Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B

For public – redacted

Technology appraisal committee D [12 July 2023]

Chair: Megan John

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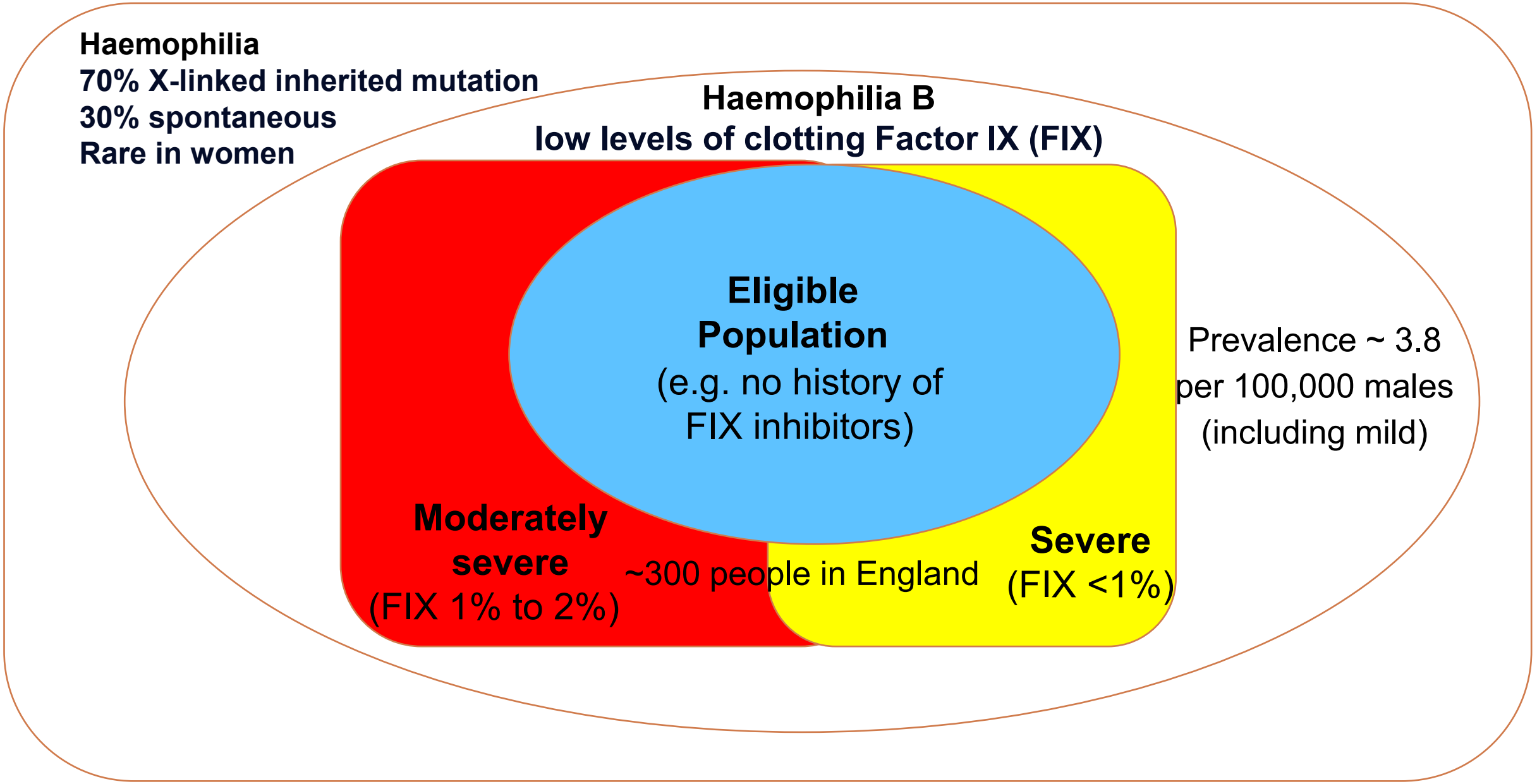
Company: CSL Behring

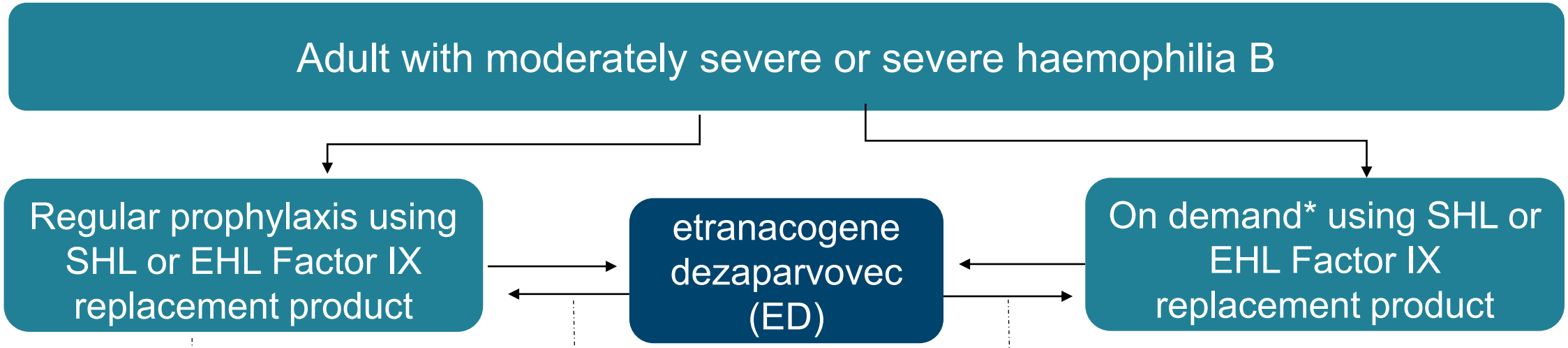
Background on moderately severe or severe haemophilia B



NICE

Treatment pathway

Proposed positioning of etranacogene dezaparvovec is mainly displacing FIX prophylaxis but "could displace on-demand treatment"



- Idelvion
- Alprolix
- Refixia
- BeneFIX

Re-introduction of prophylactic IV FIX if treatment failure on ED

Patients may receive ad- hoc FIX replacement following ED treatment

Note: 'On demand only' not included in economic model

Proposed positioning for etranacogene dezaparvovec

*Company: "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".

ED, etranacogene dezaparvovec; EHL, extended half-life; IV, intravenous; SHL, standard half-life; FIX, factor IX

Patient perspectives

Submission from The Haemophilia Society

- Having bleeds is not only painful physically but also cause great mental distress as demonstrated by 'The inherited bleeding disorders patient survey' first conducted in 2020 and repeated in 2022
- Significant impact on family-life, day-to-day activities, travelling and career
- Treatment options better than they were a few years ago but still time consuming, awkward to travel with → substantial unmet need remains
- Etranacogene dezaparvovec has potential to reduce long-term joint damage and make it easier for people to have required joint surgery, reduce pain, improve mobility, reduce burden of treatment and improve mental health
- Maintenance of FIX expression and impact on suitability for future gene therapies key considerations for people with haemophilia when deciding whether to opt for gene therapy.

"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."

"Most people with haemophilia B have anxiety or worry about their condition and many still develop joint damage over time"

ED, etranacogene dezaparvovec; FIX, factor IX

Clinical perspectives

Submission from United Kingdom Haemophilia Centre Doctors Organisation (UKHCDO)

- Current standard of care for severe haemophilia B requires the self-infusion or infusion by caregivers between 1 to 2 times a week → substantial treatment burden. Some people have challenges with venous access, requiring more than one infusion attempt
- A clinically significant response is to stop the need for regular prophylaxis without spontaneous bleeding
- Treatment aims to reduce mortality and morbidity, mainly focussed on the joints with severe disabling arthropathy
- With current regimens, people continue to have spontaneous or minimally provoked bleeds → maybe due to less than adequate regimens or adherence
- Delivery of the gene therapy requires consolidation to a few specialist centres to ensure appropriate oversight and follow up.

"Gene therapy is a paradigm shift in haemophilia care and opens up possibilities for long-term remission and potential cure"

"The patients need to be supported by the MDT team in their journey, as both success and failure have a significant psychological impact."

Potential equality and stakeholder raised issues

- Company & SH: Moderate and severe haemophilia B is rare in women and the pivotal phase III clinical trial (HOPE-B) did not include women
- SH: AAV vectors can lead to liver toxicity and consideration should be given on use in people with cirrhosis or extensive fibrosis
- SH: Dosing of etranacogene dezaparvovec is based on weight and that there is some suggestion that high doses of AAV vectors may be associated with higher risks
- SH: If the treatment is to be delivered in a small number of specialist centres, consideration should be given to ensure equitable access to treatment for those who are more distant from those centres
- Clinical experts: consideration required for people for whom English not first language, learning disabilities and for those with speech, sight or hearing impairment. Consideration also required for people with impaired mobility or who do not have the resources to attend the hospital regularly.

NICE technical team considerations

- Issues related to differences in prevalence or incidence of a disease cannot normally be addressed in a technology appraisal recommendation
- Access to treatments is an implementation issue that cannot be addressed in a technology appraisal recommendation.

AAV, adeno-associated virus; HIV, human immunodeficiency virus; SH, stakeholder scoping workshop

Key issues

Issue	Resolved?	ICER impact
Calculation of change in FIX levels	No – for discussion	None
Magnitude of clinical benefits reported in HOPE-B	No – for discussion	Unknown
Reliability of ITC	Partially – for discussion	Unknown
Definition of treatment failure	No – for discussion	Large
Durability of treatment effect	No – for discussion	Large
Health state utilities	Yes*	Small

*Updated at technical engagement using Hernandez et al. (2017) mapping function to map EQ-5D-5L from the HOPE-B trial to EQ-5D-3L values. Updated values included in both company and EAG base cases

FIX, factor IX; ITC, indirect treatment comparison

Etranacogene dezaparvovec (Hemgenix, CSL Behring)

Technology details

Marketing authorisation	• Conditional MHRA marketing authorisation granted March 2023 for "the treatment of severe and moderately severe haemophilia B in adults without a history of Factor IX (FIX) inhibitors"
Mechanism of action	• Recombinant adeno-associated virus-5-based gene therapy designed to introduce a copy of a gene encoding the Padua variant of human coagulation FIX • Administration results in cell transduction and increase in circulating FIX activity
Administration	Single-dose intravenous infusion
Price	• List price of £2,600,000 per treatment for a single-dose of etranacogene dezaparvovec (1×10^{13} genome copies/mL concentrate for solution for infusion) • Company has agreed confidential patient access scheme for etranacogene dezaparvovec

FIX, factor IX

Decision problem (1/2)

Population and intervention from the scope

	Final scope	Company	EAG comments
Population	People with moderately severe or severe haemophillia B	As per final scope	• Principal clinical evidence (HOPE-B) consistent with MA • Only 18.5% of people in the study had moderately severe disease → likely representative
Intervention	Etranacogene dezaparvovec (ED)	As per final scope	• Noted that ED would be administered in conjunction with standard care including FIX replacement therapy • Evidence presented by company suggested lower rate of FIX replacement in ED arm→ EAG noted some uncertainty about magnitude of this difference (addressed in key issue 2)

EAG, Evidence Assessment Group; ED, etranacogene dezaparvovec; FIX, factor IX; MA, marketing authorisation

Decision problem (2/2)

Comparators and outcomes from the scope

	Final scope	Company	EAG comments
Comparators	Established clinical management* (including prophylaxis and on-demand treatment)	• Mainly prophylaxis with on-demand option used in some patients • Very small cohort of patients using on-demand only FIX treatment may be eligible for ED	• Agree prophylactic FIX replacement most appropriate comparator • On demand only treatment not permitted by the clinical study (HOPE-B) inclusion criteria and not considered within company's economic model
Outcomes	Change in FIX levels; need for further treatment with FIX injections; ABR; durability of response to treatment; complications of the disease; adverse effects of treatment; HRQoL	As per final scope	Company presented evidence for all scoped outcomes

*Note: standard half-life products (e.g. BeneFIX) must be given every 2-3 days. Extended half-life products (e.g. Alprolix, Idelvion, Refixia) allow the frequency of injections to be reduced to once every 1-2 weeks.

ABR, annualised bleeding rate; EAG, Evidence Assessment Group; ED, etranacogene dezaparvovec; FIX, factor IX; HRQOL, Health-related quality of life; MA, marketing authorisation

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Key clinical trial: HOPE-B

Clinical trial designs and outcomes

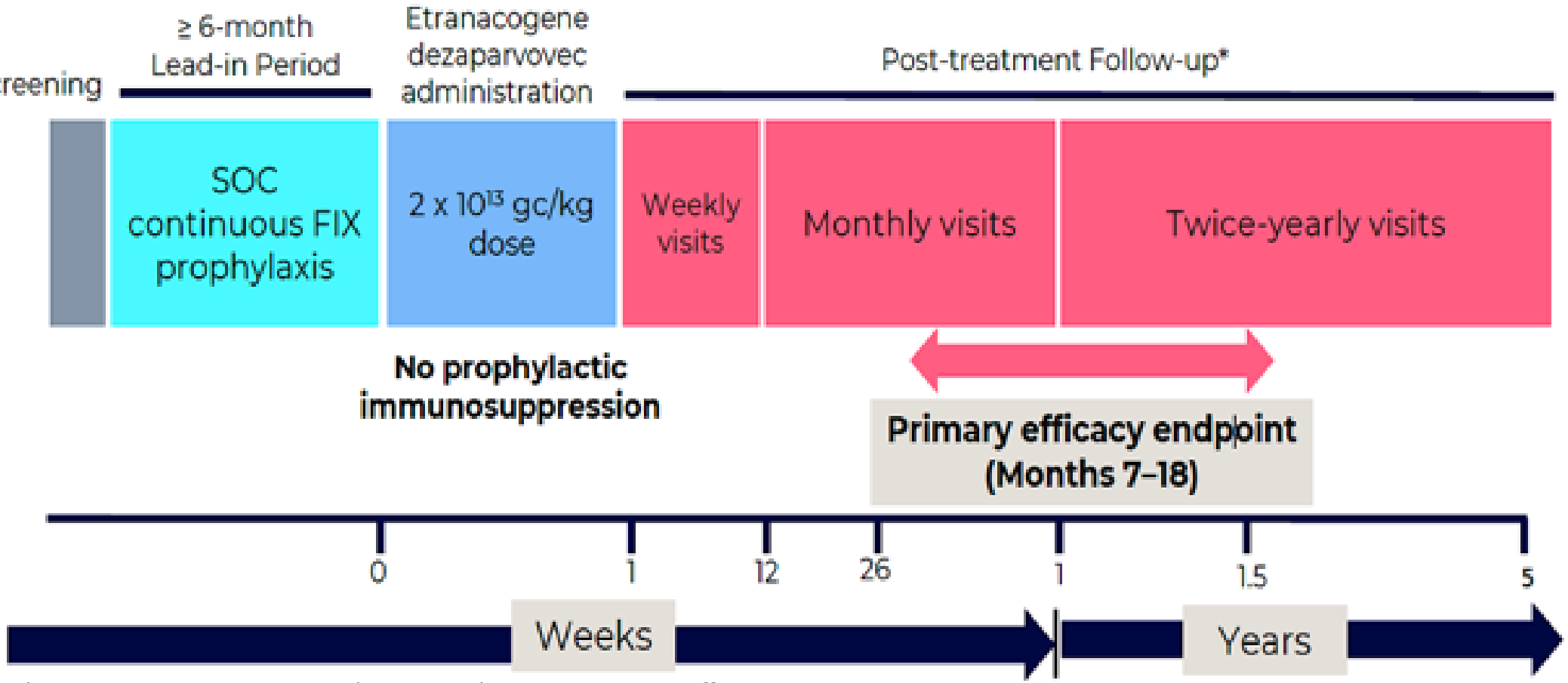
	HOPE-B, CT-AMT-061-02, NCT03569891
Design	Phase III, open label, single dose, single arm, non-inferiority trial
Population	Adult males with moderately severe or severe haemophilia B with FIX level ≤2%
Intervention	Etranacogene dezaparvovec
Comparator(s)	None. Company compared outcomes using a lead-in period (minimum of 26 weeks) when patients received EHL or SHL FIX replacement prophylaxis therapy
Duration	Ongoing; subjects are being followed for 5 years for efficacy and safety; data up to 24 months presented in company submission*
Primary outcomes	ABR and comparison of ABR between the lead-in and after administration of ED
Key secondary outcomes	FIX activity levels at 6, 12, 18 and 24 Months after ED dosing
Locations	Multicentre, 33 sites (including three sites in the UK)

*36-month data-cut likely available soon

ABR; annualised bleeding rate; ED, etranacogene dezaparvovec; EHL, extended half-life; FIX, factor IX, SHL, standard half-life

HOPE-B study design

Single arm study comparing outcomes following etranacogene dezaparvovec treatment with outcomes during a baseline lead-in phase of 6-months



*At least quarterly contact (±2 weeks) between site staff and subjects to monitor occurrence of AEs. Last subject visit planned Q1 2025.

AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HIV; human immunodeficiency virus; FIX, factor IX; Q1, quarter 1

HOPE-B primary endpoint: ABR (24 months)

64% reduction in adjusted ABR for months 7-24 following treatment compared to the lead in period

	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
7-24 months ABR	1.51 (0.83, 2.76)* Change: -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.

<u>Baseline anti-AAV5 NAb titre subgroup analysis</u>

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.

AAV5, adeno-associated viral vector of serotype 5; ABR, annualised bleeding rate; CI, confidence interval; FIX, factor IX; Nab, neutralising antibody; PP, per person

HOPE-B secondary endpoint: FIX level & FIX consumption

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

FIX activity (%) from uncontaminated central laboratory one-stage (aPTT-based) assay (FAS)

Visit[a]	Result		Change from baseline	
	N	Mean (SD)	LS Mean (SE)[b]	p-value[c]
Month 6	51	38.95 (18.72)	36.18 (2.432)	<0.0001
Month 12	50	41.48 (21.71)	38.81 (2.442)	<0.0001
Month 18	50	36.90 (21.40)	34.31 (2.444)	<0.0001
Month 24	50	36.66 (18.96)	34.13 (2.325)	<0.0001

[a]Data are from 'uncontaminated' central laboratory one-stage;
[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.

Note: Assumed baseline FIX was imputed based on patients' historical haemophilia B severity. If documented severe FIX deficiency, their baseline FIX activity level was imputed as 1%. If moderately severe FIX deficiency their baseline FIX activity level was imputed as 2%

- At 24 Months post-treatment, the increase in endogenous FIX level (least square [LS] mean value) from (assumed) baseline was 34.13 IU/dL (p<0.001)
- FIX consumption: the mean number of infusions of FIX 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 (p<0.0001).

aPTT, activated partial thromboplastin time; FAS, full analysis set; FIX, factor IX; LS, least square; SD, standard deviation; SE, standard error

HOPE-B adverse events

68.5% of people experienced at least one adverse event during the lead in period compared to 100% of people during the 24-month post-treatment period

	Lead-in period (excluding lead-in discontinuers) (n=54)		Post-treatment period, 24 months (n=54)	
	n (%)	Number of events	n (%)	Number of events
At least one AE	37 (68.5)	87	54 (100.0)	557
AEs related to study treatment	0	-	38 (70.4)	93
AEs of special notification	0	-	12 (22.2)	19
Serious AEs	4 (7.4)	5	14 (25.9)	17
Serious AEs related to study treatment	0	-	0	-
Deaths – all causes	0	-	1 (1.9)	1

Adverse events of special interest

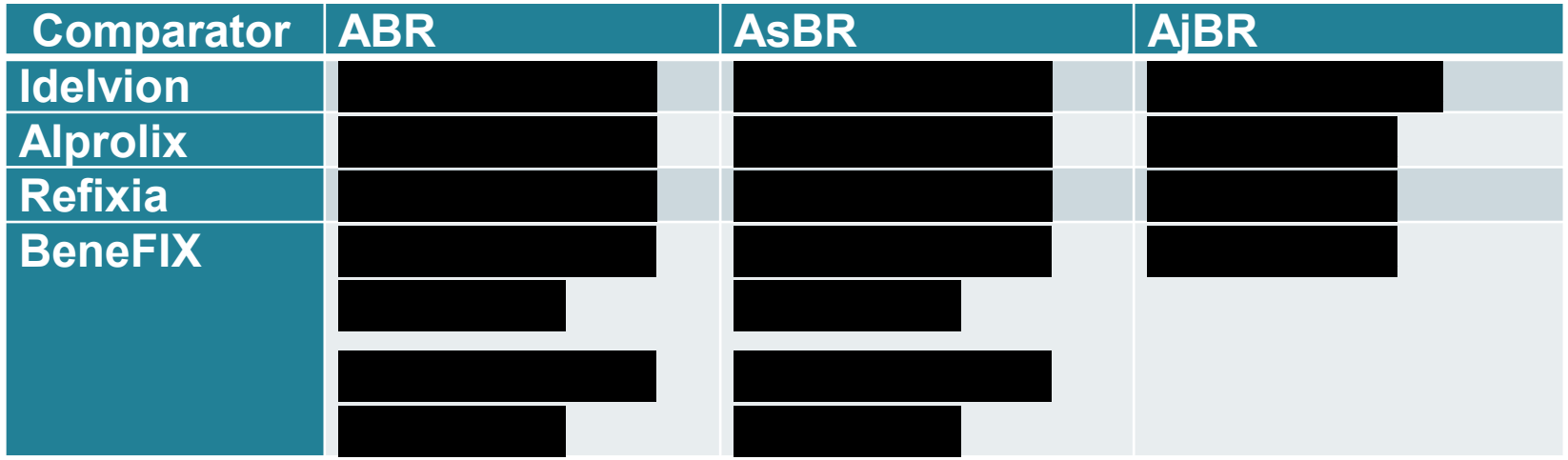
- No participants exhibited raised ALT/AST levels during the lead-in phase. Following treatment with ED, 11/54 (20.4%) and 8/54 (14.8%) participants experienced increases in ALT and AST, respectively
- Overall, 9/54 (16.7%) participants received treatment with corticosteroids for ALT/AST increases, over a mean duration of 79.8 days. No serious AEs related to use of corticosteroids
- Inhibitors to FIX were not detected in any participants during 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.

AAV5, adeno-associated viral vector of serotype 5; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ED, etranacogene dezaparvovec; FIX, factor IX; Nab, neutralising antibody

Indirect treatment comparison: results

Indirect treatment comparison results suggest statistically significant improvement in bleeding outcomes for etranacogene dezaparvovec vs comparators

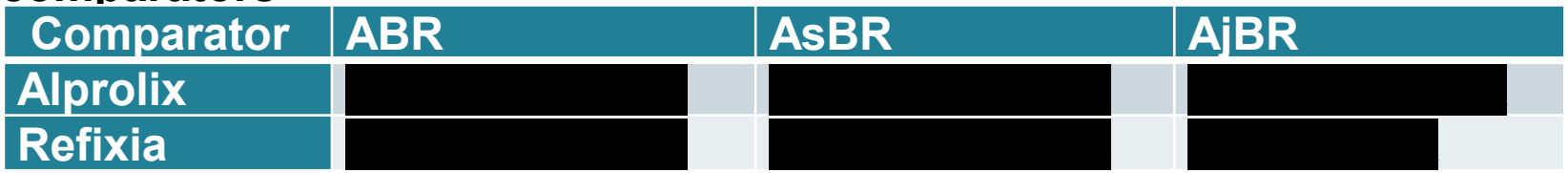
Primary analyses of indirect comparisons of etranacogene vs key comparators – 'final' multivariable adjusted comparisons.



All estimates expressed as rate ratios (95% CI)

Note: Additional analyses 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.

Secondary analyses of indirect comparisons of etranacogene vs key comparators



All estimates expressed as rate ratios (95% CI)

ABR, annualised bleeding rate; AjBR, annualised joint bleeding rate; AsBR, annualised spontaneous bleeding rate; HRQoL, health-related quality of life; CI, confidence interval; FIX, factor IX

Key issue: Calculation of change in FIX levels (1/2)

Background

- As there was no control arm, outcomes assessed during the lead-in phase were the only data to represent participant outcomes while receiving prophylactic FIX replacement
- For one key study outcome, levels of circulating FIX following treatment, company did not report FIX levels during lead-in phase but calculated change in FIX levels from baseline
- Baseline data were an estimate of what participants' FIX levels would be if they were receiving no treatment at all (i.e. company used severity of the condition to impute a FIX level)
- EAG: this approach meant it was not possible to compare FIX levels with routine prophylaxis to FIX levels following treatment with ED. An understanding of how much FIX levels changed following ED would provide an understanding about what this would mean for patients and the potential value of the treatment for their lives.

Company

- Any measure provided during lead-in phase would not be a fair representation of participants' FIX levels
- FIX levels would vary according to the type, brand, dose and frequency of FIX replacement participants were receiving, and fluctuations in FIX levels following prophylactic treatment meant that it would be challenging to identify a representative measurement
- Major benefit of ED would be reducing the peaks and troughs and having more stable FIX expression due to endogenous production → efficacy of ED compared to baseline FIX level reported as this reflects endogenous FIX production.

ED, etranacogene dezaparvovec; FIX, factor IX

Key issue: Calculation of change in FIX levels (2/2)

EAG comments

- Agree that fluctuations in FIX levels following prophylactic treatment meant that it would be challenging to identify a representative measurement, however 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
- While not perfect, other methods could have been used to represent FIX levels whilst on prophylaxis
- Understanding change in FIX levels following ED provides corroboration of the other clinical outcomes, shows the mechanism via which ED can reduce bleeds (i.e. by increasing levels of FIX) and gives an insight into how prophylactic FIX treatment uptake may change
- People with moderate and severe haemophilia almost always receive FIX replacement therapy. Comparison with no treatment is inconsistent with decision problem.

Other considerations (clinical expert and professional organisation comments)

- People receiving factor prophylaxis will have peak and trough levels, rather than a steady state level → difficult to take a single level measurement and compare it to the level after gene therapy
- FIX levels would vary according to specific regime for each patient and will vary depending on a number of variables → using lead-in phase for comparison would be difficult and potentially misleading
- Good understanding of the correlation between baseline FIX level and bleeding risk in Haemophilia B → increase in FIX level from baseline is a useful measure of the biological effect of ED.

Does the absence of FIX level measurement the during the lead-in phase result in uncertainty about the 'change in FIX levels' outcome?

EAG, Evidence Assessment Group; ED, etranacogene dezaparvovec; FIX, factor IX

Key issue: Magnitude of clinical benefits reported in HOPE-B (1/2)

Background

- COVID-19 pandemic began after study participants had received ED and resulted in a major disruption to daily activities. EAG: this may have reduced the need for study participants to receive additional FIX replacement and participants also may have had a lower risk of bleeding during this time, due to their reduced activity
- Post-treatment study procedures prohibited participants from receiving routine FIX replacement when they had circulating FIX levels of ≥5% (ad hoc FIX replacement at clinicians' discretion allowed). EAG considered that clinicians may be less likely to administer ad hoc FIX replacement within the clinical study in practice and that rates of prophylactic FIX replacement may be higher in clinical practice than in the HOPE-B study.

Company

- IPAQ, which assessed physical activity across a comprehensive set of domains during HOPE-B, suggests that there were no significant changes in physical activity during the first 12 months post-treatment
- FIX replacement consumption has remained substantially reduced up to 24 months post-treatment → not impacted by coming out of lockdown
- ABR (all bleeds) and specifically spontaneous ABRs (which are not related to trauma or activity) were reduced from baseline to Month 7–18 post-treatment, and maintained at 24-months post-treatment
- Confirmed that UK principal investigators followed usual bleed management principles in line with Good Clinical and Research Practice → did not feel restricted by study protocols when making treatment decisions.

ABR, annualised bleeding rate; EAG, Evidence Assessment Group; ED, etranacogene dezaparvovec; FIX, factor IX; iPAQ, International Physical Activity Questionnaire

Key issue: Magnitude of clinical benefits reported in HOPE-B (2/2)

EAG comments

- IPAQ questionnaire not recommended for use in small trials and no evidence for how responsive the measure is to changes in physical activity. Other published evidence has shown that activity levels were reduced in people with haemophilia B during the pandemic (Vaccaro et al. 2023)
- Reporting ABR across a period of time makes it difficult to determine patterns in the outcome over time
- Plausible that reductions in spontaneous bleeds could be more confidently associated with ED than other bleed types but EAG uncertain if it was established that changes in physical activity would not affect rate of spontaneous bleeds
- Unsure what "Good Clinical and Research Practice" was in this context. No clinician would jeopardise duty of care, but decisions about when to re-initiate prophylactic treatment may be impacted by rules of trial
- Uncertainty related more to the magnitude of the treatment effect, rather than presence of effect

Other considerations (clinical expert, patient expert and professional organisation comments)

- Maybe slight reduction in activity during the COVID-19 pandemic but in clinical practice only a small change, if any, in reporting of bleeds → impact of COVID-19 unlikely to be significant
- Decisions about whether to administer FIX based on normal clinical practice → not influenced by trial
- Patient expert: from personal experience and speaking to peers, there was an increase in activity caused by COVID-19, especially vigorous activity such as running and cycling.

What is the committee's view on the impact of COVID-19 and study procedures (related to administration of additional FIX replacement) on the magnitude of clinical benefits reported in HOPE-B?

ABR, annualised bleeding rate; EAG, Evidence Assessment Group; ED, etranacogene dezaparvovec, FIX, factor IX; iPAQ, International Physical Activity Questionnaire

Key issue: Reliability of ITC

Background

- To establish comparisons against ED, the company located four studies including relevant comparators and used these along with outcomes from the HOPE-B study to indirectly compare treatment outcomes
- EAG stated that differences between study methods seriously undermined comparability of outcomes.

Company

- ITC was performed using best methods available
- Accepted EAG assumption of gradual improvements in ED bleed rates over first 24 months to account for uncertainty (technical engagement)
- Data from ADIVO Associates, shows that out of comparators, BeneFIX (comparator for which ITC findings were deemed most unreliable by EAG) is the least commonly used prophylactic product.

EAG comments

- Main limitations with ITC were 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
- Considered that the company's methods for the ITC were the best available to them but results were unreliable
- Plausible that ED treatment would result in lower bleeding rates than FIX replacement but magnitude uncertain.

Do the committee consider the results of the ITC robust?
If not, what are implications of the uncertainty on decision making?

EAG, Evidence Assessment Group; ED, etranacogene dezaparvovec; ITC, indirect treatment comparison; FIX, factor IX

NICE

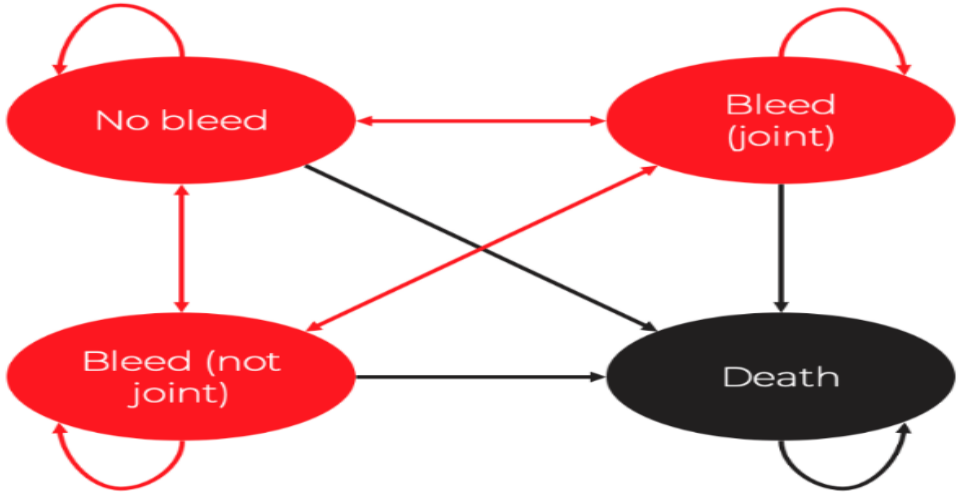
Cost effectiveness

NICE National Institute for Health and Care Excellence

Company's model overview

Model type	Markov model
Population	Adult males with congenital haemophilia B with known severe or moderately severe Factor IX deficiency aligned to HOPE-B trial population
Intervention	Etranacogene dezaparvovec (followed by IV FIX on ED failure)
Comparators	• Alprolix • BeneFIX • Idelvion • Refixia
Outcome	Incremental cost per QALY gained
Time horizon	Up to 100 years old (lifetime)
Perspective	NHS and PSS
Discounting	3.5% for health outcomes and costs

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.

-Rates of bleeding from ITC used to calculate transition probabilities
- Utilities and costs attached to each of the four health states
- In addition, a treatment-specific decrease in health utility was applied to patients receiving IV FIX (comparator)

ED, etranacogene dezaparvovec; FIX, factor IX; ITC, indirect treatment comparison; IV, intravenous; PSS, Personal Social Services; QALY, quality-adjusted life year

How company incorporated evidence into model

Input	Assumption and evidence source
Baseline characteristics	• Hope-B trial population, except age • Age updated to 18 years in line with MA at technical engagement
Intervention efficacy	• Transition probabilities based on those observed in HOPE-B*. • Predicted failure rate based on Shah et al. statistical modelling extrapolations of observed data from the HOPE-B (n=52) and AMT-061-01 (n=3) studies (total n = 55)
Comparator efficacy	Transition probabilities derived by applying rate ratios from ITCs to ED transition probabilities
Utilities	**Treatment specific utility**: EQ-5D-5L from the HOPE-B trial mapped to EQ-5D-3L values, using Hernandez et al. (2017) mapping function (updated at technical engagement) **Health state utility (bleed events):** Disutility for bleed events based on US-ICER 2022. **Adverse event disutility:** Published literature
Resource use	Advised by UK clinical experts
Costs	**Categories**: Drug acquisition costs (biomarker test for neutralising antibodies required before ED will be provided by the company free of charge), administration costs, follow-up costs for ED, monitoring costs, bleed-related management costs, adverse event costs+ **Sources**: BNF, DHSC, MIMS, National Schedule for NHS (2020/2021), and PSSRU.

*Transition rates amongst Markov state gradually decrease from the rates of comparators for 24 months until they are determined by bleeds rates from the ITC report (updated at technical engagement).
+ Costs of AEs beyond year 1 for the IV FIXes included in 'EAG-corrected company base-case' to align with adverse event utilities applied for a lifetime in post technical engagement company base case

BNF, British National Formulary; DHCS, Department of Health and Social Care; EAG, Evidence Assessment Group; ED, etranacogene dezaparvovec; EQ-5D-3L, EuroQol-5 dimensions-3 levels ; EQ-5D-5L, EuroQol-5 dimensions-5 levels; FIX, factor IX; ITC, indirect treatment comparison; IV, intravenous; MIMS, Monthly Index of Medical Specialities; MA, marketing authorisation; PSSRU, Personal Social Services Research Unit; US-ICER, Institute for Clinical and Economic Review

Key issue: Definition of treatment failure (1/2)

Background

- Company's base case durability extrapolation model was based on a resumption of IV FIX (i.e. treatment failure) at <2% FIX activity level
- Clinical advice to the EAG was that IV FIX was more likely to be reintroduced once FIX activity dropped below 5% rather than 2%

Company

- Definition of treatment failure (the FIX level at which prophylactic treatment would need to be provided) discussed with eight clinical experts
- Reinitiating prophylaxis post gene therapy is a composite decision comprising bleeding symptoms, factor level and patient preference
- Clinical experts agreed that a FIX activity level of 2% would define 'treatment failure'
- 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
- Protocol allowed for continuous use while factor levels remained below 5% but none of the responders (n=52) in the HOPE-B trial required prophylaxis.

EAG, Evidence Assessment Group; IV, intravenous; FIX, factor IX

Key issue: Definition of treatment failure (2/2)

EAG comments

- Unable to resolve the discrepancy between the views of clinicians in the advisory board and advice given to the EAG by its own expert
- 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 → 2% threshold may not be sufficient for some people treated with ED
- EAG base case model based on a resumption of IV FIX at <5% FIX activity level

Other considerations (clinical expert and professional organisation comments)

- Treatment failure defined by resumption of prophylaxis based on reappearance of spontaneous bleeding episodes or overall bleeding risk, not solely on FIX level
- Different people will have slightly different thresholds of bleeding due to their phenotype (e.g. some may need to start at higher restart prophylaxis at a higher FIX level due to worse baseline joint health)
- In most cases, people will need to restart prophylaxis if FIX levels fall below 2-3%
- UKHCDO (2021/22) data in people with Haemophilia A suggests majority of people with baseline factor levels >2% did not receive prophylactic treatment → same expected in people with Haemophilia B.

What is an appropriate definition of treatment failure?

EAG, Evidence Assessment Group; ED, etranacogene dezaparvovec ; IV, intravenous; FIX, factor IX; UKHCDO, United Kingdom Haemophilia Centres Doctor's Organisation

Key issue: Durability of treatment effect (1/2)

Background

- Company's base case model assumed a median durability of [redacted] years on the basis of modelled projections from shah et al. (failure defined as <2%). Scenario analyses also presented for failure defined as <5%.
- EAG concerned with 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
- Clinical advice to the EAG considered a durability of 6-8 years to be plausible on the basis of current thinking

Company

- Uncertainty about durability of long-acting treatments 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)
- Use of statistical extrapolation by Shah et al. 2022 was validated by eight clinical experts and most appropriate methodology using longest available trial data with ED utilised
- Highlights the need for clarity in difference between the duration of currently available trial evidence and the expectation of long-term treatment effect
- 6-year follow-up data (n=9) with similar product (AMT-060) shows that there is no waning of the treatment effect
- 18-month data (Pipe and Monahan [2023]) from HOPE-B trial shows among 52/54 patients who expressed endogenous FIX after the receipt of ED, none restarted FIX prophylaxis and FIX levels were <3 IU/dL in 3.7% of the patients and <5 IU/dL in 5.6% of the patients.

EAG, Evidence Assessment Group; ED, etranacogene dezaparvovec; IV, intravenous; FIX, factor IX

Key issue: Durability of treatment effect (2/2)

EAG comments

- High degree of uncertainty in the Shah et al. extrapolation but agrees it was appropriately conducted
- Understood that expectations of durability would be specific to the treatment and its indication and understood there to be several reasons why gene therapies using an AAV vector may experience reduced durability
- Company's claim that 6-year AMT-060 data showed no evidence of treatment waning cannot be demonstrated statistically at conventional levels of significance due to small sample size → crude mean of mean FIX activity level over years 1 - 3 was [redacted]%, whilst over years 3.5 - 6 was [redacted]% → may suggest declining treatment effect
- Acknowledged uncertainty was the lowest possible level subject to the available evidence, but the 'lowest possible' still represented a great deal of decision uncertainty

Other considerations (clinical expert and professional organisation comments)

- Very difficult to extrapolate durability based on a model, as this does not take into account many factors
- Cannot make assumptions on durability based on model until long term efficacy data available
- 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).

AAV, adeno-associated virus; EAG, Evidence Assessment Group; FIX, factor IX

Shah et al. treatment durability extrapolations

2% definition of treatment failure (company base case)

5% definition of treatment failure (EAG base case)

What are the committee's views on the durability of treatment effect?
Are the shah et al. extrapolations plausible?

NICE

Summary of company and EAG base case assumptions

Agreed upon assumptions

Parameter	Assumption
ED effectiveness	A gradual 24-month phase of a reduction in bleeding rates following ED administration
Health state utilities	EQ-5D-5L from HOPE-B mapped to EQ-5D-3L, using Hernandez et al. (2017) mapping function
Model starting age	18 years old (align with MA)
Adverse event costs and utilities	Inclusion of AE costs and disutilities beyond one year for ED and comparators (EAG noted that AE costs after year 1 for IV FIXes had been omitted. The EAG therefore corrected this in the company's decision model).

Differing assumptions between company and EAG

Assumption	Company base case	EAG base case
Treatment failure	< 2% FIX	<5% FIX
Durability (i.e. point at which IV FIX was resumed)	Durability function based on Shah et al. (results in median durability of [redacted] mean durability [redacted]	Conducted scenario analyses to identify minimum durability required to yield ICER below £20,000 and £30,000* but analysis demonstrated that overall shape of durability function is critical to determining cost-effectiveness, not just mean durability, therefore threshold analysis not presented in part 2

*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.

AE, adverse event; EAG, Evidence Assessment Group; EQ-5D-3L, EuroQol-5 dimensions-3 levels; EQ-5D-5L, EuroQol-5 dimensions-5 levels; FIX, factor IX; ICER, incremental cost-effectiveness ratio; MA, marketing authorisation

Cost-effectiveness results

Company presented fully incremental and pairwise analyses. Fully incremental and pairwise probabilistic* ICERs are reported in PART 2 slides because they include confidential comparator discounts. A summary of the cost effectiveness results is presented on the next slide.

NICE methods guide 2022: presenting expected cost-effectiveness results

Section 4.10.8: Economic evaluation results should be presented in a fully incremental analysis with technologies that are dominated (that is, more costly and less effective than another technology in the analysis) and technologies that are extendedly dominated (that is, a combination of 2 or more other technologies would be more cost effective) removed from the analysis.

Pairwise comparisons may be presented when relevant and justified (for example, when the technology is expected to specifically displace individual comparators).

*EAG: mean QALYs in the probabilistic analysis were lower for IV FIXes and higher for ED strategies than 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. 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.

Cost-effectiveness results

A summary of the cost effectiveness results is presented below.

Intervention	Comparators			
ED+ Benefix	Benefix	Refixia	Alprolix	Idelvion
ED+ Refixia				
ED+ Alprolix				
ED+ Idelvion				

- In a fully incremental analysis, ED + each of the 4 IV prophylactic FIX treatments are compared against each of the 4 IV prophylactic FIX treatments alone. This results in 8 treatment strategies in the fully incremental analysis.
- In the fully incremental analysis (including confidential prices) in both the company and EAG base-case, ED* was not the most cost-effective treatment strategy (ICER well in excess of £30,000 per QALY gained).
- In a pairwise analysis (including CMU prices) with the most frequently used^ IV prophylaxis treatment: ED* dominates (lower total costs and higher QALYs)

*ED plus IV prophylactic FIX treatments; ^ according to data from NHS England

Managed Access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

Managed Access

Feasibility of Managed Access

This topics is not currently eligible for managed access as the company did not provide a managed access proposal and therefore there is no full feasibility assessment.

The MAA team consider that further data collection could potentially reduce uncertainty around the durability of the treatment effect. There are 3 potential data sources:

- HOPE-B, collecting outcome data up to 5 years after dosing
- CT-AMT-060-01 open-label extension study
    - NOTE: the expression cassette within AMT-060 was a predecessor to etranacogene dezaparvovec
- The National Haemophilia Database could be used to provide real-world evidence of longer-term outcomes

Is 5 years, the maximum allowable length of managed access data collection, sufficient to resolve uncertainties?

Does the committee wish to ask the company for a managed access proposal? Which uncertainties should be resolved?

Key issues

Issue	Resolved?	ICER impact
Calculation of change in FIX levels	No – for discussion	None
Magnitude of clinical benefits reported in HOPE-B	No – for discussion	Unknown
Reliability of ITC	Partially – for discussion	Unknown
Definition of treatment failure	No – for discussion	Large
Durability of treatment effect	No – for discussion	Large
Health state utilities*	Yes*	Small

*Updated at technical engagement using Hernandez et al. (2017) mapping function to map EQ-5D-5L from the HOPE-B trial to EQ-5D-3L values. Updated values included in both company and EAG base cases

FIX, factor IX; ITC, indirect treatment comparison

What is the model assuming about the relative treatment effect throughout the time horizon?

- **Treatment effect persists beyond observed period** (no treatment effect waning)
- **Treatment effect wanes after observed period, either by:**
  - choice of extrapolation, OR
  - introduction of explicit waning assumption

Is the assumption plausible?

Consider:

1. Is the modelled treatment effect consistent with the observed data?
2. Is clinical trial follow-up long enough to provide estimate of treatment effect waning (also consider observational and real-world data)?
3. Is there evidence to support a sustained treatment effect or effect waning from another technology with same or similar mechanism of action?
4. Does a stopping rule apply? Is treatment effect likely to continue following treatment discontinuation?
5. Are the hazard rates of key clinical inputs plausible? Consider the plots of smoothed empirical time-varying hazard ratios from pivotal trial or MAIC.
6. Are the model outputs plausible? Are they supported by clinical expert opinion?
7. What impact do scenarios of different treatment effect waning assumptions have?

Back up slides

HOPE-B trial baseline characteristics

Baseline characteristics for HOPE-B

Characteristic	ED (n=54)	EAG comments
Male, n(%)	54 (100.0)	-
Age mean (SD, min-max),years	41.5 (15.8, 19–75)	Treatment with ED may be expected to have a lower impact on the broader HRQoL of older people
Severity of haemophilia B at time of diagnosis, n (%) Severe Moderately severe	 44 (81.5) 10 (18.5)	Clinical advice that the anticipated benefits of treatment may be less for those with mild or moderately severe haemophilia B, and so any discrepancy between the study make-up and the target population may be affect generalisability
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 Standard half-life	 31 (57.4) 23 (42.6)	Clinical advice that this may not be representative of current clinical practice because more people in the NHS are now receiving the longer acting therapies.

EAG; Evidence Assessment Group; ED, etranacogene dezaparvovec; FIX, factor IX; HIV; human immunodeficiency virus; HRQoL, health-related quality of life; SD, standard deviation

HOPE-B key inclusion and exclusion criteria

Key inclusion 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

Key exclusion criteria

ALT, AST, total bilirubin (except if caused by Gilbert disease), ALP or creatinine >2 times upper normal limit; 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

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HIV; human immunodeficiency virus; FIX, factor IX

HOPE-B secondary endpoints: consumption of FIX & joint health

Significant reduction in consumption of FIX replacement therapy and small statistically significant improvement in Haemophilia Joint Health Score (HJHS) following treatment

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

At final follow-up (months 19-24), [redacted] of participants were receiving FIX replacement, each receiving a mean of 3.2 infusions

Joint health

- Small, statistically significant improvement in HJHS following treatment with ED
- The LS mean difference in the first 12 months was [redacted] (p-value [redacted]) and between 12–24 months was -[redacted] (p-value [redacted])
- EAG: unable to identify a minimally clinical importance difference 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.

EAG, Evidence Assessment Group; ED, etranacogene dezaparvovec; FIX, factor IX; HJHS, Haemophilia Joint Health Score; LS, least square

HOPE-B secondary endpoints: HRQoL and functions

Varying impact of treatment dependent on patient reported outcome tool used

EQ5D- 5L

- A numerical benefit in EQ-5D-5L scores was reported at the 24-month follow-up with an LS mean difference of [redacted] (p value: [redacted]
- EAG: difference in score was under the threshold considered to be a meaningful change in HRQoL for people with haemophilia

Haem-A-QoL

- Statistically significant mean differences vs the lead-in period in the Total Score and the domains regarding 'Work/School', 'Feelings', 'Treatment' and 'Future' at 24 Months post-treatment
- EAG: One paper reported a minimally clinical importance difference 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 was demonstrated for the 'feelings' domain, the 'treatment' domain, and the 'dealing with haemophilia' domain at 24-months

Other

No differences in scores on the WPAI (work productivity), BPI (pain), and HAL (functional ability) following treatment with ED.

BPI, Brief Pain Inventory; EAG, Evidence Assessment Group; ED, etranacogene dezaparvovec ; EQ5D-5L, EuroQol-5 dimensions-5 levels; Haem-A-QoL, Haemophilia Quality of Life Questionnaire for Adults ; HAL, Haemophilia Activities List; HRQoL, health-related quality of life; LS, least square; WPAI, Work Productivity and Activity Impairment Questionnaire

Indirect treatment comparisons (1/2)

In the absence of head-to-head evidence, Indirect treatment comparisons were conducted to determine comparative efficacy of etranacogene dezaparvovec to comparators

- Company used four studies which included relevant comparators
- Methods used for the indirect comparison depended on the study used and the availability of participant-level data
- 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
- Because all comparisons were non-randomised, a range of matching and adjusting approaches were taken:
- Inverse probability of treatment weights(IPTW) method relies on considering how patient characteristics 'predict' membership to either treatment group, and then reweighting patients to balance characteristics between groups
- Matching-Adjusted Indirect Comparison (MAIC) involves re-weighting Individual Patient Data from one study to the baseline summary statistics of another, to provide greater adjustment for observed trial differences.

ED, etranacogene dezaparvovec; IPTW, Inverse probability of treatment weighting; MAIC, matching-adjusted indirect comparison

Indirect treatment comparisons (2/2)

Comparator & study	ITC method	EAG comments
Idelvion. PROLONG-9FP (relevant n=40)	IPTW. Patients from PROLONG-9FP 'unique' to that study, excluded from analyses. Comparison included the richest set of factors for adjustment, specifically severity of haemophilia B, prior ABR, and age	Analysis generated improvements in many, but not all factors
Alprolix. B-LONG (relevant n=63)	MAIC. Primary analyses included subset of patients with prior prophylaxis, adjusting only for prior ABR. Secondary analyses used full populations, with additional variables used in adjustment	Lack of data available to compare balance of covariates between groups in primary analyses → limits credibility of analyses. Major differences in populations by prior prophylaxis in secondary analyses → not likely to be probative
Refixia Paradigm-2 (relevant n=29)	MAIC. Primary analyses included subset of patients with prior prophylaxis, adjusting for prior ABR and prior FIX product class. Secondary analyses used full population, with additional variables used in adjustment	Primary analyses inconsistently able to adjust for both prior ABR and prior FIX product class → not possible to ascertain covariate balance. Secondary analyses not likely to be reliable because inclusion of full population
BeneFIX NCT00093171 (relevant n=34)	MAIC. Only age and prior FIX product class available for adjustment. Analyses required imputation of standard errors for outcomes (not reported)	Analyses especially tenuous. Limited by limited by a lack of baseline data, ambiguities in outcome definitions and addition to a lack of precision estimates. Also not possible to ascertain covariate balance.

ABR, annualised bleeding rate; EAG, Evidence Assessment Group; FIX, factor IX; IPTW, Inverse probability of treatment weighting; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison

Durability of treatment effect

Company believe ED has a long-term therapeutic effect based on the following:

- Most recently published follow-up of the earliest successful haemophilia B gene therapy trial, demonstrated stable therapeutic expression FIX over a period of 8 years → rAAV-based vector used, similarly to ED, contained a codon-optimised FIX gene, under control of a liver specific promoter
- During a presentation at the Congrès Français d'Hemostase (CFH) in 2021, Dr Nathwani stated that the dose-dependent, multiyear increase in FIX was sustained in an rAAV-based trial, with the longest follow-up being up to 10 years
- 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

ED, etranacogene dezaparvovec; FIX, factor IX; rAAV, recombinant adeno-associated viral vector