Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B]

For public – contains redacted information

Technology appraisal committee D 2nd committee meeting [13th September 2023]

Chairs Presentation

Chair: Megan John

External assessment group: Peninsula Technology Assessment Group (PenTAG)

Technical team: Vicky Gillis-Elliott, Victoria Kelly, Linda Landells

Company: CSL Behring

Summary of appraisal to date

Recommendation after ACM 1

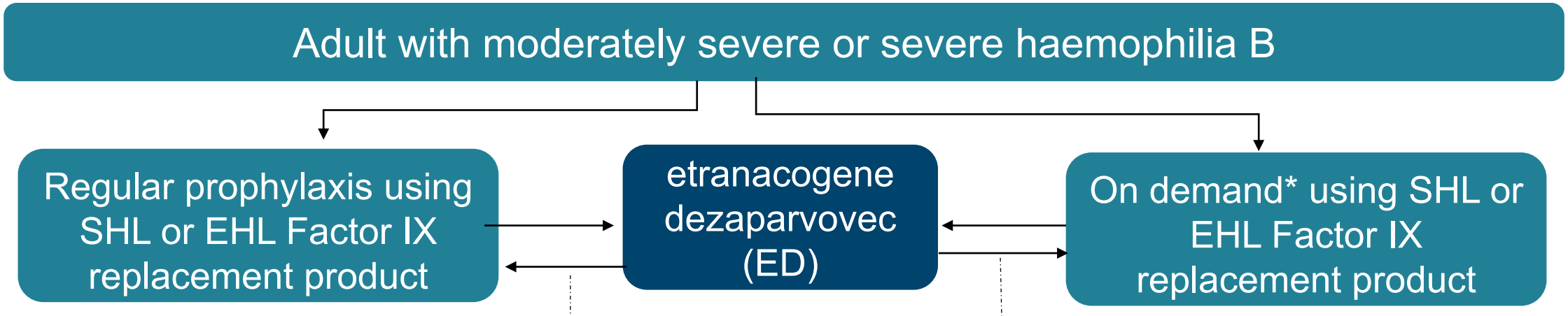
Etranacogene dezaparvovec is not recommended, within its marketing authorisation, for treating moderately severe or severe haemophilia B (congenital factor IX deficiency) in adults without a history of factor IX inhibitors (antibodies against factor IX)

Additional analyses requested by the committee

- A scenario analysis using a 'basket of comparators' weighted by market share
- A scenario analysis where FIX prophylaxis treatment is restarted at 3%
- A scenario analysis incorporating missing patient data from Shah et al. (2020) including:
  - The person who had a partial dose to reflect clinical practice
  - the person with poor response to treatment with a high AAV5 neutralising antibody titre

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".

Committee concluded FIX prophylaxis treatment was the most appropriate comparator

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

Etranacogene dezaparvovec (Hemgenix, CSL Behring)

Recap

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 a revised confidential patient access scheme for etranacogene dezaparvovec

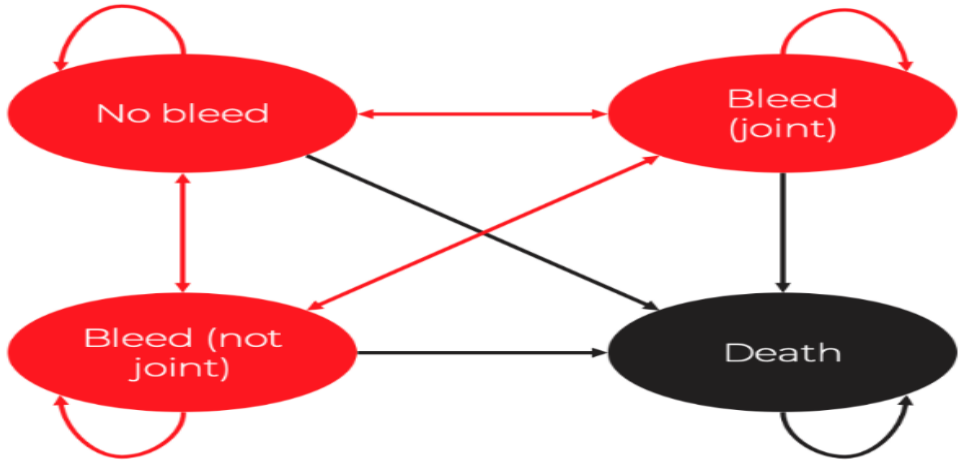
FIX, factor IX; MHRA, Medicines and Healthcare products Regulatory Authority

Company's model overview

Recap

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)

Committee concluded the company's model structure was appropriate for decision making

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

Key issues

Issue	Resolved?	ICER impact
Comparators in the economic model	No – for discussion	Large
Durability of treatment effect: • **Shah et al (2022) analyses - uncertainties** • **Excluded patient(s) scenario analyses**	No – for discussion	Unknown
Divergence of probabilistic and deterministic ICERs	No – for discussion	Large
Managed access proposal and feasibility assessment	For discussion	Not applicable

Summary of committee conclusions after first meeting

Issue	Committee discussion and conclusion	Addressed in responses?
Comparators in the economic model	• People having ED in HOPE-B were also given FIX on-demand for ad-hoc bleeding episodes • Company compared ED and FIX prophylaxis after ED failure with FIX prophylaxis. But in clinical practice choice of FIX prophylaxis is based on various factors so committee requested a scenario analysis for a 'basket of comparators' weighted by NHS market share	Yes. Company provided scenario analyses for a basket of comparators
Definition of treatment failure	• Company and EAG assumptions on level at which prophylaxis FIX should be resumed differed • Company set level below 2% and EAG set it below 5% • Committee considered prophylaxis FIX could restart between 2 and 3% so requested a scenario analysis for restarting at FIX level of 3%	Yes. Company provided scenario analysis restarting prophylaxis at 3%
Durability of treatment effect	• Company used data from Shah et al (2022) to estimate long term durability of ED. But committee noted excluding 2 participants from HOPE-B in the analyses could bias estimates • It requested 2 scenario analyses to explore the uncertainty	Yes. Company updated model functionality to include/ exclude participants

ED, etranacogene dezaparvovec; FIX, factor IX;

HOPE-B primary endpoint: Annualised Bleeding Rate (36 months)

Updated data cut for ACM2 [not included in modelling]

64% reduction in adjusted ABR unchanged from earlier data cut

	All bleeds	Joint bleeds	Spontaneous	FIX-treated
Lead-in phase ABR (N=54)	4.17 (3.20, 5.44)	2.34 (1.74, 3.16)	1.52 (1.01, 2.30)	3.62 (2.79, 4.71)
Median [range] bleeds per person	2 [0-10]	-	-	-
Total bleeds (>6 months period)	136	77	50	118
People who had bleeds	40/54 (74.1%)	32/54 (59.3%)	24/54 (44.4%)	39/52 (75%)
Up to 36 months	[redacted]	[redacted]	[redacted]	[redacted]
Total bleeds	Year 2: 48 [redacted]	Year 2: 18 [redacted]	Year 2: 14 [redacted]	Year 2: 29 [redacted]
People who had bleeds	Year 2: 21/54 (38.9) [redacted]	Year 2: 10/54 (18.5%) [redacted]	Year 2: 9/54 (16.7%) [redacted]	Year 2: 19/52 (36.5%) [redacted]

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ABR, annualised bleeding rate; CI, confidence interval; FIX, factor IX; P-value, probability value

Consultation responses

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Consultation responses

Received from:

- **Company:** CSL Behring
- **Clinical and Patient organisations (n=2):** The Haemophilia Society (THS) and the United Kingdom Haemophilia Centre Doctors Organisation (UKHCDO)
- **Web comments (n=1, Cell and Gene Therapy Catapult)**

Clinical and Patient organisations and web comments (1)

Comparison

- FIX at baseline compared to FIX after gene therapy is a valid comparison.
- Comparison with FIX level on standard prophylaxis is difficult or impossible because levels vary from 70% to 3% during the interval between doses
- Prophylaxis does not have set doses and frequencies and instead can be tailored to ensure suitably high troughs and for peaks to coincide with days of particular activity
- The required trough level and required levels over time will also vary based on lifestyle, physiology and bleeding phenotype.

FIX levels

- Prophylaxis should not be offered based solely on FIX levels. Most patients will likely start experiencing bleeds when their levels are between 1 and 2%.

Impact of Haemophilia B

- Draft guidance does not explain how substantial effect of Haemophilia B has on peoples lives.
- People with severe haemophilia B still have painful bleeds, some of which require lengthy recovery periods, hospital visits and potentially hospital stays. Over time these bleeds will lead to joint damage, pain and disability. Treatment could lead to fewer hospital visits, better joint health and lower rates of disability over time.

FIX, factor IX;

Clinical and Patient organisations and web comments (2)

Treatment burden

- Management of haemophilia B with factor replacement therapy has a high burden of treatment due to the required frequency of intravenous infusions
- Many people with haemophilia are restricted in the jobs and leisure activities they can engage in.
- A long-term treatment for haemophilia B offers the chance to escape that.

Eligible patients

- Patients with significant antibodies to vector would be screened out and not offered gene therapy.
- An intention to treat analysis to the trial data to include such patients and those offered only a tenth of the intended dose, appears counterintuitive and inappropriate

Durability

- Earlier clinical trials with longer follow-up suggest that once established haemophilia B gene therapy is very durable over >8 years, in contrast to gene therapy for haemophilia A.
- Do not have information about the impact of fatty liver on the durability but concerned about identifying the risk factors that contribute to the potential for liver cancer in patients.
- A longer potential treatment effect is suggested by clinical trials for other AAV gene therapies that deliver factor IX transgenes to the liver. This includes the St. Jude Children's Research Hospital study (NCT00979238) by Nathwani et al.* which reported that “transgenic FIX activity levels have remained stable in all 10 subjects treated in the initial dose escalation/extension arm over a median follow-up of 6.7±1.0 years

Equalities

Background after ACM1

Section 3.16 of DG states:

“haemophilia B is rare in women and HOPE-B did not include women. The committee was aware of clinical advice received by the EAG that the few women who experience severe and moderately severe haemophilia B would be affected similarly as men. The committee considered that any recommendation made would not need to differentiate between men and women.”

Company response to DGC

- Agree few women who experience severe and moderately severe haemophilia B would be affected
- The effects of ED on male fertility were studied but no studies have been carried out to substantiate whether use in women of childbearing age and during pregnancy could be harmful for a newborn child
- SmPC states ED is not recommended in women of childbearing potential and ED should not be used during pregnancy or during breastfeeding

Other comments from patient organisations

- Important to ensure people excluded from the trial due to HIV or hepatitis but would otherwise be eligible for treatment will be able to access the therapy if approved. The same applies to women
- It is it difficult for people not on prophylaxis to be given factor infusions or to self-infuse. This group may benefit disproportionally from the treatment

Shah et al. (2022) Long term durability (1)

Company methodology to estimate durability – Shah et al [recap]:

- Combined observed data from HOPE-B (52/54) and AMT-061-01 (n=3), a phase 2b trial of etranacogene dezaparvovec (total n=55).
- Model predicted FIX levels for up to 25.5 years at an individual and population level.
- Model estimated no more than 6 out of 55 people (10.9%) would have FIX levels below 2%, up to 25.5 years post-infusion.
- Company extended to 60 years in its economic model.

EAG Concerns [recap]

- Low participant numbers
- short follow-up: 24 months follow-up data available [36 months provided but not included in model for ACM2]
- 2 patients excluded from Hope B – committee requested inclusion [see key issue slide 16]
- Other EAG concerns about the long-term durability of ED included:
  - the rate of cell turnover in the body targeted by ED, and subsequent illnesses and other treatments that affect these areas of the body or the broader mechanisms of treatment, may lead to reduced efficacy over time
  - A subset of patients who have had corticosteroids to treat transaminase increases, people who developed AAV5 neutralising antibodies and people with moderate or severe liver steatosis at baseline – may have reduced efficacy based on data from HOPE-B

Shah et al. (2022) Long term durability (2)

Recap from first committee meeting

Further methodological issues with Shah et al were identified and discussed by committee at ACM1:

- Limited information provided by the company on how the extrapolation was carried out:
    - observations on FIX levels excluded from analysis if taken up to 5 half-lives (equivalent to 5 days) following administration of exogenous FIX. Clinicians were free to provide exogenous FIX to patients at any time. If “failure” events (defined as Factor IX levels falling below 3%) are being extrapolated, this seems invalid, since clinicians were permitted to intervene to prevent failure.
- A mixed model for repeated measures was used for modelling durability
    - a key assumption is that data is missing at random so if FIX levels are being modelled, potentially the analysis is invalid as investigators did not randomly administer exogenous FIX irrespective of endogenous FIX levels.

Company response to DG

- 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

FIX, factor IX, rAAV, Recombinant adeno-associated virus

Key issue: Durability of treatment effect

Analyses requested after ACM 1

- 2 participants in HOPE-B had been excluded from the analyses:
  - 1 patient excluded due to receiving a partial dose
  - 1 patient excluded with poor response to treatment and high AAV5 neutralising antibody titre
- Committee were concerned the excluded data could bias estimates – requested updated analyses including these patients

Company response to DG

- 2 participants excluded for methodological reasons – because uncontaminated FIX levels were required to perform the statistical analysis
- Company provided 2 requested scenario analyses after ACM1.
- Cautions against using the scenario including patient with high AAV5 neutralising antibody titre. Notes that principal investigators carrying out HOPE-B had noted neutralising antibodies titres >1:678 would be an exclusion criterion and would not be eligible for ED treatment

EAG response

- High antibody titre not an exclusion in SmPC so people with high titre are not prevented from being offered ED in routine clinical practice
- However it does state that antibodies above a titre of 1:678 may reduce efficacy of ED

Is it appropriate to include both patients in the Shah et al analysis?

DGC, draft guidance; ED, etranacogene dezaparvovec; FIX: factor IX, IV, intravenous, SmPC, summary of product characteristics

Key issue: Durability of treatment effect (cont.)

EAG response continued.

- EAG originally tried step function to conduct a one-way sensitivity analysis, varying the durability from 0 to 60 years – but due to shape of durability function results were not useful.
- New scenario provided truncating it at various time points
- Results show that at list price for the comparators, ED remains the most CE strategy at [redacted] (mean durability [redacted]). This result is insensitive to the inclusion of additional patients.
- When the confidential comparator prices are included there are no scenarios in which ED is the most cost-effective treatment strategy.

EAG: Sensitivity analysis on durability function

- Shah extrapolation (blue solid line) truncated at 60 years. EAG's previous step function (red dotted) was varied between 1 and 60 years (example shown with 20 year durability). EAG's revised step function (green dashed line) follows the Shah extrapolation until the cut point, which is varied between 1 and 60 years (example shown with 30 year durability).

DGC, draft guidance; ED, etranacogene dezaparvovec; FIX: factor IX, IV, intravenous, SmPC, summary of product characteristics

Key issue: Comparators in the economic model

Background after ACM1

- Company base case compared treatment with ED to 4 IV FIX products used in clinical practice
- Company provided a pairwise analysis comparing ED to 4 IV FIX products and in fully incremental analyses for the 4 comparators as prophylactic treatment plus the 4 comparators as on-demand treatment
- In clinical practice the most frequently prescribed treatments are extended half-life treatments
- Committee noted various factors contributed to the choice of FIX treatment so requested a scenario analysis using a 'basket of comparators' weighted by NHS market share data

Company response to DGC

- Provided analysis using a 'basket of comparators' weighted by market share in the NHS
- This better reflects choices in clinical practice for treating moderately severe and severe haemophilia B

EAG response

- Retained a fully incremental analysis
  - Binary choice between a basket of treatments or ED can create misleading conclusions, and result in incorrect application of incremental analysis
  - Data upon which NHS market share was derived unclear – timing and sample size may effect overall results.

Which analyses of comparators' is most appropriate?

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ACM, appraisal committee meeting; DGC, draft guidance for consultation; ED, etranacogene dezaparvovec; FIX: factor IX, IV, intravenous

Additional uncertainty: Divergence in probabilistic and deterministic ICERs

Background: Probabilistic and deterministic ICERs vary considerably due to a difference in QALYS of [redacted]

- EAG considered the divergence was due to the way the health state utilities were input.
- Utility values were input as independent beta distributions when it is best practice to model a baseline utility and an incremental utility. Latter approach provides structural correlation between health state utilities which is considered more plausible than independence.

Company response: Divergence <1% and do not consider this excessive

- Probabilistic utility values determined by the minimum function of the value of the beta distribution of comparator or ED (whichever is lower) - the structural correlation between the health state utilities which is advocated by the EAG is already included in the model.
- SHs all agree that QoL with ED is superior to QoL with Factor IX replacement therapies.

EAG response: Company approach inappropriate, Suggest committee consider the deterministic ICERs:

- Does not sample from the full uncertainty distribution of IV FIX health state utility - biases the health state utility estimate for IV FIX downwards, causing underestimate of the QALYs accrued in the IV FIX arms, and a lower ICER for ED
- Difference in health state utility not statistically significant: 95% confidence interval [redacted]
- Provides further evidence to reject the company's model assumptions fixing the health state utility of IV FIX to be always below that of ED – time constraints mean EAG cannot re run all analyses to provide less biased estimates.

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Is the company approach appropriate?

Additional comments raised on draft guidance

Issue and section in DGC	Company response	EAG critique
Annualised bleeding rate and change in FIX levels (3.4)	Queried DG data reported a reduced magnitude of benefit of ED (average bleeds per person 2.7 at 7–24 months post-treatment and 3.4 bleeds lead in period)	Reviewed data and consider it is correct • DGC refers to average number of bleeds in 6-month lead-in phase (total bleeds/number having a bleed) • Company refers to annualised rates of bleeds (extrapolated to 12-months based on total bleeds/time at risk)

DGC, draft guidance for consultation; ED, etranacogene dezaparvovec; FIX: factor IX;

Summary of company and EAG base case assumptions

Agreed upon assumptions in company and EAG base case

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 disutility 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).
Definition of treatment failure**	The FIX level at which FIX prophylaxis treatment would be restarted: 3% (as requested in DG)
Scenarios	• Basket of comparators weighted by market share • Inclusion of patient who received partial dose • Inclusion of patient who received partial dose and patient who had high nAB

* Retained from ACM 1; ** updated at consultation

ACM, appraisal committee meeting; nAB, neutralising antibodies

Managed access (1)

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 (2)

Managed access details of company proposal

- Company maintain routine commissioning most appropriate as uncertainty over durability of treatment is much longer than can be collected over the maximum timeframe of managed access
- Company proposes 5-year managed access agreement with data collected through:
    - Ongoing clinical trial programme
    - Clinical practice from the National Haemophilia Database (NHD) and the United Kingdom Haemophilia Centre Doctors Organisation (UKHCDO)
- Managed access team consider data collection is feasible but note:
    - Key uncertainty is durability of treatment effect. Any further data would be helpful, but an additional 5-years is unlikely to substantially impact the assumptions used over the lifetime of the model.
    - It would not be possible to collect meaningful data on the proportion who restart FIX prophylaxis in clinical practice within the timeframe of a managed access agreement
    - Evidence about sub-optimal dosage could be collected in clinical practice

Is ED suitable for consideration in managed access?

Cost-effectiveness results

All deterministic and probabilistic ICERs are reported in PART 2 slides because they include confidential comparator discounts

Type of analysis	Scenarios	Impact
Fully incremental analysis of ED compared with each IV FIX • Using a 3% definition of treatment failure	• Exclusion of 2 participants [as per company original base case in ACM1] • including participant having partial dose • Including participant with high levels of antibodies **and** participant having partial dose	ED not the most CE treatment strategy – ICER compared with cheapest IV FIX well in excess of £30,000 per QALY gained
Pairwise analysis of ED compared with a basket of comparators weighted by market share^ • Using a 3% definition of treatment failure	• Exclusion of 2 participants [as per company original base case in ACM1] • including participant having partial dose • Including participant with high levels of antibodies **and** participant having partial dose	ED dominates*

EAG consider the deterministic results provide a more plausible estimate than probabilistic results

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ED, etranacogene dezaparvovec; FIX: factor IX, IV, intravenous

* has lower total costs and higher QALYs; ^according to data from NHS England

Key issues

Issue	Resolved?	ICER impact
Comparators in the economic model	No – for discussion	Large
Durability of treatment effect: • **Shah et al (2022) analyses - uncertainties** • **Excluded patient(s) scenario analyses**	No – for discussion	Unknown
Divergence of probabilistic and deterministic ICERs	No – for discussion	Large
Managed access proposal and feasibility assessment	For discussion	Not applicable

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Thank you.