated with removing the lifelong cost of prophylaxis factor IX treatments, which can result in the net reduction of the cost to the health service.
- The important difference in etranacogene dezaparvovec administration versus currently available prophylaxis factor IX treatments is that it is administered only once over patients' lifetime. The prophylaxis factor IX treatments, on the other hand, have to be administered regularly, around once or twice a week, depending on the treatment.

Uncertainty

- As mentioned previously, the durability of the effect of etranacogene dezaparvovec is a crucial input in the health economic model. The long-term data is not yet available, and hence had to be statistically extrapolated and confirmed by the opinion of clinicians experienced in the management of haemophilia B.
- We have tested alternative assumptions regarding the durability of etranacogene dezaparvovec effect, and it had the largest effect on the cost effectiveness estimates out of all variables in the model.
- There are smaller clinical trials (43), which have duration longer than HOPE-B trial, which provide support for the longer-term durability of etranacogene dezaparvovec effect. The statistical extrapolation of the results was published and reviewed in a peer reviewed scientific journal (44). This extrapolation was further validated and confirmed by the advisory board of clinical experts in haemophilia B (45).

Cost effectiveness results

- As explained beforehand, there is no additional benefit to overall survival. The incremental quality-adjusted life years (QALYs) against most efficacious comparator is 0.9 QALYs. A QALY is a measure of the state of health of a person (see Glossary [Section 4b] for more information).

Additional factors

- The benefits of avoiding long-term joint damage are not represented in the model, as including this would require making a number of assumptions, for which there is no clinical data yet. The model results can therefore be seen as a conservative estimate, and the real value of etranacogene dezaparvovec is higher than the one presented in the model.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Etranacogene dezaparvovec can represent a step-change in the management of people with moderately severe or severe haemophilia B, as a single-infusion gene therapy that induces stable Factor IX expression, potentially eliminating regular intravenous injections with current prophylaxis as well as reducing long-term complications associated with the disease. A trial participant explained why they had taken part of the etranacogene dezaparvovec study, highlighting the potential of this gene therapy in changing the lives of eligible people with haemophilia B (30): "*I've done it for the next generation. I don't want anyone to have to go through what I went through.*"

In the HOPE-B trial, a single dose of etranacogene dezaparvovec significantly reduced the risk of experiencing a bleeding episode compared with that with burdensome and time-consuming intravenous prophylaxis (see Document B, Section B2).

As outlined in section 3i, the benefits of avoiding long-term joint damage are not represented in the model, due to the lack of data.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
There are two potential equality considerations associated with patients' human immunodeficiency virus (HIV) status and sex. The pivotal Phase III trial for etranacogene dezaparvovec (HOPE-B) excludes women, people with positive HIV test at screening, not controlled with antiviral therapy (as shown by CD4 counts ≤200 µL) and active infection with hepatitis B or C virus at screening. This may present a potential equality consideration for the Committee to discuss. It is also suggested that NICE consider its recommendations for people with HIV or hepatitis B or C infection.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
• Miesbach W. Final analysis from the pivotal Phase 3 HOPE-B gene therapy trial: stable steady-state efficacy and safety of etranacogene dezaparvovec in adults with severe or moderately severe haemophilia B. Oral presentation at EAHAD 2022: https://www.uniqure.com/assets/uploads/doc/eahad2022-hope-b-oral-presentation-20220204.pdf • Pipe SW, et al. 52 week efficacy and safety of etranacogene dezaparvovec in adults with severe or moderate-severe hemophilia b: data from the Phase 3 HOPE-B gene therapy trial. Abstract Number: PB0653. Presented at ISTH 2021 Congress: https://abstracts.isth.org/abstract/52-week-efficacy-and-safety-of-etranacogene-dezaparvovec-in-adults-with-severe-or-moderate-severe-hemophilia-b-data-from-the-phase-3-hope-b-gene-therapy-trial/

- Pipe SW, et al. First data from the Phase 3 HOPE-B gene therapy trial: efficacy and safety of etranacogene dezaparvovec (AAV5-Padua hFIX variant; AMT-061) in adults with severe or moderate-severe hemophilia B treated irrespective of pre-existing anti-capsid neutralizing antibodies. Blood 2020; 136 (Supplement_2): LBA–6. doi: https://doi.org/10.1182/blood-2020-143560
- ClinicalTrial.gov. HOPE-B: Trial of AMT-061 in Severe or Moderately Severe Hemophilia B Patients: https://clinicaltrials.gov/ct2/show/NCT03569891

4b) Glossary of terms

- Annualised bleeding rate (abbreviated as ABR): estimation of the number of bleeding events a patient experiences per year to assess the efficacy of a haemophilia treatment.
- Factor IX: one of the proteins that promotes the clotting of blood. Deficiency (lack) of this protein causes haemophilia B
- Gene therapy: a treatment approach that modifies a person's genes to treat or cure disease by correcting the underlying cause.
- Haemarthrosis: bleeding into a joint.
- Indirect treatment comparison: statistical comparison of data from different clinical trials with treatments of interest used to demonstrate which options can offer more benefit. This approach is used when direct evidence (such as a single trial including all relevant treatments) does not exist.
- On-demand treatment: the administration of Factor IX therapy at the time of a bleeding event.
- Prophylaxis treatment: the regular administration of Factor IX with the aim to prevent bleeds.
- Quality-adjusted life years (abbreviated as QALYs): a type of economic analysis. A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life (the ability to carry out daily activities and freedom from pain or mental disturbance). The QALY allows comparisons between new and existing treatments to understand whether the new treatment brings additional QALYs (a QALY gain).

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B [ID3812]

Clarification questions

February 2023

File name	Version	Contains confidential information	Date
ID3812 etranacogene dezaparvovec clarification question responses	**2.0**	**Yes [AIC, CIC redacted]**	**21/02/2023**

Section A: Clarification on effectiveness data

A1. On page 17 of the CS, it is stated that at the time of submission (January 2023) etranacogene was still awaiting a decision from the EMA. However, the EAG understood that the treatment received a conditional marketing authorisation from the EMA in December 2022. Can you please confirm if the text on p.17 of the CS is incorrect or whether you anticipate changes to the licence from the EMA in [redacted]?

The text in page 17 is correct although it omits the granting of conditional marketing authorisation. On 15 December 2022, the Committee for Medicinal Products for Human Use (CHMP) granted a conditional marketing authorisation for etranacogene dezaparvovec for the treatment of severe and moderately severe haemophilia B (congenital Factor IX deficiency) in adult patients without a history of Factor IX inhibitors.[1] The EMA conditional marketing authorisation in the above indication is anticipated to be granted in [redacted]. The Great Britain (GB) conditional marketing authorisation application was submitted in December 2022 and a decision is expected in [redacted].

A2. Are further data cuts from HOPE-B planned? If so, when will they be available?

As per Section B.2.11 in the CS, the next readout of HOPE-B will be at 36 months for which follow-up visits will be completed by May 2023, with the analysed and validated data to become externally available 3-6 months later. This data will not be available in time for the committee meeting.

A3. We would request further data on the use of corticosteroids during the trial follow-up please. Can you please include the number of participants who required one period of corticosteroid treatment, the dose and duration of this, the number of repeat treatments needed with their dose and duration?

Of the 54 HOPE-B participants who received etranacogene dezaparvovec, 11 participants reported 12 adverse events of alanine transaminase (ALT) elevation (six

mild, five moderate, one severe), of which 9/54 (16.7%) patients received oral steroids for elevated transaminases.[2]

The mean corticosteroid treatment duration for those patients was 81.4 days. All treatment-emergent adverse events of elevated ALTs were non-serious and resolved within 3 to 127 days.[3] Participants who received corticosteroids maintained pre-steroid levels of Factor IX activity and no participants who had ALT elevations returned to continuous Factor IX prophylaxis over 24 months of follow-up.[4]

All corticosteroid use is detailed in Section 10.4.2. of the 24-month HOPE-B CSR.[2] Please note that the model has accounted only for the steroid use associated with etranacogene dezaparvovec treatment.

Recently, a poster by Astermark et al. presented at the 16th Annual Congress of the European Association for Haemophilia and Allied Disorders (EAHAD) on 7–10 February 2023 further reported on the use of corticosteroids due to ALT elevations during the HOPE-B trial:[5]

- Mean (SD) time to first elevated ALT (per laboratory protocol definition) was 44.1 (28.6) days (range: 22–120 days).
- The mean (SD) oral corticosteroid dose administrated was 27.6 (±5.35) mg/day.
- The mean (SD) time from etranacogene dezaparvovec infusion to last corticosteroid treatment was 119.3 days (+31.2).
- All participants discontinued corticosteroid treatment between days 85–170 after etranacogene dezaparvovec infusion.
- No corticosteroid-related serious adverse events were reported.
- Per-patient data of the acute corticosteroid use for participants experiencing ALT elevations after receiving etranacogene dezaparvovec infusion are listed in Table 1.[5]

Table 1. Per-patient data of corticosteroid use for the treatment of ALT elevations post-etranacogene dezaparvovec infusion

Participant	Time from infusion to first corticosteroid use, days	Duration of corticosteroid use, days	Mean daily corticosteroid use, mg/day	Time from infusion to last corticosteroid use, days
1	22	64	25.8	85
2	24	83	23.9	106
3	36	51	35.9	86
4	49	101	33.2	149
5	-	-	-	-
6	31	117	27.3	147
7	-	-	-	-
8	43	56	21.3	98
9	43	57	25.9	99
10	41	130	33.4	170
11	61	74	21.7	134

Source: Astermark et al., 2023.[5]

A4. How would you describe the monitoring requirements for transaminase elevations following treatment and over the lives of people treated?

Liver function tests (LFTs) should be performed weekly for the first three months post-treatment. A course of corticosteroid taper should be considered if the ALT levels increase to above the upper limit of normal or to double the patient's baseline levels, along with human Factor IX activity examinations. From Month 4 until Month 12 (Year 1) post-treatment, ALT levels should be checked every 6 months for patients with Factor IX activity levels >5 IU/dL, with more frequent monitoring considered in patients with Factor IX activity levels ≤5 IU/dL in consultation with their treating physician. After Year 2, measurement of ALT levels should be checked every 12 months for patients with Factor IX activity levels >5 IU/dL, with more frequent monitoring considered in patients with Factor IX activity levels ≤5 IU/dL in consultation with their treating physician. Further details on the post-treatment monitoring of transaminase elevations are available in the SmPC.[3]

Please note that the frequency of long-term liver health monitoring, after the first 3 months post-treatment, is not dissimilar to the current frequency of contact for patients with severe/moderately severe haemophilia.

Section B: Clarification on cost-effectiveness data

B1. Please provide citations for the two published systematic reviews referred to in the first bullet point, section B.3.1 p.138.

The two published systematic reviews are:

- Berger K, Schopohl D, Hilger A, et al. Research in haemophilia B – approaching the request for high evidence levels in a rare disease. Haemophilia. 2015;21;4-20[6]
- Thorat T, Neumann PJ, Chambers JD. Hemophilia Burden of Disease: A Systematic Review of the Cost-Utility Literature for Hemophilia. Journal of managed care & specialty pharmacy. 2018;24(7):632-642[7]

Please note that, although the PDFs were included in the original reference pack accompanying the CS, the PDFs are also added to the reference pack accompanying these responses for your convenience and completeness.

B2. We have identified an inaccuracy in Table 24 (B.3.1) of the CS: it is stated that Bolous et al. do not report results, though full results are shown in Table 3 of their report (although erroneously reports average cost per QALYs, the reported ICER appears correct). Please can you review the contents of this table and correct this and any other omissions?

Thank you for flagging, the table has been updated appropriately and the relevant section is reported as Table 2 below. No other omissions have been identified.

Table 2 : Summary list of published cost-effectiveness studies with updated Bolous et al. (2021) erroneous reporting row only

Study	Year	Summary	Patient Population	QALY	Costs	ICER
Bolous et al. (US, USD) AAV-FIX Padua gene therapy On-demand FIX replacement therapy Primary FIX prophylaxis	2021	Microsimulation Markov model: Three health states: "Alive", "Alive with Joint Damage" and "Dead". Time horizon: Lifetime	500,000 simulated cohort of male patients with severe haemophilia B	Gene Therapy standard half- life FIX Approach E vs. Prophylaxis Standard half- life FIX Approach C: QALY gain: 1.05	Gene Therapy standard half- life FIX Approach E vs. Prophylaxis Standard half- life FIX Approach C: Incremental cost: $-447,565	ICER negative, meaning Gene Therapy standard half- life FIX Approach E dominates Prophylaxis Standard half- life FIX Approach C:

B3. PRIORITY QUESTION. The annualised bleeding rate (ABR) and annualised joint bleeding rate (AjBR) used in the model for etranacogene are [redacted] and [redacted] (assuming this is per person per year?), as reported in Doc B Table 28.

- Can you please confirm that these rates are per person per year?
- We find discrepancies between the bleeding rates in the model compared to the data reported in the clinical effectiveness section of the CS. Can you please explain the discrepancies between the figures in the question and those listed below for the HOPE-B data cut off 7–24 months post-dose?
    - ABR is reported to be 1.51 (Table 10, p.68)
    - AsBR (annualised *spontaneous* bleeding rate) is reported to be [redacted] (p.68)
    - AjBR is reported to be [redacted] (p.68)
- Can you please explain the way in which ABR, AjBR and AsBR are used in the model?

The outlined assumption is correct, as the bleed rates are per person per year. The discrepancy between rates from the pivotal trial and those used in the model are due to differences in the definition of bleeds in HOPE-B and the indirect treatment comparison (ITC) analysis.

Table 10 on page 68 of the CS presents the adjusted ABR, AsBR and AjBR for all bleeding episodes after stable Factor IX expression in the Full Analysis Set (FAS) population (n=54), these rates are taken from the HOPE-B trial and are based on 7-18 Months post-treatment.

The ABR and AjBR values used in the model are taken from *Table 3.16: Bleeding outcomes (ABR, AsBR, AjBR) for HOPE-B and B-LONG trials* from the ITC report. They are the ABR, per Sensitivity Analysis 6 from HOPE-B and AjBR, per Sensitivity Analysis 6 from HOPE-B. Furthermore, these rates are taken from the HOPE-B trial and are directly from Months 7–24 post-treatment data and are estimated with an intercept-only negative binomial model.

The discrepancies between the two sets of bleed rates, is that the ITC used a different definition of bleeds as “the definition for ABR from sensitivity analysis 6 was selected as this best matches the definitions defined in other comparator trials.” (p. 56). Appendix C of the ITC report defines bleeds as any bleeding event that occurs between stable Factor IX expression and study completion or early withdrawal that were both treated with exogenous Factor IX and determined to be new and true (p. 142, Appendix C). The model uses the ITC reported rates as they better compare to the bleed rates of the comparators and Table 10 of the CS reports the trial specific rates, in line with the context of Section B.2.6.1.

In the model, the AjBR is transformed using formula 1 of the CS to derive the transitional probability to the health-state of joint bleed and, as per question B6, the EAG was able to replicate the calculation. The answer to question B6 provides a clarification on how the transitional probability to the state of non-joint bleeds was calculated and this includes the use of ABR and AjBR. The implications of patient outcomes corresponding to those health states are beyond the scope of the question, but the EAG accepts the modelling approach.

B4. PRIORITY QUESTION. Section B.3.3.2 states that the transition probabilities, utilities and costs for those patients requiring prophylaxis once etranacogene has worn off are a weighted average of market shares. Please clarify what those market shares are and show these calculations. Please include rationale for why BeneFIX is assumed in the base case to have a 100% market share.

Thank you for flagging the typographical error. The text should read as follows; “The bleed rates and therefore the associated transitional probabilities, utilities, and costs for etranacogene dezaparvovec treated patients who require Factor IX *treatment* at any point *are associated with the comparator that the intervention is being compared against.*” (p.151 – *updated*). Implicitly, this means that the model assumes a 100% market share for BeneFIX for all on-demand and prophylaxis Factor IX treatment as required by etranacogene dezaparvovec treated patients, in a pairwise comparison against BeneFIX.

This was the simplest modelling approach that could be used to generate the most robust results. For clarity, all tables provide the respective comparator product on their column headings. The total costs and QALYs of etranacogene dezaparvovec vary according to the comparator of comparison, as the Factor IX treatments vary in their costs and effectiveness. Pairwise comparisons between etranacogene dezaparvovec and each relevant comparator are presented in Tables 45, 46, 48-58 of the CS.

B5. Calculated transition probabilities (provided in Table 29 of the report) only appear to provide transition probabilities from the ‘no bleed’ health state. We considered if this is because the model assumes that bleeds last for only one cycle and thus bleed states are effectively tunnel states (the EAG notes reference to the duration of bleeds is stated at 2 and 4 days in Table 44), but Figure 38 (P147, Doc B) shows patients can remain in these states for more than one cycle. Please provide a full state transition matrix (unadjusted for death) for each treatment to and from every state (except death).

Bleed states, formally health states 2 and 3, are not effectively tunnel states.

Figure 38 on page 147 of the CS indeed shows how patients can remain in these states for more than one cycle and the model is adequately equipped for those possibilities and their effects. The way in which a patient remains in the joint bleed health state, is where they can experience a joint bleed in the current cycle and subsequent cycle.

The CS did not elaborate that the transitional probabilities are presumed to be bi-directional with equal likelihoods. This means that the probability of experiencing a joint bleed in the succeeding cycle is independent of the health state a patient is in the current cycle (except the health state of death). Thereby, the transitional probabilities in Table 29 of the CS provide a holistic and comprehensive outlook on all transitional probabilities used in the model. As the EAG notes, for completeness mortality needs to be considered and that values for etranacogene dezaparvovec need to be augmented for the durability of etranacogene dezaparvovec at a particular cycle of interest, which is described in section B.3.3.

This is a modelling simplification approach as the examination of the bleeding rates, following the occurrence of bleeds, were not recorded in the HOPE-B trial. If the assumed bi-directional transitional probabilities with equal likelihood assumption would have been augmented by ‘perfect’ data sets, the qualitative results of the modelling would have not changed. This is demonstrated by the analyses in the DSA and PSA sections of the CS. **Table 3** below provides the full transition matrix as requested by the EAG.

Table 3: Transition probability matrix

Markov state of origin and technology	Markov state of destination		
	No bleeds	Non-Joint bleeds	Joint bleed
Etranacogene dezaparvovec – no bleeds	[redacted]%	[redacted]%	[redacted]%
Etranacogene dezaparvovec – non-joint bleeds	[redacted]%	[redacted]%	[redacted]%
Etranacogene dezaparvovec – joint bleeds	[redacted]%	[redacted]%	[redacted]%
BeneFIX – no bleeds	92.12%	6.31%	1.57%
BeneFIX – non- joint bleeds	92.12%	6.31%	1.57%
BeneFIX – joint bleeds	92.12%	6.31%	1.57%
Alprolix – no bleeds	96.18%	1.99%	1.82%
Alprolix – non-joint bleed	96.18%	1.99%	1.82%
Alprolix – joint bleed	96.18%	1.99%	1.82%
Idelvion – no bleeds	96.27%	0.69%	3.04%
Idelvion – non-joint bleed	96.27%	0.69%	3.04%
Idelvion – joint bleed	96.27%	0.69%	3.04%
Refixia – no bleeds	97.61%	1.51%	0.88%
Refixia – non-joint bleed	97.61%	1.51%	0.88%
Refixia – joint bleed	97.61%	1.51%	0.88%

B6. PRIORITY QUESTION. The EAG is able to replicate the calculations for weekly probability of joint bleed of 0.27% from AjBR of [redacted], but not 0.46% from ABR of [redacted]. Please clarify the way this was calculated?

This method for the calculation of the transitional probabilities is outlined in the CS in Section B.3.3.3 as well as on p.151: “The r value for calculating the probability of a

non-joint bleed is the difference between the ABR and AjBR for the comparator of interest."

These calculations are also presented in the columns O-R in the Markov traces, with values for etranacogene dezaparvovec being augmented by mean durability at the cycle of interest. The probability of a patient experiencing a non-joint bleed is given by the expression of formula 1 in terms of the relevant bleed rates:

1-exp(-(ABR-AjBR)/52.14)

B7. Please justify why health state utilities are applied to treatment arm rather than to health states?

Health state utilities are applied to the health states and differ by treatment arm. There are two treatment arms, the gene therapy arm corresponding to the administration of etranacogene dezaparvovec and the Factor IX arm corresponding to the administration of the Factor IX comparators. The health state utility for the gene therapy arm is higher than the health state utility for the Factor IX arm, key opinion leaders have validated an outright utility gain for patients receiving a gene therapy over Factor IX treatments, stating the gains are 'conservative and a minimum, but reasonable' p.155 of the CS.

The gene therapy can offer benefits on EQ-5D dimensions, which are specifically outlined in Section B.2.12 and validated by key opinion leaders. These include:

- Lesser pain – caused by regular Factor IX treatment
- Greater ability to do usual activities – caused by not attending regular Factor IX treatments
- Lesser depression – caused by not attending regular Factor IX treatments

Further differences between the health state utilities and how they vary by the intervention and comparators are provided in the response to question B10.

B8. PRIORITY QUESTION. The EAG notes that the difference in EQ5D-5L van-Hout utility was [redacted] at 12m post treatment (not statistically significant), rising

to [redacted] (statistically significant) at 24m. It is stated on p.81-82 of the CS that a potential explanation for this trend is "due to the relatively intensive follow-up period in the first-year post-treatment". However, the decision model appears to assume patients obtain the full benefit of treatment from day Can you please provide a rationale for this decision?

The choice to assume constant health-related quality-of-life gains of etranacogene dezaparvovec as a gene therapy, over the comparators from day one is a modelling simplification. There is data from earlier data collection points of the HOPE-B study, which indicates that the difference in utility between etranacogene dezaparvovec and the comparators is lower than at the endpoint 24-month utilities. CSL can use more granular utility data if the EAG believes such a scenario to be more appropriate.

However, section B.3.10.3.2 outlines a conservative scenario, exploring the impact of no incremental gains in quality-of-life offered by etranacogene dezaparvovec as a gene therapy. The quantitative results of this scenario are still considerably in favour of etranacogene dezaparvovec which retains its dominance over the comparators, such that analysis of 'delayed' quality-of-life gains from an intensive follow-up period are not going to change any conclusion for the intervention in question.

B9. PRIORITY QUESTION. EQ5D-5L van-Hout utility values for etranacogene and comparators are reported as [redacted] and [redacted], respectively, in Table 15, but the values used in the model are [redacted] and [redacted] (as shown in Table 32 and in the model decision model). Please can you explain the difference?

Section B.2.6.6 does not mention mapping which means that utility values in Table 15 of the CS are consistent with the reported EQ-5D-5L index scores outlined for the lead-in period and 7–24 months post-treatment period, from the HOPE-B trial. These index scores are expressed in terms of the standard English EQ-5D-5L value set of Delvin et al. (2018). It was considered good practice to report EQ-5D-5L utility values from the HOPE-B trial as 'raw', meaning, without mapping. Admittedly, there should have been a clearer indication that utilities specified before section B.3.4.2, which refers to mapping, were not mapped.

The utility values in Table 32 of the CS are consistent with the utility values of Table 15 of the CS, in the sense that they are an expression of the same EQ-5D-5L index scores outlined for the Lead-in period and 7–24 Months post-treatment period from the HOPE-B trial. The key difference is that the utility values in Table 32 of the CS correspond to the EQ-5D-3L value set by the way of the mapping function developed by van Hout et al. (2012).

Section B.4.3.16 of NICE guidance and methods does not recommend the use of the van Hout et al. mapping function, or the EQ-5D-5L value set for England published by Delvin et al. (2018). CSL Behring are currently deriving utilities that are mapped in accordance with NICE guidance and methods as per the Hernández Alava et al. 2017, using the 'EEPRU dataset' (Hernández Alava et al. 2020). The mapped utilities will be available and provided in CSL Behring's response to the EAG report and technical engagement. CSL Behring made NICE aware of a delay with this when submitting the dossier (Friday 20 January 2023), and for transparency have included this update in the latest communication with NICE that accompanies this response.

B10. Table 32 reports the same health state utility for no bleeds, non-joint bleed and joint bleed. Is this a typographical error? (The EAG notes disutilities for the two bleed types are reported lower in the table)

There are no typographical errors in Table 32 of the CS. The second column lists the next four rows of the utility values for etranacogene dezaparvovec to the corresponding four health states. In accordance with the answers provided to questions B7, B8 and B9, sections B.2.12 and B.3.4.5 more generally, alongside key opinion leader input: as a gene therapy etranacogene dezaparvovec offers inherent quality of life benefits over the comparators which are Factor IX prophylaxis treatments. The variance of utility between the health states amongst the same technology stem from the fact that disutility of non-joint (joint) bleeds are applied to non-joint (joint) health states, also as outlined per the sources mentioned.

A major factor contributing to the modelling decision of technology dependant health state utilities, is that patients on the comparators still face the quality-of-life burdens of attending and administrating their regular Factor IX prophylaxis treatments in a

given cycle, independent of whether a non-joint (joint) bleed has occurred in that cycle.

For completeness, the third column of Table 32 of the CS lists the next four rows of the utility values for the comparators to the corresponding four health states. **Table 4** below provides the same analysis as Table 32 of the CS but including the adjustment of the non-joint (joint) health state utility for disutility of a non-joint (joint) bleed. Note that the SE for etranacogene dezaparvovec and the comparators for the non-joint bleed and joint bleed states utilities are calculated as SE of the respective no bleed state utility minus the relevant disutility SE. The SE of the disutility of bleeds are not known and a value of 20% of mean was attributed.

Table 4 : Health state utilities by technology adjusted for bleeding disutility

Health state	Utility values for etranacogene dezaparvovec: (SE)	Utility values for comparators (SE)	95% CI etranacogene dezaparvovec	95% CI comparator	Section in CS
No bleeds	[redacted]	[redacted]	[redacted]	[redacted]	B.2.6.6.1
Non-joint bleed	[redacted]	[redacted]	[redacted]	[redacted]	B.2.6.6.1
Joint bleed	[redacted]	[redacted]	[redacted]	[redacted]	B.2.6.6.1
Death	0	0	-	-	B.2.6.6.1

Justification for all: HOPE-B[2]

B11. Can you please explain how you accounted for uncertainty in disutilities in the model? This appears not to have been accounted for, and in which case can you please provide a rationale for this approach?

The disutilities in question are the ones for non-joint and joint bleeds, initially reported in Table 32 of the CS. Table 32 of the CS presents the standard errors for these to be "**-**" which is a typographical error.

The exact standard errors for these disutilities are unknown, and as such in the 'Model Parameters' sheet they have been assigned a standard error of 20% of their respective means. The 'control' column has an input of '0' in the rows for these two

bleeds, which means the uncertainty surrounding these values has been accounted for in the DSA and PSA outputs.

B12. The CS states that the biomarker test required for treatment with etranacogene dezaparvovec will be provided by the company free of charge, and therefore the model should include only the costs associated with delivering the test in practice. Can you please confirm the costs you expect to be incurred by the NHS?

The cost expected to be incurred by the NHS is an assumed hour of nurse time relating to the handling of the biomarker test results from the manufacturer. Table 5 below is an extension of Table 34 in the CS and provides the details of the total administrative costs that etranacogene dezaparvovec is expected to incur to the NHS, now including the additional nurse time.

Table 5 : The administrative cost of etranacogene dezaparvovec including the additional nurse time

Resource	Inflated cost (£)
Delivery of etranacogene dezaparvovec	133.92
Initial screening cost (FibroScan)	225.00
Blood test	3.78
Abdominal ultrasound	396.47
Nurse time for the biomarker test results	39.17
Steroids and/or diphenhydramine	6.50
Wound management products	0.02
Total	808.62

This additional cost is very small with respect to the total costs incurred by the cohort and will not affect the outcomes of the cost-effectiveness results. Note this table also includes the response to question B13.

B13. The EAG notes the SmPC recommends diluted etranacogene is infused at 500ml/hour, which the EAG assumed would be delivered as an outpatient procedure. This does not appear to be included in the list of cost items in Table 34. Please can you clarify your rationale for excluding this?

Thank you for highlighting. The costs of the delivery of etranacogene dezaparvovec was mistakenly omitted from Table 34 of the CS. The outpatient procedure cost,

which is included in Table 5, is taken as the average non-consultant led unit cost for an outpatient procedure as per NHS NCCI 2020/2021.

As with the response to question B12, the additional cost is very small with respect to the total costs incurred by the cohort and will not affect the outcomes of the cost-effectiveness results.

B14. PRIORITY QUESTION. The EAG notes the SmPC states that "haemostatic support with exogenous human Factor IX may be needed during the first weeks after etranacogene dezaparvovec infusion to provide sufficient Factor IX coverage for the initial days post-treatment" (CS, Appendix C1.1, SmPC). Please can you clarify whether this was included in the model (costs, effects and health state utilities)? If not, can you please provide your rationale?

The modelling fully accounts for the SmPC recommendations. Cell G42 of the 'Settings' sheet (expressed annually) outlines that three weeks are needed for etranacogene dezaparvovec patients to reach the full impact of the dose. Accordingly, the costs, effects and health state utilities for etranacogene dezaparvovec patients in those first three weeks are those taken from the active comparator and this approach is explained in the answers to questions B4 and B20. The active comparator values are added on top of the initial list price of etranacogene dezaparvovec when calculating total costs and thereafter etranacogene dezaparvovec values take place for the remaining cycles according to the durability of etranacogene dezaparvovec over the time horizon.

B15. Table 35 assumes all people who receive etranacogene would receive regular follow-up appointments with a nurse during year 1. Was this assumption based on evidence or clinical opinion that a nurse would conduct these appointments as opposed to another staff member?

This assumption was validated by eight English haemophilia centre directors in an advisory board conducted in November 2022, who confirmed a nurse would conduct these appointments as opposed to another staff member.

B16. Please clarify that costs reported in Section B.3.5.4 are incurred by all patients equally in all arms, therefore the incremental impact of these is zero?

Incremental impact is indeed zero. P.164 states “disease monitoring costs are incurred by all haemophilia B patients”.

B17. PRIORITY QUESTION. Please can you confirm the approach used to account for uncertainty around transition probabilities? Our view is that this is best reflected using a Dirichlet distribution.

For clarity, transition probabilities are a transformation of annual bleed rates according to formula 1, as expanded in the answer to question B6. Measures of statistical uncertainty of the bleed rates are available since the standard errors are reported by the ITC report, as expanded by the answer to question B3. The uncertainty of the bleed rates thereby became the uncertainty of the transitional probabilities, and their characterisation was accounted for in the DSA and PSA analyses.

CSL Behring agrees with the view of the EAG that the Dirichlet distribution is the most appropriate method of accounting for uncertainty of transitional probabilities. The reason that it was not utilised in the above analyses was because of structural difficulty in relation to the derivation of the weekly transitional probabilities from annual bleed rates. To the best of our knowledge, the modelling of the Dirichlet distribution in Excel for the transitional probabilities of a certain comparator could have been conducted in the manner of:

Let X = RAND()

Let Y = the mean of the transitional probability of interest

Let Z = the standard error of the transitional probability of interest

Gamma value = GAMMA.INV(X, Y/beta , Z^2/Y), for all transitional probabilities.

The final characterisation to the realised transitional probability would have been to normalise the gamma value with respect to all the other gamma values of interest.

However, this process could not have been applied as the method of calculating the Z variable is not known. Considering the equation outlined in the response to question B6, one requires knowledge of how the standard errors of the ABR and AjBR react following the transformation applied by formula 1 and scaling to weekly cycles from annual rates in; 1-exp(-(ABR-AjBR)/52.14) [for non-joint bleed rates]. CSL Behring welcomes the input of the EAG to clarify the computation of correlated standard errors following a non-linear transformation from rates to probabilities.

The approach to accounting for the uncertainty of transitional probability was applied prior to the application of formula 1, as the bleed rates were made probabilistic or varied deterministically with the aid of directly observed clinical variables in the form of ABRs and AjBRs. The approach of accounting for the uncertainty of transitional probability by the EAG is not disputed, but the structure of the transition probabilities does not allow for the application of the Dirichlet distribution directly. Regardless of the method chosen, the difference between the currently used method to account for the uncertainty of transition probabilities versus the proposed Dirichlet distribution, would have negligible impact on the transition probabilities (as this uncertainty is already accounted for via uncertainty of bleed rates) and therefore would not impact the conclusions stemming from the cost-effectiveness analysis.

B18. Can you please review and confirm the hyperparameters reported in Table 47 for the distribution of intervention administration cost? A Gamma (127,25) has a mean of £3175, not £635.55.

Thank you for highlighting this typographical error. The alpha and beta for that distribution in the model are 25 and 25.42 respectively.

B19. PRIORITY QUESTION. In Table 47, a combination of standard errors and standard deviations are reported in column 2. It is critical for the PSA to have consistent values. Can you please provide SE for all values where SD is

currently provided?

The model does have consistent values for the PSA and DSA as all presented uncertainty metrics are standard errors unless they are confidence intervals. All instances which refer to SD in the CS are a typographical error.

B20. Can you please explain the meaning of this statement on p.190 of the CS? – "The PSA results are presented in **Error! Reference source not found.** *with etranacogene dezaparvovec as a function of Refixia*".

Full explanation of the meaning of "etranacogene dezaparvovec as a function of Refixia" is explained in the response to question B10. To confirm, the meaning of this statement is to explain that the PSA was conducted with Refixia as the active comparator and accounts for 100% of the market share. Refixia inherited all the responsibility for providing etranacogene dezaparvovec patients with on-demand Factor IX treatment for every bleed, and regular Factor IX treatment as for patients who waned off etranacogene dezaparvovec durability.

As per section B.3.9.1 of the CS, Refixia is identified as the most expensive comparator. The response to question B10 explains that the total costs of etranacogene dezaparvovec vary in comparisons as dependants of other comparators. Therefore, a PSA conducted under these circumstances can be classified as a conservative approach to characterising the uncertainty of etranacogene dezaparvovec. The probability of being cost-effective for etranacogene dezaparvovec at a particular threshold would have been higher if another comparator was designated in this role. A similar description of events can be found on p.190 of the CS, with the first reference to etranacogene dezaparvovec as a 'function' of comparators stated on p.183.

B21. Can you please provide more detail the way the durability scenarios reported in Table 50 of the CS were conducted, and how you interpret the findings? The EAG notes that scenario 3 is only moderately worse than the base case with waning

commencing in year 6 rather than year 7, yet the result swings from extremely favourable to etranacogene (dominating) to extremely unfavourable (£656,728).

To clarify, the base case results are in terms of durability presented by Shah et al. (2022) for a 2% threshold, with all of these values outlined in Table 43 of the CS for all of the years of analysis.

The durability scenarios were conducted in the following way. Scenarios were numbered and they reflected a set of values of the durability (the proportion of etranacogene dezaparvovec patients expressing cost and effect values associated with etranacogene dezaparvovec, and values for the active comparator otherwise) for the various years of the analysis. Scenario 1 is synonymous with perfect and never-ending effect of etranacogene dezaparvovec over the patient's lifetime in the model. Thereby, the results in Table 50 of the CS for scenario 1 represent the best possible outcomes for etranacogene dezaparvovec, surpassing the dominance shown by the base case.

Scenario 2 is similar to the base case. Scenario 2 is the durability presented by Shah et al. (2022) for a 5% threshold. The threshold refers to mean Factor IX level activity in haemophilia B patients and indicate the start of regular Factor IX prophylaxis. This scenario is worse than the base case, and key opinion leaders have forwarded their unanimous support for the base case values. Like the base case and scenario 1, scenario 2 presumes the effect of etranacogene dezaparvovec for 60 years although like the base case it naturally wanes. The results in Table 50 for scenario 2 are worse than for the base case but still dominant.

There is a significant difference between scenarios 2 and 3, as reflected in the graphs. The base case, scenario 1 and scenario 2 are common in that they have varying durability over a long-time horizon. Scenario 3 is a short-term durability scenario. The values for this scenario are the presented in Table 6 and Figure **1** below, depicting the two scenarios mapped over the time horizon.

Figure 1 : Comparison of scenario 2 and scenario 3

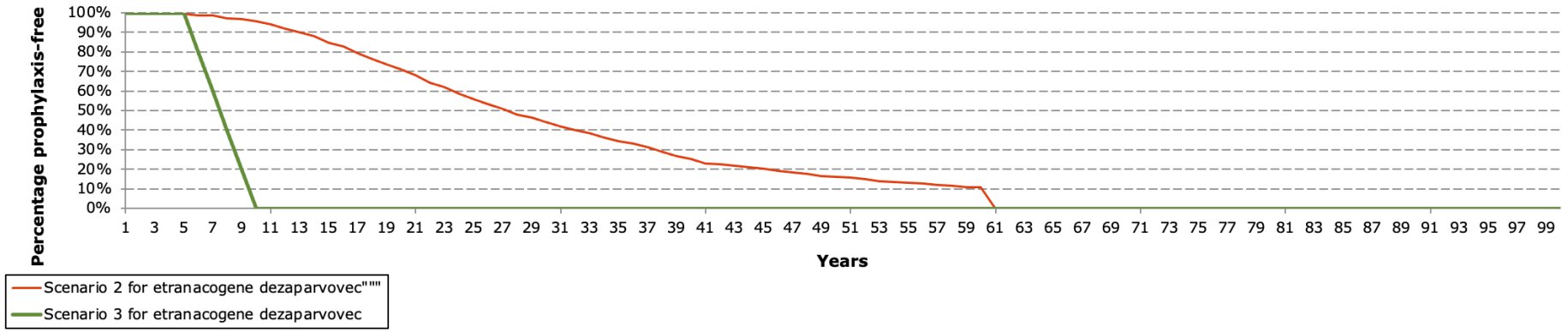

Table 6 : Scenario 2 and scenario 3 durability values per year

	Durability values for scenario 2	Durability values for scenario 3
Year	**Durability**	
1	100%	100%
2	99.90%	100%
3	99.80%	100%
4	99.60%	100%
5	99.50%	100%
6	98.80%	80%
7	98.50%	60%
8	97.20%	40%
9	96.90%	20%
10 and beyond	Extrapolated decline from 95.60%	0%

This scenario considers the improbable situation in which following the observed durability for patients in the 5-year phase 2b HOPE-B trial, patients started suddenly and rapidly losing the benefits of etranacogene dezaparvovec. As per Table 6, there are assumed no gains in etranacogene dezaparvovec for years ten and beyond, despite the intervention being a gene therapy which is only administered once, as per the SmPC. Furthermore, this contradicts statistical extrapolations. This is the cause of the extreme swing of cost-effectiveness between scenarios 2 and 3. It must be stressed that this scenario is beyond pessimistic guess work and only reported for the transparency of the modelling approaches. To reiterate, the key opinion leaders unanimously and only support the base case durability which leads to domineering outcomes.

Scenario 4 falls in the same category as scenario 3 but even more unrealistic. It represents a situation that contradicts observed evidence for the durability of etranacogene dezaparvovec, that at 24-month following treatment patients start to suddenly and rapidly losing the benefits of etranacogene dezaparvovec with a linear decline like shown in Table 6. Scenario 4 offers no benefits for etranacogene dezaparvovec patients following year 6 and beyond. The conclusions of scenario 4 are similar quantitatively to the conclusions of scenario 3, the incremental cost-effectiveness ratio is far above the cost-effectiveness threshold.

B22. We note the discrepancy between the starting age in the model (aged 42 years) and the eligibility for etranacogene which begins at 18 years old. We appreciate that to some extent this will reflect a changing target population; however, we would be interested to see a sensitivity analysis showing the impact on the cost effectiveness of etranacogene if it were started at an earlier starting age. Are you able to provide that please?

Table 7 provides the pairwise incremental cost effectiveness results for a cohort of patients aged 18, for 4328 cycle iterations which is equal to 83 years such that the cohort reaches death at the end of their 100th year of life.

Table 7 : Pairwise incremental cost-effectiveness results for a cohort of 18-year-olds up to their 100th year of life inclusive

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Etranacogene dezaparvovec (BeneFIX)	[redacted]	25.584	[redacted]	-	-	-	-	-
BeneFIX	[redacted]	25.584	[redacted]	[redacted]	0	[redacted]	Dominating	Dominating
Etranacogene dezaparvovec (Alprolix)	[redacted]	25.584	[redacted]	-	-	-	-	-
Alprolix	[redacted]	25.584	[redacted]	[redacted]	0	[redacted]	Dominating	Dominating
Etranacogene dezaparvovec (Idelvion)	[redacted]	25.584	[redacted]	-	-	-	-	-
Idelvion	[redacted]	25.584	[redacted]	[redacted]	0	[redacted]	Dominating	Dominating
Etranacogene dezaparvovec (Refixia)	[redacted]	25.584	[redacted]	-	-		-	-
Refixia	[redacted]	25.584	[redacted]	[redacted]	0	[redacted]	Dominating	Dominating

*Table accurate to whole pound in terms of costs and three significant figures for QALYs.

Etranacogene dezaparvovec extends the dominance over all comparators in all pairwise comparisons relative to the base case. This occurs because mortality in the earlier decades of modelling is low and durability is high, whereas when durability wanes to low levels the weight assigned to those years in terms of their share of the total analysis is low due to discounting. Furthermore, these results occur with a conservative approach to the durability as the base case durability used is now limited, since Shah et al. (2022) only expanded their extrapolation to 60 years. What this means for a cohort of 18-year-olds is that etranacogene dezaparvovec halts to non-existent durability at the age of 78 of the cohort, whereas the simulated durability for year 60 is 21.5%. Table 8 provides the same analysis as Table 7 but including the PAS discount, where these results further the points made regarding Table 7.

Table 8 :Pairwise PAS incremental cost-effectiveness results for a cohort of 18-year-olds up to their 100th year of life inclusive

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	ICER incremental (£/QALY)
Etranacogene dezaparvovec (BeneFIX)	[redacted]	25.584	[redacted]	-	-	-	-	-
BeneFIX	[redacted]	25.584	[redacted]	[redacted]	0	[redacted]	[redacted]	[redacted]
Etranacogene dezaparvovec (Alprolix)	[redacted]	25.584	[redacted]	-	-	-	-	-
Alprolix	[redacted]	25.584	[redacted]	[redacted]	0	[redacted]	[redacted]	[redacted]
Etranacogene dezaparvovec (Idelvion)	[redacted]	25.584	[redacted]	-	-	-	-	-
Idelvion	[redacted]	25.584	[redacted]	[redacted]	0	[redacted]	[redacted]	[redacted]
Etranacogene dezaparvovec (Refixia)	[redacted]	25.584	[redacted]	-	-		-	-
Refixia	[redacted]	25.584	[redacted]	[redacted]	0	[redacted]	[redacted]	[redacted]

*Table accurate to whole pound in terms of costs and three significant figures for QALYs

Section C: Textual clarification and additional points

Errors in Decision Model Mechanics

C1. PRIORITY QUESTION. Errors when changing default settings (1). Changing the time horizon of the model (Settings!G19) generates a type-mismatch error. This is caused by the character 'i' in Settings!A:A. Can you please correct this?

Thank you for highlighting the type-mismatch error when changing the time horizon of the model. The updated model includes working time horizon and age settings. The previous macro was removed, and the Markov traces have been expanded to include the possibility of modelling of cohorts 18 years old and older up to the age of 100, as seen in Table 7.

C2. PRIORITY QUESTION. Errors when changing default settings (2). Switching to health-state dependent health state utilities (rather than treatment-dependent) generates errors. The EAG believes that this is due to errors in Model Parameters!E197:E202, which do not link to any cell – utilities by health state appear to have been deleted from sheet "Quality of Life Inputs". Please can you provide the relevant data?

The utilities by health-state to which the EAG is referring, were reported for Markov states in a different disease area as the model was adapted from a different indication. These utilities by health-state are thereby not relevant to the decision problem. The updated model (included with the response to the clarification questions) no longer includes that setting.

C3. PRIORITY QUESTION. Errors when changing default settings (3). Changing the durability effect to replicate the durability scenarios (Clinical Inputs!E39) appears not to change anything in the model. Please can you review ALL switches within the code and ensure they are all fully functional.

To replicate durability scenarios, it is required to input 'User-defined' from drop down in E38 of cost inputs and then change values in G65 downwards. Two percent threshold from Shah et al. (2022) extrapolation over 60 years is the base case and

5% threshold from Shah et al. (2022) is the other option in the drop-down box. Use Table 1 of the document in reference to scenario 3.

Miscellaneous clarification points

C4. Please supply the RIS file for the CS report references. Please also ensure that the supplied pdf files for references are complete (e.g. Shah et al. 2022, Liu et al. 2020 and Liu et al. 2021 are missing).

Thank you for highlighting that only the first 100 references were included in the original CS reference pack. Please see the full CS reference pack and the associated RIS file, named as '*ID3812 Company Submission RIS'* and '*ID3812 Company Submission Reference Pack'*, accompanying this clarification question response for completeness.

Please note that Liu et al. (2021) was included in the original reference pack, while Liu et al. (2020) is not referenced in the CS and thus is not included in the reference pack.

Also please note that this clarification question response document also has its own reference pack and RIS file, which are included as '*ID3812 CQ response RIS'* and '*ID3812 CQ response reference pack'*.

C5. Appendix D, Figure 1. Three records appear to go missing by the end of the PRISMA diagram (353 + 25 = 381), please can you review the numbers reported?

Each stage of the Appendix D, Figure 1 PRISMA numbering has been checked, with no missing records identified:

2064 – 1237 = 827

827 – 474 = 353

353 + 25 = 378

378 – 131 = 247

C6. It appears as if references to section B.2.6.6.2 reported in Table 32 should actually be to B.2.6.6.1 (EQ5D5L not Haem-A-QoL). Can you please confirm and correct if needed?

Thank you for highlighting; Table 32 should reference Section B.2.6.6.1.

C7. Please can you cite Neufeld 2012, Mazza 2016 and Fischer 2016 (p.153) and include these in your reference pack?

The full citations are as follows, with the PDFs supplied in the accompanying reference pack (*CQ Responses Reference Pack*):

- Neufeld EJ, Recht M, Sabio H, et al. Effect of acute bleeding on daily quality of life assessments in patients with congenital hemophilia with inhibitors and their families: observations from the dosing observational study in hemophilia. Value in Health. 2012;15(6):916-925[8]
- Mazza G, O'Hara J, Carroll L, Camp C, Hoxer CS, Wilkinson L. The impact of severe haemophilia and the presence of target joints on health-related quality-of-life. Health and Quality of Life Outcomes. 2018; 2;16(1):84[9]
    - Please note that Mazza et al. (2016) is an abstract from the Professional Society for Health Economics and Outcomes Research (ISPOR) conference held in November 2016. The research was subsequently published by O'Hara et al. in 2018:
        - O'Hara J, Walsh S, Camp C, Mazza G, Carroll L, Hoxer C, Wilkinson L. The impact of severe haemophilia and the presence of target joints on health-related quality-of-life. Health Qual Life Outcomes. 2018 May 2;16(1):84. doi: 10.1186/s12955-018-0908-9[10]
    - For completeness, both have been included in the accompanying reference pack.
- Fischer K, de Kleijn P, Negrier C, et al. The association of haemophilic arthropathy with Health-Related Quality of Life: a post hoc analysis. Haemophilia. 2016;22(6):833-840[11]

C8. In Table 43, the header to column 3 is “confidence interval (distribution)” yet this is not reflected in the column contents. Is this an error? If possible, can you please provide SE rather than SD for model variables.

With respect to the column header, thank you for highlighting this error. The column contents are correct for a column header titled ‘Measurement of uncertainty and values’.

All variables that have a distribution assigned to them in the PSA are outlined in Table 47 of the CS. With respect to the reporting of SE versus SD, please refer to the response to the question of B19.

C9. We note an error in the calculation of Figure 39, which shows that every comparator dominates etranacogene. Can you please review this?

Figure 39 and by extension Figure 41 of the CS which is the same analysis but with the PAS discount in place, once reviewed we note that etranacogene dezaparvovec dominates all comparators in all but one iteration. The dots highlight where etranacogene dezaparvovec lays with respect to the comparator of interest all of whom, are situated at the origin. Therefore, as per the broader picture of the PSA results in section B.3.10.1 of the CS, etranacogene dezaparvovec dominates the comparators in the vast majority of cases, see Tables 48 and 49 of the CS.

C10. Figures 43-50 are challenging to interpret. If possible, can you please re-submit these as bar charts that show NMB across all five comparators simultaneously?

As clarified during the NICE/EAG meeting on Friday 10 February 2023, the latest version of the model, which has been included with this clarification response, features a fixed x-axis such that the NMB for all DSA comparisons can be visually seen on the diagram.

References

1. European Medicines Agency. Hemgenix (etranacogene dezaparvovec). https://www.ema.europa.eu/en/medicines/human/summaries-opinion/hemgenix. Accessed 10 February, 2023.
2. CSL Behring. HOPE-B Study Results Overview: 24-month data [data on file]. 2022.
3. CSL Behring. Hemgenix (etranacogene dezaparvovec) SmPC 2022.
4. Coppens M, Pipe S, Miesbach W, et al. Adults with haemophilia B receiving etranacogene dezaparvovec in the HOPE-B phase 3 trial experience a stable increase in mean Factor IX activity and durable haemostatic protection after 24 months follow-up. 16th Annual Congress of the European Association for Haemophilia and Allied Disorders (EAHAD); 2023.
5. Astermark J, Lucas S, Chen L, Monahan PE, Recht M. Analysis of elevated alanine transaminase in HOPE-B, a phase 3 recombinant adeno-associated viral 5 gene therapy trial in people with haemophilia B – PO040 poster abstract. Annual Congress of European Association for Haemophilia and Allied Disorders (16th, 2023); 2023; Manchester.
6. Berger K, Schopohl D, Hilger A, et al. Research in haemophilia B--approaching the request for high evidence levels in a rare disease. *Haemophilia.* 2015;21(1):4-20.
7. Thorat T, Neumann PJ, Chambers JD. Hemophilia Burden of Disease: A Systematic Review of the Cost-Utility Literature for Hemophilia. *J Manag Care Spec Pharm.* 2018;24(7):632-642.
8. Neufeld EJ, Recht M, Sabio H, et al. Effect of acute bleeding on daily quality of life assessments in patients with congenital hemophilia with inhibitors and their families: observations from the dosing observational study in hemophilia. *Value Health.* 2012;15(6):916-925.
9. Mazza G, O'Hara J, Carroll L, Camp C, Stentoft Hoxer C, Wilkinson L. The Impact of Haemophilia Complications on Health-Related Quality of Life for Adults with Severe Haemophilia. ISPOR 2016; 2016.
10. O'Hara J, Walsh S, Camp C, et al. The impact of severe haemophilia and the presence of target joints on health-related quality-of-life. *Health Qual Life Outcomes.* 2018;16(1):84.
11. Fischer K, de Kleijn P, Negrier C, et al. The association of haemophilic arthropathy with Health-Related Quality of Life: a post hoc analysis. *Haemophilia.* 2016;22(6):833-840.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B [ID3812]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	The Haemophilia Society
3. Job title or position	Policy and Public Affairs Manager
4a. Brief description of the organisation (including who funds it). How many members does it have?	The Haemophilia Society (THS) is the only UK-wide charity and free membership organisation for everyone affected by a bleeding disorder. We have over 4,700 members. At THS we want to empower everyone affected by a bleeding disorder to live life to the full, whatever stage you are at. We offer free member events, a local group network and online communities to share advice and experiences, as well as the latest news and access to specialist resources. Many people with a bleeding disorder are undiagnosed or are diagnosed late, because of a lack of understanding about these rare conditions. Our community rallies together to raise awareness about bleeding disorders, giving hope to everyone affected. THS also campaigns and advocates for what matters to our community; lobbying government, the NHS and clinicians to demand excellent care and safe and effective treatment, which is available to everyone affected by a genetic bleeding disorder.
4b. Has the organisation received any funding from the company bringing the	Yes, The Haemophilia Society receives funding from a number of companies involved in the development, manufacture, marketing and distribution of treatments for haemophilia and other bleeding disorders. I have included the detailed information for the financial year 21/22 below.

<table>
<tr>
<td>treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]
If so, please state the name of the company, amount, and purpose of funding.</td>
<td>
<table>
<tr><th>Company</th><th>Amount (£)</th><th>Purpose</th></tr>
<tr><td>CSL Behring</td><td>35,000</td><td>Core Funding</td></tr>
<tr><td>Novo Nordisk</td><td>23,500</td><td>Centre Engagement, Member Magazine, AGM and Core Funding</td></tr>
<tr><td>Sobi</td><td>47,588</td><td>CRM system, centre engagement, booklets and local groups</td></tr>
<tr><td>Sanofi</td><td>5,000</td><td>Patient Survey</td></tr>
<tr><td>Roche/Chugai</td><td>21,125</td><td>Patient Survey, Website, AGM and Journal Access</td></tr>
<tr><td>Takeda</td><td>25,000</td><td>Patient Survey, AGM, Newly Diagnosed Weekends and Talking Red</td></tr>
</table>
</td>
</tr>
<tr>
<td>4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?</td>
<td>No</td>
</tr>
<tr>
<td>5. How did you gather information about the experiences of patients and carers to include in your submission?</td>
<td>The Haemophilia Society regularly speaks to and corresponds with its members collecting and amplifying their views and needs.
We have an active Facebook group where people share experiences of living with a bleeding disorder and their treatment and care. People also engage with us on other social media including Instagram and Twitter. We have a range of ambassadors, trustees and other patient experts who have contributed to or reviewed this submission. Specifically for this appraisal we convened a working group of people with haemophilia B or parents of children with haemophilia B to better understand their views on gene therapy for haemophilia B and the most important measures of success, unmet need and concerns.</td>
</tr>
</table>

	Our members events include discussion of treatment options, and advice on living with their condition and approaches to life.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Our ambassador describes how living with haemophilia is difficult, having bleeds are not only painful physically but cause great mental distress. You have to adapt your life and this means stopping or not being able to do certain things in life including certain sports, travelling and a number of jobs. This includes not being able to move to certain places for fear of being too far away from a treatment centre. On a day-to-day level walking in a major crowd can be worrying too. The time and money spent on the condition should not be forgotten. Going to a treatment centre even if only for regular appointments a few times a year can cost hundreds of pounds and take you away from work, school and other events. Then, when things go wrong, which on average occurs 3-4 times a year you end up with multiple trips or days spent in hospital.

7. What do patients or carers think of current treatments and care available on the NHS?	Since the 90s people with severe haemophilia B have moved from plasma-derived factor products to recombinant factor IX and most recently on to so-called extended or enhanced half-life products. This has reduced the frequency with which people need to infuse from every second or third day to weekly for most people. Our members have described how currently, the treatments are better than they were a few years ago. However, they are not perfect and still leave a lot to be desired. Treatments, are still time consuming, awkward to travel with and not pleasant especially for younger members of the community. The way these treatments are provided and administered mean that people need to arrange this lives around their treatment. We are often told of people at home waiting for deliveries. They are required to time their treatments with physical activity to ensure they have more protection at those times but leaving them with lower levels at other points. If they want to leave the country or travel away from home they must ensure that they have enough treatment for holidays. Additionally there is a burden in detailed tracking of treatments in an app or elsewhere. In general the current treatments reduce spontaneity and require people with severe haemophilia B to plan meticulously or risk missing out.

8. Is there an unmet need for patients with this condition?	The inherited bleeding disorders patient survey first conducted in 2020 and repeated in 2022 showed that a majority of people with a bleeding disorders feel anxious because of their condition and up to 25% said they felt anxious “a lot” in the last 12 months. In both surveys almost half of respondents said that they had felt depressed in the last 12 months because of their condition. In the 2022 survey we asked a series of questions on pain which showed that only a third of people with bleeding disorders lived a life free from pain as a result of their condition. Around a quarter said this was chronic long-term pain that they felt every day. The Haemophilia Society provides it’s members with advice on pain management and this is a common area of concern for clinicians managing the condition of people with haemophilia. Pain is highly prevalent in people with haemophilia with studies reporting acute pain being experienced by 20–68%. A detailed investigation on what impact pain in people in the UK with haemophilia has on their lives has shown that people make major changes to their life and that their experience of pain is a complex bio-medical and social construct. (P. McLaughlin, M. Hurley, P. Chowdary, D. Stephensen & K. Khair (2022) How does a lifetime of painful experiences influence sensations and beliefs about pain in adults with severe haemophilia? A qualitative study, Disability and Rehabilitation, 44:26, 8412-8419, https://www.tandfonline.com/doi/pdf/10.1080/09638288.2021.2018053) People with severe haemophilia still have painful bleeds requiring additional treatment and often rehabilitation. These bleeds mean that most people with severe haemophilia still develop joint damage impacting on their quality of life (O’Hara, J., Walsh, S., Camp, C. et al. The impact of severe haemophilia and the presence of target joints on health-related quality-of-life. Health Qual Life Outcomes 16, 84 (2018). https://doi.org/10.1186/s12955-018-0908-9) One parent of someone with haemophilia B described how a gene therapy could increase his factor level to a consistent level rather than the up and down levels provided by current treatments. They said

	it would greatly enhance their son's sporting and travelling opportunities, and reduce the continual worry in the back of one's mind of an accident occurring, particularly a head injury at the wrong time of the week. A number of people with haemophilia have spoken to us about how despite their current treatment they do not have full confidence to walk in crowds and will adapt their lives to avoid bumping into people and the risk of bleeds and bruising. For example they will make changes to their plans to ensure they go to the supermarket at less busy times. People with haemophilia do not have the confidence to take whatever career path or social activities they want. Some people with haemophilia, particularly those affected by the scandal of contaminated blood products in the 70s and 80s, are put off by frequent attendance at hospital where they or their family members were prescribed or treated with blood products that gave them HIV and Hepatitis C leading to liver damage and premature death. This treatment could allow some to have their haemophilia treated in a way that could in time reduce their reliance on hospital management and care of their condition.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The new technology has the potential to create stable long-term factor IX expression which could reduce long-term joint damage and make it easier for people to have required joint surgery, reduce pain and improve mobility This is backed up by published data on factor expression such as that presented here:https://ash.confex.com/ash/2022/webprogram/Paper166135.html. It could see a vastly reduced burden of treatment, with a positive impact on family life, career progression and a reduction in anxiety and improve mental health. This is reflected in the conclusions of a paper presented last year which showed significant increases in health related quality of life for people for people treated with the new technology. (Itzler R, Miller J, Robson R, Monahan P, Pipe S. Improvements in Health-Related Quality of Life in Adults with Severe or Moderately Severe Hemophilia B After Receiving Etranacogene Dezaparvovec Gene Therapy [abstract]. https://abstracts.isth.org/abstract/improvements-in-health-related-quality-of-life-in-adults-with-severe-or-moderately-severe-hemophilia-b-after-receiving-etranacogene-dezaparvovec-gene-therapy/)

10. What do patients or carers think are the disadvantages of the technology?	The biggest problem many people see is the unpredictability of the outcome. In the trial data levels achieved at the end of year 2 varied. For some people on the trial the treatment failed entirely. In is also unclear for how long those levels will be maintained and if they will at some point need to move back to prophylaxis with factor concentrates. The impression from our members is that most people will only want to go through the process if they are likely to have good levels for more than five years. Some who are keen for gene therapy will however want to wait for future generations of gene therapies for haemophilia B with some people being put off that if they have this product they may be unable to have future gene therapies using the same or similar vectors. For those that have been on the trials for this treatment an important issue they note is having to be closely monitored for up to a year post treatment and that many of them had acute liver issues which are usually managed with steroids. Steroids can affect mood and lead to weight gain. This a potential major impact of treatment with the product in the first 6 months to a year. An article published by a group of leading people with haemophilia who work closely with the Haemophilia Society at the European Haemophilia Consortium and the Irish Haemophilia Society published an article in 2021 which summarises well the known and unknown risks of the treatment. Alongside the issues of steroids and variability of outcomes mentioned above they also discuss Long-term risk of liver damage potentially leading to cancer, neurotoxicity and that while the vector for this treatment is a non-integrating vector there is a low rate of integration due to the high initial dose of the transgene carrying virus. It is unclear what impact these integration events will have over time and whether there are any other long-term health impacts. Kaczmarek R, Pierce GF, Noone D, O'Mahony B, Page D, Skinner MW. Eliminating Panglossian thinking in development of AAV therapeutics. Mol Ther. 2021 Dec 1;29(12):3325-3327. doi:

	10.1016/j.ymthe.2021.10.025. Epub 2021 Nov 10. PMID: 34758292; PMCID: PMC8636166. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8636166/

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	This treatment won't be right for everyone with severe or moderately severe haemophilia B. It is likely that people whose condition is well-managed on current factor replacement treatments may be less keen to move to a new approach that has less long-term data particularly on risks and side effects. If someone adheres well to their current treatment and is very comfortable with regular self-infusions it may not be as big a priority to move to this treatment. However, for people with venous-access issues or problems with mobility due to bleeds in wrists and elbows difficulty of adherence to current treatment will be much higher and they may see a far greater benefit from this technology. Having the treatment earlier may reduce the long-term impact of joint damage and the treatment may be best suited to people at particular life stages. But we also heard powerful descriptions from people who were retired and had gene therapy because they wanted to be more comfortable and flexible to travel. Some of the people we spoke to with severe haemophilia B who had young children wanted to free up their time to look after their children and worry less about managing their condition. Haemophilia has a major impact on families and on people's decisions to start families. We have been in contact with some people who have delayed or avoided having children due to concerns about their haemophilia and difficulties managing their condition. Others who were younger and had already gone through the process, explained that it was an important option for them to have as it strongly impacted on their future life options. Some people with pre-existing antibodies to the vector won't be able to have the treatment. People with past or present inhibitors (a complication of treatment where the body produces antibodies to factor IX) may also be unable to have the treatment.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	If the treatment is to be delivered in a small number of specialist centres it must be ensure that people who are more distant from those centres still get equitable access to the treatment.

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Despite good treatment options for Haemophilia B being available to patients in England, substantial unmet need remains. • Current treatment options have a major burden of treatment. • Most people with haemophilia B have anxiety or worry about their condition and many still develop joint damage over time. • Even when well-managed with current treatment Haemophilia B continues to be a condition that restricts people's day to day activities and life options • Etranacogene Dezaparvovec will be a good treatment option for some people with severe or moderately severe haemophilia B.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B [ID3812]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

NICE National Institute for Health and Care Excellence

1. Your name	[redacted]
2. Name of organisation	United Kingdom Haemophilia Centre Doctors Organisation (UKHCDO)
3. Job title or position	Chairperson
4. Are you (please select Yes or No):	An employee or **representative** of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The United Kingdom Haemophilia Doctors organisation (UKHCDO) is a professional membership organisation that brings together Haematologists focusing on patients with inherited bleeding disorders. The organisation aims to consider the contemporaneous uncertainties in managing individuals with bleeding disorders, enhance the understanding of inherited bleeding disorders and their management and improve the quality of care for this group of people. The UKHCDO aims to provide guidance where reliable evidence is available, either as a stakeholder in other organisations or under the auspices of the British Society of Haematology and works with other organisations in this space, including professional and patient organisations. In the absence of good evidence, it provides a forum for examining existing information, exchanging opinions and experience and articulating a consensus on the potential approaches to deal with challenges reported in routine clinical practice. Moreover, deliberations within UKHCDO facilitate the characterisation of the unmet needs or issues that require the attention and focus of the organisation and the broader scientific community. The organisation is a registered charity, and expenses are met through income generated from hosting the UKHCDO annual general body meeting, which receives sponsorship from the pharmaceutical industry.

5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	The UKHCDO also owns the UKHCDO Limited, which runs the national haemophilia database (NHD). The NHD receives funds from commissioners and unrestricted grants from the industry for research projects and also undertakes an analysis of NHD data for specific questions funded by the industry.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The treatment aims to reduce mortality and morbidity, mainly focussed on the joints with severe disabling arthropathy. The aim of etranacogene dezaparvovec [ID3812] is to provide remission from the disease phenotype for extended periods, i.e. years. There is potential for a long-term cure, but data on the longevity of expression is currently limited to 7 to 10 years. The treatment prevents further progression of arthropathy by preventing joint bleeds and confers protection against bleed related mortality.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	In the context of the severity classification of Haemohilia and the current management principles, a clinically significant response (CSR) needs to result in an expression level that stops the need for regular prophylaxis (i.e. self infusion of FIX between 1 to 2 times a week) without any spontaneous bleeding. This is likely to be achieved with levels of 3%. However, taking into account the day-to-day variability of assays, the expression levels need to be between 3 to 5% over a 6 to 12-month period for assurance of the above outcome. The next big step is the cessation of top-up prophylaxis for strenuous activities or sports, and levels of 10% or greater ensure this is not required. Levels of around 30%, patients do not require treatment for minor surgeries. Levels of 50% or greater, patients do not require treatment for major surgery.

8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	The management of factor IX deficiency requires replacement with FIX protein, i.e. protein replacement therapy. This has done by intravenous infusion of FIX by patients, caregivers and health care professionals and starts in the first couple of years for patients with severe deficiency. The current standard of care in severe patients requires the self infusion or infusion by caregivers between 1 to 2 times a week, with a substantial treatment burden. Further, some patients have challenges with venous access, requiring more than one infusion attempt. With current prophylaxis regimens, patients continue to have spontaneous or minimally provoked bleeds, which may be due to less than adequate regimens or adherence and the treatment burden of more intense regimens. There is an increasing understanding of the concept of rationalised non-adherence or 'treatment breaks or holidays' as a coping mechanism from patients. Further, an often quoted definition of good adherence is 80 to 85% of the prescribed medication which we know is ineffective in Haemophilia. Many patients who have undergone gene therapy describe freedom or a haemophilia-free mind, which is related to the ongoing risk assessment the patients need to take to ensure the infusions and the fall-off match their activity.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Haemophilia B is an X-linked inherited bleeding disorder characterised by a deficiency of factor IX (FIX), The degree of deficiency largely determines a patient's clinical bleeding phenotype, with those with severe

	haemophilia (F IX <1 IU/dL) typically presenting with recurrent joint and muscle bleeds; these patients may also experience spontaneous and potentially fatal bleeds in any tissue. The classification of disease severity has been established for over 20 years and is detailed below. Severe: <1% of normal (<1 IU/dL) Spontaneous bleeding Joints or muscles Predominantly in the absence of identifiable haemostatic challenge Bleeding into any tissue and organ Post-trauma and surgical bleeding Moderate: 1–5%, (1–5 IU/dL) Occasional spontaneous bleeding Prolonged bleeding with minor trauma or surgery Mild: 5 to <40% (5–40 IU/dL) Spontaneous bleeding is rare Prolonged bleeding with major trauma or surgery The current standard of care for patients with severe deficiency is prevention of bleeding, i.e. prophylaxis, and numerous studies have established its benefits in children and adults. People with severe haemophilia and those with moderate haemophilia with FXI <3% at risk of spontaneous bleeding are encouraged to have regular prophylaxis with recombinant FXI to reduce the risk of joint bleeding. To maintain prophylaxis, standard half-life factor IX products must be administered intravenously every 48-72 hours; in the last few years, extended FIX half-life products have become available, allowing many patients to have 'good' prophylaxis with weekly injections. The primary goal of prophylaxis is the prevention of joint damage in addition to the prevention of fatal bleeds. This requires, at a minimum, zero spontaneous bleeds and, ideally, where possible, patients should have no bleeds in relation to regular physical activity. Despite an improved understanding of the factors underpinning a good prophylactic outcome, patients on prophylaxis can still experience breakthrough bleeds that impact joint health, so there is considerable potential to improve treatment effectiveness. Some challenges that contribute

	to poor outcomes include access to adequate treatment, treatment burden and the impact of the disease on mobility, pain, participation in society and quality of life. Further, the patient's FIX levels still 'see-saw' with intravenous prophylaxis and trough levels are generally below 10% for several days. Patients need to consider additional infusions/more frequent prophylaxis depending on activity levels and access to additional factors for breakthrough bleeds or surgery. Prophylaxis is typically started in the second year of life before the onset of recurrent joint bleeds, i.e. <2 years of age, which can reduce the risk of joint damage over time. Treatment is typically given on-demand in patients with moderate and mild haemophilia, i.e. as needed for prevention of bleeding in relation to surgery or management of bleeding in relation to trauma or other activities.
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes UK guidelines: Guidelines on the use of prophylactic factor replacement for children and adults with Haemophilia A and B. Rayment R et al; British Journal of Haematology 2020. World Federation of Haemophilia Guidelines (WFH): WFH Guidelines for the Management of Hemophilia, 3rd edition. Srivastava et al; Haemophilia 2020.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Yes, there is consensus on the implementation of the most appropriate treatment regimen as per disease severity and the most appropriate follow-up. The challenges are related to adherence and funding for comprehensive care at individual centres.
9c. What impact would the technology have on the current pathway of care?	To undertake gene therapy safely and effectively for patients, it will be essential that a well-informed MDT supports patients: to explore treatment options, including other novel haemophilia treatments, explain the process of gene therapy and potential benefits as well as risks, and actively follow up including both intensive

	follow up and longer-term potential toxicities, and for this data to be collected to review and improve management continuously. This will require a change in our traditional haemophilia service models. The EHC and EAHAD have issued guidance on care models for Europe. The hub and spoke model has been suggested, considering that experience in gene therapies has been restricted to small select centres with clinical trial sites. The model acknowledges the need for intense monitoring, building experience and ensuring the best patient outcomes. The UKHCDO gene therapy working party are currently writing a guideline about the care model and patient pathways within the UK. This document will expand and define the role of hub and spokes, the role of an MDT and the need for data collection following the use of gene therapy in regular clinical practice. We also explore the specific challenges that require attention in gene therapy delivery in routine clinical care.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	We expect the infusion to be restricted to use in specific sites, and the license will determine indications for use.
10a. How does healthcare resource use differ between technology and current care?	A single infusion of the therapeutic product should then have an effect for many years. The patients must travel to a 'Hub' gene therapy dosing centre. Follow-up will be very intense initially, and most patients are currently on routine 6-month follow-up. Post-gene therapy patients will need weekly bloods for at least three months and potentially six months, and then more regular follow-up for the next two years (e.g. monthly until 12 months, then quarterly until two years. If patients have complications of liver inflammation due to immune response to gene therapy, they will be started on immunosuppression and need more frequent monitoring and follow-up. This will be directed by the 'Hub'. As this is a new therapy, it will be crucial to record data, e.g. weekly blood results on a national registry. We believe a national MDT will be required to support safe, effective and equitable care nationally. This will be increased the workload for clinical teams (data manager, nursing and medical). It is essential to have psychological support available for patients, and not all haemophilia centres currently have funding for a psychologist.
10b. In what clinical setting should the technology be used? (For example, primary or	Designated centres with previous experience in gene therapy.

secondary care, specialist clinics.)	
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The facilities must follow recommendations from the advanced medicinal products group.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes,
11a. Do you expect the technology to increase length of life more than current care?	Yes, as it will address adherence issues.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes, patients with good responses are delighted with the outcomes from a disease perspective and quality of life. They believe the guessing – is this a bleed or not a bleed, has decreased, and they can focus all their energies on their professional and personal life.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Some patients struggle with regular infusions, and this group is likely to benefit more than others.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	The treatment burden for patients and clinicians' oversight will diminish significantly over time. Some patients may not wish to have immunosuppresion or be suitable for short-term immunosuppression, which might make them ineligible for the studies.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Tests for evaluation of previous exposure to the AAV virus may be required. The treatment is irreversible.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes, elaborated in 11b.
16. Do you consider the technology to be	As elaborated in 13.

innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
16a. Is the technology a 'step-change' in the management of the condition?	Yes, it is a single infusion with potential benefits for up to 10 years.
16b. Does the use of the technology address any particular unmet need of the patient population?	11b
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The most important side effects are; 1. Infusion reactions at the time of infusion that are easily managed, 2. Immune response to the gene therapy that needs monitoring and immune suppression as required 3. The long-term risk of cancer is considered theoretical but requires monitoring.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	Not applicable

18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Expression of factor IX and yes were measured in the trials as well as the bleed rate.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Yes, see 18b.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	None are available at the moment

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
21b. Consider whether these issues are different from issues with current care and why.	

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Gene therapy is a paradigm shift in haemophilia care and opens up possibilities for long-term remission and potential cure • The therapies are transformations, and for individual patients, the benefits are immense • The delivery of the GT requires consolidation to a few specialist centres to ensure appropriate oversight and follow up • There is a need for a long-term registry to ensure to capture of real-world data • The patients need to be supported by the MDT team in their journey, as both success and failure have a significant psychological impact.

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Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B [ID3812]:

A Single Technology Appraisal

Produced by

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Author Contributions:

Caroline Farmer	Project lead, critical appraisal of the company submission, writing and editorial input
Elham Nikram	Critical appraisal of the economic evidence and analysis submitted by the company, conducted additional economic analyses and drafted sections of the report
Laura A Trigg	Critical appraisal of the economic evidence and analysis submitted by the company and drafted sections of the report
Sophie Robinson	Critical appraisal of the company's literature search strategies
Jason Coppell	Expert clinical advice about haemophilia B and its treatment
Madhusubramanian Muthukumar	Review and QC of model and EAG analyses
G.J. Melendez-Torres	Critique of the company's indirect treatment comparison

Edward CF Wilson	Health economic lead, critical appraisal of the company submission and analysis, conducted additional economic analyses and drafted sections of the report. Report Guarantor.

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1. EXECUTIVE SUMMARY

This summary provides an overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1. Overview of the EAG's key issues

A brief overview of the key issues identified by the EAG in their appraisal of the company submission (CS) is provided in Table 1. Further detail of the issues is provided in Sections 1.3, to 1.6.

Broadly speaking the key clinical issues stemmed from the lack of a randomised trial for ED (specifically a lack of a reliable comparison between ED and current treatment options), and gaps in the evidence base submitted by the company in their submission. Notably, the EAG considered there to be a risk that the effect of ED in the key study, HOPE-B, may be overstated. In terms of cost effectiveness issues, the EAG noted that the definition of ED treatment failure was set at a very low FIX activity level (<2%), the durability extrapolation excluded non-responders and was associated with a great deal of uncertainty due to small numbers and limited follow-up, and that the treatment-related utility of ED vs. IV FIX may be overestimated. Most significantly, the likelihood that ED was cost effective was highly impacted by assumptions surrounding the durability of ED treatment response in the model.

Table 1: Summary of key issues

ID	Summary of issues	Report sections
Key Issue 1	The company did not report evidence for the true change in FIX levels following treatment with ED in the HOPE-B	3.2.2.5

ID	Summary of issues	Report sections
Key Issue 2	Clinical outcomes in the HOPE-B study may overstate the potential benefits of ED	3.2.2.3; 3.2.2.4; 3.2.2.6 and 6.2.2; 6.2.3; 6.2.10.1
Key Issue 3	Comparative efficacy estimates of ED and prophylactic FIX treatments were unreliable	3.3; 3.4
Key Issue 4	Definition of treatment failure was at a low FIX activity level	6.2.2
Key Issue 5	The durability extrapolation model was based on limited data and excluded non-responders	4.2.6.1; 5.2.3.16.2.3; 6.2.10.1; 6.3.1
Key Issue 6	Health state utilities were associated with treatment rather than health states, and the difference may be overestimated.	4.2.7.1; 6.2.5

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are outlined in Table 2.

Table 2: Key differences between the company's preferred assumptions and EAG's preferred assumptions

	Company's preferred assumption	EAG preferred assumption	Report Sections
IV FIX taken alongside ED and post ED failure	Various for pairwise comparisons, Refixia for fully incremental analysis	Only fully incremental analyses conducted, assuming Refixia alongside ED in all cases	4.2.4
FIX activity threshold at which prophylactic IV FIX is resumed ("treatment failure")	2%	5%	4.2.6.2; 6.2.3
Time to steady state	3 weeks	6 months	4.2.6.3; 6.2.4
Disutility of IV FIX treatment compared with ED	[redacted]	0.042	4.2.7.1; 6.2.5
Duration of adverse event costs and consequences from ED.	1-year post-ED administration	Whilst durability of ED continues	6.1; 6.2.9

Abbreviations: ED, etranacogene dezaparvovec; FIX, Factor IX; IV, intravenous

1.2. Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every extra QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increased health state utility associated with receiving a once-only injection of ED compared with (once or twice weekly) IV injections of FIX.
- Reduced risk of bleeds with ED compared with IV FIX.

Overall, the technology is modelled to affect costs by:

- Lower lifetime acquisition cost of ED versus other FIX products.

The modelling assumptions that have the greatest effect on the ICER are:

- Durability of ED (i.e. time before prophylactic IV FIX is resumed)
- 'Treatment associated' health utility bonus from a single injection of ED versus repeated IV FIX injections.

1.3. The decision problem: summary of the EAG's key issues

The EAG did not identify any key issues related to the company's definition of the decision problem.

1.4. The clinical effectiveness evidence: summary of the EAG's key issues

Key Issue 1: The company did not report evidence for the true change in FIX levels following treatment with ED in the HOPE-B study

Report sections	3.2.2.5
Description of issue and why the EAG has identified it as important	The HOPE-B study was a single-arm study that compared outcomes following treatment with ED with participants' outcomes during a baseline lead-in phase of 6-months. As there was no control arm, outcomes assessed during the lead-in phase were the only data to represent participant outcomes while receiving a comparator treatment (prophylactic FIX replacement). One of the key study outcomes, levels of circulating FIX following treatment, was an important outcome for determining the effect of the treatment, and how the condition affects people's lives, including the need for

	additional FIX replacement therapies. However, the company did not report FIX levels during the lead-in phase, and therefore it was not possible for the EAG to determine to what extent FIX levels changed following treatment with ED. The company calculated change in FIX levels from baseline, however the baseline data used for these calculations were not based on data from the lead-in phase, but were rather an estimate of what participants' FIX levels would be if they were receiving no treatment at all (i.e. they used the severity of their condition to impute a FIX level). The EAG considered this approach to be inconsistent with the decision problem for this appraisal, and that the presentation of these findings could potentially be misleading.
What alternative approach has the EAG suggested?	The company did not provide a rationale for why true FIX levels from the lead-in phase of the HOPE-B study were not used to calculate the change in FIX following treatment with ED. The EAG was aware that FIX levels following prophylactic FIX replacement fluctuate with high levels following treatment administration and low levels in the 'trough' before another dose is administered. For this reason, it may be that the company were uncertain how to select a representative FIX level for the lead-in phase from which to calculate the change outcome. However, the EAG considered that the company could have provided descriptive data for the lead-in phase and provided an analysis of change in FIX levels as compared to mean, highest and lowest FIX levels during the lead-in phase. This would have given an indication of the extent to which ED affected circulating FIX, and would be useful given limitations in bleeding and FIX replacement outcomes described in Key Issue 2.
What is the expected effect on the cost-effectiveness estimates?	FIX levels were not directly included as part of the decision modelling, although failure of ED was defined as a circulating FIX activity level of <2% in the company's durability extrapolation. Understanding of the difference in FIX levels between the lead-in phase and following treatment with ED may reduce uncertainty in the reliability of bleeding outcomes that were used in the model (Key Issue 2).
What additional evidence or analyses might help to resolve this key issue?	The company should provide true baseline FIX levels for the lead-in phase of HOPE-B. Useful analyses would be the difference in FIX levels following treatment with ED as compared to mean, minimum and maximum FIX levels during the lead-in phase.

Abbreviations: EAG, External Assessment Group; ED, etranacogene dezaparvovec; FIX, factor IX

Key Issue 2: Clinical outcomes in the HOPE-B study may overstate the potential benefits of ED

Report sections	3.2.2.3; 3.2.2.4; 3.2.2.6**;** 6.2.2; 6.2.3; 6.2.10.1
Description of issue and why the EAG has identified it as important	HOPE-B was a single-arm study that compared outcomes following treatment with ED with participants' outcomes during a baseline lead-in phase of 6-months. As there was no control

	arm, the comparability of outcomes measured in the lead-in phase and following treatment were crucial for determining the clinical effectiveness of ED. The EAG had two main concerns about the comparability of outcomes may affect the reliability of the study evidence: 1. The COVID-19 pandemic began after study participants had received ED and resulted in major disruption to the daily activities of people in the UK. Those with HIV, hepatitis or those receiving immunosuppression were included in advice to shield, whereas others may have experienced significant reductions in activities outside of their homes, including sports and travel. The EAG expected that these changes may have reduced the level of circulating FIX people with haemophilia B needed to do their daily activities, which may have therefore reduced the need for study participants to receive additional FIX replacement during the study. They may also have had a lower risk of bleeding during this time, due to their reduced activity. 2. The study procedures prohibited participants from receiving routine FIX replacement when they had circulating FIX levels of ≥5%. In these circumstances, investigating clinicians were permitted to administer ad hoc FIX replacement at their discretion, though the EAG considered that clinicians may be less likely to do this within the clinical study than they may do in practice, so as to adhere as closely as possible to the preferred study procedures. This requirement was not in place during the lead-in phase, and the EAG considered it plausible that rates of prophylactic FIX replacement would be higher in clinical practice than in the HOPE-B study.
What alternative approach has the EAG suggested?	The EAG explored the impact of changes to the clinical efficacy of ED and of increasing prophylactic FIX replacement in the EAG model through a number of scenarios (sections 6.2.2, 6.2.3 and 6.2.10.1)
What is the expected effect on the cost-effectiveness estimates?	Overstating the effectiveness of ED will both overestimate QALYs gained and underestimate cost through underestimation of IV FIX ultimately consumed by patients in the ED arm of the model.
What additional evidence or analyses might help to resolve this key issue?	As lives return towards normal in the years following the COVID-19 pandemic, study participants' daily activities may become more comparable with those during the lead-in phase. This may mean that subsequent data cuts of the HOPE-B study may provide a more representative view of the potential benefit of ED. To inform if and to what extent the use of FIX replacement therapy would be higher in clinical practice than in the HOPE-B study, the EAG would be interested to see the proportion of participants in HOPE-B with circulating FIX levels at alternative thresholds. The EAG would then seek clinical opinion on how many people at each threshold may choose to receive

	additional FIX therapy according to safety and/or personal preference.

Abbreviations: EAG, External Assessment Group; ED, etranacogene dezaparvovec; FIX, factor IX

Key Issue 3: Comparative efficacy estimates of ED and prophylactic FIX treatments were unreliable

Report sections	3.3; 3.4
Description of issue and why the EAG has identified it as important	The company identified four studies that reported outcomes for the main comparators to ED and used these along with outcomes from the HOPE-B study to indirectly compare treatment outcomes. There were no head-to-head comparisons of different FIX therapies, and most comparative studies compare prophylactic vs. on-demand treatment. Moreover, differences between the methods used in the studies seriously undermined the comparability of the outcomes. The company used matching of population characteristics to improve the quality of their ITC, but this process was itself highly limited due to the information available to them in the comparator studies. Overall, while the EAG considered that the company's methods for the ITC were the best available to them, the results were nevertheless unreliable and it therefore had little confidence in the results. The findings were most unreliable for BeneFIX, which [redacted].
What alternative approach has the EAG suggested?	The main difficulty with the company's ITC was the poor quality of evidence for prophylactic FIX and the differences in methods between the HOPE-B and comparator studies, including the definition and measurement of bleeding outcomes. This could not be resolved by the EAG. On the combined evidence of the HOPE-B study and the company's ITC, the EAG considered it plausible that treatment with ED would result in lower bleeding rates than FIX replacement. However, the EAG considered that the magnitude of that reduction was uncertain.
What is the expected effect on the cost-effectiveness estimates?	Overstating the effectiveness of ED will both overestimate QALYs gained and underestimate cost through underestimation of IV FIX ultimately consumed by patients in the ED arm of the model.
What additional evidence or analyses might help to resolve this key issue?	The company's methods were the best available to them with the current evidence. New, high-quality, comparative evidence to compare outcomes following treatment with ED vs. prophylactic FIX therapy was needed to resolve this issue.

Abbreviations: EAG, External Assessment Group; ED, etranacogene dezaparvovec; FIX, factor IX; ITC, indirect treatment comparison

1.5. The cost effectiveness evidence: summary of the EAG's key issues

Key Issue 4: Definition of treatment failure was at a low FIX activity level

Report sections	6.2.2
Description of issue and why the EAG has identified it as important	Treatment failure in the company model was effectively defined as resumption of prophylactic IV FIX. The company's base case durability extrapolation model was based on a resumption of IV FIX at <2% FIX activity level, however clinical advice to the EAG was that IV FIX was more likely to be reintroduced once FIX activity dropped below 5% rather than 2%. Durability of treatment effect (i.e. time to resumption of IV FIX) was fundamental to estimation of incremental costs and QALYs gained from ED.
What alternative approach has the EAG suggested?	The EAG base case utilises 5% as the threshold for reintroducing IV prophylactic FIX.
What is the expected effect on the cost-effectiveness estimates?	The use of a 2% threshold was considered to underestimate the ICER and thus overstate the cost-effectiveness of ED compared with IV FIX.
What additional evidence or analyses might help to resolve this key issue?	Wider consultation with clinical experts as to FIX activity levels at which they would reinstate prophylactic IV FIX would be informative.

Abbreviations: EAG, External Assessment Group; ED, etranacogene dezaparvovec; QALY, Quality Adjusted Life Year

Key Issue 5: The durability extrapolation model was based on limited data and excluded non-responders

Report sections	4.2.6.1; 5.2.3.16.2.3; 6.2.10.1; 6.3.1
Description of issue and why the EAG has identified it as important	Durability of the ED treatment effect was fundamental to the cost-effectiveness of ED. The extrapolation model used was based on small sample sizes and a very short follow-up relative to the extrapolation period.
What alternative approach has the EAG suggested?	The EAG conducted a threshold analysis to determine the minimum durability of ED required to yield an ICER below £20,000 and below £30,000 per QALY gained.
What is the expected effect on the cost-effectiveness estimates?	Overstating durability will overestimate incremental QALYs gained and underestimate incremental cost.
What additional evidence or analyses might help to resolve this key issue?	Due to the rarity of the disease, sample size limitations were unsurmountable. However, longer follow up of existing cohorts was considered essential to reducing uncertainty in durability.

Abbreviations: EAG, External Assessment Group; ED, etranacogene dezaparvovec; QALY, Quality Adjusted Life Year

Key Issue 6: Health state utilities were associated with treatment rather than health states, and the difference may be overestimated.

Report sections	4.2.7.1; 6.2.5
Description of issue and why the EAG has identified it as important	As a general principle, the EAG preferred health state utilities attached to states of health rather than treatment received because allowing treatment-driven utilities as well as differences in transition probabilities in a model risks double counting the impact of a treatment and thus overstating cost-effectiveness. However, the EAG agreed with the company that there may be a difference in utility by treatment over and above that associated with bleed rates and which was not otherwise captured in the decision model, namely a psychological benefit from receiving a once-in-a-lifetime treatment compared with frequent, repeat IV treatments. Nevertheless, the EAG considered the value applied to be overly optimistic.
What alternative approach has the EAG suggested?	The EAG considered that a lower treatment-related utility difference was more appropriate
What is the expected effect on the cost-effectiveness estimates?	Overestimating the utility difference would overestimate incremental QALYs and therefore underestimate the ICER
What additional evidence or analyses might help to resolve this key issue?	More evidence was needed to support the use and magnitude of a treatment-specific utility. Health state utilities based on EQ-5D collected alongside a randomised comparison of ED versus IV FIX would be the most appropriate evidence, though given the lack of an existing randomised study of ED the EAG considered that this was unlikely within the timeline of the appraisal. The EAG was unaware of an indirect population that would be suitable.

Abbreviations: EAG, External Assessment Group; ED, etranacogene dezaparvovec; QALY, quality-adjusted life-year

1.6. Other key issues: summary of the EAG's views

The EAG did not identify any other key issues.

1.7. Summary of EAG's preferred assumptions and resulting ICER

The EAG submitted a revised model correcting a number of errors. This also included a number of undocumented changes to the company base case made by the company at clarification. The results of the corrected company base case and the EAG preferred assumptions incorporating a patient access scheme (PAS) discount for ED of [redacted] are shown in Table 3.

Modelling errors identified and corrected by the EAG are described in section 6.1. For further details of the exploratory and sensitivity analyses done by the EAG, see section 6.2

Table 3: Summary of EAG's preferred assumptions and ICER (probabilistic results)

Preferred assumption	Section in EAG report	Comparators	Costs	QALYs	ICERs	NMB @ £20k	NMB @ £30k
EAG corrected company base case (excl. ED+mkt share)	6.1	ED+Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Benefix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG preferred base case assumptions							
5% FIX activity definition of failure	6.2.2	ED+Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Benefix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 month time to steady state	6.2.4	ED+Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Benefix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disutility of IV FIX treatment of 0.042	6.2.5	ED+Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Benefix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adding AE cost and disutility to ED after first year	6.2.9	ED+Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Benefix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative		ED+Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Benefix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ED, etranacogene dezaparvovec; FIX, factor IX; IV, intravenous; mkt, market

2. INTRODUCTION AND BACKGROUND

2.1. Introduction

In this report, the External Assessment Group (EAG) provides a review of the evidence submitted by CSL Behring '(the company') for etranacogene dezaparvovec (ED) for the treatment of severe and moderately severe haemophilia B. This report is accompanied by an appendix that contains the company and EAG analyses using confidential prices for comparators to ED. As these prices are not included in the analyses within this report, the findings are indicative only and do not represent current NHS funding for comparators to ED.

2.2. Critique of the company's description of the underlying health problem

The company's description of the condition highlighted key areas for understanding the humanistic burden of severe and moderately severe haemophilia B. For the most part, the EAG considered the company's description to be appropriate, though noted the following additional points:

- The EAG noted a minor typo on p.25 of the CS – "in rare cases, women can have [*severe and moderately severe*] haemophilia B". The EAG agreed with the company's description about the role of gender in the condition and received feedback from its clinical expert that the few females who experience severe and moderately severe haemophilia B would be affected similarly as males.

- The company described the incidence and impact of joint bleeding and arthropathy, which significantly impacts the lives of people with haemophilia B and is associated with delayed or insufficient treatment to maintain sufficient FIX levels and prevent bleeds. As an addition to the company description, the EAG noted that the younger cohort of people with haemophilia B in England will have a much lower risk of joint bleeds and arthropathy in their lifetimes due to earlier access to prophylactic FIX replacement. Clinical advice to the EAG was that the older cohort who did not have access to prophylactic treatment typically have received at least one joint replacement and experience significant disability, whereas the majority of those in the younger cohort are much less likely to have severe joint problems and require replacements. This is likely to lead to higher lifetime health-related quality of life (HRQoL) in the younger cohort.

- Further to the information provided by the company about the risk of mortality in those with haemophilia B, the EAG noted that mortality risk for the condition will have changed over the past several decades. This will be due in part to increased access to prophylactic FIX replacement, but also because those treated in the 1970-80s may have been exposed to contaminated blood products during FIX replacement and were at a higher risk of mortality due to infections such as HIV and hepatitis. The EAG considered it likely that mortality rates in the younger cohort of people in England with haemophilia B are likely to be much lower. Clinical advice to the EAG was that life expectancy in England may now be similar to the general population.

- The EAG considered that the company's description of the way in which the condition affects people's HRQoL lacked evidence for how HRQoL varies across the population. The EAG was aware that HRQoL is poorest for people with haemophilia B who develop inhibitors to FIX, meaning that they cannot receive FIX replacement therapy and their health outcomes and the impact of the condition on their life will be much greater. Overall, evidence suggests that HRQoL is worse for those with higher disease severity, though people of all disease severities can report high levels of HRQoL[2]. This may be because of differences in the impact of the condition on people's preferred lifestyles, and/or because people adapt to their condition and its management. Experiencing joint pain is also associated with poorer HRQoL[2]. The EAG understood that the condition does not cause people to feel unwell on a daily basis, and that therefore deficits in HRQoL are primarily driven by the impact of the condition on their joints (e.g. chronic pain), the psychological impact associated with the risk of bleeds and the lifestyle modifications required to manage the disease safely, and by the burden of treatment.

- The company stated that carers may experience both humanistic and economic burden (CS section B.1.3.3). Four studies[3-6] cited by the company reported that carers experience financial expenses due to their loved one's condition, though three studies were based in the US and not directly applicable, while the other reported overall indirect costs associated with people with either haemophilia A or B and did not separate out costs incurred by carers as compared to other indirect costs (e.g. loss of earnings). The EAG further noted that the two studies[7 8] cited by the company to support the humanistic burden of haemophilia B for carers were restricted to considering the burden amongst the carers of children with haemophilia, who are outside the target indication for this appraisal. The EAG therefore concluded that the company had not provided evidence to support its assertions concerning

the HRQoL impacts for the carers of those with haemophilia B. The EAG considered it plausible that carers would experience a detrimental impact from their loved one's condition, though expected that the detriment would be much greater for the carers of children and young adults who may be required to facilitate access to healthcare appointments and have greater responsibility in ensuring that their loved one is safe. For adults with haemophilia, the EAG considered it plausible that limitations on the lifestyles of those with the condition would be expected to have some impact on the carers of adults with haemophilia, and anxiety related to the risk and impact of bleeds is also likely to be felt by a person's carers.

- The company estimated that there were 242 people with severe disease registered in the UK and 271 with moderate disease, of whom a sub-population will have moderately severe disease (defined within the HOPE-B study as ≤2% FIX levels; p. 24 & p.33) The company did not report a breakdown of the number of people considered to have moderately severe disease, though the figures provided by the company suggested that this would be a small population. The EAG was unable to identify other figures for the incidence of severe vs. moderately severe disease to validate the company figures, though clinical advice to the EAG agreed that this would be a small population. The EAG noted that 'moderately severe' was not an established threshold in NHS practice, though it has been used in studies of IV FIX replacement therapies.

- The company estimated there to be [redacted] people in England who would be eligible to receive ED. This calculation was based on UKHCDO data for the number of registered people in England with severe and moderately severe disease minus those who would not have been eligible for treatment with ED in the HOPE-B study. The EAG noted that the numbers reported in the CS (p.34) did not tally with the final numbers, however the difference was minimal and was assumed to be due to a typo.

2.3. Critique of the company's overview of current service provision

Overall, the EAG considered the company's description of the current treatment pathway for the target population to be accurate.

2.4. Critique of company's definition of decision problem

The EAG considered that the CS was consistent with the NICE scope and decision problem for this appraisal. The approved product licence for ED aligned with the population in the key study

for ED (HOPE-B) and was therefore considered to be representative of the target population. The EAG also clarified that ED was intended to be delivered alongside standard care, which would include routine prophylactic FIX replacement if/when the treatment effect of ED wanes, and on-demand FIX replacement as required. The EAG also considered it plausible that some people may receive additional prophylactic FIX replacement, depending on their response to ED. The EAG appraisal of the company's definition of the decision problem is provided in Table 4.

Table 4: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	People with moderately severe* or severe haemophilia B	As per final scope	Not applicable	The principal clinical evidence for ED was the HOPE-B study, which included evidence from people with both moderately severe and severe haemophilia B, as consistent with the expected licence for ED. However, only 18.5% of people in the study had moderately severe disease. The company presented some data that suggested that this was reflective of the true population, though the data was not provided in full for validation. On the basis of the evidence presented, the EAG concluded that the study was likely representative, though noted that the generalisability of the evidence would be in question if this was not the case. This was because clinical advice to the EAG was that the relative treatment effect of ED would likely be smaller in those with moderately severe disease compared to severe disease.
Intervention	Etranacogene dezaparvovec (ED)	As per final scope	Not applicable	The company's evidence was consistent with the NICE scope and decision problem for this appraisal, though the EAG noted that ED would be administered in conjunction with standard care, including Factor IX (FIX) replacement therapy (the comparator). The evidence presented by the company suggested that FIX replacement would be administered at a lower rate than in the comparator arm, though the EAG noted some uncertainty about the magnitude of this difference

				(Key Issue 2). The way that FIX replacement therapy would be expected to be delivered alongside ED is discussed in Section 3.2.2.3
Comparator(s)	Established clinical management (including prophylaxis and on-demand treatment)	As per final scope, comparator was IV prophylaxis with on-demand option used in some patients	FIX prophylaxis was the most relevant comparator used in clinical practice. A very small cohort of patients using on-demand FIX treatment may be eligible for ED, i.e. those who are eligible for prophylaxis but continue to treat on-demand due to patient choice or clinical challenges	The EAG agreed that prophylactic FIX replacement was the most appropriate comparator, as this was considered to be the best available treatment for the target population. As stated by the company, a small number of people in practice choose to use on-demand treatment due to personal preference or clinical issues with administering prophylactic treatment, however this was not permitted by the clinical study inclusion criteria and was not considered within the company's model. Nearly half of participants in HOPE-B were receiving standard-life FIX replacement for prophylaxis at baseline. A market share report provided by the company suggested [redacted] clinical advice to the EAG was that more people may begin to use extended life products in future. Short-life products would be associated with more instability in FIX levels and higher resource use, though extended life products have a much greater cost. This issue is discussed in Section 3.2.2.4.
Outcomes	The outcome measures to be considered include: • change in FIX levels • need for further treatment with FIX injections • annualised bleeding rate	As per final scope	Not applicable	The EAG considered that the company had presented evidence for all of the scoped outcomes. Data tables for the CSR of the HOPE-B study were not provided with the CS, and therefore full data for all outcomes were not available. Notably, baseline data from HOPE-B for change in FIX levels (which represented the

	• durability of response to treatment • complications of the disease (e.g., joint problems and joint surgeries) • adverse effects of treatment • health-related quality of life.			comparator to ED) were not reported in the CS.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The use of ED is conditional on the presence of a specific biomarker (currently considered confidential by the company). The economic	As per final scope, noting that the use of ED is conditional on the test result for a biomarker.	The clarification included in the previous column intends to flag that patients will require to undertake a specific biomarker test for neutralising antibodies before receiving ED. Clinicians will consider the use of ED based on the test result (no cut-off values defined). The company will provide the test free of charge, which is not routinely performed in the NHS, and therefore its costs are not included in the cost-effectiveness model. The company assumes that indirect costs associated with testing patients (e.g., staff time) will not be substantial, as testing will take place as part of routine clinic follow-up.	The economic analysis broadly followed the NICE reference case. The company presented a series of pair-wise comparisons against each comparator in its deterministic base case, with fully incremental analyses presented in the PSA. The EAG considered pairwise comparisons inappropriate for decision making and therefore presented fully incremental analyses as a modification of the company base case. However, this was complicated by the choice of FIX once ED fails (i.e. people return to routine prophylaxis). This is discussed further in Section 6.

	modelling should include the costs associated with diagnostic testing for biomarkers in people with haemophilia B who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.			
Subgroups	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	As per final scope	Not applicable	ED had received CMA by the EMA and, more recently, from the MHRA for use in the UK. The company presented evidence from a number of subgroup analyses, and a further subgroup analysis (relating to the use of corticosteroids during the study) was identified from the EMA report. As the sample size from ED studies was low, there was limited power to explore potential variation in treatment effect across participants.
Special considerations including issues related to equity or equality	None in the final scope.	None in the final scope	Not applicable	The clinical studies for ED included only male participants. The EAG understood that females with haemophilia B typically have mild disease, and very few females would meet the criteria for moderately severe or severe disease. Clinical advice to the EAG was that disease characteristics were similar between males and females, and that the study evidence was generalisable to females who met the eligibility criteria for ED.

Abbreviations: CMA, conditional marketing authorisation; CSR, clinical study report; EAG, External Assessment Group; ED, etranacogene dezaparvovec; FIX, Factor IX replacement therapy; NICE, National Institute for Health and Care Excellence; PSA, probabilistic sensitivity analysis

3. CLINICAL EFFECTIVENESS

3.1. Critique of the methods of review(s)

The company undertook a systematic literature review (SLR) to identify evidence for the clinical effectiveness and safety of treatments used for haemophilia B. A literature search strategy was used to capture evidence published between March 2013 and October 2022, and two published SLRs[9 10] were used to capture evidence published before these dates.

Table 5: Summary of EAG's critique of the methods implemented by the company to identify evidence relevant to the decision problem

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix D	Searches were well conducted with a variety of keywords and subject headings used in a range of databases. A variety of grey literature sources were also searched. There was some discrepancy in the sources searched in the original searches of August 2021 and then in the update searches of October 2022; most notably the Cochrane Database of Systematic Reviews (CDSR) was searched in the update searches but not in the original searches. Adverse reactions were searched for at the same time as clinical effectiveness evidence (Appendix F).
Inclusion criteria	Appendix D1.1	The inclusion criteria were clear and appropriate to the review aims
Screening	Appendix D1.1	The methods used were consistent with best practice.
Data extraction	Appendix D1.1	The methods used were consistent with best practice.
Tool for quality assessment of included study or studies	Appendix D1.3	Quality assessment of RCTs was conducted using the modified CRD checklist recommended by NICE[11] and quality assessment of uncontrolled studies was conducted using the Downs and Black checklist[12] both of which were appropriate. However, the checklist was not completed to a high standard and the EAG did not consider it to be useful for determining the presence of bias in the studies.
Evidence synthesis	CS Doc B, Section B.2.9 and Appendix D1.2	The company did not pool data from the HOPE-B study with the other phase IIb and I/II studies as it considered the latter studies not to be relevant for decision-making. As the company nevertheless reported data from these studies and referred to the data to support some of its assertions about ED, the EAG considered that the company should have provided a qualitative comparison between the study outcomes. However, as AMT-060 was with a different formulation of ED, and the other study included only 3 participants, the EAG did not consider that any quantitative pooling of data would have been meaningful. The company conducted ITCs to compare ED with routine FIX replacement strategies where evidence for these was

		identified by its SLR. There was a high degree of heterogeneity between the methods used by the ED and FIX replacement studies, including variation in the definition and measurement of outcomes. The company used the best possible approach to account for the available data, though the EAG considered that the underlying evidence resulted in unreliable results (see Key Issue 3).

Abbreviations: CRD, centre for reviews and dissemination; CS, Company submission; EAG, External Assessment Group; ED, etranacogene dezaparvovec; FIX, factor IX; ITC, indirect treatment comparisons; RCT, randomised controlled trial; SLR, systematic literature review

3.2. Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1. Studies included in the clinical effectiveness review

The CS described three studies (Table 6). These comprised a phase I/II single arm study of AMT-060 (N=10), an early form of ED using the same vector and cassette design, but with a wild-type Factor IX transgene instead of the hFIXco-Padua gene variant later incorporated into ED. Two clinical studies of ED were reported, including one Phase IIb single arm study (N=3) and Hope-B, which was a Phase III single arm study (N=67).

Table 6: Clinical evidence for ED included in the CS

Study name and acronym	Study design	Population	Intervention	Comparator	Follow-up	Study type
HOPE-B **NCT03569891**[13]	Phase III, open label, single arm, multicentre	Adult patients with moderately severe or severe haemophilia B with Factor IX level ≤2% (N=67)	ED (single dose, 2×10^{13} GC)	Lead in study phase while participants received prophylactic Factor IX treatment (≥26 weeks)	2 years*	Clinical efficacy, safety, utility
CT-AMT-061-01 **NCT03489291**[14 15]	Phase IIb, open label, single arm	N=3	ED (single dose, 2×10^{13} GC)	NA	3 years*	Dose-comparison. Clinical efficacy, safety
CT-AMT-060-01 **NCT02396342**[16]	Phase I/II, open-label trial with ongoing extension	N=10	AMT-060 • Cohort 1: 5×10^{12} GC • Cohort 2: 2×10^{13} GC	NA	5 years*	Clinical efficacy, safety

Abbreviations: ED, etranacogene dezaparvovec; GC, genome copy; RCT, NA, not applicable; randomised controlled trial

*Latest follow-up available for this submission. Up to five years' data collection is planned. The next data cut will be 36-months' follow-up, which will become available Q3-Q4 2023.

The company did not submit a complete Clinical study report (CSR) for HOPE-B; while the main body of an updated CSR (to 24-month follow-up) was supplied[13], the data tables accompanying this document were not provided. The EAG assumed that the main body of the CSR was complete, though as it was labelled as an amendment to the original CSR, the EAG considered it possible that some information was retained only in the original. Moreover, while the company supplied CSRs for CT-AMT-060 and CT-AMT-061, these were also supplied without full data tables. As a consequence, the EAG did not have access to the full clinical effectiveness outcome data from the company studies. The EAG was uncertain if data identified as missing from the CS, such as FIX levels during the lead-in phase (Key Issue 1) and adverse events occurring following ≥1 year follow-up (Section 3.2.3.1), were reported in those data tables.

3.2.2. Description and critique of the design of the studies

3.2.2.1. Design of the studies

At the time of the appraisal there was a limited evidence base available for ED. Given the difference in composition between AMT-060 and ED, and the small sample sizes of the Phase I/II and Phase IIb studies, the company and the EAG each considered the principle evidence base for this appraisal to be the HOPE-B study. However, the EAG noted that data from the Phase IIb study (N=3) was used alongside that from HOPE-B in the Shah et al[17] 2022 analysis to predict the durability of the ED effect.

HOPE-B study was a small, single arm prospective cohort study with limited follow-up currently available. While up to five years of follow-up was planned, data in the submission was based on 24-months' of follow-up only (follow-up was a minimum of 24-months in all participants, though the company did not report the average follow-up across participants). The next planned data cut, which would provide 36-months follow-up, was not expected by the company to be available until Q3-Q4 2023. To support assumptions regarding the long-term durability of ED, the company referenced data from the Phase I/II of AMT-060, which measured outcomes at up to five years following treatment (CS p.48). The EAG had concerns about the reliability of these data as used for this purpose. This issue is discussed further in Section 4.2.6.1 and in Key Issue 5.

Given the rare nature of moderately severe and severe haemophilia B, the EAG acknowledged that the small sample size of HOPE-B was to be expected. Nevertheless, it presented challenges for interpreting the clinical efficacy of treatment, particularly given that treatment response appeared to vary across the population (see Section 3.2.3.1). The study was conducted internationally at 33 sites, including 3 sites in the UK, 17 sites in the US and 13 sites in the EU. Clinical advice to the EAG was that international variation in health outcomes for people with haemophilia B was largely due to the poor availability of FIX replacement therapies in low- and middle-income countries.[18] Given the procedures within the study, the EAG did not identify any reason why outcomes could not be generalised to the UK population.

As HOPE-B was a single-arm study, the company compared outcomes following treatment with ED with outcomes assessed during a lead-in phase of 26-weeks. This approach was generally preferred by the EAG as compared to no comparison or a naïve comparison with the findings in other samples; however, variations in care between the lead-in phase and following treatment with ED meant this comparison had limitations (see Section 3.2.2.4). In brief, protocols for the

use of standard care varied between the two time periods, and the EAG also considered that the onset of the COVID-19 pandemic following the lead-in phase would have likely impacted the lifestyles and treatments received by participants. These issues are discussed in Section 3.2.2.3 and Key Issue 2.

Following administration of ED, the company appeared to differentiate between the subsequent 6-months' of follow-up, during which time they stated that FIX levels needed to stabilise following treatment. Throughout the CS, the company generally reported clinical outcomes limited to data collected outside of this period, such as during months 7-18 and 7-24 after treatment only. Where data for the 0-6 month period following treatment were reported, this was not merged with the later follow-up timepoints (e.g. 0-24 months' following treatment). The EAG considered this to be an unusual approach, since outcomes immediately following treatment are just as meaningful to people receiving treatment and to understanding the treatment effect of ED. Excluding this time period also reduced the comparability of ED with comparator treatments in the company's indirect treatment comparison (ITC; Sections 3.3 – 3.4). Where feasible, the EAG sought to identify clinical data for the 0-6 month period following treatment from the study CSR, though this was rarely possible. On the basis of the evidence available, the EAG considered it plausible that bleed rates would be higher during months 0-6 after ED as compared to subsequent time periods.

3.2.2.2. Population

Study eligibility criteria

Adult males with severe or moderately severe haemophilia B (as indicated by ≤2% of normal circulating FIX) who were receiving continuous routine prophylactic FIX therapy and without a history of FIX inhibitors were eligible for inclusion. Inclusion criteria also specified that participants who showed high compliance with outcome measures during the lead-in phase were included. A number of exclusion criteria that may be relevant to evaluating the efficacy and safety of ED were also specified, and are summarised in Table 7. The EAG made the following observations:

- The study targeted people with severe and moderately severe haemophilia B, which corresponded with the anticipated licence for ED in England. Clinical advice to the EAG was that this was the most appropriate population since the expected benefit of

treatment may not be meaningful for those with mild or moderate disease who have a lower frequency of spontaneous bleeds.

- Clinical advice to the EAG was that the restriction of the clinical studies to male participants was acceptable. As haemophilia B is a recessive disorder linked to the X chromosome, females almost always have one healthy copy of the gene. Where women have haemophilia, they typically have mild or moderate disease. The EAG was advised that the study evidence could be generalised to any females who met the eligibility criteria.
- Clinical advice to the EAG was that the exclusion of people with a history of inhibitors to FIX was appropriate and unlikely to exclude many people, since the presence of inhibitors in haemophilia B was rare (estimated to be 1% - 3%). The EAG was advised that if a person were to develop inhibitors, this would be identified during childhood, before ED would be considered.
- The exclusion of people with active HIV, hepatitis B or C may affect the population of people with haemophilia B affected by contaminated blood products during the 1970s-1980s, some of whom were children at the time. While many of those affected have now died and the EAG assumed most others have received treatments to manage the conditions, this may still affect an unknown minority of people in the UK with haemophilia B. Clinical advice to the EAG was that this was likely to be a relatively small number of patients in 2023.
- The conditional marketing authorisation (CMA) for ED awarded by the European Medicines Agency (EMA) did not preclude the use of ED in those with elevated liver transaminase, however the SmPC for ED notes the potential risks of treatment with ED for liver function. That EAG therefore noted that outcomes related to liver function reported in the study were based on a sample without any pre-existing impairment in liver function, and that these outcomes may not be generalisable to those who would not have been eligible for inclusion in the study. Clinical advice to the EAG stated that liver complications were not more prevalent amongst patients with haemophilia B *per se*, but that around 90% of older patients exposed to contaminated blood products in the 1970s and 80s developed hepatitis C.
- The exclusion of participants who were anticipated to require chronic treatment with steroids was relevant as a minority of participants in the study required corticosteroids to treat injection site reactions and elevated transaminase levels. As treatment with corticosteroids following ED may affect treatment response (see Section 3.2.3.1), the

study findings may not be generalisable to those participants eligible to receive ED in practice but who would have been excluded from the study due to corticosteroid use. The EAG also considered that unexpected use of corticosteroids during the lifetime of the person treated may affect treatment response(Section 3.2.3.2), although clinical advice to the EAG was that in general, corticosteroid use amongst patients with haemophilia B would not be any different from that in the general population.

- In addition, participants were not permitted to have received a previous gene therapy treatment. The EAG understood that receipt of a gene therapy may not automatically prevent people from receiving a subsequent gene therapy, however it expected that this may be a requirement of gene therapy clinical study eligibility or future medical licences. Moreover, people may develop resistance to the vector used to deliver the gene therapy (as was the case following receipt of ED, CS p.128), which may mean that they are unable to receive gene therapies using the same vector or may experience reduced benefit.
- The study eligibility criteria did not exclude people on the basis of pre-existing neutralising antibodies to AAV, which may be present in 30-50% of the general population[19] and may interfere with vector administration. The company assessed levels of AAV antibodies at baseline and considered the impact of this on treatment outcomes in subgroup analyses.

Table 7: Selected participant exclusion criteria from HOPE-B

- ALT >2 times upper normal limit (i.e., upper limit of normal [ULN])
- AST >2 times ULN
- Total bilirubin >2 times ULN (except if caused by Gilbert disease)
- ALP >2 times ULN
- Creatinine >2 times ULN
- Hepatitis B or C infection requiring treatment
- Uncontrolled HIV infection
- Another known coagulation disorder
- Thrombocytopenia
- Known history of allergy to corticosteroids
- Known medical condition that would require chronic administration of steroids
- Known medical condition that may impact the intended transduction of the vector and/or expression of the protein

• Known severe infection or medical disorder that may interfere with tolerance or adherence to the study procedures

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; HIV, human immunodeficiency virus

A breakdown of why eight people screened for HOPE-B were deemed ineligible for participation was not provided in the CS or other submitted documents. Likewise, a breakdown of the reasons for why a further 13 participants discontinued following screening was not provided: a list of reasons was provided in the CS, though the number of participants discontinuing for each reason was not given (the reasons included ineligible liver test as assessed by FibroScan, concomitant medications and comorbidities). In the CSR[20], the text noted that [redacted] participants discontinued following a positive FibroScan result for liver fibrosis. Overall, given the uncertainty in the reasons for participants not entering the study, the EAG concluded that up to 28% of people (21/75) who were interested in participating in HOPE-B were ineligible due to the study eligibility criteria. At the time of writing, any forthcoming licence and conditions for the use of ED in England was unknown, though if the licence were to match the study eligibility criteria, then a significant minority of people with severe and moderately severe haemophilia B would not be eligible. If more relaxed eligibility criteria were used, this minority population would not have been included in the HOPE-B study and therefore their outcomes may vary. The conditional licence awarded by the EMA specified that treatment would be contraindicated in those with active infections (acute or chronic) and people with known advanced liver fibrosis or cirrhosis (SmPC, p. 3-4), and would not be recommended for us in those with other significant hepatic disorders (p.3).

Comparable population inclusion criteria were used in both of the previous Phase IIb and Phase I/II studies.

Baseline characteristics

Select baseline characteristics for HOPE-B were reported in Table 8 of the CS (p.62-63). The EAG made the following key observations:

- The sample included a broad age range, from 19 – 75 years (mean 41.5 years). The EAG was aware that health outcomes would typically vary between younger and older participants due to younger participants having had earlier access to routine FIX replacement, including long-acting prophylactic therapies, that reduce the risk of joint

damage. As joint damage is irreversible, treatment with ED may be expected to have a lower impact on the broader HRQoL of older people.

- The majority of participants had severe haemophilia (44/54; 81.5%), with only ten participants (18.5%) classified as having moderately severe disease. The EAG struggled to identify recent epidemiological data for the incidence of severe vs. moderately severe disease in the UK, though clinical advice was that this was likely to be a small population and therefore the clinical study sample may be representative. Clinical advice to the EAG was that the anticipated benefits of treatment may be less for those with mild or moderate severe, and so any discrepancy between the study make-up and the target population may be affect the generalisability of study effect estimates.

- The EAG noted that nearly half of all participants were receiving standard half-life prophylactic FIX replacement therapy prior to screening. Clinical advice to the EAG was that at the time of the HOPE-B study, standard half-life products were the most commonly used treatment for prophylaxis though this may not be representative of current practice as more people in the NHS are now receiving the longer acting therapies. Within their practice, the last person switched to a longer acting treatment within the past 12-months. In practice, there may be geographical variation in the availability of treatments, but preferences and lifestyle choices of participants also affects choice of half-life product.

- A sizeable minority (38.9%) of participants exhibited neutralising antibodies to AAV5 at baseline, which were found in the company's subgroup analyses to affect treatment response (Section 3.2.3.1).

Further baseline characteristics were provided in additional documentation,[13] which revealed that:

- Only a small minority of participants were receiving on-demand FIX replacement therapy at baseline compared to prophylactic (CS, p.82), which the EAG understood to be representative of current practice in the NHS.

- [redacted] of participants ([redacted]%) were experiencing 0 – 3 bleeding episodes per year prior to screening, with remaining participants distributed at rates between [redacted] to [redacted] (p.82).

- Of bleeding episodes experienced in the year prior to screening, 55.6% were joint bleeds, 59.3% were spontaneous bleeds, and 37.0% were traumatic bleeds (p.82).

Clinical advice to the EAG was that the annual incidence of bleeding episodes was consistent with that observed in their clinical practice, albeit with the caveat that small patient numbers lead to a lot of uncertainty in percentage estimates.

3.2.2.3. Intervention

ED was intended to be administered as a single intravenous (IV) infusion of 2×10^{13} GC/kg of body weight, which corresponds to 2mL/kg of body weight (CS, p.18). Administration occurred as planned for the vast majority of participants in HOPE-B, though 3/54 (5.6%) of participants required a dose interruption due to an infusion reaction, of whom 1/54 (1.9%) were unable to receive the full dose. The same dose and administration were used in study AMT-061-01. In study AMT-060-01, the treatment administered was AMT-060, an earlier formulation of ED that according to the company used the same protein capsid and cassette deign, but a different amino acid to the Padua FIX variant. Two doses of AMT-060 were evaluated, including the same dose as used in the other studies (2×10^{13} GC/kg) and a higher dose of 5×10^{12} GC.

In the HOPE-B study, participants could continue with their routine FIX replacement on the day of treatment with ED and in the following weeks to ensure that FIX levels were sufficiently high. This allowed time for FIX levels to increase and stabilise following treatment with ED. During follow-up visits, FIX levels were assessed, and the use of continuous routine FIX replacement was withdrawn if participants' FIX levels were >5% of normal activity. Clinical advice to the EAG was that FIX levels of 3-5% of normal activity would be the lowest acceptable level while receiving treatment, and that clinicians would likely treat before FIX levels reached 5% where possible. Moreover, whilst a FIX level of 5% would be adequate for most 'normal' activities, it would be insufficient for higher-risk sport and physical activity, and therefore some people with haemophilia B would seek FIX replacement to maintain a higher FIX level, (or alternatively schedule their dosing to coincide with the high-risk activities to ensure they are at a peak level). The CS stated that while routine continuous FIX replacement was discouraged in those with FIX levels >5% of normal, "further management was based on the Investigator's clinical judgement and subject preference" (CS p.54). The EAG therefore considered it plausible that on-demand FIX replacement therapy was administered to those with FIX levels >5% of normal, though data to confirm that were not provided in the CS, and it was therefore unclear whether any on-demand treatment was comparable with the FIX replacement that would have been

administered in practice. Overall, the EAG considered it plausible that clinicians would administer more FIX replacement in clinical practice than they did in the clinical study, either because of patient preference and/or because they would typically seek to attain a higher FIX threshold than was permitted during the study.

Moreover, the EAG noted that the COVID-19 pandemic began during study follow-up, which drastically limited the daily activities of people in the UK. People with haemophilia B who were receiving immunosuppression or had hepatitis or HIV infections were also advised to shield, whereas others will have experienced various levels of lockdown. The company did not present any data that the EAG could use to determine whether study outcomes may have been affected by the onset of the pandemic, though a market share analysis commissioned by the company [redacted]. In addition, clinicians may have been reluctant to administer FIX replacement unless absolutely necessary due to concerns about the risk of thrombogenic events linked to COVID-19. Finally, due to reduced activities, people may also have been at a lower risk of bleeds. Overall, the EAG considered it plausible that the onset of the pandemic may have resulted in a reduced risk of bleeding and fewer doses of prophylactic FIX being administered to participants than would be normal in clinical practice.

The EAG considered whether participants who responded to ED would nevertheless continue to receive FIX replacement to further 'top-up' their FIX levels. While the need to attend once or twice weekly appointments to receive IV FIX was associated with a notable treatment burden for people with haemophilia B, the EAG considered it plausible that some people may choose to receive further IV FIX on a regular or semi-regular basis. The choice to do this may allow people to engage in activities not typically recommended for those with haemophilia B, such as more active sports. As part of Key Issue 2, the EAG has identified the potential benefit of further evidence for the number of people in HOPE-B with circulating FIX levels at different thresholds of normal. With this information, clinicians may be able to advise whether they think a proportion of people in clinical practice would request further FIX replacement therapy in addition to ED.

FIX infusions were also not recommended by the investigators if FIX levels were ≥40% of normal activity (i.e. the threshold for non-haemophilic levels of FIX). Clinical advice to the EAG was that a threshold of 40% was sufficient to protect against bleeding events for most everyday

activities and concurred with the company that higher rates of FIX were associated with thrombosis. The EAG therefore concluded that this requirement was not a concern for the generalisability of the study.

3.2.2.4. Comparator

The comparator to ED was participants' outcomes during the ≥6-month lead-in phase prior to dosing with ED. Prior to the start of the lead-in phase, participants underwent a washout period for their usual FIX replacement therapy: this was 3 days for normal half-life products and 10 days for extended half-life products. The EAG did not consider it to be clear in the CS whether treatment during the lead-in phase was aligned with the care participants were receiving prior to study participation, or whether the lead-in phase was also subject to the same controls over use of FIX replacement as applied following treatment with ED. However, on the basis of a statement in the study CSR[20] ("with standard of care continuous routine FIX prophylaxis", CSR p. 44), the EAG concluded that it was the former: i.e. participants received regular prophylactic treatment as per usual care. As noted in Section 3.2.2.2, nearly half of participants were receiving standard half-life therapy at baseline. The EAG assumed that participants continued to receive their usual FIX replacement treatment during the lead-in phase (as was stated to be the case for following treatment with ED). Clinical advice to the EAG was that whilst probably representative of clinical practice at the time of the HOPE-B study, the use of standard half-life products in the NHS was declining, as the extended half-life products can reduce treatment burden and prolong the treatment effect, thus providing people with improved coverage (though these are significantly more expensive). The company provided a report[1] of the market share of FIX replacement products in the UK from 2020 that suggested that a standard half-life product accounted [redacted]. The EAG therefore considered it possible that treatment outcomes during the lead-in phase could be conservative.

3.2.2.5. Outcomes

A broad number of clinical outcomes were evaluated in the HOPE-B study, including a variety of bleeding outcomes that accounted for different bleed types, outcomes specific to joint health, use of FIX replacement therapies, circulating FIX activity, safety and pharmacokinetic outcomes, health-related quality of life (HRQoL) and various patient-reported outcomes (PROs). The EAG considered that the outcomes included the principle metrics for determining the

efficacy of ED. However, the EAG identified two major concerns with the way outcomes were defined and measured:

- Clinical outcomes (i.e. not safety) typically excluded data measured during the 6-month time period following treatment with ED, which the company described as the period during which time stable FIX levels were established following treatment. The EAG strongly disagreed with this approach. The EAG attempted to identify clinical outcomes that included the initial 6-month time period after treatment, though this was not feasible for some outcomes. It was not clear to what extent this would affect the interpretation of the clinical results, however while ED begins to exert its mechanism of action, the EAG considered it plausible that circulating FIX levels would be lower, people may be at an increased risk of bleeding, and people would be more likely to receive FIX replacement therapy.
- The company reported change from baseline in circulating FIX levels, however did not use data from the lead-in phase in these outcomes. Instead, the company calculated an estimate of FIX activity to represent a comparison as if participants were not receiving any treatment for their condition. To do this, for each participant they imputed a baseline FIX level based on their condition severity (i.e. <1% of normal activity for those with diagnosed severe disease). The EAG considered these analyses to be inconsistent with the decision problem for this appraisal, and that the presentation of these data was potentially misleading. This issue is addressed in Key Issue 1.

In addition, the EAG noted the following minor issue:

- The company reported the proportion of participants with FIX levels <12%. This threshold was specified *a priori* in the study protocol, though no rationale was given for the choice. The Clinical advice to the EAG was that mild haemophilia B was defined as FIX levels between 5% and 40%. The EAG considered that the proportion of participants at different thresholds of disease would be a useful outcome; i.e. the number of people with severe haemophilia who became moderately severe, moderate and mild etc. Clinical advice was that approximate thresholds can be used to guide the minimum FIX levels for safe engagement in certain activities (e.g. certain sports), on the basis that thresholds are understood to represent varying risk of bleeding and the likely impact of the condition on people's lives. This data was identified as potentially useful to reduce uncertainty in Key Issue 2.

3.2.2.6. Critical appraisal of the design of the studies

Full critical appraisal for HOPE-B was reported in the CS Appendix D. The company used an appropriate checklist for considering the potential for bias in the study, though item responses lacked detail and consideration. Standardised critical appraisal checklists are intended to capture the most common types of bias present in the relevant study designs, though they are not intended to be comprehensive, and researchers are expected to consider potential risks of bias that may exist beyond those covered by the tool, or explicitly prompted in signalling questions. This was clearly not done in this appraisal.

Key points noted by the company appraisal included a lack of information about participants who dropped out from the study and a lack of information about the population from which the participants were recruited. It was also reported that it was not possible to assess whether the statistical tests used to assess the main outcomes were appropriate or if the study had sufficient power. The company appraisal did not provide insight into whether the company considered the population to be representative of the target population and usual treatment in the NHS. The appraisal focused on procedures following treatment with ED, without consideration of potential bias during the lead-in phase and in the comparability of the two periods. Moreover, there was no evidence that the company considered the potential for bias to vary across outcomes and (where relevant) subgroups.

The HOPE-B study was a single-arm, open-label study where change in outcomes was based on a historical comparison, and as such this was low-quality evidence[21]. Historical comparisons are always challenging because of the potential for change in factors other than the administration of treatment to influence participant outcomes. In this case, and as addressed in Key Issue 2, study procedures varied between the lead-in phase and following treatment, and the onset of the COVID-19 pandemic may have influenced outcomes. Without a concurrent comparison arm, the true effect of treatment was therefore uncertain.

As an open-label study, outcomes were also subject to performance bias, meaning that the care participants received may have been different because of knowledge that they had received ED. In addition, the assessment of outcomes can be affected by study participation and knowledge of the intervention being received (or in the case of the lead-in phase, not being received). This type of bias particularly affects subjective outcomes, such as diary entries of bleeding events completed by participants and the assessment of adverse events.

Overall, the EAG considered that the treatment effects reported were of a significant magnitude to suggest that they represented a true benefit of ED as compared to standard care with prophylactic FIX replacement. However, the study design and the unexpected start of the COVID-19 pandemic was considered by the EAG to introduce a risk of bias in favour of ED. The true treatment effect of ED may therefore be smaller than shown, and so study findings should be interpreted with caution.

3.2.3. Description and critique of the results of the studies

3.2.3.1. Clinical effectiveness results

Annualised bleeding rate (ABR)

The company reported a series of outcomes to assess bleeding rates in HOPE-B, which are reported in Table 11 of the CS (p.70), and included various types of bleeding (all, joint, spontaneous, traumatic, FIX-treated, new and true) and two types of analysis (unadjusted and adjusted). With the exception of bleeding episodes in people who tested positive for anti-AAV5 NAb (discussed later in this section under Subgroup Analyses, p44), bleeding rates were lower following treatment with ED than they were during the lead-in phase. Rate ratios across bleeding outcomes (i.e. adjusted ABR / lead-in ABR) for the ITT population ranged between 0.13 – 0.36, and 95% Cis around these were generally all within the range that the EAG considered a meaningful average reduction. The number of people experiencing bleeds (any bleed) also reduced following treatment with ED, from 74.1% during the lead in phase to 37% during months 7-18 and 50% for months 7-24.

Table 8: Annualised bleeding rates in HOPE-B

	All bleeds	**Joint bleeds**	**Spontaneous**	**FIX-treated**
Lead-in phase ABR	4.19 (3.22, 5.45)	2.35 (1.74, 3.16)*	1.52 (1.01, 2.30)	3.65 (2.82, 4.74)*
Total bleeds	136	77	50	118
People who had bleeds	40 (3.4/pp); 74.1%	32 (2.4/pp); 59%	24 (2.1/pp); 44.4%	37
7-18 months ABR	1.51 (0.81, 2.82)* Δ-64% (95%CI 36, 80)	0.51 (0.23, 1.12)	0.44 (0.17, 1.12)	0.84 (0.41, 1.73)* Δ77% (95%CI 54, 88)
Total bleeds	54	19	14	30

	All bleeds	Joint bleeds	Spontaneous	FIX-treated
People who had bleeds	20 (2.7/pp); 37%	11 (1.7); 20.3%	9 (1.6/pp); 16.7%	15
7-24 months ABR	1.51 (0.83, 2.76)* Δ-64% (95%CI 37, 79)	0.46 (0.24, 0.89)*	0.38 (0.16, 0.89)	0.99 (0.48, 2.03)*
Total bleeds	74	26	18	43
People who had bleeds	27 (2.7/pp); 50%	15 (1.7/pp); 27.8%	11 (1.6); 20.4%	19

*adjusted ABR: generalized estimating equations negative binomial regression model accounting for the paired design of the study with an offset parameter to account for the differential collection periods. Treatment period was included as a categorical covariate.

Source: Company submission Document B; HOPE-B CSR[13]

FIX levels

During the lead-in phase, the company reported that 79.6% of participants had FIX levels <12% of normal, which changed to 7.8% after 3 months, 8.0% at 12 months, 6% at 18 months, and 10% following 24-months of treatment.

The company also reported change in mean FIX levels; however, the EAG noted that the baseline FIX levels reported in the CS (i.e. Table 12, p.73) and used to calculate change from baseline represented an estimate of FIX levels as if participants were not receiving FIX replacement therapy, rather than FIX levels assessed during the lead-in phase. This estimate was based on the conventional FIX threshhold for each of the participants' diagnosed disease severity, i.e. a participant with severe disease (FIX levels <1%) was awarded a baseline FIX level of 1%. FIX levels during the lead-in phase were not reported in the CS and the EAG was unable to identify these during its appraisal. The EAG considered the company's approach to be unusual and one that could be potentially misleading.

Clinical advice to the EAG was that the target with prophylactic FIX replacement therapy was to keep trough (i.e. minimum) levels of circulating FIX between 3 – 5% of normal, though following each treatment FIX levels may initially be much greater. Studies evaluating the efficacy of prophylactic FIX replcement therapies reported FIX levels in the normal range following treatment, which then returned to the trough level over hours or days (depending on whether the treatment is a short- or extended half-life product). [22, 23, 24, 25, 26] Without knowing true baseline FIX levels during the lead in phase, the EAG was only able to comment on absolute FIX levels

after treatment with ED, without comment on whether the level of FIX after treatment was meaningfully different from treatment with prophylactic FIX replacement.

On the basis of the data provided, the EAG was able to make the following observations:

- Mean FIX levels reported following administration of ED were >35%, which was above the threshold for mild haemophilia B.
- FIX levels varied widely across participants, ranging from a minimum of 4.5%, which was within the threshold for moderate disease severity, to above 100% of normal.
- FIX levels appeared to remain consistent between 6-months and 24-months following treatment.

FIX levels in AMT-061-01 appeared relatively stable until final follow-up (N=3). In the study of AMT-060-01, FIX levels also appeared [redacted] (see Figure 1). Overall, acknolwedging the small samples, the EAG considered these data to support a plausible maintenance of treatment effect up to five years' following treatment.

Figure 1: FIX Levels up to 5-years following treatment with AMT-060

Source: Study CSR [16]. Data is from participants in Cohort B.

Consumption of FIX replacement therapy

During the lead-in phase, 100% of participants in HOPE-B were receiving FIX replacements at a mean of 44.1 infusions per participant. Throughout the post-treatment period, including the 0-6 months immediately following treatment with ED, FIX replacement reduced and stayed reasonably stable to 24 months. By the time of the final follow-up (months 19-24), 24.5% of participants were receiving FIX replacement, each receiving a mean of 3.2 infusions. The EAG considered that this reduction represented a potential major reduction in healthcare resource use and treatment burden. However, as discussed in Section 3.2.2.3, the EAG considered it plausible that rates of FIX replacement following ED would be somewhat higher in practice.

Joint health

There was a very small, statistically significant improvement in Haemophilia Joint Health Score (HJHS) following treatment with ED. The EAG was unable to identify a minimally clinical importance difference (MCID) for the HJHS, though a LS mean change of [redacted] on a scale of 0-124 may be unlikely to demonstrate a major change in joint health. The EAG understood that joint damage occurs following years of joint bleeds, and that this damage would not be reversible. Within the short timeframe of the available data from HOPE-B, the EAG therefore did not consider it surprising that there was no clear difference in joint health as measured by the HJHS. If ED was found to lead to improvements in joint health, this may be evident at the latest follow-up timepoints of the study not yet collected, though may be better represented by long-term follow-up data from the HOPE-B study in comparison with naturalistic studies of joint health in people with the target condition. The company did not report data for the prevalence and resolution of target joints in the CS, and the tables containing these data were not supplied with the HOPE-B CSR. From the text in the amended CSR provided[20], it appeared as if [redacted], though the wording was somewhat unclear.

Health-related quality of life and funcion

A numerical benefit in EQ-5D-5L scores was reported at the 24-month follow-up, though the difference in score was under the threshold considered to be a meaningful change in HRQoL for people with haemophilia[27].

The EAG was unable to identify an established MCID threshold for the Haem-A-QoL, which would determine what change in scores would be clinically meaningful for people with haemophilia B. One paper[28] reported a MCID threshold of 7 points for the total score and 10 points for two domains (physical health sports and leisure). Using these thresholds for those subscales and an arbitrary threshold of 7 points for the other domains, a benefit of ED was demonstrated for the 'feelings' domain at 12- and 24-months, the 'treatment' domain at 12- and 24-months, and the 'dealing with haemophilia' domain at 24-months (though the latter was not statistically significant). These domains would suggest that study participants felt less emotional burden from their haemophilia, had reduced treatment burden and may also feel more able to manage their condition. The company stated that a statistically significant change in scores was noted for the 'work and school' and 'future' domains. The EAG was unclear if these changes were clinically meaningful, but if so, it would suggest that those treated with ED felt more able to go to school/work, and were less concerned about the impact of haemophilia on their future lives. There was no change in total Haem-A-QoL scores or in the other domains: participants' physical health, engagement in sports/leisure, view of themselves (including impact of the disease on their current lives), family planning, or personal relationships.

There were no differences in scores on the WPAI (work productivity), BPI (pain), and HAL (functional ability) following treatment with ED.

3.2.3.2. Subgroup analyses

Results of the company's planned subgroup analyses for ABR were shown in Figure 13 of the CS (p.86). Across subgroups, ED was associated with a benefit for ABR as compared to the lead-in phase with the exception of a subgroup of participants aged ≥60 years, in whom ABRs were shown to increase following treatment with ED. The company did not discuss the potential interpretation of this finding except to note the small sample size of this group (N=8). The EAG acknowledged that the small sample for the subgroup meant that there was uncertainty in the finding, as evidenced by the wide 95%Cis around the effect, though noted that the effect was large (RR 1.90, 95%CI 0.38, 9.57). Conversely however, absolute ABR rates reported for older participants reported in the study CSR[20] appeared to show an overall reduction in bleeding between the lead-in phase and follow-up after treatment with ED, and subgroup analyses for older participants reported in the study CSR showed that FIX levels increased and FIX replacement reduced following treatment with ED. The EAG therefore considered it possible that the increase in ABR shown in Figure 13 of the CS for participants aged ≥60 years could be a data inputting error. Nevertheless, as there also appeared to be some numerical difference in

the size of effect for ABR between age groups generally, this may suggest that the age of participants affects treatment outcome. Given the uncertainty surrounding the effect for older participants, and the pattern of effect across groups which could not be plausibly explained, the EAG did not feel able to conclude about the presence or lack of a difference in effect according to age.

ED showed a beneficial effect for ABR compared to the lead-in phase for participants both with and without neutralising antibodies to AAV, though the effect for those with antibodies was somewhat smaller in magnitude. There was also a reduced effect for those with ≥grade 2 liver steatosis (i.e. moderate or severe). In response to a request from the EMA, the company submitted a subgroup analysis comparing ABR between those who did and did not receive corticosteroid treatment due to elevated transaminase[29]. The results were comparable across groups. However, those who received corticosteroid treatment during the study follow-up reported lower mean FIX levels: 14.30 (SD 7.65) at 24-months compared to 40.12 (SD 17.55)[29].

3.2.3.3. Safety

Administration of ED

Six people in HOPE-B (6/54, 11.1%) experienced an infusion reaction to ED, of whom three (3/54, 5.6%) required a dose interruption. One participant (1/54, 1.9%) did not receive the full dose of ED due to the reaction (10% of dose received only).

Deaths

There was one death (1/54, 1.9%) following administration of ED, which the company stated was due to a bacterial urinary infection followed by cardiogenic shock. The study investigator did not consider this death to be related to treatment with ED, and the EMA assessment was that there was no evidence to refute this conclusion[29]. There was one death in AMT-060-01 that occurred following the end of the five-year follow-up. This death was also considered by the study investigator to be unrelated to treatment with ED.

Serious adverse events

During the lead-in phase, four participants (4/54, 7.4%) experienced a serious adverse event compared to fourteen participants (14/54, 25.9%) following treatment with ED. A total of 17 serious adverse events occurred during the follow-up period, compared to five in the lead-in phase. Despite the increase in events, the company stated in the CS that none of these events

were related to treatment. The CS did not list the types of severe event experienced by participants, though the study CSR[13] provided more detail. Of the events reports, , [redacted] were considered severe and [redacted] were considered mild or moderate. Events included two cases of blood loss anaemia, hepatocellular carcinoma, acute myocardial infarction, COVID-19, jaw fracture, haemophilic arthropathy, cardiogenic shock, upper gastrointestinal haemorrhage, muscle haemorrhage and cellulitis. The EMA assessment of these events was that there was no evidence that these events were caused by ED, though it could not rule out the possibility of instances where ED had exacerbated a condition, thus leading to the event.

All adverse events

All study participants experienced at least one adverse event following treatment with ED, compared to 68.5% (37/54) of people during the lead-in phase. Events showing a marked increase included nasopharyngitis, arthralgia, back pain, extremity pain, fatigue, toothache, diarrhoea, ALS and ALT increases, creatinine increase, and headaches.

Treatment-related adverse events

As the potential implications of gene therapies for broader processes in the body were yet unknown, understanding the potential for adverse effects following these types of therapies was more uncertain. Of the 557 adverse events reported following treatment with ED, 93 (16.7%) were considered by the investigator to be related to ED. Treatment-related AEs affected 38/54 (70.4%) of study participants. A full breakdown of the treatment-related adverse events was not provided in the CS and the data table accompanying the study CSR was also not provided. The CS stated that the majority were mild or moderate in severity, with only [redacted] experiencing [redacted]. The most commonly reported treatment-related event was an increase in ALT (experienced by 9/54, 16.7% of participants).

Adverse events of special interest

No participants exhibited raised ALT/AST levels during the lead-in phase. Following treatment with ED, 11/54 (20.4%) and 8/54 (14.8%) participants experienced increases in ALT and AST, respectively. Of these, 8/54 (14.8%) and 5/54 (9.3%) ALT and AST increases were more than twice baseline levels, and of these almost all were considered by the company to be treatment-related. The company reported that only one event was considered to be severe, though based on discussion in the EMA report of ED (p.110, [29]), there was some uncertainty about the severity classifications of AST and ALT increases, with similar increases described as severe,

moderate and mild across different participants. Overall, 9/54 (16.7%) participants received treatment with corticosteroids, including prednisone, prednisolone, and methylprednisolone, for ALT/AST increases, over a mean duration of 79.8 days (SD 26.6; range 51 - 130)[20 29]. The company stated that all participants discontinued corticosteroids between 85 – 170 days following ED, and that all ALT/AST increases were resolved within 3 to 127 days. However, the EAG was unable to resolve that against information in the SmPC for ED where it was reported that "onset of ALT elevations [in the clinical studies] ranged from day 22 to 787 post-dose" (p. 13). All events were described as non-serious and resolved with treatment; however, clinical advice to the EAG was that late-onset increases in ALT/AST were more concerning as these could result in repeat events and further need for immunosuppression therapy, potentially throughout participants' lives.

No serious adverse events related to the use of corticosteroids were reported, though a list of adverse events of other severity levels associated with corticosteroid use were not provided in the CS or identified by the EAG elsewhere.

Eligibility criteria for the study required participants not to exhibit inhibitors to FIX at screening. Following treatment with ED, inhibitors to FIX were not detected in any participants, suggesting that treatment did not result in the development of inhibitors during the study follow-up. Anti-AAV5 NAbs were identified in 38.9% of participants at baseline, and in 100% of participants from week three onwards following treatment with ED.

3.3. Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

To establish comparisons against ED, the company located four studies including relevant comparators: PROLONG-9FP for Idelvion (relevant n=40); B-LONG for Alprolix (relevant n=63); Paradigm-2 for Refixia (relevant n=29); and NCT00093171 for BeneFIX (relevant n=34). Study-level details are presented in CS Appendix D, Table 22, and bleeding outcomes from these studies are reported in Table 11 of this report.

The included studies differed from HOPE-B in several important ways, principally relating to analysis populations, outcome definitions and background care. First, comparator studies often included different analysis populations. Most notably, B-LONG and Paradigm-2 included significant numbers of patients who would not have been classed as having prior prophylaxis, which significantly limited the number of patients relevant for each group. Thus, the patients available in the most relevant subgroups for B-LONG and Paradigm-2 were 33 and 17,

respectively. These small sample sizes meant that comparisons were more imprecise, and subject to imbalance in subsequent matched adjusted indirect comparisons, than with larger sample sizes.

Second, outcome definitions and time at risk varied between studies. This was especially important with respect to bleeds and was a common issue across all studies. For example, in B-LONG, the time at risk for a bleed was defined with respect to all follow-up, whereas the company noted that HOPE-B limited follow-up time to exclude a period following FIX use. The inclusion of bleeds also differed between studies. In PROLONG-9FP and B-LONG, the validation of individual bleeds used different clinical algorithms than in HOPE-B, where bleeds were investigator assessed. In Paradigm-2, included bleeding events were counted only if they were identified as spontaneous or traumatic, whereas in HOPE-B all bleeding events were counted. The combined impacts of these differences are hard to quantify. While the company presented a range of sensitivity analyses using different definitions of outcomes, these were naïve in nature and thus it was not clear what the impacts would be on a 'target randomised study'.

Third, it is difficult to understand what the standard of care was for the different analyses presented, as the time range of these studies and the range of populations included may have meant different standards of care were in place. Again, it was difficult to quantify the totality of these impacts on estimates of effectiveness.

The EAG identified a further study, NCT01335061 (Kavakli et al., 2015), that was excluded by the company in their SLR. The reason for exclusion given by the company was that the population was not relevant, but the EAG considered the population eligibility criteria to be comparable with other included studies and the inclusion criteria for review question 2 outlined in the CS appendix D1.1.1.

3.4. Critique of the indirect comparison and/or multiple treatment comparison

The methods used for the indirect comparison depended on the study used. As a rule, because all comparisons were non-randomised, a range of matching and adjusting approaches were taken. The EAG noted that while the statistical methods used to undertake these were of an appropriate standard, the inconsistency between comparisons in variables available for adjustment creates significant variability in the credibility of different analyses used, as does the

differing interpretations of estimates from indirect comparisons. The EAG also regarded that comparisons with BeneFIX were especially uncertain for reasons detailed by the company.

3.4.1. Statistical methods

Methods used to undertake comparisons differed by the availability of participant-level data. Of four indirect comparisons undertaken, only comparisons with Idelvion included participant-level data both for ED and Idelvion. Comparisons with Alprolix, Refixia and BeneFIX relied on summary data for comparator treatments. A strength of the company's approach was the transparency of sensitivity analyses presented, including sensitivity analyses where relevant on different outcome definitions.

3.4.1.1. Comparisons with Idelvion

Methods used to create comparisons with Idelvion relied on first excluding patients from PROLONG-9FP that were 'unique' to that study, i.e. adolescent patients and patients with different thresholds for ALT/AST values, and then estimating inverse probability of treatment weights (IPTW). IPTW relies on considering how patient characteristics 'predict' membership to either treatment group, and then reweighting patients to balance characteristics between groups. In this analysis, patients were reweighted from PROLONG-9FP to be similar to patients in HOPE-B. This is an important point of incommensurability between the different indirect comparisons undertaken.

Because of the availability of patient-level data for both studies, this comparison included the richest set of factors for adjustment, specifically severity of haemophilia B, prior ABR, and age, though prior FIX product class, BMI, weight, ALT/AST thresholds, HIV status, total bilirubin threshold, family with FIX inhibitor antibodies and duration of diagnosed haemophilia B were also considered. Based on estimates provided in Table 5.1 of the report of indirect comparisons[30 31], it was clear that IPTW analysis generated improvements in many, but not all factors; notable differences between groups in BMI, prior FIX product class, ALT/AST thresholds, and HIV status (among other characteristics) remained significantly imbalanced. The optimal combination of covariates for adjustment was selected after ranking covariates and considering trade-off between improvement in balance, effective sample size and overall balance of groups. After estimation of IPTW, differences between groups were estimated using standard regression models.

3.4.1.2. Comparisons with Alprolix, Refixia and BeneFIX

In contrast, methods used to create comparisons with Alprolix, Refixia and BeneFIX relied on a combination of matching populations by inclusion criteria and then adjusting using weights estimated on the HOPE-B patient-level data to create a HOPE-B group similar in mean and distribution of key variables as in the summary data available from comparator studies. This is an important point of incommensurability between these comparisons and the comparisons estimated against Idelvion; in the present comparisons, the interpretation of the effect is the average treatment effect on the comparator population.

Matching and adjusting HOPE-B data to B-LONG, which was the study for Alprolix, relied on first selecting a subset of patients in B-LONG with prior prophylaxis. The EAG regarded that this was appropriate to ensure balance on this key moderator, though this limited the number of additional variables used for comparison; in particular, primary analyses relied on adjusting only for prior ABR. Secondary analyses using the full B-LONG dataset included additional variables, but the EAG regarded that these analyses were not likely to be probative given major differences in populations by prior prophylaxis. Importantly, very few data were available to compare balance of covariates between groups in the primary analysis, which the EAG regards as a significant threat to the credibility of the analysis.

Matching and adjusting HOPE-B data to Paradigm-2, which was the study for Refixia, relied on a subset of patients with prior prophylaxis as primary analysis. As above, the EAG noted that this was appropriate (and relatedly that full-population secondary analyses were not likely to be reliable), but acknowledged that these primary analyses were only inconsistently able to adjust for both prior ABR and prior FIX product class. Correspondingly, it was not possible to ascertain covariate balance in the primary analysis.

Finally, comparison of data from HOPE-B and NCT00093171, which was the source of clinical data for BeneFIX, was limited by a lack of baseline data and ambiguities in outcome definitions, in addition to a lack of precision estimates (i.e. standard errors) for outcomes. Analyses thus required imputation of standard errors. Only age and prior FIX product class were available for adjustment, and it was not possible to ascertain covariate balance. The EAG thus regarded these analyses as especially tenuous. The company also reported pre-post analyses for patients from HOPE-B who were previously on BeneFIX but the EAG regarded these as being even less probative for decision-making than the MAICs given the lack of a comparator group.

3.4.2. Results of indirect comparisons

We report primary analyses for indirect treatment comparisons below, focusing on ABR, AsBR and AjBR as key outcomes, and reporting 'final' multivariable adjusted comparisons (Table 9). Additional analyses (not reported here) were undertaken for percentage with no ABR, with no AsBR, and with no AjBR; consumption of FIX; and for HRQoL estimates. All estimates suggest superiority of etranacogene against comparators in reducing the rate of key outcomes.

Table 9: Primary analyses of indirect comparisons of etranacogene vs key comparators

	ABR	AsBR	AjBR
Idelvion	[redacted]	[redacted]	[redacted]
Alprolix	[redacted]	[redacted]	[redacted]
Refixia	[redacted]	[redacted]	[redacted]
BeneFIX	[redacted]	[redacted]	[redacted]

Note: All estimates are expressed as rate ratios (95% CI).

Of note is that in Document B, the company reports secondary analyses for some comparisons instead of primary analyses; and these secondary analyses often include outcomes for which primary analyses are not available (e.g. AsBR for etranacogene vs Alprolix). No secondary analyses were reported for comparisons with Idelvion. However, as noted above, the EAG regards that the dissimilarity in populations to be too large for these analyses to be meaningful. These are nevertheless provided in summary form below (Table 12). These reflect a similar pattern of effects as for primary analyses above.

Table 10: Secondary analyses of indirect comparisons of etranacogene vs key comparators

	ABR	AsBR	AjBR
Alprolix	[redacted]	[redacted]	[redacted]
Refixia	[redacted]	[redacted]	[redacted]

Note: All estimates are expressed as rate ratios (95% CI).

3.5. Additional work conducted by the EAG

Clinical outcomes of prophylactic FIX replacement therapies as identified by the company and the EAG are shown in Table 11. Note that, for simplicity, the EAG has reported a small selection of effect estimates from the cited studies; a broader range of estimates (e.g. for different groups/regimens) were reported in CS appendix D and the cited publications. In some cases,

alternative estimates were used by the company in their ITC, which may have been as part of an effort to select populations that were most comparable. All studies were conducted with people with moderately severe and severe haemophilia B.

Table 11: Annualised bleeding rates following treatment with prophylactic FIX replacement vs etranacogene dezaparvovec

Study and product	ABR	ASBR	AJBR	Number of participants with bleeds requiring treatment (follow-up)
PROLONG-9FP[22] Extended-action FIX replacement; 7-day regimen N=40	1.58 (95%CI 1.02, 2.44)*	0.65 (95%CI 0.37, 1.13)*	NR	75% (26 weeks)
B-LONG[23] Short-acting FIX replacement; 7-day regimen N=63	3.12 (95%CI 2.46, 3.95)*	Median 1.0 (IQR 0.0, 2.22)	Median 1.1 (IQR 0.0, 4.0)	77% (median 12 months)
Paradigm-2[24] Extended-action FIX replacement; 7-day regimen N=29	2.51 (95% CI 1.42, 4.43)*	1.22 (0.48, 3.10)	NR	55% (12 months)
NCT00093171[25] Short-acting FIX replacement; 1->3 times weekly N=17	Mean 3.11 (SD 3.76)	Mean 0.72 (SD NR)	NR	64.7% (median 32 weeks)
NCT01335061[26] Short-acting FIX replacement; 7-day regimen N=25	Median 2.0 (range 0, 13.8)	Median 1.0 (range 0, 13.8)	Median 0.0 (range 0, 9.8	64.0% (12 months)
HOPE-B ED[13] N=52	1.51 (0.83, 2.76)*	0.38 (0.16, 0.89)	0.46 (0.24, 0.89)*	50% (7-24 months)

Abbreviations: ABR, annualised bleed rate; AJBR, annualised joint bleed rate; ASBR, annualised spontaneous bleed rate; CI, confidence interval; ED, etranacogene dezaparvovec; FIX, factor IX; IQR, interquartile range; NR, not reported; SD, standard deviation

Note: *estimated rate based on author's choice of statistical model

3.6. Conclusions of the clinical effectiveness section

3.6.1. Evidence quality

There was a small, low-quality evidence base for ED and the EAG had significant concerns about the reliability of the findings. The best available evidence was from the HOPE-B study, though the EAG identified a number of serious risk of bias concerns that could favour ED in the results. A major cause of concern in the HOPE-B study was the potential impact that the onset of the COVID-19 pandemic had on the risk of bleeding in the study, and the EAG considered that forthcoming follow-up data from the study (i.e. once participants daily activities had begun to return to levels comparable with the lead-in phase) may be more reliable. The phase IIb and phase I/II studies of ED were of limited value for decision-making, and the EAG was sceptical about their value in supporting the durability of the ED treatment effect given the difference in the treatment formulation (the phase I/II study) and the small sample size (phase IIb study[32]). The company's approach to the ITC were the best available to them, but the evidence base for the efficacy of prophylactic FIX replacement was limited and variations in the methods used by included studies resulted in unreliable relative effects.

3.6.2. Clinical benefits of ED

The EAG considered that the uncertainty in the findings due to evidence quality concerned the magnitude of the treatment effect, rather than its presence *per se*. Despite the lack of baseline data for FIX levels in the lead-in phase, FIX levels after treatment with ED were at a level considered to offer a meaningful benefit to people with severe and moderately severe haemophilia B. These FIX levels appeared to be stable over the study follow-up and would likely have benefits for people from having safer and more stable FIX activity. Bleeding rates were reduced for those receiving ED as compared to the lead-in phase of HOPE-B and in naïve comparisons with the best available evidence for routine prophylactic FIX replacement. While absolute ABRs were not drastically lower following ED than for its comparators, there appeared to be a major increase in the number of people who were without bleeds. Moreover, while acknowledging the limitations in the data about rates of FIX replacement, the EAG considered it likely that treatment with ED would result in a reduction in FIX replacement treatments than they would have in usual practice. Some minimal benefits in PROs were reported in HOPE-B, and the EAG expected that, with time, these benefits may increase (e.g. as people adjust to the new normal with their condition).

3.6.3. Reduced treatment benefit for some populations

Following treatment with ED, cells in the liver are directed to produce FIX. Subgroup analysis in the HOPE-B study suggested that participants with moderate or severe liver steatosis at baseline had reduced benefit of ED, as did those who required corticosteroid treatment (e.g. to treat elevated transaminase elevations). People with serious liver conditions were ineligible to participate in HOPE-B, though it may be that people affected by less severe liver conditions may also experience reduced benefits. The EAG considered that the onset of liver conditions at any time following treatment with ED could also affect the durability of the treatment response. Subgroup analysis also suggested that there may be reduced benefit for people with pre-existing neutralising antibodies to AAV. Given the immaturity of the evidence base and the broader uncertainties about the mechanisms involved in gene therapy, the EAG considered it plausible that other as yet unknown factors may moderate the treatment effect.

3.6.4. Potential for long-term clinical benefits

Evidence for the durability of the ED treatment effect was limited to the 2-year follow-up of the HOPE-B study since the EAG did not consider the longer follow-up evidence from the Phase I/II and Phase IIb studies to be useful in this regard, nor did it consider the durability model presented by the company (Shah 2022)[17] to be informative given the lack of available data. The potential for gene therapies to deliver long-term, even lifelong, clinical benefits was an area of significant clinical interest. To date, the evidence for long-term effects of gene therapies was lacking across indications, and the EAG understood that the presence of a long-term effect in one gene therapy would not necessarily confer benefit in another. Researches have posited that various factors may influence the potential for long-term gene expression, including the rate of cell turnover, patient demographics, and immune-response[33]. Illnesses experienced by people who have received a gene therapy, and any treatments that they receive, may also affect the durability of a gene therapy treatment response. On the basis of the evidence available and current thinking about gene therapies, the EAG considered it both plausble that ED could have a lifelong effect or that the treatment effect of ED could last only a few years until (for example) liver cell turnover has progressed and/or people experience conditions that affect liver function or the body's immune response. Clinical advice to the EAG was that this was an area of great uncertainty, considered that a 6 – 8 year duration of effect was plausible based on the current evidence. The EAG noted that the uncertainty in this issue was unlikely to be resolved without further data collection, though the EAG explored the potential impact that variation in the durability of treatment response has on the cost effectiveness of ED in Section 6.2.2.

3.6.5. Safety

Overall, ED was not associated with significant safety concerns during the studies; those adverse events reported appeared to be mild or were considered to be unrelated to treatment. An exception to this was the risk of transaminase elevations, which affected a significant minority of study participants. The EMA highlighted inconsistencies in the decisions made by the study investigators about whether these elevations were caused by ED, and the EAG considered it reasonable to assume that treatment with ED did result in an increased risk of ALT/AST increases that require immunosuppressive treatment. The data presented by the company suggested that all these events responded to treatment and were resolved within the first year after ED, however evidence reported by the EMA suggested that this was not the case and further elevations occurred more than one year following treatment. Pending further clarification from the company on this point, this would suggest that people receiving ED are at an increased risk of repeated transaminase elevations that require corticosteroid treatment, and which may therefore have long-term impacts on their health.

4. COST-EFFECTIVENESS

4.1. EAG comment on company's review of cost-effectiveness evidence

The company conducted a SLR to identify existing evidence to support this appraisal, including published cost effectiveness analyses and studies reporting cost, resource use, and HRQoL data. Overall, the methods used by the company were appropriate. A summary of the EAG's assessment is provided in Table 12.

Table 12: Summary of EAG's critique of the methods implemented by the company to identify cost-effectiveness, cost and resource, and HRQoL evidence

Systematic review step	Section of CS in which methods are reported	EAG assessment of robustness of methods
Searches	Appendix D1.1 and G	Searches were well conducted with a variety of keywords and subject headings used in a range of databases. A variety of grey literature sources were also searched. There was some discrepancy in the sources searched in the original searches of August 2021 and then in the update searches of October 2022. One search strategy was used to search for economic, cost and HRQoL evidence simultaneously.
Inclusion criteria	Appendix D1.1.1	The inclusion criteria were appropriately and appeared sufficiently broad to capture all relevant evidence
Screening	Appendix D1.1.2	The methods used were consistent with best practice.
Data extraction	Appendix D1.1.2	The methods used were consistent with best practice.
QA of included studies	NA	Quality assessment was not conducted

Abbreviations: CS, Company Submission; EAG, External Assessment Group; HRQoL, health-related quality of life; NA, not applicable; QA, quality assessment

4.2. Summary and critique of company's submitted economic evaluation by the EAG

4.2.1. NICE reference case checklist

Table 13: NICE reference case checklist

Attribute	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	QALYs were used as appropriate and captured the health benefit to patients. Adverse events disutility was corporated

Attribute	Reference case	EAG comment on company's submission
		into the company's model.
Perspective on costs	NHS and PSS	NHS and PSS, as appropriate.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The company submitted a cost utility analysis. The company made multiple pairwise comparisons rather than a fully incremental analysis in its deterministic base case, but presented a fully incremental analysis in the PSA. Comparisons were complicated by changing the IV FIX treatment used post-failuire of ED for each scenario.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model incorporated a time horizon of 59 years until the cohort of patients reached an age of 100 years. The EAG considered this to be sufficiently long enough to capture important differences in costs and benefits between the intervention and comparators.
Synthesis of evidence on health effects	Based on systematic review	Bleeding rates and consequently transition probabilities in the economic analysis for ED were estimated from the HOPE-B study, and comparator arms via ITC[30 31].
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Outcomes were reported in QALYs as per the reference case.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Utility associated with ED treatment was taken from EQ-5D-5L data at 24 months from HOPE-B. A lower utility was assigned to IV FIX based on expert opinion. Disutilities for bleed events were taken from US-ICER 2022[34].
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The population of the HOPE-B study were generally representative of the target haemophilia B population in the UK..
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Women were excluded from the study, though clinical experts to the EAG advised that evidence from the studies could nevertheless be generalised to the small minority of females with severe disease.

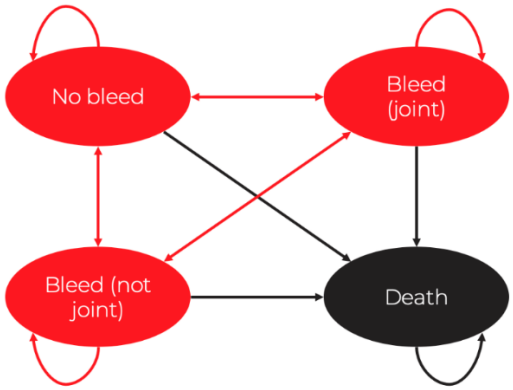
Attribute	Reference case	EAG comment on company's submission
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Resource use and costs were based on NHS Costs 2019/2020 and PSSRU 2021. It was unclear whether prices were adjusted to a common price year, but the EAG considered this unlikely to be of consequence to the results in this case.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Costs and benefits were discounted at 3.5%.

Abbreviations: EQ-5D, EuroQol 5 dimension; HRQoL: health-related quality of life; NHS, National Health Service; PSS, Pseronal Social Services; QALY: quality-adjusted life year; TA: technology appraisal

4.2.2. Model structure

The company presented a cohort-based Markov model whereby patients moved through four health states (Figure 2). Health states were based on bleeding events, and each health state was associated with specific costs and utilitites. The company defined health states as 'no bleed', 'non-joint bleed', 'joint bleed' and 'death'. All patients started from the 'no bleed' health state and the cycle length was seven days.

Figure 2: Model structure



Source: CS Document B, page 147

Rates of bleeding were used to calculate transition probabilities between the health states. Utilities were attached to each of the four health states. In addition, a treatment-specific decrease in health utility was applied to patients receiving IV FIX to account for the inconvenience of regular (i.e. once or twice weekly) IV injections versus a once only administration of ED.

The cycle length of one week was in line with the adminstration of routine prophylactic IV FIX. The EAG's clinical expert also noted that duration of bleeding events and their management was highly unlikely to be more than a week. Hence the EAG believed that the cycle length in the model was appropriate.

Overall the EAG considered that the company's approach to defining health states according to bleeding events was likely to be appropriate.

4.2.3. Population

Modelled baseline characteristics for participants in the HOPE-B study are outlined in Table 14. The EAG noted that the mean age of participants in HOPE-B was 41.5 years old whilst the expected indication for ED was for people over the age of 18 (CS B p.51).

Table 14: Patient baseline characteristics

Patient characteristics	
Male	100% (N=54)
Age mean (SD, min-max), years	41.5 (15.8, 19-75)
Severity of haemophilia B at time of diagnosis, n (%)	
• Severe (Factor IX <1%)	44 (81.5)
• Moderately severe (Factor IX ≥1% and ≤2%)	10 (18.5)
• Positive HIV status, n (%)	3 (5.6)
• Prior hepatitis B infection, n (%)	9 (16.7)
• Prior or ongoing hepatitis C infection, n (%)	31 (57.4)
Pre-screening Factor IX prophylaxis therapy n (%)	
• Extended half-life	31 (57.4)
• Standard half-life	23 (42.6)

Abbreviations: SD, standard deviation; HIV, human immunodeficiency virus

Source: CS Document B, Table 8

4.2.4. Interventions and comparators

The company compared treatment with ED followed by IV FIX on ED failure versus four IV FIX products available in the NHS (BeneFIX [standard half-life] and Alprolix, Idelvion and Refixia [all

extended half-life]). The EAG noted that people who receive ED may receive supplementary IV FIX on demand, and therefore the comparison may be considered ED+IV FIX followed by IV FIX on ED failure as compared with four IV FIXes (see Section 2.4). The decision model excluded on demand FIX as this would be expected to be equal between arms, which the EAG agreed with, albeit noting that the incremental cost may be affected where a different FIX treatment was used as an on-demand therapy than was considered in the comparator arm because of variability in the price of different FIX treatments (e.g. ED+Refixia should be compared with Refixia). For simplicity, we refer to the variations of the ED arm as ED+BeneFIX, ED+Alprolix etc.

In its base case, rather than presenting a comparison of all five strategies, the company presented a series of four pairwise comparisons. In each case, ED was compared with a specific FIX treatment, thus the pairwise comparisons were ED+BeneFIX vs BeneFIX, ED+Alprolix vs Alprolix etc. In each case, the FIX treatment used was also the treatment administered to all patients after ED failure. The EAG understood the logic of this approach, however, multiple pairwise comparisons in the presence of multiple comparators can lead to misleading conclusions. The correct way to analyse this decision problem would have been to compare all options simultaneously against each other, excluding dominated and extended dominated strategies. This is the approach NICE refers to as a 'fully incremental' analysis. The EAG noted that a fully incremental analysis was presented in the company's probabilistic sensitivity analysis (PSA), where the ED arm was defined as ED+Refixia. This was the most expensive IV FIX treatment and thus represented a conservative (least favourable) estimate of the cost-effectiveness of ED.

Clinical experts advised the EAG that a large number of people with haemophilia B were indeed receiving Refixia in the NHS, due to its longer half-life compared with BeneFIX resulting in reduced treatment burden. The EAG's preferred approach was based on a five-way comparison with ED+Refixia as the ED arm, but with some additional sensitivity analysis around the choice of IV FIX on failure of ED (see Section 6).

4.2.5. Perspective, time horizon and discounting

The economic analysis was conducted from an NHS and PSS perspective, as was consistent with the NICE reference case.

The time horizon used in the economic analysis was patient life-time (up to age 100). The EAG considered this appropriate to capture all relevant differences in cost and outcomes between arms. However, the EAG noted that the starting age applied in model was 41.5 years' of age, whilst the anticipated indication was adults aged ≥18 years. In response to clarification, the company provided incremental cost effectiveness results for a cohort of patients aged 18-years with a life-time horizon. The results showed that ED was still dominant over all comparators. However, to investigate the effect of age in combination with other scenarios, the EAG also included it in EAG base case (see Section 6.3).

Costs and benefits were discounted at the NICE reference case rate of 3.5%.

4.2.6. Treatment effectiveness and extrapolation

4.2.6.1. Durability of ED

The decision model included a predicted failure rate of ED (durability function) based on extrapolations of observed data, with failure in the company base case defined as FIX activity <2%. Once ED failed, the model assumed that patients resumed prophylactic treatment with one of the IV FIX treatments. This was modelled by calculation of a weighted average of the ED and relevant IV FIX costs and health state utilities in each cycle.

The company stated that the median durability of ED was [redacted] years (CS B p150) on the basis of modelled projections (Shah 2022a & 2022b[17 35]), although the EAG noted this is a presumed typographical error as the median stated in Shah et al. was [redacted] years.

Shah et al.[17] combined observed data from the HOPE-B (n=52) and AMT-061-01 (n=3) studies (total n = 55) and modelled extrapolations using Bayesian and frequentist linear mixed models. The 52 participants from the HOPE-B data were those who received the full dose of ED, excluding one person who received only 10% of the dose due to a reaction to treatment, and one participant who responded poorly to treatment and continued to require routine prophylactic FIX treatments. Baseline was defined as FIX activity levels at 6 months post-treatment, with failure defined as a predicted FIX activity of <2%. Predicted failure rates were extrapolated to 25.5 years, with a supplementary analysis extending to 60 years (Shah 2022b).

The EAG considered the source data for the extrapolation to be appropriate, drawing on the two studies using the hFIXco-Padua gene variant and excluding AMT-060 (wild-type Factor IX transgene). Whilst the statistical modelling technique was considered reasonable, the EAG was concerned with the low participant numbers available to inform the model and the short follow-

up of the source data: 24 months follow-up data were available for only 6/55 (10.9%) participants in the analysis, and 30 months for 3/55 (5.45%), which were then extrapolated out to 60 years. The EAG also did not consider it appropriate to exclude the participant who did not have a satisfactory response to ED and continued to require prophylactic therapy; while Shah stated that this person had high levels of neutralising antibodies to AAV at baseline, the EAG understood that the presence of such antibodies was common in the general population and people with high levels were not currently expected to be ineligible for treatment with ED. Overall, the EAG considered that there was a high degree of uncertainty in the extrapolation.

There were limited long-term data available to determine the potential durability of gene therapy treatment effects, both within haemophilia and in other conditions, due to their relatively recent development. The EAG understood that expectations of durability would be specific to the treatment and its indication, and that evidence of durability in other gene therapies (even those using a similar vector) may not be indicative. Long-term extrapolations of treatment effect beyond the study follow-up period were therefore highly uncertain. Clinical advice to the EAG acknowledged this limitation but considered a durability of 6-8 years to be plausible on the basis of current thinking.

Within haemophilia, the EAG understood there to be several reasons why gene therapies using an AAV vector may experience reduced durability[33]. Evidence from the HOPE-B study suggested that specific subgroups of people treated with ED may experience a reduced treatment effect and the EAG considered it plausible that they may be more susceptible to reductions in treatment efficacy over time. This included people who received corticosteroids to treat transaminase increases, people who develop AAV antibodies, and those with moderate or severe liver steatosis at baseline(Section 3.2.3.2).[29] It had also been posited that the rate of cell turnover in the areas of the body that receive the treatment, and subsequent illnesses and treatments that interfere with that area of the body or the broader mechanisms of treatment, may lead to reduced efficacy over time[33]. Following ED, cells in the liver becomes responsible for producing FIX, and study participants with liver conditions were either excluded from the study or else showed reduced treatment efficacy. The EAG also understood that the liver was known to have a higher rate of cell turnover compared to other areas of the body. Overall, the EAG understood that there are reasons why the ED treatment effect may not sustain over time, and that further evidence would be needed to demonstrate its durability.

Given their impact on the cost-effectiveness estimates, the EAG explored a number of assumptions around durability, including threshold analyses to identify the minimum duration of effect for ED to be considered cost-effective (sections 6.2.3 and 6.2.10.1).

4.2.6.2. Definition of ED failure

The company base case set a threshold for the re-introduction of prophylactic IV FIX when patients' levels of circulating FIX were ≤2% of normal, which was highlighted by the company as a typical FIX activity level considered for prophylactic treatment (CS B p150). However, clinical advice to the EAG stated that a 2% - 5% FIX activity level would be considered as a 'trough' (i.e. minimum level of FIX activity when people are routinely receiving FIX therapy), and that this may be too low to engage safely in some routine activities (e.g. certain sports). Furthermore, following administration of ED, participants in HOPE-B only discontinued IV FIX once FIX levels were >5% of normal activity (Section 3.2.2.3). Therefore, the EAG considered that the 2% threshold may underestimate the proportion of patients returning to prophylactic IV FIX. Shah et al.[17] calculated the durability function (described in Section 4.2.6.1 above) at a 5% FIX activity level threshold, resulting in a median durability of [redacted] years. The EAG considered a 5% FIX activity level to be a more plausible threshold at which prophylactic IV FIX would be recommenced.

4.2.6.3. Response to ED in the first six months post administration

The EAG noted that participants in HOPE-B continued to receive IV FIX post administration of ED until their FIX levels had stabilised at >5% of normal activity and that the clinical outcomes reported in the CS excluded data measured during the initial 6-month period post-administration, which the company stated was to allow participants' circulating FIX levels to stabilise (see Section 3.2.2.5). In contrast, the company base case assumed 100% durability of ED from the first model cycle in terms of risk of bleeds but included cost of 3 weeks of IV FIX immediately following ED administration.

As there may be greater need for people receiving ED to receive prophylactic FIX treatments in the initial 6-months after treatment, the EAG considered that the company base case was optimistic and so the EAG explored the impact of a longer 'induction period'.

4.2.6.4. Transition probabilities for bleeds

The clinical data to derive transition probabilities for the ED arm were based on those observed in the HOPE-B study, with comparisons with IV FIX based on rate ratios estimated via several

ITCs [30 31] (Section 3.4). Given the limitations of the data (Section 3.4), and the risk of overestimation of the treatment effect of ED (Key Issue 2), the EAG explored the impact on the ICER of reduced treatment efficacy of ED comparative to prophylactic FIX replacement.

4.2.7. Health-related quality of life

The company model assumed that patients receiving ED had a higher utility than those receiving IV FIX. Bleed health states are associated with a disutility penalty and adverse events also incur a disutility. These are discussed in turn below.

4.2.7.1. Treatment-specific health utility

Health utility for patients receiving ED was based on EQ-5D-5L data from HOPE-B at 24 month follow-up. Health profiles were converted to utilities using the Van Hout cross-walk algorithm[36], yielding a utility of [redacted] for patients in the 'no bleed' health state. The EAG considered this an appropriate algorithm.

The EAG noted that the utility estimate was applied from the first model cycle and therefore may have overestimated utility during the first cycles post-administration while patients were still receiving IV FIX.

Health utility for patients receiving IV FIX was defined as the utility for ED less [redacted] (i.e. [redacted]) to represent "patients living a precautionary life, as they fear bleeding events and lack of freedom to enjoy usual activities, as described in the dimensions of EQ-5D" (CS p156). The source of the quoted disutility was expert opinion, described as "conservative and a minimum, but reasonable" (CS p156). The methods for deriving the clinical expert opinion were not reported and it was unclear how the SE was estimated.

The EAG noted that the utility decrement associated with 'some problems with performing usual activities' in the MVH algorithm (NICE's preferred preference weightings for the EQ-5D-3L) was 0.036, rising to 0.363 for 'unable to perform usual activities' (calculated as $2\beta_3 + \beta_8 + \beta_{11}$ as per Equation 1, Dolan 1997[37]). The availability of FIX replacement therapies, particularly regular prophylactic treatment, was associated with a major benefit for survival and HRQoL in people with haemophilia B. However, ED may have further benefits for HRQoL over and above this, for example by reducing treatment burden and benefits for functioning and psychological wellbeing of a higher and more stable circulating FIX level. This implied that an appropriate upper estimate for the disutility associated IV FIX compared with ED would be 0.036 (per the MVH algorithm for a 'some problems performing usual activities'), somewhat below the company's

base case assumption. However, allowing for additional impact above and beyond this from being free of injections whilst ED remains active, the EAG preferred an estimate of 0.042 for the disutility associated with IV FIX compared with ED.

4.2.7.2. Health state utility (bleed events)

In the model, patients experiencing a bleed event experienced a reduction in health state utility, incorporated in the model as the treatment-associated utility less the disutility of a joint or non-joint bleed, as appropriate. Based on the company's expert opinion, the non-joint bleeds lasted up to two days and joint bleeds up to four days. The EAG considered the company's reasoning for how to model the bleeding events disutility was appropriate. The data relevant to disutilities came from US-ICER 2022[34]. Table 15 provides the summary of disutility values of bleeding events.

Table 15: Summary of disutility values of bleeding events

Bleed type	Disutility
Disutility of non-joint bleed per cycle	0.05 (-)
Disutility of joint bleed per cycle	0.16 (-)

Abbreviations: ED, etranacogene dezaparvovec

Source: Table 32 from Document B of CS

4.2.7.3. Adverse events disutility

The company reported disutilities associated with ED and IV FIX treatment, sourced from various literature (CS p154-5). Weekly probabilities for ED were taken from the HOBE-B study and for IV FIX from a study relating to BeneFIX (source not stated), which was then assumed equal across all IV FIXes. The company stated that the impact of AEs from all treatments was "captured in the model via the application of disutility values and estimated AE duration, where necessary" (CS p153), but the time over which patients were at risk of AEs was not stated. The EAG noted that the company's initial model included a life-time duration for adverse events in ED, but that the version submitted post clarification altered this to the first year only with no rationale provided (see Section 6.1).

The EAG considered that the disutility estimates were appropriate but the lack of clarity over the source of IV FIX disutilities increased uncertainty. The EAG explored the impact of altering the assumption over duration of AEs in Section 6.2.9.

4.2.8. Resources and costs

The company conducted a SLR to identify cost and healthcare resource use for ED and its comparators. Model costs were separated into the following types:

- Drug acquisition costs
- Administration costs
- Follow-up cost for etranacogene dezaparvovec
- Monitoring costs
- Bleed-related management costs
- Adverse event costs

Follow-up costs were presented in Table 35 of the CS, with weekly/monthly follow-up sessions assumed to be with a nurse in the hospital and a liver function test carried out twice weekly, presumably at home. The EAG considered there to be uncertainty around whether follow-up sessions would be with a nurse or consultant haematologist. The EAG explored the impact of this in a scenario analysis (see Section 6.2.8).

The company presented the cost per bleed for the intervention and comparators in Table 38 of the CS (note that these costs did not consider any confidential discounts to the NHS for these treatments). This reported that the cost for Refixia (an extended half-life treatment increasingly used in the NHS) was £8,247.89 per bleed.

Section 3.5.4.1 of the company CS highlighted societal costs associated with treatments, including estimates of the workdays lost due to bleeding events (CS Table 42). The company included these costs in a scenario analysis presented in CS Section 3.10.3, concluding that as ED is associated with fewer bleeds, the incremental costs are even lower compared with any of the IV FIXes, thus reinforcing the conclusions of the NHS+PSS (NICE reference case) analysis.

5. COST-EFFECTIVENESS RESULTS

5.1. Company's cost-effectiveness results

5.1.1.1. Base case results

The company's base case comprised pairwise comparison of ED with each of the four IV FIXes (Table 1). In each case, the IV FIX used alongside ED and post ED failure was changed to be the relevant comparator. As stated in Section 4.2.4, where there were more than two treatment strategies being compared a fully incremental analysis was required, taking into account dominance and extended dominance. Changing the IV FIX used alongside ED complicated this but the company did present a fully incremental analysis for its PSA, assuming Refixia was used alongside ED.

The figures reported included the company's PAS discount but list prices for IV FIXes. Results including confidential discounts for all drugs are reported in the confidential appendix to this report. In the company's base case, ED dominated all IV FIXes. The PSA showed that ED had a [redacted] probability of being the most cost-effective of all five comparators at a willingness to pay of £30,000/QALY. The EAG's critique of the PSA is in Section 5.2.2.

Table 16: Company base case results (including PAS price for ED)

	Discounted costs	Discounted QALYs	Incremental discounted costs	Incremental discounted QALYs	Cost per QALY gained
Company deterministic base case					
ED followed by Alprolix	[redacted]	[redacted]	-	-	-
Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ED followed by BeneFIX	[redacted]	[redacted]			
BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ED followed by Idelvion	[redacted]	[redacted]			
Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
ED followed by Refixia	[redacted]	[redacted]			

Refixia	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Company probabilistic base case					
ED followed by Refixia	[redacted]	[redacted]	-		-
BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Refixia	[redacted]	[redacted]	[redacted]	[redacted]	Dominated

Abbreviations: QALYs, quality adjusted life years

5.2. Company's sensitivity analyses

5.2.1. One-way sensitivity analysis (OWSA)

The company conducted pairwise OWSA varying a number of model parameters by +/-20% including annual bleeding rates, treatment costs, utilities, disease monitoring cost, disease follow up cost, disease management cost, disutility of adverse events and non-joint and joint bleeding events. Result were presented as tornado diagrams of NMB rather than ICERs for greater clarity when ICERs are negative (CS p197-200). The results were most sensitive to variation in IV FIX annual bleed rates and subsequent costs, except for Refixia where the two most important parameters were cost of treatment of bleeds and total disease monitoring cost (rather than bleed rates).

The EAG preferred to see five-way comparisons of ED and IV FIXES (i.e. comparing net monetary benefit with each treatment option). However, in all cases the model conclusions were insensitive to changes in the input parameters, and the EAG believed this was true for multi-way comparisons.

5.2.2. Probabilistic sensitivity analysis

Parametric distributions were assigned to all model inputs except for HOPE-B demographics (e.g age), list prices, dosing regimens, durability and mortality. The EAG noted measures of variability were reported as a mix of standard deviations and standard errors (CS B p186-90). In its response to clarification question B19 the company confirmed that all variability measures

were standard errors. The PSA was run for 10,000 simulations. Results are reported in section 5.1.1.1 above.

The company reported the PSA results as a fully incremental analysis, which was more appropriate for decision making than the pairwise analysis presented in the deterministic base case (NICE manual section 4.10.8[38]). The EAG agreed with the company's decision to include the assumption of a 100% market share of Refixia following treatment with ED. Whilst this may not be a full representation of real world practice, clinical advice to the EAG was that individuals were more commonly switching to Refixia due to the need for less frequent treatments.

The EAG considered the parameterisations broadly appropriate, although it was unclear how standard errors and hyperparameters were defined for costs and adverse event incidences, utilities and costs. Given the relatively low incidence of AEs and low influence on the cost-effectiveness results the EAG considered this to be of minor consequence.

The EAG agreed that HOPE-B demographics, list prices and mortality were appropriately entered in the model as constants, and noted that durability was handled in a separate scenario analysis. However, not allowing dosing regimens to vary may have underestimated uncertainty.

In summary, the EAG considered that the PSA was appropriately performed but that assuming fixed dosing regimens may have underestimated uncertainty.

5.2.3. Scenario analyses

Scenario analyses explored a number of assumptions over durability, utilities, model time horizon and societal costs, each of which is discussed below.

5.2.3.1. Durability

The durability scenario analyses compared ED with BeneFIX only, assuming (1) 100% lifetime durability, (2) reintroduction of IV FIX at a 5% FIX activity threshold, (3) 100% durability for five years followed by a 20% drop in durability over five years and (4) 100% durability for 24 months followed by a 20% drop in durability over five years. Results showed that a 5 year durability (followed by 20% decline over the next 5) yielded an ICER of [redacted] (with PAS discount) compared with BeneFIX, substantially in excess of the £20,000 to £30,000 wilingness to pay threshold used by NICE in the STA programme. Whilst useful, the EAG preferred to see simultaneous comparison of ED versus all four IV FIXes, and so conducted additional threshold

analyses to identify the minimum durability for ED to yield an ICER below £20,000 and below £30,000 per QALY (Section 6.2.10.1).

5.2.3.2. Utilities

The company presented a scenario analysis without the treatment-specific health utility difference (see Section 4.2.7.1 and CS p.206), although it was unclear whether the ED utility (of [redacted]) was applied to IV FIX, or the IV FIX utility (of [redacted]) applied to ED. Nevertheless, the results were insensitive to this scenario: ED remained dominant. As expected, the scenario did not affect incremental cost, but reduced the incremental QALYs. The EAG noted presentation of the results as pairwise comparisons rather than fully incremental and explored alternative estimates of the utility difference between ED and IV FIX (see Sections 4.2.7.1 and 6.2.5).

5.2.3.3. Time Horizon

The company explored the impact of 5-, 10- and 20-year time horizons of ED compared with BeneFIX. Over 5 years, the ICER was [redacted] (including PAS discount), reducing to [redacted] at 10 and 20 years.

The EAG considered the shorter time horizons to be inappropriate as they were not considered long enough to capture all differences in cost and outcomes. The EAG noted the company's preferred base case had a life-time horizon.

5.2.3.4. Societal costs

The company did not make an argument for the inclusion of a broader cost perspective including societal costs, therefore the EAG provides no comment on this scenario.

5.3. Model validation and face validity check

The model structure and key inputs were assessed for face validity by the company's clinical experts and reviewed by an external agency, following which minor adjustments were made.

6. EVIDENCE ASSESSMENT GROUP'S ADDITIONAL ANALYSES

The EAG identified a number of limitations within the company's base case and explored the impact of parameter values and assumptions that the EAG believed were more plausible.

This section is organised as follows: Section 6.1 details the impact of errors identified in the EAG's validation of the executable model. Section 6.2 details a series of scenario analyses exploring the robustness of the cost-effectiveness results to specific assumptions and additional uncertainties identified by the EAG. These analyses were conducted within the company corrected base-case analysis. Section 6.3 identifies the EAG's preferred base case based on a combination of the exploratory analyses presented in Section 6.2. A summary of the decision modelling results is then in Section 6.4.

6.1. EAG corrections and adjustments to the company's base case model

Due to a number of mechanical errors in the company model the EAG was unable to fully explore the submitted version of the model. The company supplied a revised model file following clarification, however, the EAG noticed several undocumented changes in the calculations in this model leading to small changes in the base case. These were:

- Reduction in the unit cost of Refixia from £1221.50 to £1211.50
- Increase in the administration cost of ED from £635.55 to £808.64
- Cessation of costs and quality of life impact associated with adverse events from ED after one year

The EAG noted that the change in unit cost of Refixia appeared erroneous: the list price supplied to the EAG by NICE was £1221.50 and so the EAG reverted the price to the original (this adds approximately £3000 to the annual cost of treatment with Refixia).

In its clarification response, the company stated that the cost of administration was omitted from Table 34 of the company submission (CS Table 34, p159) and it presented a revised version (clarification response, Table 5, p15) stating a revised administration cost for ED (£808.64, reported as £808.62). However, the EAG noted that this was also omitted from the original model submission but were added by the company post clarification. The additional costs of £133.92 and £39.17 represented an outpatient procedure and one hour of nursing time

(covering time required to handle biomarker test results), yielding the increased figure of £808.64.

The EAG noted the change to the model assumptions regarding duration of adverse events post administration of ED, but also noted that there was no explanation or justification for this in the company's clarification response. The company submission (CS p153) stated that the impact of AEs from all treatments was "captured in the model via the application of disutility values and estimated AE duration, where necessary", but without further elaboration. The EAG explored the reintroduction of adverse events cost and disutility after the first year of treatment as a scenario (Sections 6.2.5 and 6.2.9).

Therefore, the EAG corrected base case (Table 17) comprised the company base case results reported in the revised model file (including the increased administration cost of ED, duration of AEs associated with ED lasting one year only but with a reverted unit cost for Refixia). The EAG reproduced the pairwise comparisons as per the deterministic company base case, but also presented deterministic and probabilistic fully incremental analyses, with Refixia used alongside ED. Due to resource constraints within the timeline of the appraisal, PSA results are presented based on 1,000 iterations rather than the 10,000 used in the CS.

Table 17: EAG-corrected company base case results (including ED PAS price)

	Discounted costs	**Discounted QALYs**	**Incremental discounted costs**	**Incremental discounted QALYs**	**Cost per QALY gained**
*EAG-corrected company **deterministic** base case*					
ED followed by Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ED followed by BeneFIX	[redacted]	[redacted]			
BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ED followed by Idelvion	[redacted]	[redacted]			
Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ED followed by Refixia	[redacted]	[redacted]			
Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
*EAG-corrected company **deterministic** base case (fully incremental)*					

ED followed by Refixia	[redacted]	[redacted]	[redacted]		[redacted]
BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
*EAG-corrected company **probabilistic** base case (run by EAG)*					
ED followed by Refixia	[redacted]	[redacted]			
BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: QALYs, quality adjusted life years

6.2. Exploratory and sensitivity analyses undertaken by the EAG

The EAG conducted a number of scenario analyses to test the impact of alternative model assumptions on the ICER. These are discussed in the Sections below. The first scenario analysis explored sensitivity to the IV FIX used alongside ED / post ED failure. The EAG's preferred IV FIX was Refixia, so all subsequent analyses show ED+Refixia for the intervention arm.

6.2.1. IV FIX taken alongside ED and post ED failure

In its base case, the company provided four pairwise comparisons rather than a fully incremental analysis, each time changing the IV FIX used alongside ED to the relevant comparator. The EAG preferred a fully incremental analysis but this required a decision on the IV FIX (see Section 4.2.4). Based on discussions with its clinical expert, the EAG preferred Refixia. However, the company submitted market share data of IV FIX for 2020, and so the EAG explored the impact of assuming a weighted average by market share in a scenario analysis. This was included as an additional comparator (ED+mkt share), alongside ED+Refixia and the four IV FIXes in Table 18 and Table 19.

6.2.2. Definition of ED failure

The company base case assumed prophylactic IV FIX was reinstated once FIX activity levels fall below 2%. As discussed in Section 3.2.2.4, this may be lower than would be used in clinical practice. The EAG therefore calculated a scenario where prophylactic IV FIX was resumed at 5% FIX activity level.

6.2.3. Durability of ED

Due to the small sample size and limited follow-up of the available evidence, the durability of ED treatment effect was a key area of uncertainty. The company's base case assumed a median durability of [redacted] years (reported in the CS as [redacted] years), based on a definition of failure of 2% FIX activity levels. At a 5% FIX activity definition of failure, median durability using the company analysis was [redacted] years (see Sections 4.2.6.1 and 4.2.6.2). The EAG's clinical expert acknowledged the uncertainty in this area, though anticipated that a much lower duration of effect of around 6 to 8 years may be plausible. As discussed in Section 3.6.4, the EAG was aware of reasons why treatment with ED may not have lifetime durability, and therefore considered the assumption in the company model to be uncertain. The EAG conducted a threshold analysis calculating the minimum durability required to achieve an ICER below £20,000 and £30,000 per QALY.

6.2.4. Time to steady state

The company base case allowed for a three-week period during which IV FIX was maintained post administration of ED, adjusting costs and bleed rates accordingly. However, the company did not supply data pertaining to bleed rates for months 0-6 post administration. The EAG therefore explored a scenario where all patients maintained IV FIX for six months rather than three weeks.

6.2.5. Utility assumptions

The EAG conducted additional scenario analyses comprising (a) a disutility for IV FIX of 0.042 in place of the company's base case of [redacted], and (b) equal utility associated with treatment with ED and all IV FIXes (set to [redacted]). An additional scenario assuming disutility for adverse events continues beyond the first year is described in Section 6.2.9 below.

At clarification, the company stated that the benefits of the intervention gradually improved to get to its maximum value at month 24. Hence, the EAG calculated an additional scenario (c)

setting utility equal to [redacted] for the first 24 months[redacted]. This approximated a gradual improvement in utility over the first two years post administration.

6.2.6. Estimation of transition probabilities for bleeds

Given the uncertainty in the company's ITCs (Section 3.4) and the risk of overestimation of the treatment effect of ED (Key Issue 2), the EAG conducted two scenario analyses assuming equal probabilities of bleeds across all five treatments, one ('low bleed rate scenario') setting ABR and AjBR bleed rates to the treatment with the lowest ABR (ED) and one ('moderate bleed rate scenario') setting rates to those of Refixia.

To explore the impact of a gradual increase in ED effectiveness, the EAG also presented a scenario analysis with a gradual reduction in bleed rates from that associated with Refixia to that associated with ED over a period of 24 months. Note that this scenario overlapped with the 'time to steady state' scenario (Section 6.2.4) which explored the impact on cost and bleed rates of continuation of IV FIX for a period of six months. This scenario assumed the company base case continuation of prophylactic IV FIX (3 weeks) and focussed on the impact of assuming a gradual 24 month time period for bleed rates to reach those estimated for ED. The cost and QALY impact of bleeds were as per the company base case (including IV FIX).

6.2.7. Age at administration of the intervention

The company base case assumed an age of 41.5 years at ED administration, whilst it was anticipated that the licence would specify a minimum age of 18 years. The EAG was aware of qualitative evidence that suggested that the decision to receive a gene therapy was complex, and that people weigh up a number of considerations before taking a decision to receive a treatment[39 40]. The decision to receive a gene therapy may also be influenced by the extent to which treatment precludes any future gene therapy treatment; in which case, people may choose to wait until evidence was available for several gene therapies (given that there are more gene therapies for haemophilia B in the pipeline) before making a choice. Those who find their disease difficult to manage with prophylactic FIX replacement (for example, where their lifestyle means that regular treatments are challenging) may be more likely to opt for a gene therapy earlier in their lives. The EAG therefore considered it plausible that some people may choose to receive treatment at aged 18 years while others may wait several years before deciding to do so. In its clarification response (question B22), the company provided an analysis with age at administration of 18. This did not affect the conclusions of the model but increased

the magnitude of costs and QALYs in each arm. The EAG repeated this with its corrected base case.

6.2.8. Follow-up visit with haematologist rather than nurse

The company base case assumed follow-up care post administration of ED would be provided by a nurse. The EAG explored a scenario where this follow-up care was provided by a haematologist.

6.2.9. Adverse Events continue whilst ED durability persists

The EAG explored a scenario that reverts to the company base case assuming adverse events continued (and so imposed costs and disutility penalties) whilst ED durability continued.

6.2.10. Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

The EAG made the changes described in Sections 6.2.1 to 6.2.9. Each change was made individually. The results of the EAG's exploratory analyses are provided in Table 18 (deterministic) and

Table 19 (probabilistic). In each case, to facilitate fully incremental analysis, the comparators are listed in order of increasing cost, which may lead to a change in the ordering of interventions listed. The highest NMB at £20,000 and £30,000 thresholds are highlighted in bold. Deterministic and probabilistic results of the durability threshold analysis are presented in the text below

Table 19. Results presented here include PAS prices for ED and list prices for all IV FIXes. Results including confidential discounts for all treatments are reported in the confidential appendix to this report.

Table 18: Deterministic EAG scenario analyses

Scenario	Section in EAG report	Comparators	Costs	QALYs	ICER	NMB @ £20k	NMB @ £30k
EAG corrected company base case	6.1	ED+mkt share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		ED+Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Section in EAG report	Comparators	Costs	QALYs	ICER	NMB @ £20k	NMB @ £30k
		Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5% FIX activity definition of failure	6.2.2	ED+Refixia	[redacted]	[redacted]		[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 month time to steady state	6.2.4	ED+Refixia	[redacted]	[redacted]		[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility assumptions							
a. Disutility of IV FIX treatment of 0.042	6.2.5	ED+Refixia	[redacted]	[redacted]		[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b. Equal utility in all arms	6.2.5	ED+Refixia	[redacted]	[redacted]		[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
c. ED utility 0.815 for the first 24 months	6.2.5	ED+Refixia	[redacted]	[redacted]		[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Transition probabilities for bleed							
a. Low bleed rates scenario	6.2.6	ED+Refixia	[redacted]	[redacted]		[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b. Moderate bleed rate scenario	6.2.6	ED+Refixia	[redacted]	[redacted]		[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Section in EAG report	Comparators	Costs	QALYs	ICER	NMB @ £20k	NMB @ £30k
		Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
c. Gradual improvement with ED over 24m	6.2.6	ED+Refixia	[redacted]	[redacted]		[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 at admin	6.2.7	ED+Refixia	[redacted]	[redacted]		[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow up visit with haematologist	6.2.8	ED+Refixia	[redacted]	[redacted]		[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adding AE cost and disutility to ED after first year	6.2.9	ED+Refixia	[redacted]	[redacted]		[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse events; EAG, External Assessment Group; ED, etranacogene dezaparvovec; FIX, factor IX; ICER, incremental cost-effectiveness ratio; mkt, market; NMB, net monetary benefit; QALY, quality adjusted life year

Table 19: Probabilistic EAG scenario analyses

Scenario	Section in EAG report	Comparators	Costs	QALYs	ICER	NMB @ £20k	NMB @ £30k
EAG corrected company base case	6.1	ED+mkt share	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		ED+Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Section in EAG report	Comparators	Costs	QALYs	ICER	NMB @ £20k	NMB @ £30k
		Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5% FIX activity definition of failure	6.2.2	ED+Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 month time to steady state	6.2.4	ED+Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Utility assumptions							
a. Disutility of IV FIX treatment of 0.042	6.2.5	ED+Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b. Equal utility in all arms	6.2.5	ED+Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
c. ED utility 0.815 for the first 24 months	6.2.5	ED+Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Transition probabilities for bleed							
a. Low bleed rates scenario	6.2.6	ED+Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
b. Moderate bleed rate scenario	6.2.6	ED+Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Scenario	Section in EAG report	Comparators	Costs	QALYs	ICER	NMB @ £20k	NMB @ £30k
		Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
c. Gradual improvement with ED over 24m	6.2.6	ED+Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 at admin	6.2.7	ED+Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Follow up visit with haematologist	6.2.8	ED+Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adding AE cost and disutility to ED after first year	6.2.9	ED+Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse events; EAG, External Assessment Group; ED, etranacogene dezaparvovec; FIX, factor IX; ICER, incremental cost-effectiveness ratio; mkt, market; NMB, net monetary benefit; QALY, quality adjusted life year

6.2.10.1. Durability threshold analysis results

To perform the threshold analysis, rather than adjusting the durability model used in the company's base case (Shah et al. 2022a & 2022b[17 35]), the EAG assumed a simple 'cliff edge' whereby durability was assumed to persist at 100% (i.e. where no ED patients require prophylactic IV FIX) until n years had elapsed, after which durability dropped to 0% (where all ED patients require prophylactic IV FIX). This represented an optimistic scenario for ED as a gradual decline over a number of years was considered to be more plausible, starting within a few years post administration (as per the Shah et al. extrapolation in the company's base case).

The identified minimum durability should therefore be seen as absolute minima required for ED to be cost-effective. Durability that exceeded this length of time would be regarded as increasing confidence that ED was cost-effective. Full results are reported in Appendix A in this report.

Figure 3 and Figure 4 below show that under the company's base case assumptions, ED durability needs to be maintained for a minimum of 17 to 18 years to yield an ICER below £20,000 and £30,000 (the results are mostly insensitive to varying the WTP threshold between £20,000 and £30,000).

Figure 3: NMB as a function of ED durability (EAG corrected company base case, NMB at £20,000 / QALY)

Figure shows net monetary benefit of each of the five comparators as a function of durability of ED. The vertical line identifies the point where ED yields the highest net monetary benefit at a WTP threshold of £20,000 per QALY.

Figure 4: NMB as a function of ED durability (EAG corrected company base case NMB at £30,000 / QALY)

Figure shows net monetary benefit of each of the five comparators as a function of durability of ED. The vertical line identifies the point where ED yields the highest net monetary benefit at a WTP threshold of £30,000 per QALY.

6.3. EAG's preferred assumptions

The EAG preferred deterministic and probabilistic base case ICERs are provided in Table 20 and Table 21. Incremental costs including comparator PAS prices are provided in the confidential appendix to this report.

Table 20: EAG's deterministic preferred model assumptions

Preferred assumption	Section in EAG report	Comparators	Costs	QALYs	ICERs	ICER change from base case	NMB @ £20k	NMB @ £30k
EAG corrected company base case (excl. ED+mkt share)	6.1	ED+Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
EAG preferred base case assumptions								
5% FIX activity definition of failure	6.2.2	ED+Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
6 month time to steady state	6.2.4	ED+Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Disutility of IV FIX	6.2.5	ED+Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]

treatment of 0.042		Alprolix	[redacted]					
		Idelvion	[redacted]					
		Refixia	[redacted]					
Adding AE cost and disutility to ED after first year	6.2.9	ED+Refixia	[redacted]					
		BeneFIX	[redacted]					
		Alprolix	[redacted]					
		Idelvion	[redacted]					
		Refixia	[redacted]					
Cumulative		ED+Refixia	[redacted]					
		BeneFIX	[redacted]					
		Alprolix	[redacted]					
		Idelvion	[redacted]					
		Refixia	[redacted]					

Abbreviations: AE, adverse events; EAG, External Assessment Group; ED, etranacogene dezaparvovec; ICER, incremental cost-effectiveness ratio; mkt, market; NMB, net monetary benefit; QALY, quality adjusted life year

Table 21: EAG's probabilistic preferred model assumptions

Preferred assumption	Section in EAG report	Comparators	Costs	QALYs	ICERs	ICER change from base case	NMB @ £20k	NMB @ £30k
EAG corrected company base case (excl. ED+mkt share)	6.1	ED+Refixia	[redacted]					
		BeneFIX	[redacted]					
		Alprolix	[redacted]					
		Idelvion	[redacted]					
		Refixia	[redacted]					
EAG preferred base case assumptions								
5% FIX activity definition of failure	6.2.2	ED+Refixia	[redacted]					
		BeneFIX	[redacted]					
		Alprolix	[redacted]					
		Idelvion	[redacted]					
		Refixia	[redacted]					
6m time to steady state	6.2.4	ED+Refixia	[redacted]					
		BeneFIX	[redacted]					
		Alprolix	[redacted]					
		Idelvion	[redacted]					

		Refixia	[redacted]					
Disutility of IV FIX treatment of 0.042	6.2.5	ED+Refixia	[redacted]					
		BeneFIX	[redacted]					
		Alprolix	[redacted]					
		Idelvion	[redacted]					
		Refixia	[redacted]					
Adding AE cost and disutility to ED after first year	6.2.9	ED+Refixia	[redacted]					
		BeneFIX	[redacted]					
		Alprolix	[redacted]					
		Idelvion	[redacted]					
		Refixia	[redacted]					
Cumulative		ED+Refixia	[redacted]					
		BeneFIX	[redacted]					
		Alprolix	[redacted]					
		Idelvion	[redacted]					
		Refixia	[redacted]					

Abbreviations: AE, adverse events; EAG, External Assessment Group; ED, etranacogene dezaparvovec; ICER, incremental cost-effectiveness ratio; mkt, market; NMB, net monetary benefit; QALY, quality adjusted life year

6.3.1. Durability threshold analysis around EAG's preferred base case

Figure 5 and Figure 6 below show that under the EAG's preferred base case assumptions, ED durability needs to be maintained at 100% for a minimum of 18-19 years to yield an ICER below £20,000 and £30,000 (the results are mostly insensitive to varying the WTP threshold between £20,000 and £30,000).

Figure 5: NMB as a function of ED durability (EAG base case, NMB at £20,000 / QALY)

Figure shows net monetary benefit of each of the five comparators as a function of durability of ED. The vertical line identifies the point where ED yields the highest net monetary benefit at a WTP threshold of £20,000 per QALY.

Figure 6: NMB as a function of ED durability (EAG base case NMB at £30,000 / QALY)

Figure shows net monetary benefit of each of the five comparators as a function of durability of ED. The vertical line identifies the point where ED yields the highest net monetary benefit at a WTP threshold of £30,000 per QALY.

6.4. Conclusions of the cost-effectiveness section

The EAG considered that the overall methodological approach used by the company in its analysis was mostly sound. However, several of its base case assumptions were unduly optimistic, and the analysis was severely limited by the quantity and quality of data available (in part, a consequence of the rarity of the disease) and the short follow-up period (which will be resolved by time). Individually the EAG's exploratory analyses did not alter the conclusions of the model and ED dominated all FIX replacement treatments. However, the EAG analyses demonstrated that the cost effectiveness of ED depended largely on assumptions concerning the durability of its effect. The EAG did not consider that the Shah analysis provided by the company was a reliable source of evidence for durability, given the lack of available data, and therefore the cost effectiveness of ED depended almost entirely upon conjecture about long-term durability. Relatedly, the definition of treatment failure in the model, which informed assumptions concerning treatment costs and utilities, also influenced cost effectiveness. Results varied substantially with the results of analyses including the confidential comparator prices (included in the confidential appendix to this report), though durability assumptions remained a significant issue.

7. QALY MODIFIER

The company stated that there was no excess mortality for people with haemophilia B and therefore the technology did not meet the criteria for the severity modifier (CS B.3.6, p166).

References

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Appendix A: Threshold analysis on durability of ED

This appendix shows the full results of the threshold analysis presented in Figure 3: NMB as a function of ED durability (EAG corrected company base case, NMB at £20,000 / QALY)Figure 3 to Figure 6, showing how the cost-effectiveness of ED and its comparators varies with assumptions over the durability of ED (presented as net monetary benefit, NMB). The durability function assumed for this analysis was a 'cliff-edge' function, whereby 100% durability was assumed until year n, dropping instantly to 0% the following year. It is thus an approximation of a more plausible gradual tailing off of durability. The EAG adopted this approach to avoid assuming a specific parametric form for the durability function.

Table 22 shows the NMB of the four IV FIXes at £20,000 and £30,000 per QALY gained. These do not change as durability of ED changes. Table 23 shows how the cost and QALYs gained with ED change as the durability of ED increased. The option with the highest NMB ('winner') is mathematically identical to identifying the most cost-effective option with an ICER below the threshold taking account of dominance and extended dominance.

The same data are shown in Table 24 and Table 25 for the EAG-preferred base case.

Table 22: Net Monetary benefit for IV FIXes at £20,000 and £30,000/QALY thresholds (deterministic, EAG corrected company base case, ED PAS discount)

IV FIX	NMB @ £20,000 / QALY	NMB @ £30,000 / QALY
Benefix	[redacted]	[redacted]
Alprolix	[redacted]	[redacted]
Idelvion	[redacted]	[redacted]
Refixia	[redacted]	[redacted]

Table 23: Threshold analysis varying durability of ED (deterministic, EAG corrected company base case, ED PAS discount)

	ED+Refixia		NMB (£20,000/QALY)			NMB (£30,000/QALY)		
Years	**£**	**QALY**	**ED**	**Max**	**Winner**	**ED**	**Max**	**Winner**
1	[redacted]	[redacted]	[redacted]	[redacted]	Benefix	[redacted]	[redacted]	Benefix
2					Benefix			Benefix
3					Benefix			Benefix

4	[redacted]	[redacted]	[redacted]	[redacted]	Benefix	[redacted]	Benefix
5					Benefix		Benefix
6					Benefix		Benefix
7					Benefix		Benefix
8					Benefix		Benefix
9					Benefix		Benefix
10					Benefix		Benefix
11					Benefix		Benefix
12					Benefix		Benefix
13					Benefix		Benefix
14					Benefix		Benefix
15					Benefix		Benefix
16					Benefix		Benefix
17					Benefix		Benefix
18					ED		ED
19					ED		ED
20					ED		ED
21					ED		ED
22					ED		ED
23					ED		ED
24					ED		ED
25					ED		ED
26					ED		ED
27					ED		ED
28					ED		ED
29					ED		ED
30					ED		ED
31					ED		ED
32					ED		ED
33					ED		ED
34					ED		ED
35					ED		ED
36					ED		ED
37					ED		ED
38					ED		ED
39					ED		ED
40					ED		ED
41					ED		ED
42					ED		ED
43					ED		ED
44					ED		ED
45					ED		ED
46					ED		ED
47					ED		ED
48					ED		ED
49					ED		ED
50					ED		ED

Table 24: Net Monetary benefit for IV FIXes at £20,000 and £30,000/QALY thresholds (deterministic, EAG preferred base case, ED PAS discount)

IV FIX	NMB @ £20,000 / QALY	NMB @ £30,000 / QALY
Benefix	[redacted]	[redacted]
Alprolix	[redacted]	[redacted]
Idelvion	[redacted]	[redacted]
Refixia	[redacted]	[redacted]

Table 25: Threshold analysis varying durability of ED (deterministic, EAG preferred base case, ED PAS discount)

	ED+Refixia		NMB (£20,000/QALY)			NMB (£30,000/QALY)		
Years	£	QALY	ED	Max	Winner	ED	Max	Winner
1	[redacted]	[redacted]	[redacted]	[redacted]	Benefix	[redacted]	[redacted]	Benefix
2					Benefix			Benefix
3		[redacted]	[redacted]	[redacted]	Benefix	[redacted]	[redacted]	Benefix
4					Benefix			Benefix
5	[redacted]	[redacted]	[redacted]	[redacted]	Benefix	[redacted]	[redacted]	Benefix
6					Benefix			Benefix
7	[redacted]	[redacted]	[redacted]	[redacted]	Benefix	[redacted]	[redacted]	Benefix
8					Benefix			Benefix
9	[redacted]	[redacted]	[redacted]	[redacted]	Benefix	[redacted]	[redacted]	Benefix
10					Benefix			Benefix
11	[redacted]	[redacted]	[redacted]	[redacted]	Benefix	[redacted]	[redacted]	Benefix
12					Benefix			Benefix
13	[redacted]	[redacted]	[redacted]	[redacted]	Benefix	[redacted]	[redacted]	Benefix
14					Benefix			Benefix
15					Benefix			Benefix
16					Benefix			Benefix
17					Benefix			Benefix
18					Benefix			Benefix
19					ED			ED
20					ED			ED
21					ED			ED
22					ED			ED
23					ED			ED
24					ED			ED
25					ED			ED
26					ED			ED
27					ED			ED
28					ED			ED

29	[redacted]				ED	[redacted]		ED
30					ED			ED
31					ED			ED
32					ED			ED
33					ED			ED
34					ED			ED
35					ED			ED
36					ED			ED
37					ED			ED
38					ED			ED
39					ED			ED
40					ED			ED
41					ED			ED
42					ED			ED
43					ED			ED
44					ED			ED
45					ED			ED
46					ED			ED
47					ED			ED
48					ED			ED
49					ED			ED
50					ED			ED

Single Technology Appraisal

Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B [ID3812]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 14 April 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Misleading inclusion of on-demand treatment since prophylaxis is the relevant comparator

Description of problem	Description of proposed amendment	Company justification for amendment	EAG response
Page 15, Key Issue 3 table, column 2, row 2, line 16 — misleading market share proportion	Please replace: The findings were most unreliable for BeneFIX, which [redacted] (Adivo report [data on file]). with the following: The findings were most unreliable for BeneFIX, which [redacted] (Adivo report [data on file]).	The report describes BeneFIX as [redacted] FIX replacement treatment option and references an Adivo prophylactic market share report. However, this is incorrect as Adivo data during this time period reported BeneFIX to be the least commonly used FIX prophylaxis product out of those considered in the evidence submission (ALPROLIX, IDELVION, Refixia, BeneFIX). The provided comparative evidence with etranacogene dezaparvovec (ED) considered treatments for prophylaxis only, not on-demand options, therefore only prophylaxis treatments	The EAG are puzzled by this issue raised by the company, as the graph in the Adivo report (p.5) provided by the company clearly shows that BeneFIX was [redacted] as correctly stated by the EAG in its report. The data in the Adivo report does not differentiate between prophylactic and on demand FIX replacement, and therefore the EAG is unable to determine if the company's proposed correction is factually correct. The EAG have therefore not made this amendment.

		should be considered when discussing market share based on the Adivo report.	
Pages 24–25, column 5, row 2, paragraph 2, lines 1–3 — lack of clarity on FIX replacement options	Please replace: Nearly half of participants in HOPE-B were receiving standard-life FIX replacement at baseline. with the following: Nearly half of participants in HOPE-B were receiving standard-life FIX replacement for prophylaxis at baseline.	Improve clarity of Factor IX replacement use as prophylaxis or on-demand, considering that the former is relevant for this appraisal.	The EAG agrees that this amendment would improve clarity and has made the proposed change (p.24).
Page 36, second bullet point, lines 2–5 — misleading market share proportion	Please clarify whether use refers to prophylaxis or on-demand treatment: Clinical advice to the EAG was that at the time of the HOPE-B study, standard half-life products were the most commonly used treatment though this may not be representative of current practice as more people in the NHS are now receiving the longer acting therapies.	Improve clarity of Factor IX replacement use as prophylaxis or on-demand, considering that the former is relevant for this appraisal.	As above, the EAG agrees and has made the proposed amendment (p.35).

Page 45, paragraph 1, lines 4–5	Please add: ED treatment was associated with a significant decrease (by 96%) in mean unadjusted annualised Factor IX consumption (prophylaxis therapy plus on-demand use) at Month 24 post dose, compared with the 6-month lead-in period. after following statement: By the time of the final follow-up (months 19-24), 24.5% of participants were receiving FIX replacement, each receiving a mean of 3.2 infusions.	As per before.	This is not a factual inaccuracy and no amendment has been made to the EAG report.

Issue 2 Missing data sources

Description of problem	Description of proposed amendment	Company justification for amendment	EAG response
Page 20, bullet point 3, lines 3–5 — missing evidence provided	In addition to the two studies mentioned (references 3. Burke et al., 2021 and 4. O'Hara et al., 2017) cited for carers' financial expenses, the submission also referenced the following two studies:	Amendment for completeness	Thank you for raising this, we have noted the two additional studies (p.20)

	• Schwartz CE, Stark RB, Michael W, Rapkin BD. Understanding haemophilia caregiver burden: does appraisal buffer the impact of haemophilia on caregivers over time? Psychol Health. 2020;35(12):1516-1530. • Cutter S, Molter D, Dunn S, et al. Impact of mild to severe hemophilia on education and work by US men, women, and caregivers of children with hemophilia B: The Bridging Hemophilia B Experiences, Results and Opportunities into Solutions (B-HERO-S) study. Eur J Haematol. 2017;98 Suppl 86:18-24.		

Issue 3 Licensed indication now confirmed following granted marketing authorisation

Description of problem	Description of proposed amendment	Company justification for amendment	EAG response
Page 21, paragraph 3, lines 6–9	Please consider removing the following statement: ED was awaiting a licence for use in England and it was yet unclear whether the licence would restrict	At the time of submission, ED was not licensed; however, its conditional GB market authorisation was granted on the 22 March 2023 for the	Thank you for raising this. The MHRA licence was released in the final days before submission of the EAG report, and

	use of ED to those meeting the HOPE-B eligibility criteria. If not, the EAG noted that the number of people in England eligible to receive ED may be up to [redacted].	treatment of severe and moderately severe haemophilia B (congenital Factor IX deficiency) in adult patients without a history of Factor IX inhibitors (Summary of Product Characteristics available here). This is aligned with the information provided in the submitted Appendix L, in which the company noted that the marketing authorisation was expected to be granted in March 2023.	was missed during preparation. We have amended the text as suggested (p.21).
Page 22, Section 2.4, lines 2–4 — licence now confirmed	Please consider replacing: As the final product licence for ED was not confirmed, there was some uncertainty about whether the population in the key study for ED (HOPE-B) was representative of the target population. with the following: The approved product licence for ED aligns with the population in the key study for ED (HOPE-B),	As per above.	We have amended the text to reflect the new product licence (p.22).

	meaning the trial patients were representative of the target population.		
Page 23, Table 4, column 5, row 2, paragraph 2, lines 1–2 — licence now confirmed	Please consider removing the following statement: The final product licence for ED was not yet determined, and therefore it was unclear whether certain population exclusion criteria used in the HOPE-B study will be applied. If not, then the EAG considered that treatment outcomes reported in the study may not generalise to those who were excluded from the study, e.g. those with liver conditions and those requiring chronic corticosteroid treatment.	As per above.	We have removed this text (p.23).
Page 26, column 5, row 2, lines 1–3 — licence now confirmed	Please consider replacing: The approved product ED had received CMA by the EMA but did not currently hold a licence for use in the UK. with the following: The approved product ED had received CMA by the EMA and,	As per above.	We have amended the text (p.26)

	more recently, from the MHRA for use in the UK.		

Issue 4 Lack of clarity that ED will be used as a single-dose, standalone treatment

Description of problem	Description of proposed amendment	Company justification for amendment	EAG response
Page 22, lines 4–6 — statement implies concomitant use of standard of care with ED	Please remove 'as required and' in the following statement: The EAG also clarified that ED was intended to be delivered alongside standard care, which would include routine prophylactic FIX replacement ~~as required and~~ if/when the treatment effect of ED wanes.	ED is indicated as a single-dose, standalone treatment and prophylactic FIX replacement treatment should only be used if treatment effect wanes.	Thank you for raising this point. In its report the EAG have raised the possibility that some people who receive ED may continue to receive prophylactic FIX replacement treatment depending on their response to treatment. The EAG have modified this text to differentiate between prophylactic FIX replacement that may be needed if/when the effect of ED wanes, on-demand FIX replacement, and prophylactic FIX replacement that may

			continue to be used in some people (p.22).
Page 24, column 5, row 1, lines 1–7 — statement implies concomitant use of standard of care with ED	Please replace: The company's evidence was consistent with the NICE scope and decision problem for this appraisal, though the EAG noted that ED would be administered in conjunction with standard care, including Factor IX (FIX) replacement therapy (the comparator). with the following: The company's evidence was consistent with the NICE scope and decision problem for this appraisal, though the EAG noted that, if/when the effect of ED wanes, patients would be treated with standard care, including Factor IX (FIX) replacement therapy (the comparator).	As per before.	This is not a factual inaccuracy and no change has been made. As stated in this section of the table (p.24) the details of how FIX replacement was expected to be used alongside ED was discussed in a different section of the report (Section 3.2.2.3).

Issue 5 Incorrect thresholds and values for patient population and safety results

Description of problem	Description of proposed amendment	Company justification for amendment	EAG response
Page 40, 2nd bullet point, line 5 — missing less than sign	Replace '(i.e. 1% of normal activity for those with diagnosed severe disease).' with '(i.e. <1% of normal activity for those with diagnosed severe disease).'	Amendment for correctness	Thank you, we have added this
Page 40, 3rd bullet point, line 1 — incorrect less-than-or-equal-to sign	Replace '…participants with FIX levels ≤12%.' with '…participants with FIX levels <12%.'	Amendment for correctness	Thank you, we have amended this
Page 48, Section Treatment-related adverse events, line 3 — incorrect relative value of adverse events	Remove percentage within brackets as not associated with the absolute value provided	Amendment for correctness	This is not a factual inaccuracy. Of 557 adverse events reported following treatment with ED, 93 were considered by the investigator to be related to ED (as reported in the CS p.118). The % reported is therefore correct (16.7%).
Page 48, Section Treatment-related adverse events, line 4 —	Replace ratio of '28/54' with '38/54'	Amendment for correctness	Thank you, we have amended this

incorrect number of patients reporting treatment-related adverse events			

Issue 6 HE modelling factual inaccuracies

Description of problem	Description of proposed amendment	Company justification for amendment	EAG response
On page 68, it is stated that "Additionally, the company presented administrative costs per bleed of £1.26 for Refixia and £0 for other therapies. The company stated that the costs did not include home delivery costs as the treatment would be delivered in a clinical setting. The EAG considered that it was unlikely that administration costs for treatments administered in a clinical setting would be £0, unless costs such as staff costs for administration were accounted for elsewhere, but the incorporation of these was unclear. Low	[remove the paragraph]	The administrative cost of £1.26 and £0 are not a cost per bleed event but per standard prophylaxis treatment injection, which is taken 1-2 times a week, depending on the comparator. These administrations, which occur in absence of bleeds, indeed would be taken in home, and are hence have the low cost. The comment regarding the lack of home delivery cost is valid, but refers not towards the aforementioned pre-scheduled & standard FIX prophylaxis injection costs, but it was made in reference to the administration cost in case of a bleed, which due to	We thank the company for this clarification. We have deleted the paragraph.

administrative costs per bleed event we considered likely to lead to an underestimation of the costs of ED in the model."		its emergency nature would take place in a hospital. Therefore, the administrative cost of a standard injection which is self-administered in home is low as it should be, and the lack of the delivery cost is not relevant to home administrations, making the whole paragraph no longer relevant.	
Page 68-69 "The EAG noted that the company did not make an argument for inclusion of these costs within its base case thus the EAG did not comment further.	[remove the paragraph]/provide a commentary on excluding it from the base case analysis, as being in accordance with the NICE reference case.	We did argue for the importance of the inclusion of these costs as a scenario analysis. We did not argue on the inclusion of these costs within the base case as this would be a departure from the perspective of the NICE reference case. (See section 4.4.22 of NICE methods and guidance (2022)).	We thank the company for this correction. We have edited the text commenting on the results of the scenario analysis.

Issue 7 Typographical errors

Description of problem	Description of proposed amendment	Company justification for amendment	EAG response
Page 18, Table 3 and throughout — inconsistent spelling of drug name	Replace 'Benefix' with 'BeneFIX' in table and throughout the document as per drug name	Consistency in spelling of brand name	Thank you, we have made amendments on the following pages: 68, 73, 77 - 81, 84 – 86.
Page 19, Section 2.1, paragraph 1, line 3 and throughout — inconsistent use of 'and' in treatment of severe and moderately severe haemophilia B.	Replace with '…severe or moderately severe haemophilia B' consistently as per appraisal title	Consistency with terminology referring to patient population	This is not a factual inaccuracy. The EAG considers the inclusion of both severity groups to be implicit in either use.
Page 20, paragraph 2, line 4 — incorrect use of 'there'	Replace 'there' with 'their'	Minor amendment for correctness	Thank you, we have amended this.
Page 23, Table 4, column 5, row 2, **&** page 31, Section 3.2.2.1, paragraph 1, line 3 — incorrect use of term 'principle' **&** page 39, Section 3.2.2.5, paragraph 1, line 5	Replace 'principle' with 'principal'	Minor amendment for correctness	Thank you, we have amended this.

Page 31, Section 3.2.2.1, paragraph 2, lines 2, 3 and 5 **&** page 32, paragraph 2, line 2 — incorrect use of apostrophe	Remove apostrophe in term *years* in *up to five years of follow-up* & in *months* in *6 months of follow up*	Minor amendment for correctness	Thank you, we have amended this
Page 31, Section 3.2.2.1, paragraph 2, line 2 — inconsistent spelling of numerical values across the document	Use Arabic number in 'While up to 5 years…'	Minor amendment for consistency	This is not a factual inaccuracy. Typically, it is convention for the EAG to use Arabic numbers for numerical values ≥10 and text for those <10. The exception to this is where multiple numbers are reported in the same sentence, in which case a consistent approach is taken.
Page 37, Section 3.2.2.3, paragraph 2, line 5 — incorrect verb form	Replace 'was' with 'were' in 'The same dose and administration were used in study…'	Minor amendment for correctness	Thank you, we have amended this.
Page 42, Section 3.2.3.1, paragraph 1, lines 5 **&** 8 **&** page 46, Section 3.2.3.2, line 7 — incorrect	Replace 'Nab' with 'NAb' as abbreviated form of neutralising antibody **&** replace 'Cis' with 'CIs' as abbreviated form of confidential intervals.	Minor amendment for correctness	Thank you, we have amended one instance on p.41 and one on page 48 (section 3.2.2.3).

capitalisation in abbreviations			
Pages 42–43, Table 8 — use of abbreviation not spelled out	Replace ‘ppl’ (3×) with ‘people’ or introduce abbreviation in full	Minor amendment for clarity and consistency	We have amended this.
Pages 43, Section: FIX levels, paragraph 3, line 1 — misspelled word	Replace ‘propylactic’ with ‘prophylactic’	Minor amendment for correctness	Thank you, we have amended this
Page 46, paragraph 1, line 13 — duplication	Remove duplicated ‘to go’ in ‘…ED felt more able to go ~~to go~~ school/work…’	Minor amendment for correctness	We have removed the extra “go” only; i.e. “to go to school/work” (p.45).
Page 53, Section 3.4.2, paragraph 1, line 4 — misspelled abbreviation	Replace ‘HRWoL’ with ‘HRQoL’	Minor amendment for correctness	Thank you, we have amended this (p.52).

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**	**EAG response**
AIC in Section 3 and subsections.	HOPE-B results have now been published (DOI: 10.1056/NEJMoa2211644).	Suggest removing AIC marking on Section 3. This is aligned with the information provided in the submitted Appendix L, in which the company noted that a publication was expected in February 2023.	Thank you, we have removed all AIC marking in Section 3 and its subsections, except where specifically requested not to in

			items below. This has resulted in changes to the following pages: p.39, 41-42, 43, 44, 45, 46, 47, 48, 49, 53, 56
ID3812 Etranacogene EAG report 05042023KM [ACIC].docx, page 42, Section 3.2.3.1 — missing academic-in-confidence highlight and underlined information.	Please highlight the number of people experiencing bleeds prior to the treatment of etranacogene dezaparvovec.	The number of people experiencing bleeds (any bleed) also reduced following the treatment with ED, from [redacted] during the lead in phase to [redacted] during months 7-18 and [redacted] for months 7-24.	These values have AIC marking.
ID3812 Etranacogene EAG report 05042023KM [ACIC].docx, page 63, Section 4.2.6.1 — missing academic-in-confidence highlight on underlined information	Please highlight the etranacogene dezaparvovec median years post treatment Factor IX levels >2% from the Bayesian and Frequentist linear mixed model's additional analyses.	The company stated that the median durability of ED was [redacted]-years (CS B p150) on the basis of modelled projections (Shah 2022a & 2022b15 33), although the EAG noted this is a presumed typographical error as the median stated in Shah et al. was [redacted] years.	This AIC marking has been added
ID3812 Etranacogene EAG report 05042023KM [ACIC].docx, page 77, Section 6.2.3 — missing	Please highlight the etranacogene dezaparvovec median years post treatment Factor IX levels >2% from the	The company's base case assumed a median durability of [redacted]years (reported in the CS as	AIC marking has been added

academic-in-confidence highlight on underlined information	Bayesian and Frequentist linear mixed model's additional analyses:	[redacted] years), based on a definition of failure of 2% FIX activity levels.	
ID3812 Etranacogene EAG report 05042023KM [ACIC].docx, page 78, Section 6.2.5 — missing academic-in-confidence highlight on underlined information	Please highlight the EAG calculated utility value from the additional scenario as well as the definition.	Hence, the EAG calculated an additional scenario (c) setting utility equal to [redacted] for the first 24 months, [redacted].	AIC marking has been added to the value. AIC marking was already applied to the definition.
ID3812 Etranacogene EAG report 05042023KM [ACIC].docx, Appendix A, page 94, Table 22 — missing commercial in confidence highlight on underlined information	Please highlight the calculated net monetary benefit values with PAS of the EAG corrected company base case.	**IV FIX** / **NMB @ £20,000 / QALY** / **NMB @ £30,000 / QALY** **BeneFIX** [redacted] **Alprolix** [redacted] **Idelvion** [redacted] **Refixia** [redacted]	This has been added.
ID3812 Etranacogene EAG report 05042023KM [ACIC]. docx, Appendix A, Page 96, Table 24 — missing commercial in	Please highlight the calculated net monetary benefit values with PAS of the EAG preferred base case.	**IV FIX** / **NMB @ £20,000 / QALY** / **NMB @ £30,000 / QALY** **BeneFIX** [redacted] **Alprolix** [redacted]	This has been added.

confidence highlight on underlined information		**Idelvion** [redacted] [redacted] **Refixia** [redacted] [redacted]	

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B [ID3812]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **25 May 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	**Dan Betts**
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	**CSL Behring UK Ltd**
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	**N/A**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**N/A**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: The company did not report evidence for the true change in FIX levels following treatment with ED in the HOPE-B	No	Due to the nature of the disease in question, it is not deemed ethical to perform a placebo-controlled trial since no relevant active comparators exist, the trial was designed as an open-label and uncontrolled trial. Moreover, since patients with the same severity of haemophilia often have very different bleeding phenotypes, the best comparator to etranacogene dezaparvovec was deemed to be the same patient receiving current standard of care as to minimise variables (as is seen during the lead-in phase). As such it is not the standard practice in haemophilia research methodology to have randomised controlled trials. The exact FIX levels during the lead-in phase were not provided as these are dependent on several factors, including: • the type and brand of FIX replacement therapy used; • the individual dose and frequency of administration of the FIX replacement therapy; • the timing of the measurement of FIX levels in relation to the patients' dosing regimen – troughs and peaks of FIX levels are patient-specific, making standardisation of sample collection/measurements and comparisons between patients challenging and inaccurate. Moreover, if the

		sample is collected prior to completing the wash-out period of FIX replacement products (3 days for SHL and 10 days for EHL products), the sample would be contaminated with the FIX replacement products and not deemed accurate. It is worth noting that etranacogene dezaparvovec aims to replace FIX replacement therapy, rather than be used in addition to current standard of care. A major benefit of etranacogene dezaparvovec would be reducing the peaks and troughs and having more stable FIX expression due to endogenous production. Therefore, the efficacy of etranacogene dezaparvovec was compared to patients' baseline FIX level as this reflects their endogenous FIX production and would avoid fluctuating FIX levels due to the prophylaxis administered during the lead-in phase.
Key issue 2: Clinical outcomes in the HOPE-B study may overstate the potential benefits of ED	No	The EAG posed that COVID-19 lockdowns could have impacted the degree of physical activity of patients and hereby the number of bleeds and use of prophylaxis they required in this period (potentially affecting the impact of HOPE-B outcomes). However, measurements from Patient Reported Outcomes (PRO) during the HOPE-B trial suggest that there were no significant changes in physical activity of patients. The iPAQ PRO assesses physical activity undertaken across a comprehensive set of domains including leisure time, domestic and gardening (yard) activities, and work- and transport-related activity. The short form was used which was designed to provide an evaluation of daily physical activities and assessed the time spent sitting, walking, doing moderate- and vigorous intensity activity within the domains of work, transportation, domestic and gardening (yard) activities, and leisure-related activities in metabolic equivalent of task (MET) minutes/week. If COVID-19 would have had an impact on patient activities, we would expect to have seen a change in iPAQ score. However, no significant changes were observed during the first 12 months post-treatment in HOPE-B trial.

		Additionally, FIX replacement consumption has remained substantially reduced up to 24 months post-treatment. If COVID-19 would have impacted patient activity levels, coming out of lockdown would have resulted in an increase of activity and thus more bleeds and factor consumption, which is not the case. Importantly, ABR (all bleeds) and specifically spontaneous ABRs are reduced from baseline to Month 7–18 post-treatment; spontaneous bleeds are not related to activity or trauma but rather are impacted by circulating FIX levels. This indicates that any reduction in ABRs would not be due to a change in activity levels due to COVID-19. Moreover, this reduction in ABR was sustained at 24 months post-treatment, further indicating that the clinical outcomes of HOPE-B were not impacted by COVID-19 lockdowns. The absence of a rebound rise in FIX consumption and ABR between Months 18–24 compared to Months 7–18 suggests that the effects of COVID-19 was not a significant confounder. CSL Behring disagrees with the issue raised, that study investigators may have felt restricted by the study protocol when making treatment decisions on management of bleeding event. CSL Behring validated this with the UK principal investigators of the HOPE-B trial, who confirmed that they followed usual bleed management principles in line with Good Clinical and Research Practice.
Key issue 3: Comparative efficacy estimates of ED and prophylactic FIX treatments were unreliable	Yes	As there were no head-to-head comparisons of different FIX therapies, and most comparative studies compare prophylactic vs. on-demand treatment, the decision was made to perform an ITC with prophylactic treatments currently used in clinical practice. As noted by the EAG the methods used for the ITC were the best available.

		The EAG report states that '*the report findings were the most unreliable for BeneFIX, which was the most commonly used FIX replacement treatment in the UK in 2019 and 2020*'. However, this is not quite correct. The UKHCDO Annual Report (2020), on which we assume the statement in the EAG report was based, combines the use of prophylaxis and on-demand FIX replacement treatment and does not differentiate between the two uses. A report from ADIVO Associates presenting the use of FIX in the UK differentiated by prophylaxis vs on-demand use, is shown in Appendix A. This report shows that, compared to all comparators used in the ITC, BeneFIX is the least commonly used prophylactic product. Citation: UKHCDO Annual Report, 2020. http://www.ukhcdo.org/wp-content/uploads/2021/03/UKHCDO-Annual-Report-2020-2019-20-Data_FINAL.pdf ADIVO FIX market tracking: UK Q3 2020 (Appendix A)
Key issue 4: Definition of treatment failure was at a low FIX activity level	Yes	The definition of treatment failure (the FIX level at which prophylactic treatment would need to be provided) was discussed with eight clinical experts Haemophilia Comprehensive Care Centre Clinical Directors from across the NHS at the CSL Behring November 2022 advisory board. All had direct haemophilia gene therapy experience. The advisory board was conducted in line with ABPI & PMCPA guidance. The aim of the advisory board was to understand and seek alignment on the assumptions, structure, and inputs for the current economic cost-effectiveness model of etranacogene dezaparvovec. Invitations were sent to haemophilia centre directors in England, Scotland, and Wales, of which eight accepted the invitation to attend. Pre-reads, discussion guide and the PowerPoint slide deck from the advisory board are included in Appendix B. The advisory board summary also now contains unredacted names of those participants that we have been able to contact within the technical engagement timelines for consent. The advisors discussed what a clinically significant response post gene therapy is defined as and concluded that this should be a factor level expression that stops the need for prophylaxis without any spontaneous bleeding. Compared to

		prophylaxis (which is exogenous factor replacement), gene therapy results in endogenous factor expression therefore levels required are different for starting versus stopping prophylaxis. Factor assays also have limitations as they are only capable of measuring circulating factor levels and additional factor may be available in the extravascular space. Reinitiating prophylaxis post gene therapy is a composite decision comprising bleeding symptoms, factor level and patient preference. Need to restart prophylaxis would be viewed as treatment failure and the clinical experts agreed that a FIX activity level of 2% would define this. This value was used to inform the cost-effectiveness model. Although protocol allowed for continuous use while patients' factor levels remained below 5%, none of the responders (n=52) in the HOPE-B trial required prophylaxis. Following the technical engagement call advisory board participants have restated their support of the consensus document and given consent for the following part of the transcript to be shared: *"I'm not sure we are trying for more than 2% of trough levels. So I feel that and I don't think that once the patients are on gene therapy and let's assume they get a level of 10% or 20%, they're unlikely to start prophylaxis unless they drop to 2% and start seeing bleeds. I think getting patients to do regular infusions, in the absence of bleeds is next impossible and that's the key point think it is because the factor nine behaves like wild type factor 9 in terms of the extravascular distribution and XYZ. So in some ways it is very difficult to understand.* *What does the plasma level mean in the context of a part of a variant? How much of the actual factor 9 is floating outside in the extravascular space? So it may be that it although the plasma level is only 2 to 3% that it is quite effective. I can't see a patient if they have got a level of 2% and had no bleeds for over the 12 month period accepting to go on prophylaxis."*

Key issue 5: The durability extrapolation model was based on limited data and excluded non-responders	Yes	CSL Behring agrees that, when exploring the durability of a long-acting treatment such as etranacogene dezaparvovec, a level of uncertainty will remain. It should be noted, however, that this uncertainty is inherent and common to all novel advanced therapy medicinal products that have the potential to remain effective for an extended time (in the range of decades). Therefore, the most appropriate methodology to reduce this uncertainty has been established and applied in this submission: • The longest available trial data with etranacogene dezaparvovec should be utilised, as was included in the initial submission with the inclusion of AMT-061-01. To provide further long-term durability evidence, 6-year follow-up data with the AMT-060 product (the AMT-060-01 trial), which have become available since the submission date, are available in Appendix C. The data shows that there is no waning of the treatment effectiveness of AMT-060, further supporting longevity of treatment duration of etranacogene dezaparvovec due to the similarity in products. • Predictions of long-term treatment effect should be made (beyond currently available data) to inform the cost-effectiveness model. The statistical analysis by Shah et al. (2022), which is based on the longest follow-up data available at the time of the initial submission, provides this. While CSL Behring agree that, fundamentally, any statistical extrapolation is uncertain, it should be noted that the EAG did not criticise the validity of the extrapolation used, with the exception of the exclusion criteria. As stated in Shah et al. (2022), “two participants were excluded from the analysis, one participant received only a partial dose of etranacogene dezaparvovec, the other participant had a notably high AAV5 neutralising antibody (NAb) titre of 3212”. • The exclusion of the patient who received a partial dose is suitable, as it would not be appropriate to evaluate the effectiveness of etranacogene dezaparvovec based on a dose that is not in the anticipated marketing authorisation.

		• The exclusion of the patient with a notably high AAV5 NAb titre is appropriate as the SmPC for etranacogene dezaparvovec states baseline assessment of pre-existing neutralising AAV5 antibody titre should be performed and that 'pre-existing antibodies above a titre of 1:678 may impede transgene expression at desired therapeutic levels and thus reduce the efficacy of therapy'. The high titre patient would not receive commercial product, and this can be reflected in the final appraisal determination. It is important to note that only 1 out of 54 patients in the HOPE-B trial presented with an AAV5 NAb titre >1:3000, which suggests that this cut-off will likely affect a small minority of the potential recipients of etranacogene dezaparvovec. • Clinical experts should be consulted to assess their expert opinion on the extrapolated data. The use of this extrapolation in the cost-effectiveness model (by Shah et al. [2022]) was validated by eight clinical experts from Haemophilia Comprehensive Care Centre Clinical Directors across the NHS at the November 2022 CSL Behring advisory board. Therefore, while CSL Behring acknowledges that uncertainty around the durability of the treatment remains, the best practices were followed in the derivation of the durability data. Therefore, the uncertainty has been decreased to the lowest level possible with the available evidence. To provide further clarity to the issue of durability to the Committee, an additional scenario analysis was conducted and is included in the response. CSL Behring believes the EAG may have misconstrued comments from the clinical expert and UKHCDO submission provided within the technical engagement papers around the duration of data currently available for gene therapy for haemophilia B (both etranacogene dezaparvovec and other products) as the maximum durability. We note that there were subsequent comments from UKHCDO in their response, which outline "*long-term remission and potential cure"*. Similarly, stable long-term expression of haemophilia B gene therapy has been provided as a reasonable

		expectation by several international key opinion leaders at multiple international haemophilia congresses (European Association for Haemophilia and Allied Disorders [EAHAD], 2023. Second clinical expert opinion source is available upon request), which is in contrast to the 6–8 years considered as plausible by the EAG clinical expert. Rather, haemophilia A gene therapy has an expected durability of 6–8 years, with one clinician clarifying in the EAHAD webcast that gene therapy for haemophilia A and haemophilia B should be viewed separately and that haemophilia B gene therapy is expected to have stable long-term durability EAHAD, 2023). We encourage NICE to be clear about the difference between the duration of the currently available trial evidence and the expectation of long-term treatment effect when discussing treatment durability with stakeholders. To support the Committee with decision making on whether etranacogene dezaparvovec is clinically effective in the long term, CSL Behring supplies new evidence for long-term treatment duration. Please see Appendix C for the 6-year follow-up data from the AMT-060-01 trial with the AMT-060 product. Moreover, a recent published response to a comment on the long-term effects of haemophilia B gene therapy provided further data on the percentage of patients enrolled in HOPE-B who had FIX levels of <3 IU/dL and <5 IU/dL and the percentage of patients who had to restart prophylaxis (Appendix D, Pipe and Monahan [2023]). The published response stated that, among 52/54 patients who expressed endogenous Factor IX after the receipt of etranacogene dezaparvovec, none restarted Factor IX prophylaxis. Moreover, at 18 Months post-treatment, factor IX levels were <3 IU/dL in 3.7% of the patients and <5 IU/dL in 5.6% of the patients. The investigators are currently in the process of evaluating extensive post-hoc analyses of HOPE-B data that were collected at 24 months (Appendix D, Pipe and Monahan [2023])

		Citations: EAHAD Academy. Virtual roundtable webcast 15 February 2023. URL: EAHAD Academy Pipe SW, Monahan PE. Long-Term Effects of Hemophilia B Gene Therapy. Reply. N Engl J Med. 2023 May 18;388(20):1918-1919. doi: 10.1056/NEJMc2304262. PMID: 37195961. (Appendix D) Shah J, Kim H, Sivamurthy K, Monahan PE, Fries M. Comprehensive analysis and prediction of long-term durability of factor IX activity following etranacogene dezaparvovec gene therapy in the treatment of hemophilia B. Curr Med Res Opin. 2023 Feb;39(2):227-237. doi: 10.1080/03007995.2022.2133492. Epub 2022 Oct 25. PMID: 36285399. (Company submission reference pack)
Key issue 6: Health state utilities were associated with treatment rather than health states, and the difference may be overestimated.	Yes	CSL Behring can confirm that the health state utilities were associated with the health states. However, due to the difference in mode of administration of etranacogene dezaparvovec and the comparators, an additional utility benefit was applied to the etranacogene dezaparvovec arm in the cost-effectiveness model. The use of this utility benefit is supported by HOPE-B trial results. Moreover, at the November 2022 CSL Behring advisory board, eight clinical experts, Haemophilia Comprehensive Care Centre Clinical Directors from across the NHS agreed with the use of this utility benefit, and, in fact, believed this was a conservative estimate using the best and most current data available. These utility benefits are further supported by patient testimonials: • *"My haemophilia has been cured – for now – by a brand-new gene therapy called Hemgenix. It's an exciting development in treatment, which has changed my life."* Haemophilia patient, 63 (Telegraph, 2023) The same patient had previously stated "*I've had no side-effects and my factor IX level has stayed normal. After living my entire life with severe haemophilia, at the moment I don't have it."* Haemophilia patient, 63 (Irish Times, 2020) • *The trial has changed everything. Since I was 18 months old, I've had to have an injection at least once every week to manage my haemophilia – I'm now 40. But when I received this gene therapy, that changed – I haven't had to inject myself since 2019. It's amazing and I'm so glad I could be part*

		of something that will hopefully help others like me in the future." Haemophilia patient, 40 (Barts Health, 2023) • *"The condition always made me aware of my surroundings and I think that could make me quite timid sometimes, I would avoid any confrontation. On the social side it could be quite difficult as well. When I was a teenager some of my mates went travelling around the world and I can never do that. I always felt that I had been left out of things, it did affect me. I have three sons but often think about what would've happened if I had a daughter. She would have inherited the abnormal factor IX gene and therefore been a carrier for the disease. If she'd have gone on to have a son, there would have been a chance that he would have haemophilia. I think I would have had major guilt for passing the gene on. It's amazing to think that worry could be eradicated soon and that something I was told was incurable can now, be effectively managed with a single-dose treatment."* Haemophilia patient, 55 (NIHR, 2023) Additionally, the effect of this utility benefit has been tested in the initial evidence submission. In the most conservative scenario, in which no utility benefit of etranacogene dezaparvovec is assumed, the intervention still showed substantial benefit compared to the comparators and therefore any uncertainty around this utility benefit is not crucial to the reimbursement decision. Furthermore, as explained in the initial evidence submission, the utility values were mapped from EQ-5D-5L to EQ-5D-3L using the Van Hout et al. (2012) mapping function. Updated utility values, utilising the Hernandez et al. (2017) mapping function have been provided in the updated base case analysis, in accordance with the updated NICE process and methods (2022). Citations:

		Barts Health. Barts Health researchers bring hope to patients with haemophilia B. 2023. https://www.bartshealth.nhs.uk/news/barts-health-researchers-bring-hope-to-patients-with-haemophilia-b-14888 Irish Times. Irish haemophilia patients given 'functional cure'. 2020. https://www.irishtimes.com/news/health/irish-haemophilia-patients-given-functional-cure-1.4430168 Telegraph. 'I lost half my family and many friends to a rare illness but it wasn't too late for me'. 2023. https://www.telegraph.co.uk/health-fitness/body/i-lost-half-my-family-to-rare-illness-haemophilia/ National Institute for Health and Care Research. Case study: Portsmouth-born man with haemophilia-B finds new lease of life after taking part in a gene therapy clinical research study. 2023. https://local.nihr.ac.uk/case-studies/portsmouth-born-man-with-haemophilia-b-finds-new-lease-of-life-after-taking-part-in-a-gene-therapy-clinical-research-study/32785 Van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health.* 2012;15(5):708-715. Hernandez Alava M, Wailoo A, Pudney S. Methods for mapping between the EQ-5D-5L and the 3L for technology appraisal. Report by the Decision Support Unit ScHARR University of Sheffield, 2017.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Mapping function from EQ-5D-5L to EQ-5D-3L	4.2.7 (p66)	Yes	CSL Behring informed the NICE project team during the appraisal submission process that utilities would be mapped back to the 3L tool using Hernández Alava et al. (2017) as per updated NICE process and methods (2022) and would be submitted at the technical engagement stage. Please see Appendix E of mapped utilities with the included scenario analysis.
Appropriateness of the pairwise incremental analysis versus the fully incremental analysis	2.4 (EAR table 4 p24), (EAG report table 4 p25)	Yes	CSL Behring agrees with the EAG that the preferred method of analysing cost-effectiveness in the view of NICE is the fully incremental analysis (NICE, 2022). The analyses that the EAG had conducted in their report are not fully incremental as claimed and thus CSL Behring will provide fully incremental analyses for the responses to issues in Table 3 and Table 4. Furthermore, this response will provide evidence to the contrary of the EAG's claim (p.62) that CSL Behring's pairwise incremental analysis found in the company's initial submission is misleading, but in fact provide ex aequo conclusions. This approach also clearly outlines the most relevant strategies to be analysed in the evaluation of etranacogene dezaparvovec's cost-effectiveness.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Key issue 3	All company's base case assumptions, including constant bleed rates based of the ITC report.	Accepted EAG assumptions, including the gradual increase in etranacogene dezaparvovec based of bleed rates of the ITC report. Calculated the gradual improvement of the bleed rates to etranacogene dezaparvovec values for all comparators over the first 24 months. This excludes the EAG's preferred durability threshold of 5% Factor IX level (as explained in the response to the Key issue 4), and EAG's preferred assumption 6 months necessary to reach steady state FIX equilibrium (based on the clinical data which shows significant reduction in the need	Table 3 of Appendix F Etranacogene dezaparvovec (BeneFIX) Total Costs: £[redacted] Etranacogene dezaparvovec (BeneFIX) Total QALYs: [redacted] BeneFIX Total Costs: £[redacted] BeneFIX Total QALYs: [redacted] No impact – Intervention still dominating

		for FIX treatment in the first 6 months of treatment, with all responders off prophylaxis post administration).	
Key issue 6	Company's use of the EQ-5D-5L quality-of-life measure from the HOPE-B trial, mapped to the EQ-5D-3L preference-based measure of utility using the Van Hout et al. (2012) algorithm.	The use of the EQ-5D-5L quality-of-life measure from the HOPE-B trial, mapped to the EQ-5D-3L preference-based measure of utility using the Hernández Alava et al. (2017) mapping function, as per NICE process and methods (2022).	Table 5 of Appendix F Etranacogene dezaparvovec (BeneFIX) Total Costs: £[redacted] Etranacogene dezaparvovec (BeneFIX) Total QALYs: [redacted] BeneFIX Total Costs: £[redacted] BeneFIX Total QALYs: [redacted] No impact – Intervention still dominating
EAR section 4.2.3	Company's base case included an age at baseline of 41.5 years, consistent with the average age of patients in the HOPE-B trial.	The starting age of patients in the model was adjusted from 41.5 years to 18 years to align with the anticipated indication. The HOPE-B trial included a broad age range from 19 to 75 years. EAR Section 4.2.3 states 'the EAG noted that the mean age of participants in HOPE-B was 41.5 years old whilst the expected indication for etranacogene dezaparvovec was for people over the age of 18.'	Table 7 of Appendix F Etranacogene dezaparvovec (BeneFIX) Total Costs: £[redacted] Etranacogene dezaparvovec (BeneFIX) Total QALYs: [redacted] BeneFIX Total Costs: £[redacted] BeneFIX Total QALYs: [redacted] No impact – Intervention still dominating

Company's base case following technical engagement (or revised base case)	Incremental QALYs: [redacted]	Incremental costs: [redacted]	Table 7 of Appendix F No impact – Intervention still dominating

Sensitivity analyses around revised base case

Table 8 and Table 9 of Appendix F present the fully incremental and pairwise incremental analysis of sensitivity analysis which includes the use of the 5% durability threshold extrapolation by Shah et al. (2022), with otherwise revised base case inputs. Etranacogene dezaparvovec (BeneFIX) remains the most cost-effective strategy as indicated in the company submission.

Table 10 of Appendix F presents the fully incremental probabilistic sensitivity analysis with the revised base case inputs, for 1,000 iterations. Therefore, etranacogene dezaparvovec appears in four sepeatre treatment strategies, once alongside each of the comparators. Alongside the four comparators, there are overall eight strategies being stochastically examined as this is the EAGs preferred PSA method. The probability of a strategy containing etrancogene dezaprvovec being cost-effective is 99.9%, with Etranacogene dezaparvovec (BeneFIX) being cost-effective in 69.8% of the iterations.

Table 11 of Appendix F presents a paired comparison of etranacogene dezaparvovec (BeneFIX) against BeneFIX, for each year of the 2% durability threshold extrapolation by Shah et al. (2022). The durability value of the last year of the extrapolation is set to zero, total costs and total QALYs are recoreded and this process is then repeated for the next non-zero year. This sensitivity analysis shows the resistance of the cost-effectiveness of etranacogene dezaparvovec with respect to the durability of the treatment. Etranacogene dezaparvovec with Benefix. when compared to Benefix, remains the dominant treatment for as long as the durability is assumed to last at least 10 years, which is an extremally conservative assumption, as explained in the response to the Key Issue 5.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B [ID3812]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

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In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

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A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

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Clinical expert statement

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

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The deadline for your response is **5pm** on **25 May 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Clinical expert statement

NICE National Institute for Health and Care Excellence

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating moderately severe or severe haemophilia B and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Charles Percy
2. Name of organisation	Clinical Reference Group for Specialised Blood Disorders
3. Job title or position	Consultant Haematologist and Haemophilia Centre Director, University Hospitals Birmingham NHS Foundation Trust
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with haemophilia B? ☒ A specialist in the clinical evidence base for haemophilia B or etranacogene dezaparvovec? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	I have never received funding of any sort from the tobacco industry.
8. What is the main aim of treatment for moderately severe or severe haemophilia B? (For example, to stop progression, to improve mobility, to	The principle aim is to prevent bleeding, particularly joint bleeding. By achieving this, long term health problems such as joint damage causing reduced mobility and chronic pain, can be minimised and individuals can lead a life with the

cure the condition, or prevent progression or disability)	minimum of limitations.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	As a minimum a reduction in bleeding events compared to existing treatments and a reduction in joint damage. Ideally one would want no spontaneous bleeding at all. The factor IX activity required to achieve this will vary between individuals. Data from the National Haemophilia Database would imply a factor IX activity of at least 3 iu/dL or greater would be the minimum required to reduce joint damage as assessed by joint scores.
10. In your view, is there an unmet need for patients and healthcare professionals in moderately severe or severe haemophilia B?	The current licensed treatments are intravenous, therefore there is a treatment burden associated with this. Despite the use of prophylactic factor IX injections, there remain some individuals who report breakthrough bleeding episodes.
11. How is moderately severe or severe haemophilia B currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	The current standard of care is regular preventative intravenous injections of recombinant factor IX (prophylaxis). There are standard half-life products available that must be given every 2-3 days. Over the last 8 years, extended half-life products have become available that allow the frequency of injections to be reduced to once every 1-2 weeks. For all products, the exact frequency of injection is adjusted based on the trough factor IX levels (historically a minimum of 1 IU/dL, latterly more often 3 iu/dL) and whether any spontaneous breakthrough bleeding occurs. There is guidance from the UK Haemophilia Centre Doctors Organisation (UKHCDO) and British Society for Haematology (BSH). The link is: https://www.ukhcdo.org/wp-content/uploads/2020/10/Guidelines-on-the-use-of-prophylactic-factor-replacement-for-children-and-adults-with-Haemophilia-A-and-B.-A-British-Society-for-Haematology-Guideline..pdf There is a national service specification against which haemophilia services are commissioned by NHS England. This includes guidance on patient pathways, although ultimately the details of these are for providers to define locally. There is a national specialty services dashboard to evaluate services and this includes questions about prophylaxis.

	Gene therapy would significantly change the pathway of care. In the first 12 months after receiving gene therapy, the frequency of clinic appointments/contacts would be considerably more than is currently the case for an individual receiving effective prophylaxis with recombinant factor IX (in which case one would expect review once every 6 months). However, from year 2 onwards, the frequency of visits would likely reduce back to a similar frequency. The absence of the need for regular intravenous factor IX injections would reduce the treatment burden. However, depending on the factor IX activity achieved following gene therapy, the need for intravenous factor IX would not be completely removed, as this may still be required for invasive procedures or injuries (for individuals with mild haemophilia B with factor IX activity between 5 and 50 IU/dL will sometimes bleed after an injury and require intravenous factor IX to control it).
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Current intravenous factor IX is administered by patients themselves at home. On occasion it will be given by nursing staff as day attender in the haemophilia centre or clinic (or when an inpatient for any reason). The process of discussing gene therapy, administering it and then follow up would need to be at a centre with specialist expertise in managing haemophilia B. Gene therapy will need to be prepared by pharmacy staff in suitable facilities, and administered intravenously in a hospital bed be staff trained in its handling. Based on the clinical trial experience and distance patients may be travelling, there would need to be an overnight stay either on the ward or in some sort of ambulatory facility for patients to be nearby in the event of any reactions. Follow up would then be as an outpatient, potentially with some home visits from haemophilia specialist nursing staff. Oversight from the specialist centre would be required, although monitoring blood tests could be undertaken closer to a patient's home provided suitable arrangements were in place.

	In terms of investment, firstly the specialist clinical staff involved would need to have the time to advise the patient, undertake any screening investigations, obtain informed written consent from patients, attend any local or national multidisciplinary team meetings that may be required to assess patient suitability and follow up, and finally arrange the necessary follow up monitoring and act upon the results. Secondly, in some specialist centres there would need to investment in pharmacy capacity (staff and facilities) to deliver this. Finally, all staff groups involved in the process would need training relevant to their role (e.g. suitability criteria, preparation of the gene therapy product, administration of the product and the post treatment follow up).
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	In those who respond, would expect it to reduce the treatment burden and spontaneous bleeding. This should then translate into an improved quality of life. At present we do not have data to be able to conclude whether it would impact on length of life. However, unless there are unexpected and at present unknown life shortening complications in the future, I would not expect it do so.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	It would be less effective in those with inhibitors to factor IX, pre-existing antibodies to the viral vector used (AAV-5) and those with pre-existing liver fibrosis.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or	The frequency of monitoring blood tests in the first 12 months will be higher than current treatment, leading to an increased demand on the time of the clinical team and the patient to undertake those tests. The clinical team will also need to increased time to review and act upon the results. There is very high likelihood patients will develop derangements of liver enzymes, necessitating the use of steroids, and even other immunosuppressive medications where steroids do not work. These may cause their own side effects in the patients receiving them, for

monitoring needed)	example steroid induced diabetes, thus requiring additional interventions and input from other specialist teams (e.g. endocrine/diabetes teams). However, the absence of the need for regular intravenous injections will be technically easier for patients. In addition any immunosuppressive medication is likely to have been stopped by 12 months and thereafter the frequency of monitoring blood tests will reduce to that required with current existing therapy.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The absence of any factor IX inhibitors, AAV-5 antibodies and liver fibrosis will need to be confirmed before considering gene therapy. This will require additional blood tests. Assessing liver fibrosis may require a fibroscan or ultrasound. There will need to be a multidisciplinary meeting to discuss suitability (whether locally or nationally, depending on what NHSE may stipulate).
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Whilst the reduction in bleed frequency and need for intravenous factor IX will not be directly captured in the usual instruments for QALY, they will be indirectly. Studies of new treatments in haemophilia B have used standardised questionnaires, e.g EQ-5D, and they have usually demonstrated improvements despite not specifically asking about these aspects.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	For those that respond and have an enduring increase in factor IX activity, at least within the mild haemophilia B range (so 5 iu/dL and above) I would expect a significant reduction in the need to attendance at the haemophilia centre and treatment for bleeds. The latter should reduce the need for surgical interventions, use of analgesia and the long term psychological and economic burden that places on the patient. Gene therapy addresses the unmet need for a treatment that removes the need for regular intravenous injections of factor IX.
19. How do any side effects or adverse effects of the technology affect the management of the condition	Steroids for managing any increase in liver enzymes may cause side effects such as steroid induced diabetes, insomnia, psychosis, depression and an

and the patient's quality of life?	increased of infection. Whilst these side effects would resolve once steroids were withdrawn, medication may be required in the meantime to manage them. Whilst experiencing these side effects, an individual's quality of life would be reduced. If alternative immunosuppression was required due to a failure to response to steroids, the risk of infection would be increased and with long term use other problems may arise, such as an increased risk of secondary malignancies (particularly skin cancer). However, hitherto, long term use of such drugs has not been needed. The other consideration is the long term unknowns, twenty or more years after treatment, principally whether the initial liver enzyme derangement after gene therapy will predispose to liver disease in the longer term, for example and increased risk of cirrhosis or hepatocellular cancer. Where that to happen, then that would significantly negatively impact on quality of life. However, we have no data at present to indicate whether this is indeed a definite risk or not; currently remains theoretical.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Gene therapy for any congenital bleeding disorder has not hitherto been used outside of a clinical trial in there UK, therefore there is no direct comparison. However, the comparator arm in the trial where patients were receiving prophylactic intravenous infections of factor IX was in line with current UK clinical practice, although the bleed frequency in that arm was relatively high. Despite this we can infer that similar outcomes from gene therapy can be expected. The main outcome measures were the annualised bleed rate and factor IX activity achieved. What we do not know from the clinical trials is how enduring the increased in factor IX activity will be and whether there will be any adverse events that become in the very long term (e.g. twenty years hence), in particular relating to liver damage.
21. Are you aware of any relevant evidence that might	I am not aware of any evidence that would not be found at present.

not be found by a systematic review of the trial evidence?	
22. How do data on real-world experience compare with the trial data?	This can't be answered until gene therapy for haemophilia B enters to the clinical arena outside of a clinical trial.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme.	Understanding written and verbal information for those for whom English is not their first language may be difficult. Accurate translation will be essential to ensure they understand the potential benefit and risks of gene therapy. Similar issues arise for those with speech, sight or hearing impairment. Without information in a format they can understand, these groups may be less likely to decide to receive gene therapy. For those whose mobility is impaired or have limited finances to cover the cost of travel may have difficultly attending the specialist centre, in particular for follow up blood tests. Therefore appropriate arrangements with hospital transport or care closer to their home would need to be in place.

Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key issue 1: The company did not report evidence for the true change in FIX levels following treatment with ED in the HOPE-B	The change in factor IX levels relevant to the baseline when not prophylaxis (so for severe haemophilia B that is <1 IU/dL) is an appropriate measure. Therefore this is not a concern.
Key issue 2: Clinical outcomes in the HOPE-B study may overstate the potential benefits of ED	Whilst patients may have been slightly less active during the COVID-19 pandemic, in clinical practice we haven't seen a particular change in patients reporting bleeds. Therefore the impact of that is unlikely to be significant. In relation to the concern about clinicians being less likely to administer factor IX to those involved in the clinical trial, in my experience taking part in gene therapy trials, my decisions about whether to administer factor were based on the clinical situation and the patient's current factor activity and not because they

	were in a clinical trial. The same considerations apply in routine clinical practice, therefore I consider it unlikely patients were artificially under treated with intravenous factor IX in the clinical trials.
Key issue 3: Comparative efficacy estimates of ED and prophylactic FIX treatments were unreliable	Similar issues exist with other clinical trials of existing standard and extended half-life factor IX treatments. There is no easy way of addressing that.
Key issue 4: Definition of treatment failure was at a low FIX activity level	Prophylactic factor IX injections would be reintroduced based on whether the patient experienced spontaneous bleeding or their overall bleeding risk, not solely on factor IX activity.
Key issue 5: The durability extrapolation model was based on limited data and excluded non-responders	I agree this is a problem and we ultimately will now know the answer to this for many years (possibly decades) to come.
Key issue 6: Health state utilities were associated with treatment rather than health states, and the difference may be overestimated.	That is a possibility. However, the positive impact from a reduction in overall treatment burden is an important consideration.
Are there any important issues that have been missed in EAR?	No.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Gene therapy for haemophilia B offers a new treatment options for patients who do not wish or are unable to continue to receive regular intravenous factor IX.
The data suggests that it is at least as effective as good quality prophylaxis with regular intravenous factor IX in reducing the frequency of bleeding episodes.
Prevention or reduction of bleeding episodes is a significant determinant of long term quality of life and morbidity.
The long term durability and potential for unforeseen complications in the distant future remains unkown.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

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Single Technology Appraisal

Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B [ID3812]

Clinical expert statement and technical engagement response form

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Part 1: Treating moderately severe or severe haemophilia B and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Priyanka Raheja
2. Name of organisation	Royal London Hospital, Barts health NHS trust
3. Job title or position	Consultant haematologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? X A specialist in the treatment of people with haemophilia B? ☐ A specialist in the clinical evidence base for haemophilia B or etranacogene dezaparvovec? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	X Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for moderately severe or severe haemophilia B? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To prevent bleed events.

9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A reduction in bleed events
10. In your view, is there an unmet need for patients and healthcare professionals in moderately severe or severe haemophilia B?	Yes, treatment for patients without the need for recurrent IV access
11. How is moderately severe or severe haemophilia B currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	• There are British society for haematology (BSH) / United Kingdom Haemophilia Centre Doctors Organisation (UKHCDO) guidelines on the use of prophylactic factor replacement for children and adults with Haemophilia A and B. • There is a defined pathway of care and patients are now mostly receiving extended half life factors for prevention of bleeds. • The technology would change the current pathway of care as patients would no longer need to treat themselves with IV treatment on a weekly basis. Instead, they would have one gene therapy infusion and then be closely followed up for the first year. This would increase the amount of follow ups and blood tests the patients would receive in the first year after Hemegenix treatment. Although, after the first year of treatment the patients would attend the clinic in the same frequency for follow up as someone who is on the current standard of care, but they would no longer need to self inject prophylaxis. Thus, reducing treatment burden.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	• A gene therapy infusion site or dosing site is required with pharmacy capabilities to handle genetically modified product. This includes a pharmacy with aseptic capacity and capability (isolator or biosafety cabinet) and risk assessment / mitigation strategies. The patient may also require psychological counselling prior to making the decision for gene therapy. They will need to have a thorough informed consent as it's probably a once in a life time treatment that needs proper consideration. Once they have decided to have the therapy, they will need a day case bed for the infusion, with a specialised nurse to oversee it. They need close follow up of liver function

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	testing and factor IX levels after the infusion, especially in the first 3-6 months post gene therapy and close monitoring of their liver health through ultrasound / fibroscan. After the first year, their follow up can be spaced out and they would be seen in clinic in a similar frequency to standard of care. Since their baseline levels would be higher after gene therapy, they will probably be seen less for bleeding episodes. Current standard of care is prophylaxis with an intravenous extended half life factor injection on a weekly basis. Most patients are trained to perform this at home and can self treat. They only come to the hospital if they have a bleed, accident or surgery and are seen routinely on a 6 monthly basis in clinic. • This technology should be used in a haemophilia comprehensive care centre (secondary care setting). • Investment is needed in: -The set up of a pharmacy aseptic unit capable of handling genetically modified product. -Training for pharmacy, specialist nurses and haematology consultants. -Consultant time, nursing time and administrative time to closely monitor these patients after gene therapy and collect the data on side effects. -Bed space for a day case procedure. -Psychology input to counsel patients on a once in a life time therapy, discuss changes to identity, and manage expectations in case it is not successful or there are longer term side effects to liver health. -Input from specialist hepatology services to monitor acute transaminitis.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	• I expect the technology to reduce the burden of IV injections and decrease the bleeding events patients are having as patients would no longer have peaks and troughs of factor IX levels, instead they would have a steady factor IX level. • I expect the technology to improve the quality of life of patients by eliminating the need for frequent i.e. weekly IV injections.

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No, it would be similar for all those eligible (male patients with severe or moderately severe haemophilia B).
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	In the first year of treatment, it will require extra monitoring and in some case concomitant treatment with corticosteroids. But after the first year of treatment, then patients would no longer need home delivery of factor concentrates and follow up would be similar to current care.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients would need to have their liver health assessed, as those with liver fibrosis / cirrhosis cannot have the treatment, and those with hepatitis or transaminitis will need to be reviewed by a hepatologist. They would also need to be tested for high titre AAV5 antibodies and factor IX inhibitors.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Patients would be able to live life more normally, without the fear of spontaneous bleeding events. This gives them the ability to have a “haemophilia-free mind” and be able to forget about weekly intravenous injections. The burden of injections and the freedom that this treatment would give them is very difficult to assess in a QALY calculation. The psychological benefit to their mental health is hard to assess and quantify. I’ve had patients feel more relaxed about travelling to other countries without needing to carry lots of vials of factor with them and without the fear of developing a spontaneous bleed.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, the technology is a big change in the management of the condition, as it frees the patient from the burden of regular IV injections. It addresses an unmet need especially for patients with difficult venous access.

• Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	If the patient develops acute transaminitis, they will then need close follow up and possibly treatment with corticosteroids. Attending the hospital very frequently, can be detrimental to quality of life. Long term treatment with corticosteroids can cause multiple long term sequelae such as, reduction in bone health density, adrenal insufficiency, infections, myopathy, gastritis, gastric ulcer, ophthalmologic effects, hyperlipidemia, etc.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes the clinical trials are reflective of UK practice. . The most important outcomes are spontaneous bleed events and elimination of routine factor IX injections. Both of these were measured in the trial. As there is no real world experience yet, the trial data is the most accurate representation of adverse effects.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Not that I am aware of.
22. How do data on real-world experience compare with the trial data?	We do not have real world data yet.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of	Patients who are unable to attend hospital regularly for follow up due to lack of resources and patients who do not speak English or have a learning disability might be disadvantaged. It is important that there is enough resourcing available to deliver this at an NHS service level to make sure that all patients can attend regular follow ups. Patient information should be available in multiple languages

people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	and in accessible formats.

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key issue 1: The company did not report evidence for the true change in FIX levels following treatment with ED in the HOPE-B	As there is variability between individuals in the response to gene therapy, it is very difficult to do a randomised control trial with two arms comparing FIX injections to Etranacogene dezaparvovec. Therefore, gene therapy studies in haemophilia use a lead in phase as a comparator for assessing response. Regarding the FIX levels in the lead in phase, patients that are on factor prophylaxis will have peak and trough levels, rather than a steady state level. Their baseline level will be very similar throughout their life (in this case for study eligibility it was FIX<2%), which is why the study used their baseline data. Therefore, because of the peaks and troughs during weekly factor IX injections, it is difficult to take a single level measurement and compare it to the level after gene therapy. The FIX level at a single moment of time would not be a good predictor of the level over the course of a week, as there is a peak in FIX levels just after treatment with factor IX and then a steady drop until the next treatment. Thus, I don't think measuring FIX levels in the lead in phase would add any extra information to the clinical decision making process.

Clinical expert statement

Key issue 2: Clinical outcomes in the HOPE-B study may overstate the potential benefits of ED	From my perspective as an investigator on the study, the participants at our trial site were not shielding during the COVID-19 pandemic and were still active, especially doing sports outdoors. Additionally, in between the government lockdowns, there were periods of "more normal activity" and patients were able to go about their daily life. In clinical practice, unless there is a bleeding event, accident or surgical intervention, if FIX levels are above 5, clinicians are very unlikely to give FIX replacement therapy as prophylaxis. In fact, we would probably only consider prophylaxis if FIX levels were below 3 and/or if they were having spontaneous bleeding events. We would not be giving patients who had mild Haemophilia B (FIX levels above 5), factor prophylaxis. As an investigator on the study, if the FIX levels were above 5, I followed normal clinical practice and only gave patients factor IX replacement therapy if they were bleeding, had an injury / accident or were due a surgical intervention.
Key issue 3: Comparative efficacy estimates of ED and prophylactic FIX treatments were unreliable	The most commonly used factor IX replacement therapies for prophylaxis in the UK are extended half life therapies (Alprolix, Refixia and Idelvion). As on demand therapy for non-severe Haemophilia B patients, Benefix is used more often. The main appeal of Etranacogene dezaparvovec, is the ability to live without weekly or regular IV injections, this is the reason most patients chose to go on gene therapy. The other appeal, is the fact that the factor IX levels are steady and do not have peaks and troughs on a weekly basis. Therefore, I do not think that efficacy comparisons with Benefix are useful.
Key issue 4: Definition of treatment failure was at a low FIX activity level	As a haemophilia clinician, treatment failure should be defined by resumption of prophylaxis due to reappearance of spontaneous bleeding episodes, as that is what we are preventing with prophylaxis. I do not think we can put a number on that for all patients, as different patients will have slightly different thresholds of bleeding due to their phenotype. Some patients with legacy arthropathy, might have worse baseline joint health and therefore need to restart prophylaxis at a higher factor IX level. In most cases, patients will need to restart prophylaxis if there levels fall below 2-3%.
Key issue 5: The durability extrapolation model	It is very difficult to extrapolate durability based on a model, as this does not take into account many factors. We still do not have data on long term efficacy and until that data does not get published we

was based on limited data and excluded non-responders	cannot make assumptions on durability based on a model. Long term follow up studies are needed and registry data will be important once we have real world data in routine clinical practice.
Key issue 6: Health state utilities were associated with treatment rather than health states, and the difference may be overestimated.	Both EQ-5D and HRQoL were used in the study. HRQoL may show further benefits by reducsing treatment burden and improving psychological wellbeing.
Are there any important issues that have been missed in EAR?	Not that I am aware of. As part of our discussion on the first technology appraisal call, I just wanted to point out that it is not possible to compare durability between gene therapies. Please do not compare durability in gene therapy for haemophilia A with gene therapy for haemophilia B. They are very different and each medicinal product has its own durability and can vary between individual patients.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Gene therapy for haemophilia B will reduce the treatment burden of regular factor IX injections in people with severe / moderately severe haemophilia B.
This will lead to patient being able to have a haemophilia-free mind and not worry about when they carry out certain activities based on the peak / trough levels of their factor IX prophylaxis injections.
We still do not know the exact durability of the gene therapy but data based on modelling looks promising for this particular gene therapy in haemophilia B.
There is variability between individuals, which is why head to head comparator studies are difficult to perform.
Measuring the whole impact of psychological freedom from injections is difficult to do with the current standardised quality of life assessments.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

X **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B [ID3812]

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with moderately severe or severe haemophilia B or caring for a patient with moderately severe or severe haemophilia B. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR in sections 1.4 and 1.5.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

Patient expert statement

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Patient expert statement

NICE National Institute for Health and Care Excellence

The deadline for your response is **5pm** on **25 May 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Patient expert statement

Part 1: Living with this condition or caring for a patient with moderately severe or severe haemophilia B

Table 1 About you, moderately severe or severe haemophilia B, current treatments and equality

1. Your name	Ross Bennett
2. Are you (please tick all that apply)	☒ A patient with moderately severe or severe haemophilia B? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with moderately severe or severe haemophilia B? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	The Haemophilia Society
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☒ I have completed part 2 of the statement **after attending** the expert

Patient expert statement

	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with moderately severe or severe haemophilia B? **If you are a carer (for someone with moderately severe or severe haemophilia B) please share your experience of caring for them**	Having haemophilia causes several issues in my experience. It has stopped me doing activities and jobs that I would like to do such as play rugby and join the Armed Forces. I have also had over 120 bleeds in my life including a couple of four week stays in hospital as an 8 and 10 years old respectively. Due to these injuries I'm still cautious in certain situations. For example, I still don't like walking through large crowds due to the worry of someone walking into me. The difficulties this has caused my friends and family growing up should not be underappreciated with the travel, time, and money to look after me. I think this cannot be underestimated how hard this on people. The stress upon your family and friends is tough throughout life and continues to prove so. During a bleed especially and the continuous hospital visits/stays are hard work and place a large amount of impact on anyone. I also think of my four weeks stay when I was 8 and seeing my 7-year-old sister miss my parents due to looking after me. The largest pressure is always guilt as well, my mother, auntie, and granny all as carriers feel a sense of guilt that cannot be told. This would not takeaway the guilt as a treatment but would certainly help in solving the issue. This has clearly led to me missing parts of my life, I've missed holidays, school, work, and a host of other events. Having a constant level would hopefully enable this to be reduced a significant amount.
7a. What do you think of the current treatments and care available for moderately severe or severe haemophilia B on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	The treatments available have improved dramatically in recent years and the options are greater than the single SHL product I had growing up. Due to spending 15 years of my life on a SHL and only having been on an EHL for 2 years these products still seem new and fantastic to me. Having only to inject myself once a week. 7b. These views change from generation to generation. People who are 18 and older spent a lot of life with SHL compared to kids now growing up with EHLs and

	thinking one injection a week is still a large number. But people who are older find this great with only one injection a week making life easier than before.
8. If there are disadvantages for patients of current NHS treatments for moderately severe or severe haemophilia B (for example, how they are given or taken, side effects of treatment, and any others) please describe these	I haven't come across any major side-effects. Clearly the chance of having a Inhibitor is always present and this is worry. Injecting intravenously is a challenge and learning to do so is a stressful experience and still injecting yourself 52 times a year is a challenge. Joint bleeds are clearly a threat and a joint bleed in your elbow can make injecting into your arm very difficult and clearly this is similar in your wrist.
9a. If there are advantages of etranacogene dezaparvovec over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does etranacogene dezaparvovec help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	The main advantage is the reduced needle burden that the average haemophiliac would see a complete drop in injections would be a huge advantage compared to the current treatment regime. This also makes travel and reduces anxiety of levels of treatment in the case of an injury. 9b. I think the reduced anxiety would be the major benefit, yes needle burden is a great advantage as well but the mental health benefit of not worrying would be insurmountable in improving quality of life. 9c. Yes, reducing needle burden means that people who struggle with injections would have a constant treatment without having to do anything themselves.
10. If there are disadvantages of etranacogene dezaparvovec over current treatments on the NHS please describe these. For example, are there any risks with etranacogene dezaparvovec? If you are concerned about any potential side effects you have heard about, please describe them and explain why	The process of having the treatment itself is quite a process with six months plus of blood tests and having to frequent hospital on a regular basis for these tests is difficult. Also, the lack of long-term data is worrying as you don't know what will happen in the future.
11. Are there any groups of patients who might benefit more from etranacogene dezaparvovec or any who	From speaking amongst the community, a number of groups would benefit, needle phobic and people who find injections difficult would be a major benefit.

may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	People with other difficulties such as dexterity would be a huge advantage if they've had a number of joint bleeds in wrists and in elbows in particular. Also, the final group would be other difficulties that are involved in one's health. This would remove all burden and make life drastically easier.
12. Are there any potential equality issues that should be taken into account when considering moderately severe or severe haemophilia B and etranacogene dezaparvovec? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	I can't see any reason why any group would be disadvantaged.
13. Are there any other issues that you would like the committee to consider?	No

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issue(s) where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key issue 1: The company did not report evidence for the true change in FIX levels following treatment with ED in the HOPE-B	
Key issue 2: Clinical outcomes in the HOPE-B study may overstate the potential benefits of ED	This trial was done during Covid and from my own personal experience and speaking to my peers, covid saw an increase in activity especially vigorous activity such as running, cycling. So, I don't think this would overstate the benefits as we saw increase level of activity, this could arguably be the opposite and now with normal regimes returning benefits might be under appreciated.
Key issue 3: Comparative efficacy estimates of ED and	

Patient expert statement

prophylactic FIX treatments were unreliable	
Key issue 4: Definition of treatment failure was at a low FIX activity level	
Key issue 5: The durability extrapolation model was based on limited data and excluded non-responders	This is worrying as a patient. But I understand that you cannot have the 50-year data without the treatment having 50 years of data behind it and extrapolation models are still models are the end of the day. However, I think the report understates and the model overstates, and we are somewhere between the two numbers. Arguably closer to 30/35 years as a guesstimate.
We consider patient perspectives may particularly help to address this issue **Key issue 6: Health state utilities were associated with treatment rather than health states, and the difference may be overestimated.**	Treatment burden must not be underestimated as I have mentioned in my earlier statements. The stress of learning to inject oneself is hard and puts stress on your family and friends. The constant knowing of having to do something every week is hard and the fear that if something goes wrong that you do more injections. I know this product is for people who are over 18, but it must be understood that haemophiliacs aged 14-17 now, do not inject themselves as well as my generation and struggle with the fact they have to do it. This is across the community and very soon these children will become eligible to have this treatment and we must realise the generation comings needs so we can address them, and I believe this should not be forgotten even with an 18+ limit.
Are there any important issues that	No

have been missed in EAR?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Haemophilia causes several issues in my life.
- For some people injecting intravenously is a challenge and learning to do so is a stressful experience.
- The lack of information about the future is worrying.
- This Treatment will reduce needle burden.
- This treatment will be a tough experience for the first 6 months.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B [ID3812]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **25 May 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	British Society for Haematology / The Royal College of Pathologists
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	**None**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**None**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: The company did not report evidence for the true change in FIX levels following treatment with ED in the HOPE-B	No	Baseline FIX levels without treatment are constant for individual patients with Haemophilia B, but can be modified by administration of exogenous FIX (comparator treatments) or by the ED. Without such treatments, an individual's FIX levels will always return to these baseline levels. The ED achieves an increase in FIX levels which is broadly stable from day-to-day, unlike exogenous FIX, where there are large fluctuations from peak to trough FIX levels. Thus, the ED's effect is more akin to modifying the severity of the disease than to conventional FIX replacement therapy. There is a good understanding of the correlation between baseline FIX level and bleeding risk in Haemophilia B. Hence, increase in FIX level from baseline is a useful measure of the biological effect of the ED. Factor levels in the lead in period of the HOPE-B study were a function of exogenous FIX administered to patients. These would depend on individualised treatment regimens using the comparator treatments, which will have been adjusted to try to achieve an ABR as close to zero as possible. Factor levels necessary to achieve this will depend on multiple variables including physical activity levels of the treated individual, activity types and individual pharmacokinetics for the specific FIX product in the individual in question. These variables would also influence the relative importance of trough and peak FIX

		levels, which will vary considerably between individuals. Mean, peak or trough factor levels would be of limited value without this additional information. The only relevance of such factor levels is whether they were sufficient to prevent bleeding episodes. Moreover, it is perfectly possible to alter factor levels by changing dosing regimens such that virtually any biologically plausible peak, mean or trough factor level can be achieved. Treatment regimens are often individualised to diverge from the licensed dosing schedules, further undermining the utility of quoting these FIX levels from the lead in period. Finally, delay in administering a prophylactic dose of exogenous FIX (a missed dose of comparator treatment) will lead to a period with significantly lower FIX levels than would be captured by the quoting of typical trough values in lead in period. Bleeding risk is much higher in such circumstances, and missed doses are a common reason for failure of conventional FIX replacement treatment to prevent bleeding. The ED, by maintaining roughly stable FIX levels, is not prone to such issues. Quoting peak, mean and trough FIX levels from the lead in period could lead to a misleading comparison between the ED and comparator treatments for this reason.
Key issue 2: Clinical outcomes in the HOPE-B study may overstate the potential benefits of ED	Yes	As addressed in Key issue 4 (see below), real-world data from the UK National Haemophilia Database, published in the UK Haemophilia Centre Doctors Organisation annual report for 2021/22 (https://www.ukhcdo.org/wp-content/uploads/2022/12/UKHCDO-Annual-Report-2022-2021-22-Data.pdf), demonstrates that median annual factor use in patients with Haemophilia A treated with standard half-life Factor VIII with FVIII levels of 2-<3% was 6,000 units compared to 225,000 units for those with FVIII levels of <1%. Thus, median total factor usage in patients with factor levels of 2% or more was over 35-fold less than it was in those with severe disease and not compatible with regular, or semi-regular, infusions. Being a median value, this holds true for the majority of patients, but does not exclude the possibility that a minority of patients may have significantly higher factor usage.

		Some further information in this regard can be taken from the inter-quartile ranges and total ranges of reported factor VIII consumption at different factor levels. With factor levels of 2-<3%, the range of annual factor use in the top quartile was from 80,000 to around 200,000 units, demonstrating that the very highest factor users were receiving total amounts of FVIII compatible with full prophylactic treatment. However, in the group with 5-10% baseline FVIII levels, the very highest factor users received <10,000 units per year. This amount of factor use would only be compatible with episodic treatment of bleeds or prophylactic treatment prior to very rare, high-risk activities, and was comparable to the pattern of use seen in HOPE-B trial follow up. Clinical outcomes for specific factor levels are broadly equivalent between Haemophilia A and Haemophilia B. The large majority of patients treated with the ED had FIX levels of over 5% during the follow up period of the HOPE-B study, so additional factor usage could reasonably be expected to be very low in keeping with the real-world data from the UK National Haemophilia Database discussed above. In addition, the data presented in the HOPE-B study would provide support for a restrictive approach to additional factor treatment, in that annualised bleed rates in the study period were lower than those seen with conventional factor replacement strategies as used in the lead-in period, despite the limited use of additional FIX replacement in the interventional phase of the trial. This evidence could give clinicians and patients reassurance that additional use of factor, as outlined as a concern in section 3.2.2.3, would not be necessary in most scenarios whilst FIX levels remain in the range reported in the HOPE-B study. Impact of the COVID-19 pandemic on activity levels, and therefore the factor levels necessary to prevent bleeding, is difficult to estimate. The lockdowns and shielding requirements did undoubtedly reduce physical activity levels for many, although exercise was often taken at higher intensity for shorter durations as the allowance for time outside was limited during lockdowns. Such a pattern of exercise, if

		followed by study participants, would actually give a higher risk of bleeding than conventional, lower intensity activities performed for longer. From my experience as the clinical lead of an adult bleeding disorder service with patient numbers with severe Haemophilia A and B of a similar order to those included in the HOPE-B trial, there was a transient small reduction in bleeding episodes of the order of 10-20% lasting for the first 3 months of the first COVID-19 lockdown, with a return to normal levels of activity-related bleeding thereafter. Extrapolating from this, it may be that there was a minor reduction in bleed rates post-ED administration in the HOPE-B trial that related to the COVID-19 pandemic. However, the size of any such effect is likely to have been small, and much smaller than the overall benefit reported in terms of reduction of bleeding rates. Nonetheless, the reported reductions in bleed rates may represent a minor over-estimate of the benefit of ED in this regard. Further analysis of the raw trial data to give details of estimated ABR during follow up by calendar month / quarter could be helpful in further assessing any contribution of pandemic restrictions on ABR.
Key issue 3: Comparative efficacy estimates of ED and prophylactic FIX treatments were unreliable	No	The HOPE-B trials forms the majority of the evidence base for benefits of the ED. Many of the limitations of the study design are out of necessity. A blinded study would have been unethical as this would have required a control group exposed to risk of harm. The rarity of the condition means that having a control arm would have presented a significant barrier to performing a suitably powered study. In an attempt to compare efficacy of the ED with FIX treatment, data from trials of different FIX treatments were used as comparators. Attempts to adjust these data based on key patient characteristics were made, however the concern raised by the EAG regarding reliability of this approach are valid. I share the EAG's view that the evidence presented points to a likely reduction in bleeding rates with the ED compared to FIX treatment, and this is further supported by the reduction in bleeding rates seen after administration of the ED compared to the lead-in period, during which all patients in the HOPE-B trial were receiving prophylactic FIX treatment. I also agree that, owing to the lack of high-quality comparative data, the magnitude of reduction in bleeding rates is unclear.

		Nonetheless, the company's estimate of size of effect does not appear unreasonable within these limitations. In contrast, the EAG's concerns regarding real-world factor IX treatment alongside ED significantly exceeding that seen in the trial are out of keeping with real-world data on factor use in people with factor levels of 5% or more (see response to Key concern 2).
Key issue 4: Definition of treatment failure was at a low FIX activity level	Yes	The UK National Haemophilia Database gathers information on treatment of people with bleeding disorders by all UK Haemophilia Centres. Summary data from this is published on an annual basis in the UK Haemophilia Centre Doctors Organisation annual report. This includes data on quantity of factor treatment per individual with Haemophilia A of different baseline factor levels. Equivalent data are not published for Haemophilia B owing to the rarity of the condition, hence lack of meaningful patient numbers to include in the analysis. Nonetheless, it is widely accepted that severity of bleeding symptoms are broadly equivalent between Haemophilia A and Haemophilia B for equivalent factor levels and, if there is any difference in bleeding risk, it is that risk is lower in Haemophilia B than Haemophilia A with equivalent factor levels. Page 34 of the UKHCDO annual report for 2021/22 (https://www.ukhcdo.org/wp-content/uploads/2022/12/UKHCDO-Annual-Report-2022-2021-22-Data.pdf) shows that, of people treated with standard half-life factor VIII, people with factor VIII levels of <1% received a median of 225,000 units per year, those with factor levels of 1-<2% received a median of 165,000 units per year whilst those with factor levels of 2-<3% received a median of 6,000 units per year. This demonstrates that the majority of patients in the group with factor levels of 2% or higher did not receive prophylactic treatment. This suggests that, in UK real-world practice, the factor level at which prophylactic treatment would usually be initiated is <2%, accepting that this is an extrapolation from haemophilia A and in the subgroup of patients treated with standard half-life factor VIII. Thus, the company's estimate of the likely FIX level as a threshold for resumption of prophylactic treatment (or treatment failure) of <2% would appear more realistic than EAG's estimate of 5%.

		British Society for Haematology guidance suggests offering primary prophylaxis to those with factor levels of <4% on the basis of risk of development of joint damage at lower factor levels (https://onlinelibrary.wiley.com/doi/10.1111/bjh.16704). Therefore, this would be a potential alternative cut-off for considering treatment failure, although the situation of resuming prophylaxis after gene therapy is not analogous to initiating primary prophylaxis, and real-world data suggests this threshold may over-estimate the FIX level at which prophylactic treatment would usually be resumed.
Key issue 5: The durability extrapolation model was based on limited data and excluded non-responders	No	Treatment durability and threshold for treatment failure are clearly highly relevant to the total benefit of the ED, and benefit is extrapolated well beyond the duration of the HOPE-B trial by the company. The conclusions of the EAG that the company's assessment of durability was speculative and based on limited data are entirely valid. Whilst the assumptions made in the company's attempt to assess durability do not appear unreasonable, other than the decision to exclude non-responders from the analysis and the lack of evidence presented for efficacy of the ED before 6 months, the confidence in the accuracy of these predictions is severely limited by the short duration of follow up data. On the other hand, in the EAG's estimates of durability needed to achieve the £20,000 and £30,000 cost per QALY thresholds, the assumption of treatment failure at an FIX level of 5% is not in keeping with real-world evidence, as detailed in the response to Key issue 4. In addition, it is noteworthy that the majority of patients with severe Haemophilia B currently being treated with FIX prophylaxis in the UK are being treated with extended half-life FIX products, not Benefix, as detailed in the UKHCDO annual report for 2021/22 on page 54 (https://www.ukhcdo.org/wp-content/uploads/2022/12/UKHCDO-Annual-Report-2022-2021-22-Data.pdf). Thus, the cost-effectiveness comparisons to products other than Benefix are more pertinent to the current treatment landscape.
Key issue 6: Health state utilities were associated with	No	The company reports a difference in health states utility of approximately 0.06 between end of the lead-in phase and at 24 months post-ED exposure. Whilst this does not provide a high quality of evidence, it suggests that the company's

treatment rather than health states, and the difference may be overestimated.		estimate of health utility of those treated with IV FIX treatment being 0.0672 less than those treated with ED may be more valid than the EAG's estimate of 0.042. The EAG acknowledges an impact from being free from injections within its estimate, but appears to discount the impact of freedom from fear of bleeding. The impact of needing to plan IV factor administration to perform certain activities and either missing out on unplanned activities, or participating in the knowledge that bleeding may result, and its attendant impact on QoL is a topic that frequently comes up in conversations in clinic with people with Haemophilia. Therefore, discounting this aspect of things would not appear valid from experience as a Haemophilia treater. Nonetheless, the quality of evidence to inform the magnitude of this effect is limited, with the lead-in phase comparison appearing to provide the best available comparison in the absence of a randomised controlled trial. The degree of certainty of conclusions based on this would necessarily be limited.

Additional issues

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Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: The company reported the proportion of participants with FIX levels <12%. This threshold was specified a priori in the study protocol, though no rationale was given for the choice.	3.2.2.5, page 38	Yes	The 12% factor level is a well-recognised figure within the Haemophilia treatment community. It derives from an observational study of annualised joint bleed rates in people with Haemophilia A of a range of severities, and therefore baseline factor levels (https://onlinelibrary.wiley.com/doi/10.1111/j.1365-2516.2011.02539.x). This study reported that the AjBR fell to zero once factor levels were 12% or above (see Figure 2). This has been widely extrapolated as the steady-state factor level needed to abolish joint bleeding in people with Haemophilia A and, by extension, Haemophilia B. Thus, the reason for reporting this is that the treatment community recognise the 12% FIX threshold as a potentially valuable proxy for people who should have a very low risk of joint bleeding. It should be noted, however, that this adds nothing of clinical value that is not captured by measurement of bleeding rates, and these latter are appropriately used in company's and the EAG's the assessments of clinical outcomes.

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

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Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case

Technical engagement response form

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B [ID3812]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

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You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

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If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **25 May 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	United Kindom Haemophilia Centre Doctors Organisation
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	The UKHCDO also owns the UKHCDO Limited, which runs the national haemophilia database (NHD). The NHD receives funds from commissioners and unrestricted grants from the industry for research projects and also undertakes an analysis of NHD data for specific questions funded by the industry.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	Not applicable

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: The company did not report evidence for the true change in FIX levels following treatment with ED in the HOPE-B	Yes	We appreciate the opportunity to respond to the queries raised in the External assessment group report. What follows is a commentary on key aspects of the external technical report provided as part of the technical stakeholder consultation, which we contend shows a limited appreciation of the management of haemophilia B and the design of clinical trials in rare diseases. The analysis submitted for the product is comparable to that presented for other gene therapy products for Haemophilia B over the past 7 to 8 years. The incidence of haemophilia B is 1:50,000, and there are around 200 individuals with severe haemophilia B in the UK. Therefore, the suggestion that gene therapy should have been subjected to a randomised controlled trial is impractical, and the FDA and EMA have recognised this for decades. Following a recommendation from FDA, all new studies of novel products now have a lead-in phase. Clinical experts and regulators accept that a lead-in phase helps establish a baseline for safety and efficacy, permitting analysis of non-inferiority and potential superiority to the prevailing standard of care. This trial design is not limited to gene therapy but to all new interventions in this group and other cohorts of rare diseases. We do not concur with the group that factor levels (peaks and troughs) on intravenous FIX clotting factor prophylaxis are an appropriate comparator, and

		there are several reasons detailed below. The dosing of CFs in standard care (in IU/Kg) is individualised to each person with haemophilia B, with trough levels tailored and adjusted to a target in an iterative process. There is a balance between what the patients think is feasible (treatment burden) and what patients and clinicians consider acceptable outcomes regarding bleed protection and continuation of routine activity. In the lead-in phase (Pipe, Leebeek et al. 2023) of the study, 57% of the patients used extended half-life (EHL) products, and 43% used standard half-life (SHL) products. The EHL products are modified using different biotechnological approaches which impact the drug's pharmacokinetics, both half-life and volume of distribution, i.e., where the drug circulates in addition to the intravascular space. In clinical trials, annualised bleed rates (ABRs) demonstrated that higher trough levels are required for some EHL-IXs where the extravascular distribution is reduced (Collins, Young et al. 2014). Since these EHL-FIX products are non-generic, with very variable pharmacokinetics, direct comparisons are difficult and potentially misleading since the efficacy per unit and assay properties differ between products. For example, in routine clinical practice and following both national guidelines and the recommendations in the SPC based on clinical trials, prophylaxis with Benefix (SHL-IX) and Alprolix (EHL-IX), clinicians aim for trough factor IX levels ≥ 2%, whereas with Idelvion and Refixia (EHL-IX) troughs more than 7 to 10% are aimed for, and dosage adjusted accordingly. (Powell, Pasi et al. 2013, Collins, Young et al. 2014, Santagostino, Martinowitz et al. 2016)
Key issue 2: Clinical outcomes in the HOPE-B study may overstate the potential benefits of ED	Yes	We disagree with this conclusion. The concern raised is about the potential impact of COVID-19 on activity. The assumption is that it would have reduced activity and thus reduced the risk of bleeding. We contend this is a highly speculative assumption; no evidence has been put forward to support the statement. The assumption that patients were less active has no evidence base and is contrary to real-world clinical observation. Patients continued to do exercises and DIY at home actively. The most significant risk factor for bleeds is lack of prophylaxis rather than participation in the activity. Prophylaxis was continued as before, and the only reduction in factor IX use observed during the Covid Pandemic was attributable to

		the moratorium in elective surgery. There is no evidence to suggest that the Covid Pandemic significantly affected the outcomes of the Hope B trial. The behaviour of patients and clinicians in clinical trials is not unique to this study, and studies are conducted per Good Clinical Practice. Patients are under more vigilant follow-up to document adverse events, but clinical advice in response to clinical symptoms is unchanged. Similarly, patients report bleeds to the trial sponsor pre and post-intervention for the same symptoms. Indeed this is reflected by apparent 'spontaneous' bleeds at FIX levels of 30 to 40%, which is not seen in patients with mild haemophilia. With improved prophylaxis, in our experience, it takes between 12 to 36 months for patient behaviour to change. There is a period of re-learning the disease phenotype, which requires active discussion between the patients and clinicians to help patients to distinguish between the pain of a bleed and arthritic pain. Most long-term studies demonstrate a reduction of ABRs over time, plateauing after 2 to 3 years. We also want to highlight that ABR demonstrates clinical effectiveness whilst coagulation factor level was used as a surrogate marker for modelling long-term durability. The clinical trial demonstrated a marked reduction in infusions (> 90%) from 72.5 to 2.5 per year.
Key issue 3: Comparative efficacy estimates of ED and prophylactic FIX treatments were unreliable	Yes	See our response to key issue 1. The ABRs reported in the lead-in phase are comparable to real-world data. Significantly, ABR in haemophilia is related to time spent at coagulation factor levels less than 1%, hugely influenced by adherence, frequency of infusion, dose, dose-interval and activity ((Collins 2012). Missed doses have the greatest effect on breakthrough bleeding, followed by delayed doses, which has been demonstrated in clinical trials. Although World Health Organisation (WHO) suggests that 85% adherence is good compliance, this has proven inadequate in haemophilia. Indeed, recent clinical trials of clotting factor concentrates in haemophilia have reported up to 98% adherence. Indeed compliance, once the expression is established, is not an issue with gene therapy. We also note the concerns about

		the uncertainty around trial procedures reflecting clinical practice, but this is true of any drug. There has been considerable discussion about randomised studies. The haemophilia community believes inter-patient variability is higher than intra-patient variability, hence the move to personalised prophylaxis, where regimens are tailored to an individual's bleeding pattern, lifestyle and coagulation factor pharmacokinetics. Further, this impacts sample size calculation to demonstrate any differences in outcomes. In our opinion, outcomes of current standard care are being compared to outcomes with a new treatment, notwithstanding the wide variation in standard care in routine clinical practice and access to treatment. This issue is present even for randomised controlled studies undertaken in many countries where "standard care" would need to be defined because of the wide variability of routine care. The lack of intervention would be inappropriate and unethical because there is a biological basis for the disease, and outcomes of untreated disease are well documented. We appreciate that this is not the question under consideration.
Key issue 4: Definition of treatment failure was at a low FIX activity level	Yes	The study entry was patients with factor IX activity ≤2%, which has been the standard for studies in this group. The decision to start prophylaxis is based partly on the factor level and the bleeding phenotype. All patients in the UK with a baseline level <3% should be offered the opportunity to have prophylaxis, particularly children with levels between 1 and 3% where a bleeding phenotype is yet to be established (Rayment, Chalmers et al. 2020). Many moderate HB (2-5% IX) do not bleed or require regular prophylactic treatment except for surgery or trauma. Prophylaxis will be offered to patients when the baseline has returned to 2 to 3% based on the bleeding phenotype, and a factor IX level of 2% is an acceptable definition of failure. We have also noted from other gene therapy studies that continuous expression of FIX at higher levels than this leads to the resolution of synovitis and of target joints, and loss of expression does not trigger regular bleeding until factor IX levels fall to about 2%.

Key issue 5: The durability extrapolation model was based on limited data and excluded non-responders	Yes	It is our understanding that two patients were excluded from the modelling. This exclusion was appropriate for the following reasons. One patient was excluded from the efficacy analysis because he had a partial dose (10% of the planned dose) due to a reaction during the infusion. One another was excluded as he had no expression level due to high titre neutralising antibodies. This is appropriate because patients with high titres of neutralising anti-AAV-5 antibodies during pre-treatment screening will not receive the treatment in routine clinical practice. Others were excluded and did not receive a dose of gene therapy because they failed the screening. It is reasonable to base the assessment of the efficacy and durability of gene therapy only on patients who have been treated and demonstrated some initial response. Long-term follow-up is necessarily limited in the context of a clinical trial, hence the need for modelling to estimate the likely durability of gene therapy. The projections for the durability of gene therapy in haemophilia B derived from these models are plausible, if not a little conservative since there is little fall-off in factor IX expression at the end of the observation period. Furthermore, the long duration of expression appears to be a feature common to most clinical trials of gene therapy in haemophilia B (Nathwani, Reiss et al. 2014, Nathwani, Reiss et al. 2018), in contrast to clinical trials of gene therapy for haemophilia A. Some clinical trials of haemophilia B gene therapy now have follow-up periods of 10-15 yrs (unpublished data). The gene therapy results in the two diseases (haemophilia B and A) should not be conflated, and data from one cannot be extrapolated to the other. The technical barriers and the outcomes of gene therapy for these two diseases are very different. A cut-off of 2% Factor IX expression seems reasonable as a definition of ultimate treatment failure since there is clinical evidence that most patients will not bleed spontaneously at 3% or more levels. If the modelling of the duration of gene therapy expression cannot be agreed upon, we would suggest that the alternative approach to payment being used in other European countries and North America be considered.This would envisage an annual payment to be made for a fixed period or for as long as the expression is >/=2%, whichever period is shorter. This

		shifts the financial risk to the manufacturer and avoids paying for a treatment that is no longer working. Should the duration of treatment be lifelong, it will become free of charge at the end of the agreed term of the agreement.
Key issue 6: Health state utilities were associated with treatment rather than health states, and the difference may be overestimated.	Yes	We draw attention to the long-established concept of the 'disability paradox', where patients typically report greater happiness and QoL across a wide range of health conditions than healthy people under similar circumstances (Albrecht and Devlieger 1999). This phenomenon is more marked in patients with inherited disorders because they do not have a normal baseline for comparison. It has been particularly challenging to assess the change in treatment burden, as no validated tool exists for this. Patients with chronic health conditions often undertake risk-benefit analyses about their treatment adherence. They can actively decide not to follow the recommendations because of time and other considerations, i.e. rationalised or reasoned non-adherence (Demain, Goncalves et al. 2015). Quality of life instruments are not particularly sensitive, and clinical experience suggests that they fail to capture significant benefits to patients that derive from reduced treatment burden and changes towards a new and more normal life relatively unburdened by disease.

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Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

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Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
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Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **25 May 2023**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	xxxxxxxxxxx
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Novo Nordisk Ltd
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	**N/A**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**N/A**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: The company did not report evidence for the true change in FIX levels following treatment with ED in the HOPE-B	No	No comment
Key issue 2: Clinical outcomes in the HOPE-B study may overstate the potential benefits of ED	No	No comment
Key issue 3: Comparative efficacy estimates of ED and prophylactic FIX treatments were unreliable	No	We agree with the EAG regarding the robustness of prophylaxis FIX trials in health technology assessment use. The EAG identified several issues surrounding these trials and the feasibility to inform a precise indirect treatment comparison such as the small sample size, the fact that all studies had a non-randomised, single-arm design and the heterogeneity of the populations. While these are issues related to the nature and rarity of the disease, the results should be interpreted with caution to their limitations.
Key issue 4: Definition of treatment failure was at a low FIX activity level	No	No comment

Key issue 5: The durability extrapolation model was based on limited data and excluded non-responders	No	No comment
Key issue 6: Health state utilities were associated with treatment rather than health states, and the difference may be overestimated.	No	No comment

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Population relevant to the decision problem	Section 2.4, page 22	No	The SmPC states that etranacogene dezaparvovec is indicated for the treatment of adult patients, and HOPE-B included adult patients only. However, the decision problem states that the treatment can be used by all people with moderately severe or severe haemophilia B, without any restriction noted for adults and adolescents.
Additional issue 2: Adherence in factor replacement prophylactic treatment	N/A	Yes	The economic analysis did not consider any scenario where the adherence rate of people treated with prophylactic treatment is reduced. Even though there is a paucity of evidence there are recently published evidence which suggests that not all patients fully comply with the treatment regime. For example, an observational study in Spain which assessed adult patients receiving factor VIII therapy showed that the mean adherence rate at the end of follow-up was 82.5% (Bonanad et al, 2020).

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAR	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
PLEASE DESCRIBE HERE

Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B [ID3812]

A Single Technology Appraisal

EAG Review of Company's Response to Technical Engagement Response

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Produced by

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Rider on responsibility for document

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This TE response is linked to ERG report

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1. INTRODUCTION

This document provides the External Assessment Group's (EAG) critique of the company's response to the technical engagement report produced by the National Institute for Health and Care Excellence (NICE) for the appraisal of etranacogene dezaparvovec for treating moderately severe or severe haemophilia B (ID3812).

An appraisal of the EAG's key issues following the company's response to technical engagement is provided in Section 2. The company provided changes to its economic model (Section 3). EAG critique is provided in Section 4 and the preferred EAG base case is presented in Section 5.

2. EAG REVIEW OF KEY ISSUES FOLLOWING TECHNICAL ENGAGEMENT

Issue 1: The company did not report evidence for the true change in FIX levels following treatment with ED in the HOPE-B

The company did not provide true baseline FIX levels for participants in the HOPE-B study due to their concerns that any measure provided would not be a fair representation of participants' FIX levels. They noted that FIX levels would vary according to the type, brand, dose and frequency of FIX replacement participants were receiving, and that fluctuations in FIX levels following prophylactic treatment meant that it would be challenging to identify a representative measurement. The EAG agreed with the latter of the company's concerns, and this was noted in this key issue in the EAG report. However, the EAG maintained that without a comparison of FIX levels between receiving ED and FIX replacement, it was not possible to determine the effect of ED on this outcome.

As noted in the EAG report, the company could have used several methods to represent FIX levels while on prophylaxis, and while these may not have been perfect due to the measurement difficulties, it would nevertheless be an improvement on hypothetical FIX levels assuming that participants were receiving no treatment, which was not a realistic scenario. The EAG was unconvinced by the company's rationale that the appropriate comparator for FIX levels would be no FIX replacement therapy, as people with moderate and severe haemophilia almost always receive FIX replacement therapy. A comparison with no treatment is also inconsistent with the decision problem for this appraisal.

Issue 2: Clinical outcomes in the HOPE-B study may overstate the potential benefits of ED

As HOPE-B was a single-arm trial, the lack of a comparator meant that study results may be influenced to an unknown extent by factors other than the treatment administered. During HOPE-B, the COVID-19 pandemic occurred, with wide-ranging impacts on the lives of people and societies worldwide. In England, greater restriction of activity was experienced by those people with certain health conditions, including some people with haemophilia. International responses to the pandemic varied widely, and it's difficult to conceptualise fully what impact the pandemic would have had on participants in the study. HOPE-B was conducted in 17 sites in the United States (US), 13 sites in the European Union (EU), and 3 sites in the UK. The 24-

month data available was largely based on a data cut in February 2022, at which point, the EAG estimated that many imposed restrictions would have been removed but some change to individual behaviours may still have been ongoing. This issue is important for this appraisal as bleeding rates may increase with higher levels of movement and physical activity. This may necessitate greater use of FIX replacement, and people may have been less likely to attend hospital appointments for FIX replacement due to the pandemic.

In its response to technical engagement, the company claimed that the lack of reported change in participants scores on the IPAQ, which is a measure of physical activity, was consistent with the pandemic having had little impact on the behaviour of people in the trial. The company did not report these data, which were presumably provided in the clinical study report (CSR) appendices for HOPE-B, which as noted in the EAG report were not provided by the company. The IPAQ short form contains seven questions that ask participants to report the amount of time that they spent walking, sitting, and doing moderate and vigorous activities in the past seven days. It is not possible to calculate domain-specific scores from the short-form questionnaire. The IPAQ questionnaire is not recommended for use in small trials, and there is no evidence for how responsive the measure is to changes in physical activity.[1] Several studies have reported poor correlation between results on the IPAQ and objective measures of activity.[1-3] The EAG also considered that it may be challenging for the domains of the IPAQ to assess the major changes in people's activity levels during COVID; for example, a minority of people in the total sample (N=54) may be engaged in weekly vigorous activity, while more participants may have reduced their use of public transport or their time spent in public venues, which may not be captured by the measure. In contrast, other published evidence has shown that activity levels were reduced in people with haemophilia B during the pandemic.[4] Overall, the EAG did not consider the lack of a change in IPAQ to be a strong source of evidence to resolve this issue.

In its report, the EAG had suggested that longer follow-up data may help to provide more confidence about this issue, as (to a greater or lesser extent around the world) societies have returned to normal activities. The company suggest that the following patterns in the data over time reduced the likelihood that the pandemic affected participants:

- Annualised spontaneous bleeding events, which are unrelated to physical activity or trauma, reduced following treatment with ED
- The reduction in annualised (all) bleeding rate (ABR) was maintained at 24-months' follow-up

- There was no rebound in FIX consumption and ABR between months 7 – 18 and months 18-24

The EAG disagreed with the company that the above data were conclusive of no impact of the pandemic on participants' outcomes. Firstly, reporting annualised bleeding rates across a period of time (ranging from 6 to 18 months in length) makes it difficult to determine patterns in the outcome over time. It was challenging to determine what length of follow-up in the trial would be necessary to resolve this issue, given the variability in response to the COVID pandemic internationally, however a time period as far from baseline as possible would provide greater clarity. The EAG was unclear whether a comparison between 7-18 and 18-24 months would be sufficient, though in any case the company did not supply these data for the EAG to consider.

Secondly, the EAG acknowledged the point made by the company that rates of spontaneous bleeds may be less impacted by restrictions on daily activities, and that reductions in spontaneous bleeds were evident following treatment with ED. The EAG therefore considered it plausible that reductions in spontaneous bleeds could be more confidently associated with ED than other bleed types. That said, as spontaneous bleeds are those where there is no obvious cause, the EAG was uncertain if it was established that changes in physical activity would not affect the rate of spontaneous bleeds. Within the timeframe of its response, the EAG was unable to conduct a thorough literature review to identify evidence for this point. However, the EAG was not suggesting that all of the clinical benefits, including the reductions in bleeding, shown in the HOPE-B trial, were caused by changes in physical activity. As noted in the EAG report (Section 3.6.2), the uncertainty in the findings of the HOPE-B trial related more to the *magnitude* of the treatment effect, rather than the *presence* of an effect overall. The EAG considered that the evidence demonstrated that ED may have meaningful clinical benefits in in people with moderately severe and severe haemophilia B, though highlighted uncertainty in whether *some* of the shown benefit could be ascribed to other causes, such as the impact of the COVID pandemic. It is therefore entirely plausible that participants in the trial could have benefitted from reductions in spontaneous bleeding due to ED and also reductions in all cause bleeding events due to a combination of ED and other factors including a change in lifestyle and physical activity.

Overall, the EAG considered the balance of probabilities to be that the pandemic affected the lives of people with haemophilia B in ways that were likely to influence clinical outcomes to an

unknown extent. The HOPE-B trial is ongoing and trial data up to five years are planned, at which point a fuller understanding of any potential impact may be clearer.

Finally, in response to this issue the company stated that it had consulted with the UK principal investigators in the HOPE-B trial who confirmed that they had followed "Good Clinical and Research Practice" when making decisions on management of bleeding episodes. The EAG assumed that within the timeframe of technical engagement, it was not possible for the company to consult with other trial site investigators. The EAG also assumed that these conversations happened informally during the technical engagement phase, as no documents or detailed information were provided to the EAG about these conversations in the company's response. The EAG was unsure what "Good Clinical and Research Practice" was in this context, as to its knowledge this did not refer to any clinical practice guidelines for haemophilia B. The EAG accepted that no clinician would jeopardise their duty of care for a person with a bleeding event, though considered it plausible that clinicians may make different decisions about when to re-initiate prophylactic treatment within the rules of a clinical trial. This may be particularly true if there are uncertainties about the threshold at which prophylactic FIX replacement should be re-initiated (as discussed in Key Issue 4). The company proposed that the threshold for re-initiating prophylactic therapy may be different pre- and post- gene therapy treatment, though while this was proposed by clinical experts in its advisory board,[5] the EAG was not presented with evidence to substantiate this. As the rules on the use of prophylactic treatment differed between the lead-in phase and following treatment, the EAG considered that its concern that this may have contributed to the reduction in FIX replacement use was unresolved.

Issue 3: Comparative efficacy estimates of ED and prophylactic FIX treatments were unreliable

The EAG thanks the company for the provision of treatment uptake data that distinguished between prophylactic and on-demand FIX replacement. As stated in the EAG report, the outcomes of analyses with BeneFIX were particularly unreliable, though all the results of the NMAs were highly uncertain due to the lack of high-quality evidence in FIX replacement strategies. As stated previously, this issue was beyond the control of the company, who conducted the best possible analyses given the available evidence. However, this issue remained a concern.

Issue 4: Definition of treatment failure was at a low FIX activity level

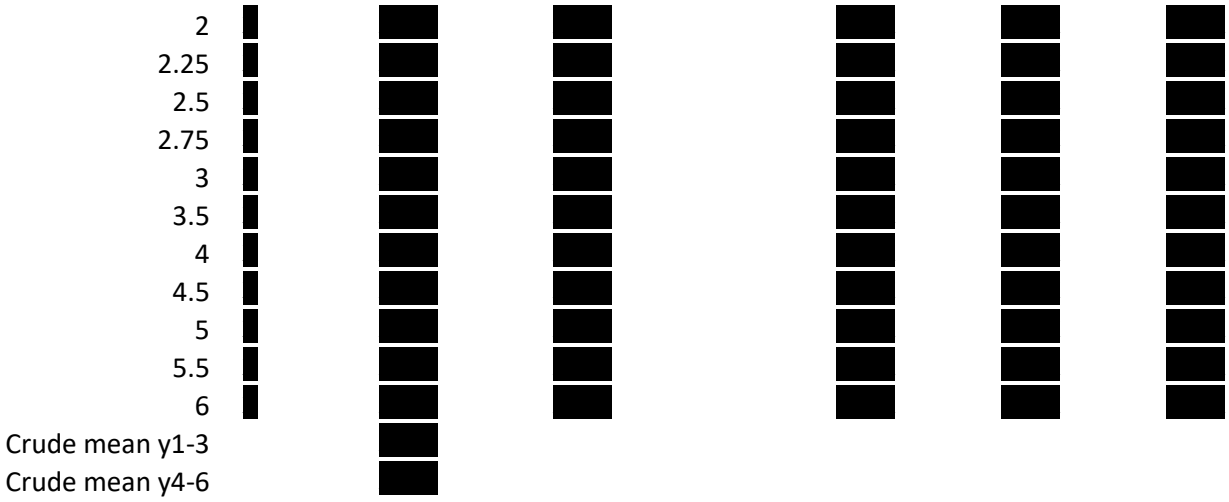
To inform this issue, the company provided details of an advisory board conducted with expert clinicians in the UK[5] along with additional quotes from the transcript that were provided in their response. As part this advisory board, the clinicians agreed with the use of a 2% threshold for re-initiating prophylactic treatment. It was noted that this may be a conservative threshold, but that treatment with ED may result in additional FIX residing in extravascular space that may mean additional efficacy. The EAG considered this evidence to be very useful and was grateful to the company for providing this, though the EAG was nevertheless unable to resolve the discrepancy between the views of clinicians in the advisory board and advice given to the EAG by its own expert. Ultimately, the EAG determined that this issue may require additional input from clinical experts, and/or additional experience with using ED in clinical practice, to resolve. Although, the EAG noted that company advisors proposed that a clinically significant response following ED was a FIX level that did not necessitate FIX replacement treatment without spontaneous bleeds, but spontaneous bleeds were still present in 20.4% of the sample in the 7 – 24 month follow-up of the HOPE-B trial. The EAG therefore considered it plausible that a 2% threshold may not be sufficient for some people treated with ED.

Issue 5: The durability extrapolation model was based on limited data and excluded non-responders

The EAG agreed that long-term data were unavoidably sparse with new treatments in rare diseases and thanks the company for providing the six-year follow up data on the nine-participant cohort study AMT-060-01. The company claimed that the data showed no evidence of treatment waning over this period. However, due to the small sample size of the cohort such a claim can never be demonstrated statistically at conventional levels of significance, thus neither a persistent nor declining treatment effect can be ruled out. The EAG noted that the crude mean of mean FIX activity level over years 1-3 was [redacted], whilst over years 3.5-6 was [redacted], which may suggest a balance of probabilities favouring a decline (Table 1).

Table 1 FIX activity by visit - one stage aPTT assay (from company TE response extracted from Appendix C, Table 14.2.1)

Year	n	Mean	SD	SE	LCL	UCL
1	[redacted]					
1.25						
1.5						
1.75						



The EAG agreed that the Shah analysis[6 7] was appropriately conducted and thanks the company for clarifications around the two exclusions from the Shah analysis. These appeared to be reasonably justified. The EAG agreed that the uncertainty was the lowest possible level subject to the available evidence, but nevertheless the 'lowest possible' still represented a great deal of decision uncertainty.

Given the uncertainty around durability, the EAG's analysis handled durability outside of its base case (using the company's base case), instead presenting a threshold analysis. Therefore, the EAG did not alter its base case in response to this.

Issue 6: Health state utilities were associated with treatment rather than health states, and the difference may be overestimated (plus additional issue raised by the company (1): Hernandez-Alva mapping function).

The EAG noted the company's use of NICE's preferred algorithm for mapping EQ-5D-5L to EQ-5D-3L (Hernandez-Alva et al.)[8] in place of the Van Hout algorithm[9], and that this reduced the treatment-related difference in health state utility from ED from approximately [redacted] to [redacted]. The EAG noted that the company did not comment on this reduction but nevertheless incorporated it into its base case. The EAG therefore updated its own base case to reflect the change.

3. UPDATED COMPANY BASE CASE ANALYSES

In response to the technical engagement report, the company presented an updated base case, the assumptions for which are reproduced here as

Table 2: Reproduction of Company TE response, Appendix F Table 1 summarising Company's revised base case with EAG comments

, with EAG comments added. In summary, the company accepted the EAG's preferred base case assumptions for (1) a gradual 24-month phase in of a reduction in bleeding rates following administration of ED and (2) inclusion of AE costs and disutilities beyond one year for ED. The company disagreed with the EAG's base case regarding (1) a 5% FIX activity definition of failure, and (2) a six-month time to steady state.

The company also provided alternative health state utilities based on the Hernandez-Alva cross-walk algorithm[8] in place of the Van Hout,[9] and incorporated two of the EAG's scenarios as their base case (follow-up visits conducted by a haematologist rather than a nurse and starting age of 18 rather than 41.5 years).

Importantly, the company included all eight discrete treatment strategies in its revised analysis and the EAG thanks the company for doing this. There were now four strategies involving ED: ED followed by BeneFIX, ED followed by Refixia, ED followed by Alprolix and ED followed by Idelvion, and four excluding ED: BeneFIX, Refixia, Alprolix and Idelvion.

The company's revised deterministic and probabilistic base case are reproduced here in Table 3 and Table 4 (showing only fully incremental analysis, excluding pair-wise comparisons). In all cases, ED followed by BeneFIX on ED failure was the most cost-effective strategy at conventional willingness to pay thresholds (£20,000 to £30,000 per QALY gained).

Table 2: Reproduction of Company TE response, Appendix F Table 1 summarising Company's revised base case with EAG comments

Submission base case	EAG preferred assumptions	Revised base case	Analysis found in table number	EAG comment
3 weeks for etranacogene dezaparvovec to a reach steady state	6-months for etranacogene dezaparvovec to a reach steady state	No change from the submission base case, given the overlap in modelling with the transition rates assumption, and the strong clinical evidence that no prophylaxis treatment is necessary in the first 6 months of the treatment.	Analysis group 1, **Error! Reference source not found.**	This issue affected the model in terms of cost of prophylactic IV FIX during the period following ED infusion. On further consideration of the data, the EAG agreed that the equivalent of 3-weeks dosing with IV FIX in the first six months was appropriate and therefore modified its base case to agree with the company.
Transition rates amongst Markov states for etranacogene dezaparvovec were determined by bleeds rates from the ITC report.	Transition rates amongst Markov state for etranacogene dezaparvovec gradually decrease from the rates of Refixia for 24 months until they are determined by bleeds rates from the ITC report.	As per EAG preferred assumption with the extension to all technologies	Analysis group 1, **Error! Reference source not found.**	No further comment.

Submission base case	EAG preferred assumptions	Revised base case	Analysis found in table number	EAG comment
Follow-up visits were conducted by an NHS nurse	Follow-up visits are conducted by a haematologist	As per EAG preferred assumption	Analysis group 1, **Error! Reference source not found.**	Whilst this was a scenario explored in the EAG's analysis, this was not a preferred assumption. However, the EAG was happy to adopt this in its own base case.
Adverse events last only the first year for the intervention and the comparator	Adverse events last a lifetime for the intervention and one year for the comparator only	Adverse events last a lifetime for the intervention and the comparators	Analysis group 1, **Error! Reference source not found.**	The EAG agreed that for consistency, AEs should also last a lifetime in the IV FIX arms. The EAG noted that whilst utilities were adjusted for this in the company's revised model, costs were not. The EAG therefore added in the costs of AEs beyond year 1 for the IV FIXes
Quality of life is sourced from the EQ-5D-5L quality of life measures from the HOPE-B, with the preference-based measures of utility being the EQ-5D-3L values, derived using the van Hout et al. (2012) mapping algorithm	0.042 utility increment of the intervention over the comparators, derived on the 'usual activity' coefficients of Dolan et al. (1997), and a plus extra for the 'further' benefits of etranacogene dezaparvovec	Quality of life is sourced from the EQ-5D-5L quality of life measures from the HOPE-B, with the preference-based measures of utility being the EQ-5D-3L values, derived using the NICE recommended Hernandez et al. (2017) mapping function.	Analysis group 2, **Error! Reference source not found.**	The EAG noted the revised health state utilities based on the Hernandez-Alva mapping function (which is the preferred mapping algorithm in the NICE manual), and that this reduced the difference in health state utility between ED and the IV FIXes from approximately 0.06 to 0.02. The EAG noted that the company incorporated this into their model and provided no commentary in its response. The EAG adopted this into its preferred base case.
Age at baseline of 41.5 years, consistent with the average age of patients in the HOPE-B trial	The EAG had raised the issue that the marketing authorisation license begins at the age of 18.	Age at baseline now reflects the marketing authorisation license	Analysis group 3, **Error! Reference source not found.**	Whilst this was a scenario explored in the EAG's analysis, this was not a preferred assumption. However, the EAG was happy to adopt this in its own base case.

Abbreviations: EAG, External Assessment Group; FIX, Factor IX; ITC, indirect treatment comparison; IV, intravenous

Table 3 Revised Company Base Case (deterministic)

Technology	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER
Etranacogene dezaparvovec (BeneFIX)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etranacogene dezaparvovec (Alprolix)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etranacogene dezaparvovec (Idelvion)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etranacogene dezaparvovec (Refixia)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-year

Source: Table 6, TE response Appendix F

Table 4 Revised company base case (probabilistic)

Technologies	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER**	**Probability of cost-effectiveness (£30,000/ QALY)**
Etranacogene dezaparvovec (BeneFIX)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etranacogene dezaparvovec (Alprolix)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER	Probability of cost-effectiveness (£30,000/ QALY)
Etranacoegene dezaparvovec (Idelvion)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etranacogene dezaparvovec (Refixia)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-year

Source: Table 10, TE response Appendix F

4. EAG CRITIQUE OF THE COMPANY ANALYSES

The EAG was able to replicate the scenarios in the company's revised base case but noted that adverse event (AE) costs after year 1 for IV FIXes had been omitted. The EAG therefore corrected this in the company's decision model. This led to a small increase in the cost of IV FIX treatments. A corrected company base case is presented in Section **Error! Reference source not found.** below.

The EAG noted that the company's revised probabilistic analysis was conducted with 1000 reps, and that this was insufficient to generate stable results; and repeated runs generated widely fluctuating estimates of costs and QALYs. The EAG therefore repeated the probabilistic analysis with 10,000 simulations. Time constraints prevented a formal assessment of stability, but repeated runs suggested a substantial improvement in stability.

The EAG noted that mean QALYs in the probabilistic analysis were lower for IV FIXes and higher for ED strategies than those reported in the deterministic results. In a non-linear model the probabilistic and deterministic results will differ, and the means from the probabilistic analysis are more informative for decision making.[10] Barring mathematical errors, the EAG believed this difference was most likely due to skewed distributions for bleeding rates but was not able to verify this within the timeframes available.

The full pathway analysis provided by the company (comprising all eight discrete strategies possible with the five treatments considered) was welcomed by the EAG, allowing identification of the most efficient overall pathway. The EAG noted that whilst pathway analyses provide a *de facto* appraisal of all treatments for a given condition, the remit of this analysis was for ED only. Thus, for ED to be cost-effective, it must be included within the most efficient pathway identified from a fully incremental analysis. Mathematically this was identical to identifying the pathway with the highest net benefit at a given willingness to pay.

Finally, the EAG accepted the company's assumption of a time to steady state of three weeks rather than six months. This assumption affected the model solely in terms of the cost of additional IV FIX during the first six months post ED administration. On further consideration of the evidence, the EAG agreed that the equivalent of three weeks' IV FIX was more consistent with the data.

5. UPDATED EAG BASE CASE ANALYSES

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER	Probability of cost-effectiveness (£30,000/ QALY)
Etranacogene dezaparvovec (BeneFIX)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etranacogene dezaparvovec (Alprolix)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etranacoegene dezaparvovec (Idelvion)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etranacogene dezaparvovec (Refixia)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Outstanding areas of disagreement between the company and EAG were (1) 5% vs 2% IV FIX activity level for the definition of treatment failure and (2) durability of the intervention.

In the following, the EAG presents a corrected version of the revised company base case, which includes the omitted AE costs for IV FIX. This comprised both deterministic (Table 5) and probabilistic (Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-year

Table 6) analyses (probabilistic analyses conducted with 10,000 simulations). Drug prices were at list prices except for ED which included the confidential PAS discount. Updated EAG base case results then follow, focusing on the definition of treatment failure and the durability threshold analysis. Analyses including confidential discounts for all drugs are provided in the confidential appendix.

5.1. Corrected company base case

The most efficient strategy was ED followed by BeneFIX: the ICER of the next most efficient option (ED followed by Alprolix) cost approximately an extra [redacted] per QALY gained, substantially above the usual maximum of £20,000 to £30,000 the NHS is typically willing to pay (Table 5 and Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-year

Table 6).

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER	Probability of cost-effectiveness (£30,000/ QALY)
Etranacogene dezaparvovec (BeneFIX)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etranacogene dezaparvovec (Alprolix)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etranacoegene dezaparvovec (Idelvion)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etranacogene dezaparvovec (Refixia)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 5 EAG corrected revised company base case (deterministic)

Technology	Total Costs (£)	Total QALYs	Incremental Costs (£)	Incremental QALYs	ICER
Etranacogene dezaparvovec (BeneFIX)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etranacogene dezaparvovec (Alprolix)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etranacogene dezaparvovec (Idelvion)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etranacogene dezaparvovec (Refixia)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-year

Table 6 EAG corrected revised company base case (probabilistic)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER	Probability of cost-effectiveness (£30,000/ QALY)
Etranacogene dezaparvovec (BeneFIX)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etranacogene dezaparvovec (Alprolix)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etranacoegene dezaparvovec (Idelvion)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etranacogene dezaparvovec (Refixia)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life-year

5.2. Updated EAG base case

The EAG accepted the company's base case assumption of a three-week time to steady state, the inclusion of impacts of adverse events for life on cost and outcomes for all treatments (ED and IV FIXes), and the calculation of health state utilities with the Hernandez-Alva algorithm.

The company accepted the EAG's preferences for a 24 month lead-in period for bleeding rates, and incorporated the EAG's scenarios regarding haematologist-led follow-up visits in place of a nurse, and a starting age of 18 years in place of 41.5.

Remaining areas of divergence were the 5% vs 2% FIX activity definition of treatment failure and durability. Table 7 and Table 8 show the impact of the 5% failure definition (deterministic and probabilistic results respectively), and durability is explored in the scenario analysis.

5.2.1. Definition of treatment failure: 2% vs 5% FIX activity levels

Results under the EAG's preferred assumptions were not materially different from the company base case: ED+BeneFIX remained the most cost-effective treatment strategy, as the next most efficient strategy (ED+Alprolix) cost approximately [redacted] for every extra QALY gained, substantially above typical willingness to pay thresholds of £20,000 to £30,000 per QALY (Table 7 and Table 8). These results were contingent on the validity of the assumed durability function, which is explored in Section 5.2.2.

Table 7 EAG's preferred model assumptions (deterministic)

Preferred assumption	Sect. in EAG report	Comparators	Costs	QALYs	ICERs	ICER change from base case	NMB @ £20k	NMB @ £30k
EAG corrected company base case	**Error! Reference source not found.**	ED+BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		ED+Alprolix	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		ED+Idelvion	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		ED+Refixia	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
EAG preferred base case assumptions								
5% FIX activity definition of failure	**Error! Reference source not found.**	ED+BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		ED+Alprolix	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		ED+Idelvion	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		ED+Refixia	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Cumulative		ED+BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		ED+Alprolix	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		ED+Idelvion	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		ED+Refixia	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]

Preferred assumption	Sect. in EAG report	Comparators	Costs	QALYs	ICERs	ICER change from base case	NMB @ £20k	NMB @ £30k
		Idelvion	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]

Abbreviations: EAG, external assessment group; ICER, incremental cost effectiveness ratio; NMB, net monetary benefit; QALY, quality-adjusted life-year

Note cumulative was identical to 5% FIX activity definition.

Table 8 EAG's preferred model assumptions (probabilistic)

Preferred assumption	Sect in EAG report	Comparators	Costs	QALYs	ICERs	ICER change from base case	NMB @ £20k	NMB @ £30k
EAG corrected company base case	**Error! Reference source not found.**	ED+BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		ED+Alprolix	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		ED+Idelvion	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		ED+Refixia	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
EAG preferred base case assumptions								
5% FIX activity definition of failure	**Error! Reference source not found.**	ED+BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		ED+Alprolix	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		ED+Idelvion	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		ED+Refixia	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		Alprolix	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
Cumulative		ED+BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		ED+Alprolix	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		ED+Idelvion	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		ED+Refixia	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		BeneFIX	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]

Preferred assumption	Sect in EAG report	Comparators	Costs	QALYs	ICERs	ICER change from base case	NMB @ £20k	NMB @ £30k
		Alprolix	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		Idelvion	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]
		Refixia	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]

Abbreviations: EAG, external assessment group; ICER, incremental cost effectiveness ratio; NMB, net monetary benefit; QALY, quality-adjusted life-year

Note cumulative was identical to 5% FIX activity definition.

5.2.2. Durability

Given the uncertainty in durability, the EAG conducted scenario analyses to identify the minimum durability required to yield an ICER below £20,000 and £30,000. Note that the definition of durability was the point at which IV FIX was resumed, and so whether this was at 2% or 5% IV FIX activity was irrelevant to this analysis.

The company's preferred durability function was based on the Shah et al.[6 7] extrapolation, comprising a gradual decline in durability over time. For ease of analysis, the EAG's durability analysis assumed a step function of 100% durability until year n, dropping to zero immediately after.

Results are presented in Figure 1 and Figure 2 with data in the Appendix. A strategy including ED became the most cost-effective at a durability of approximately 9.2 years, and this was largely insensitive to whether the threshold was £20,000 or £30,000.

Interpretation

Based on the step function, this implied that every patient must experience a durability of at least 9.2 years to yield an ICER below £20,000 per QALY. In reality, a gradual decline was more plausible. Thus, whatever the actual functional form of the durability function, as long as the mean durability was at least 9.2 years, the ICER of ED+BeneFIX vs it's next best alternative (BeneFIX alone in this case) would be below £20,000. Due to discounting of future costs and benefits, the minimum mean durability will need to be slightly above this, depending on the shape of the durability function (note the key statistic was the mean not the median durability, as functions can have the same median but very different means).

Figure 1 Durability threshold analysis, £20,000 WTP threshold

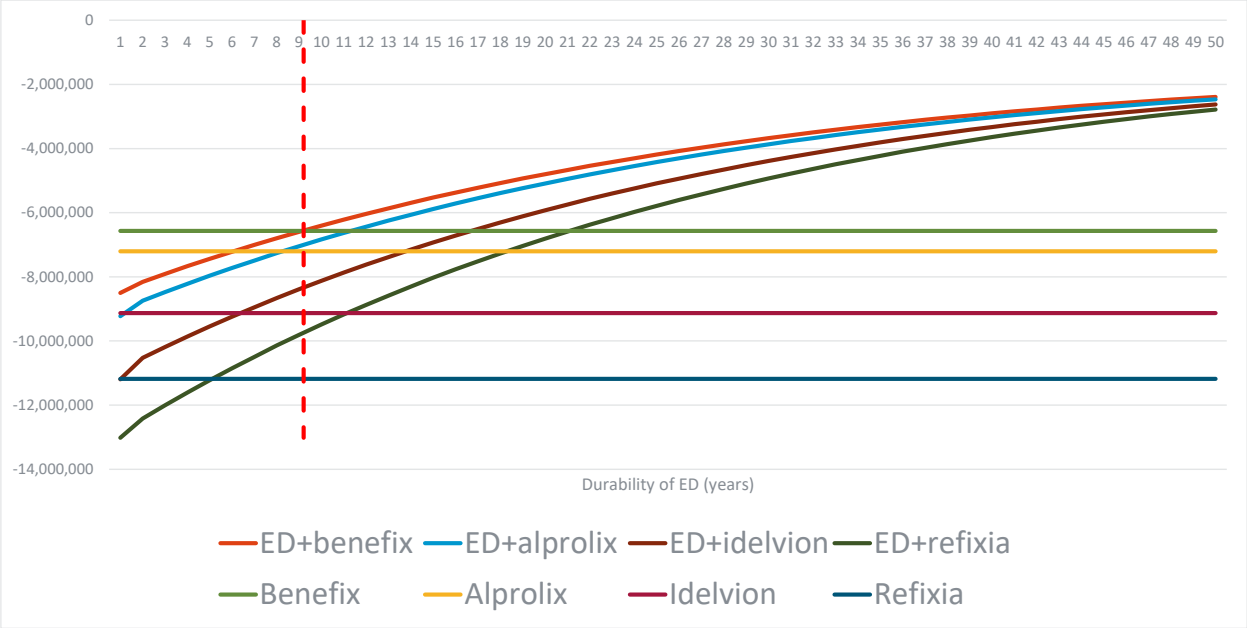
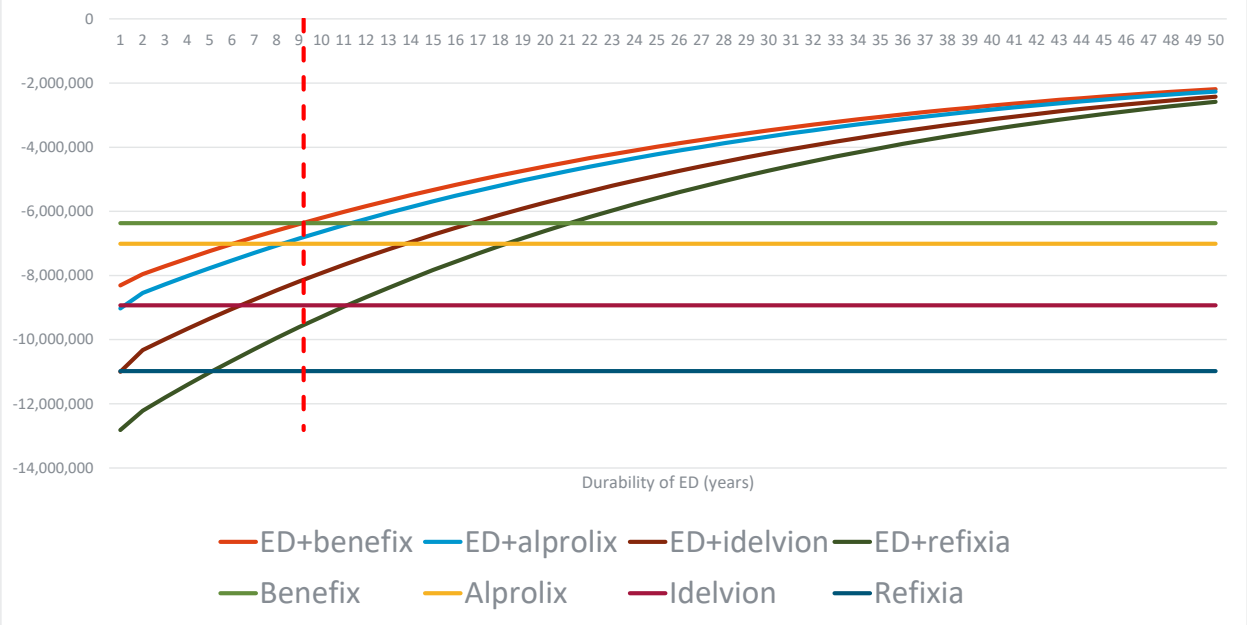


Figure 2 Durability threshold analysis, £30,000 WTP threshold



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7. APPENDIX: DURABILITY THRESHOLD ANALYSES DATA

Table 9 Durability threshold analysis, £20,000 WTP threshold

Years	NMB ED+benefix	ED+alprolix	ED+idelvion	ED+refixia	Benefix	Alprolix	Idelvion	Refixia	Winner
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Benefix
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Benefix
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Benefix
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Benefix
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Benefix
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Benefix
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Benefix
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Benefix
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Benefix
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
31	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
33	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
35	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
37	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
38	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
39	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
41	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix

	NMB								
Years	ED+benefix	ED+alprolix	ED+idelvion	ED+refixia	Benefix	Alprolix	Idelvion	Refixia	Winner
42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
43	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
46	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
47	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix

Table 10 Durability threshold analysis, £30,000 WTP threshold

	NMB								
Years	ED+benefix	ED+alprolix	ED+idelvion	ED+refixia	Benefix	Alprolix	Idelvion	Refixia	Winner
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Benefix
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Benefix
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Benefix
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Benefix
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Benefix
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Benefix
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Benefix
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Benefix
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Benefix
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
25	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
26	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
27	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix

Years	NMB ED+benefix	ED+alprolix	ED+idelvion	ED+refixia	Benefix	Alprolix	Idelvion	Refixia	Winner
28	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
29	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
31	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
32	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
33	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
34	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
35	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
37	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
38	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
39	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
40	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
41	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
43	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
44	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
46	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
47	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
48	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
49	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix
50	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	ED+benefix