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:

1. **Comments on the Draft Guidance from** CSL Behring
   a. Response to draft guidance
   b. Managed Access proposal

2. **Stakeholders comments on the Draft Guidance** from:
   a. The Haemophilia Society
   b. UKHCDO

There were no responses to the draft guidance from the invited experts

3. **Comments on the Draft Guidance received through the NICE website**

4. **External Assessment Group critique of company comments on the Draft Guidance**
   a. EAG critique of company comments
   b. Response to company email

5. **Managed Access agreement**

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

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 23 August 2023. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	CSL Behring
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**	N/A

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appraisal stakeholder list.] **Please state:** • **the name of the company** • **the amount** • **the purpose of funding including whether it related to a product mentioned in the stakeholder list** • **whether it is ongoing or has ceased.**	
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	CSL Behring has no direct or indirect links to, or funding from, the tobacco industry.
Name of commentator person completing form:	[redacted]

Comment number	Comments
	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Executive summary** CSL Behring appreciates the opportunity to provide additional evidence to address the uncertainties noted by the committee in the draft guidance consultation (DGC). In this response, we provide further information to support the following key points: • Results of the indirect treatment comparison (see section 3.7) • Shah et al. (2022) durability extrapolation including the: − small sample size − lack of long-term data − exclusion of the person who had a partial dose and

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− exclusion of the person with poor response to treatment and a notably high AAV5 neutralising antibody titre (see section 3.11).

- Further scenario analysis using a 'basket of comparators' weighted by market share in the NHS.
- A scenario in which FIX prophylaxis treatment is restarted at a FIX level of 3%.
- Two scenario analyses which include:
    - the person who had a partial dose because this would be more reflective of clinical practice
    - all participants including the person who had a partial dose and the person with poor response to treatment and a notably high neutralising anti-AAV5 antibody titre

CSL Behring is currently in discussions with NICE Commercial Liaison Team to explore commercial options that may address and alleviate the above uncertainties and have submitted a new revised Simple Patient Access Scheme (PAS) for consideration, which has been accepted.

All analyses are provided in Appendix A and B.

General overview response

- *Has all of the relevant evidence been taken into account?*

Yes, CSL Behring has submitted all relevant evidence, including the most recent data cut-off of the HOPE-B trial (36 months post-treatment) which is provided in Appendix C. Please note that no CSR will be developed for this data cut-off, hence Appendix C contains the tables and figures of the TFLs. The listings of the TFLs are not included in Appendix C as these contain patient identifiable data. This data indicates that a single dose of etranacogene dezaparvovec reduced the ABR for all bleeds by [redacted]% at Months 7 to 18 (p = 0.0002), Months 7 to 24 (p = 0.0002; not adjusted for multiplicity), and Months 7 to 36 post-dose (p = [redacted]; not adjusted for multiplicity) compared to standard of care continuous FIX prophylaxis during the ≥ 6-month Lead-in Period. FIX activity increased to statistically significant and clinically relevant levels, with mean FIX activity remaining stable at [redacted]% (standard deviation [redacted]) through to Month 36 post-dose. [redacted] subjects treated remained free of FIX prophylaxis at Month 36 post-dose.

Due to the time available and comparability to original submission, we have submitted this response using the data-cut at 24-month post-treatment, as was used in the original submission.

- *Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?*

Yes, the interpretation of the evidence is deemed reasonable. The EAG and CSL Behring largely agreed with the conclusions drawn during the committee meeting, resulting in a well-aligned positioning and agreement on the interpretation of evidence.

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	• *Are the recommendations sound and a suitable basis for guidance to the NHS?* Etranacogene dezaparvovec is a highly innovative therapy, with potential long-term benefits. CSL Behring remain committed to collaborating with NICE, NHS England and all other health system partners to ensure that eligible patients with haemophilia B have more choice in how their condition is managed. The current recommendation does not reflect what NICE aim to achieve with its guidance particularly in relation to NICE's principle 8: *Support innovation in the provision and organisation of health and social care services*.[1] Principle 8 further states that 'NICE aims to support this innovation by encouraging interventions that provide substantial distinctive benefits that may not be captured by measuring health gain (that is, the estimated QALYs gained).'[1] As per section 3.17, the committee noted benefits of etranacogene dezaparvovec that were not included in the economic model. *"It noted that etranacogene dezaparvovec is expected to reduce long-term joint damage because it reduces bleeding events which are associated with joint damage. It also noted that etranacogene dezaparvovec might lower mortality, which would lead to higher QALY benefit."* • *Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?* Please see CSL Behring's comments on section 3.16.
2	**Why committee made these recommendations** *People with moderately severe or severe haemophilia B usually have long-term treatment with Factor IX (FIX) concentrates to prevent bleeding episodes (prophylaxis) and on-demand FIX concentrates to stop bleeding during a bleeding episode. A small number of people with the condition opt to only have on-demand treatment.* **CSL Behring response – see comments 3.4** *Evidence from a clinical trial suggests that etranacogene dezaparvovec reduces the number of bleeding episodes a person has each year. But there is not enough evidence on how well it works in the long term.* **CSL Behring response – see comments 3.7, 3.10, 3.11, 3.12** *An indirect comparison of etranacogene dezaparvovec with FIX prophylaxis treatments suggests that it improves bleeding outcomes. But there are problems with this evidence, such as differences between studies in the methods used, and the definition and measurement of bleeding outcomes. So, the indirect comparison results are highly uncertain.* **CSL Behring response – see comments 3.7**

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	The cost-effectiveness estimates for etranacogene dezaparvovec are uncertain because of uncertainties in the long-term clinical evidence and some of the assumptions used to estimate cost effectiveness. They are also above what NICE considers an acceptable use of NHS resources. So etranacogene dezaparvovec is not recommended. **CSL Behring response – see comments 3.10, 3.11, 3.12, 3.13, 3.14**
3.1	**Details of the condition** Thank you. No further comment, CSL Behring endorses the summary of the patient experience and agrees with the committee conclusions
3.2	**Treatment pathway and proposed positioning** Thank you. No further comment, CSL Behring agrees with the committee conclusions.
3.3	**The HOPE-B trial** Thank you. No further comment, CSL Behring agrees with the committee summary.
3.4	**Annualised bleeding rate and change in FIX levels** In section 3.4 the committee noted that *"at 7 to 24 months post-treatment, 27 out of 54 people had bleeds (average of 2.7 bleeds per person). It noted that the average number of bleeds after treatment was not substantially different from the lead-in period (average of 3.4 bleeds per person)."* **CSL Behring response:** CSL Behring agrees with the committee's final conclusion but would like to seek clarification on the data highlighted in the report as it is inconsistent with the data we have submitted and could risk presenting reduced magnitude of benefit. ABR for all bleeds reduced significantly from 4.19 (lead in period) to 1.51 (at 7–24 months post treatment). 136 total bleeds in the lead in period (≥6 months) which reduced to 55 during Year 1, 48 during Year 2 and 37 in Year 3 post-treatment. Median [range] bleeds per subjects decreased from 2.0 [0–10] during the lead-in period and remained stable to 0.0 [0–4] during Year 1, 0.0 [0–10] during Year 2 and 0.0 [0–8] during Year 3. Percentage of subjects with zero bleeding episodes increased following treatment from 25.9% (n=14/54) during the ≥6-month lead-in period to 63.0% (n=34/54) and 50.0% (n=27/54) during the Month 7–18 and Month 7–24 post-treatment periods. Therefore, it would be important for CSL Behring to understand how the committee calculated their average bleeds per person of 2.7 bleed at 7–24 months post-treatment and 3.4 bleeds in the lead in period. CSL Behring politely asks the committee to review and revise if appropriate.
3.5	**Calculation of change in FIX levels** No further comment, CSL Behring thanks the committee for recognising the rationale and approach taken with regards to FIX levels and agree with the discussions and conclusion.

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3.6	**Magnitude of clinical benefits** Thank you. No further comment, CSL Behring agrees with the committee discussions and conclusion.
3.7	**Indirect treatment comparisons** In section 3.7 it states that the committee *"understood the EAG's concerns but acknowledged these limitations related to the quality of the studies used in the indirect treatment comparisons rather than the methods used to do the indirect treatment comparisons. The committee concluded that the magnitude of improvement in bleeding outcomes for etranacogene dezaparvovec compared with FIX prophylaxis treatments was uncertain and would take this into account in its decision making."* **CSL Behring response –** CSL Behring would like to highlight that there are no quality concerns with the pivotal, HOPE-B trial and that all stakeholders recognise that the best methods available were utilised to identify the treatment comparisons. These are key facts to consider, especially in the context that the quality of the clinical trials used to determine the efficacy of the current standard of care, (Factor IX replacement therapies) are limited and they have not undergone a NICE health technology appraisal process. CSL Behring has nevertheless been proactive around this uncertainty in its modelling approach and has adopted into its revised base case the EAG supported, gradual improvement of etranacogene dezaparvovec bleed rates for the first 24 months of modelling. This is despite observed evidence from all the data cuts of the trial that etranacogene dezaparvovec significantly reduces bleed rates (see also 3.4). Furthermore, various scenario analyses throughout the submission have indicated the insensitivity of the bleed rates on the ICER.
3.8	**Company's modelling approach** Thank you. No further comment, CSL Behring agrees with the committee discussions.
3.9	**Comparators in the economic model** Thank you. No further comment, CSL Behring agrees with the committee discussions. Please see Appendix A and B for the analysis of etranacogene dezaparvovec followed by a "basket of comparators" in a pairwise comparison. This comparison should on average be a better reflection wholistically, of the choices that the clinicians face in treating patients with moderately severe and severe haemophilia B in practice, particularly when considering the fact of the declining use of standard half-life Factor IX products in the NHS.
3.10	**Definition of treatment failure**

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	"In section 3.10 it states that the committee "*concluded that it is appropriate to model restarting FIX prophylaxis treatment at a FIX level between 2% and 3%. It requested the company also provide a scenario in which FIX prophylaxis treatment is restarted at a FIX level of 3%.* *The EAG also noted that people in HOPE-B only stopped FIX prophylaxis treatment when FIX levels were more than 5%."* **CSL Behring response –** CSL Behring has conducted an analysis to address this concern and provided a scenario in which FIX prophylaxis treatment is restarted at a FIX level of 3%, which is provided in Appendices A and B.
3.11	**Durability of treatment effect** **Shah et al. analysis** It is stated in section 3.11 that the committee *"was concerned that the excluded data could bias the estimates and that the company provide 2 scenario analyses which include:* • *the person who had a partial dose because this would be more reflective of clinical practice* • *all participants including the person who had a partial dose and the person with poor response to treatment and a notably high neutralising anti-AAV5 antibody titre.* **CSL Behring response –** Data from the two patients were excluded from the original analysis for methodological reasons, as uncontaminated FIX levels were required to perform the statistical analysis. However, following section 3.10 and the above comment of the committee, CSL Behring has conducted an analysis to address this concern. The cost-effectiveness model now includes an option to have the new Shah 3% durability threshold extrapolation to include/exclude the ITT population and the patient with a high AAV5 NAb titre. However, we would politely ask the committee to seek clinical expert opinion on whether a patient with neutralising antibodies titres >1:678 would receive treatment in the UK, as the study's clinical principal investigators, of which one is UK-based, have stated that this would be an exclusion criterion. Moreover, it is our understanding that there will be further guidance issued by UKHCDO, in which this would be an exclusion criterion. This is in keeping with the statement in the SmPC suggesting reduced efficacy for these patients in order to guide clinician decision. Therefore, it may be clinically appropriate to exclude the patient with a high AAV5 neutralising antibody titre from the model. The impact of these changes on the cost-effectiveness results can be seen in Appendix A and Appendix B

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3.12	**Long term treatment durability** In section 3.12 it was noted that *"Evidence from HOPE-B suggested that treatment effect may be reduced in specific subgroups of people who have etranacogene dezaparvovec. These subgroups included people who had corticosteroids to treat transaminase increases, people who developed AAV5 neutralising antibodies and people with moderate or severe liver steatosis at baseline. The EAG considered it plausible that reduced treatment effect over time may be more likely in these groups. The EAG also noted it received expert advice that suggested that the rate of cell turnover in the areas of the body targeted by etranacogene dezaparvovec, 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. Cells in the liver are responsible for producing FIX, and study participants with liver conditions were either excluded from the study or showed reduced treatment efficacy. The EAG also understood that the liver has a higher rate of cell turnover than other areas of the body. The committee concluded that the long-term durability of etranacogene dezaparvovec was a considerable uncertainty, which had a notable impact on the cost-effectiveness estimates."* **CSL Behring response -** 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.[2]
3.13	**Acceptable ICER** In section 3.13, the committee stated, *"Because of the high level of uncertainty in the clinical and economic evidence, the committee agreed that an acceptable ICER would be towards the lower end of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per quality adjusted life year [QALY] gained)."* **CSL Behring response –** CSL Behring believe that etranacogene dezaparvovec can meet the willingness to pay threshold of £20,000 per QALY due to the substantial value it provides to patients and the NHS. CSL Behring is currently in discussions with NICE Commercial Liaison Team to explore commercial options that may address and alleviate the above uncertainties and have submitted a new revised Simple PAS for consideration, which has been accepted. Based on this new accepted PAS, the uncertainty and the ICERs will reach an acceptable level making etranacogene dezaparvovec dominant against all comparators. CSL Behring believes that the new revised PAS goes above what is needed to reach the threshold but will help to manage concerns around the uncertainty.
3.14	**Cost-effectiveness estimates** In section 3.14 it states *"The committee agreed that it would prefer to see the following scenarios:* • *a 'basket of comparators' weighted by use in the NHS (see section 3.9).*

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	• *treatment failure defined as FIX level of 3% (see section 3.10).* • *updated Shah et al. (2022) analysis to include the person who had a partial treatment dose (see section 3.11) and a further scenario which also includes both the person who had a partial dose and the person with poor response to treatment and a notably high AAV5 neutralising antibody titre (see section 3.11).”* **CSL Behring response –** CSL Behring is happy to provide the committee with its preferred scenarios. Please see Appendix A and Appendix B In section 3.14 it states *“Both ICERs were above £100,000 per QALY gained.”* **CSL Behring response –** CSL Behring would like to highlight that due to the uncaptured quality of life benefits, the incremental total QALYs are small which in turn act as a small denominator in the ICER calculations. In this case, net monetary benefit is a more stable metric of the cost-effectiveness estimates than the ICER. The net monetary benefit of the strategy consisting of etranacogene dezaparvovec followed by a basket of Factor IX prophylaxis comparators, is vastly greater, than the net monetary benefit of the strategy consisting of a basket of Factor IX prophylaxis comparators only. This conclusion is true in terms of the committee’s preferred assumptions as outlined in this section.
3.15	**Other considerations** **Managed access** In section 3.15 it states *“The committee was aware that NICE’s health technology evaluations manual states that a recommendation with managed access can be an option for patient access to medicines when immature evidence or evidence gaps results in significant uncertainty for committee decision making. It recognised that etranacogene dezaparvovec is a promising treatment and that the ongoing HOPE-B trial could provide further data to address some of the uncertainty about the treatment’s long-term durability.”* **CSL Behring response –** Prior to the 1st Committee, CSL Behring engaged with the NICE Managed Access team regarding the potential of a managed access agreement and it was decided collectively with the stakeholders that submitting a managed access proposal was not the most appropriate route. Post 1st Committee, CSL Behring have engaged further with NICE and have submitted a managed access proposal for NICE to undertake a feasibility assessment, which is provided in Appendix D. CSL Behring believes that a technology appraisal recommendation for routine commissioning is still the most appropriate route of optimal patient access for etranacogene dezaparvovec.

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3.16	**Equality** The committee noted, as per section 3.16 that "haemophilia B is rare in women and HOPE-B did not include women. It 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." **CSL Behring response** – While CSL Behring agrees that the few women who experience severe and moderately severe haemophilia B would be affected similarly as men, the company would like to clarify that, while the effects of etranacogene dezaparvovec on male fertility and the viral shedding in semen were studied, no dedicated animal fertility/embryofoetal studies have been conducted to substantiate whether the use in women of childbearing potential and during pregnancy could be harmful for the newborn child.[3] The SmPC of etranacogene dezaparvovec states that no data are available to recommend a specific duration of contraceptive measures in women of childbearing potential, and, therefore, etranacogene dezaparvovec is not recommended in women of childbearing potential.[3] Moreover, since it is not known whether etranacogene dezaparvovec can affect reproductive capacity, cause foetal harm (when administered to a pregnant woman), or can be excreted in human milk, etranacogene dezaparvovec should not be used during pregnancy or during breastfeeding.[3]
3.17	**Uncaptured benefits** Thank you. No further comment, CSL Behring agrees with the committee discussions.

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Appendix A

Following the committee request described in Section 3.14, the cost-effectiveness modelling results are provided in the tables below. These results are for an increased patient access scheme (PAS) discount value of [redacted].

Table 1. Pairwise incremental analysis of etranacogene dezaparvovec followed by a basket of comparators, against a basket of comparators, for the Shah 3% durability threshold.

Technology	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Etranacogene dezaparvovec (Basket of comparators)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Basket of comparators	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 2. Pairwise incremental analysis of etranacogene dezaparvovec followed by a basket of comparators, against a basket of comparators, for the Shah 3% ITT durability threshold

Technology	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Etranacogene dezaparvovec (Basket of comparators)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Basket of comparators	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 3. Pairwise incremental analysis of etranacogene dezaparvovec followed by a basket of comparators, against a basket of comparators, for the Shah 3% ITT and high Nab titre patient exclusion durability threshold

Technology	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Etranacogene dezaparvovec (Basket of comparators)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Basket of comparators	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 4. Fully incremental analysis of all non-blended comparators, with etranacogene dezaparvovec having the Shah 3% durability threshold

Technology	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)

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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]

Table 5. Fully incremental analysis of all non-blended comparators, with etranacogene dezaparvovec having the Shah 3% ITT durability threshold

Technology	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
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]

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Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 6. Fully incremental analysis of all non-blended comparators, with etranacogene dezaparvovec having the Shah 3% ITT and high Nab titre patient exclusion durability threshold

Technology	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
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]

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Appendix B

The probabilistic sensitivity analyses for the blended and non-blended scenarios that CSL Behring believe to be the most appropriate for decision making are provided below, and herein constitute the post-committee revised base case. Please refer to section 3.11. These results are for an increased patient access scheme (PAS) discount value of [redacted].

Table 7. 10,000 iteration probability sensitivity analysis for the pairwise incremental analysis of etranacogene dezaparvovec followed by a basket of comparators, against a basket of comparators, for the Shah 3% ITT durability threshold

Technology	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs	NMB @ £30,000/QALY	% of Cost-effectiveness @ £30,000/QALY
Etranacogene dezaparvovec (Basket of comparators)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Basket of comparators	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 8. 10,000 iteration probability sensitivity analysis for the fully incremental analysis of all non-blended comparators, with etranacogene dezaparvovec having the Shah 3% ITT durability threshold

Technology	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs	NMB @ £20,000/QALY	% of Cost-effectiveness @ £30,000/QALY
Etranacogene dezaparvovec (Benefix)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etranacogene dezaparvovec (Alprolix)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etranacogene 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]

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 23 August 2023. Please submit via NICE Docs.

Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Appendix C

See separately provided document for Appendix C (HOPE-B data at 36-month post-treatment).

Appendix D

See separately provided document for Appendix D (managed access agreement proposal).

Appendix E

See separately provided document for Appendix E (revised economic model).

Appendix F

See separately provided document for Appendix F (confidentiality checklist).

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 23 August 2023. Please submit via NICE Docs.

Checklist

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations 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.

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Appendix D: Managed Access Proposal

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

[ID3812]

CSL Behring

23 August 2023

Is the technology eligible for managed access?

As requested by the National Institute of Health and Care Excellence (NICE), CSL Behring have provided a draft managed access proposal for NICE to undertake a feasibility assessment to consider if it concludes that a recommendation is not supported, and a recommendation with managed access through the Innovative Medicines Fund (IMF) is appropriate.

Is the technology suitable for managed access?

CSL Behring believe routine commissioning is the most appropriate route for etranacogene dezaparvovec, as the uncertainty with durability, which is the key driver of cost effectiveness, is over a longer term rather than the maximum 5 years covered by managed access via the IMF.

CSL Behring have also engaged with the NICE Managed Access Team to discuss if etranacogene dezaparvovec was suitable for a managed access agreement prior to the 1st Committee and it was decided collectively with the stakeholders that submitting a managed access proposal was not the most appropriate route.

For etranacogene dezaparvovec, phase 3 data (CT-AMT-061-02, HOPE-B) is available for up to 3 years in 54 patients. This is the largest number of participants in haemophilia B gene therapy trials to date. Moreover, the treatment durability of etranacogene dezaparvovec is supported by a phase 2b trial (CT-AMT-061-01) in 3 patients which have been followed up for 4 years and a phase 1/2 trial (CT-AMT-060-01) with the AMT-060 product for up to 7 years (5 years + 2 years open label extension (OLE) to date). AMT-060 is a gene therapy product with the same vector and cassette design as etranacogene dezaparvovec but using a wildtype Factor IX transgene, which differs from Factor IX Padua variant used in etranacogene dezaparvovec.

All 3 trials in our clinical development programme have a 5-year trial period followed by 5 years of OLE, as agreed with regulatory authorities. Therefore, each trial will only offer a maximum of 10 years of data, meaning that the likelihood of data collection sufficiently resolving this key uncertainty within the maximum of 5 years and lead to a positive NICE decision at the point etranacogene dezaparvovec exits managed access may not be possible.

It has been noted by clinical experts that other gene therapy trials using AAV vectors for haemophilia B show durability of expression for over 12 years. The final read-outs of the phase 2b and phase 3 OLE studies are expected in Q3 2028 and Q2 2030, respectively. As these data-cuts fall beyond the maximum of 5 years covered by managed access, the uncertainty with durability will not be sufficiently resolved, even if patients from the phase 1–3 studies would be included.

However, CSL Behring acknowledge uncertainty may remain in the cost-effectiveness analysis due to the durability data for etranacogene dezaparvovec and are engaging with the NICE Commercial Liaison (PASLU) team to discuss how our value proposition could be made cost-effective to address this uncertainty and allow a routine commissioning recommendation.

Unmet need/severity

The following information is sourced from Section A.1 (Document A) of the company submission.

Haemophilia B is a rare X chromosome-linked congenital bleeding disorder characterised by deficiency of coagulation Factor IX.[1] The majority (70%) of haemophilia cases are inherited, while approximately 30% result from spontaneous mutations.[2,3]

The severity of haemophilia B generally correlates with the degree of clotting-factor deficiency and is categorised as severe (Factor IX <1%), moderate (Factor IX 1–5%) or mild (Factor IX 5–40%).[3-5] People with a severe bleeding phenotype may experience spontaneous bleeds, or bleeding after an injury or surgery.[3,6] Joint bleeds (haemarthrosis) are the most common spontaneous bleeding manifestation.[7]

Haemophilia B is associated with a reduced quality of life (QoL) due to symptoms including chronic pain, functional impairment, anxiety and depression and disability caused by joint damage.[8] 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.[9]

The mainstay of treatment of haemophilia B comprises Factor IX replacement therapy, either as prophylaxis therapy or on-demand treatment, to prevent and/or manage bleeding episodes.[3,10] Although current treatments have improved clinical outcomes, they do not eliminate the risk of all bleeding events, resulting in disease progression and poor QoL.[3,11]

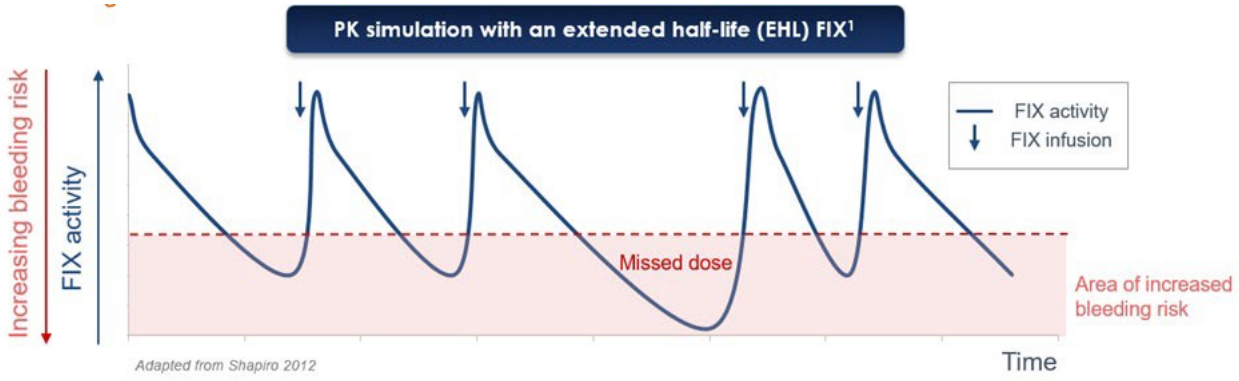
The following information is sourced from Section B.1.3.4 (Document B) of the company submission.

Burdensome and time consuming intravenous (IV) injections with prophylaxis therapy 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.[12-14] 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.[13] Furthermore, frequent IV injections can affect adherence to treatment, which in turn is critical to the risk of developing arthropathy.[15] 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 1). 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 1. 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[16]

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.[17] Such demands can be stressful for the caregiver, not only physically, but also emotionally, psychologically, and financially.[17] 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.[18]

Frequent intravenous injections are associated with several complications and reduced QoL.[19] 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.[20,21]

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, was 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.[22,23]

Clinically significant benefits of technology

The following information is sourced from Section A.4 (Document A) of the company submission.

Etranacogene dezaparvovec is a gene therapy product designed to introduce a copy of the human Factor IX coding deoxyribonucleic acid (DNA) sequence into hepatocytes to address the root cause of the Haemophilia B disease. The technology 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.[24]

Severity

The modelling assumes that haemophilia B patients experience no excess mortality, and this technology does not meet the criteria for the severity modifier. This is further highlighted in the below section on incremental QALYs, whose magnitude does not constitute severity in large part due to the uncaptured quality-of-life benefits in the EQ-5D generic preference-based measure.

Incremental QALYs gained within the base-case increment cost-effectiveness analysis results

The below table shows in part the incremental QALYs between the eight strategies, for an assumption requested by the committee following the first committee meeting. Therefore, the strategies containing etranacogene dezaparvovec express the Shah 3% intent-to-treat (ITT) population durability threshold. Costs are included to identify the next non-dominated comparator as that is how incremental values are typically expressed.

Table 1. Fully incremental analysis of all non-blended comparators, with etranacogene dezaparvovec having the Shah 3% ITT durability threshold, for the post-committee with new revised Simple PAS

Strategy	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
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; ITT, intent-to-treat; PAS, patient access scheme; QALY; quality-adjusted life year

Key uncertainties and data sources

Uncertainties

The appraisal committee identified the following key area of uncertainty in the draft consultation:

- The committee concluded that the long-term durability of etranacogene dezaparvovec was a considerable uncertainty, which had a notable impact on the

cost-effectiveness estimates. It considered that the AMT-060 sample size was too small to support robust conclusions on the long-term durability of etranacogene dezaparvovec. It further concluded that the uncertainty relating to longer-term durability of etranacogene dezaparvovec would only be reduced by longer-term data collection.

- Etranacogene dezaparvovec is a promising treatment and that the ongoing HOPE-B trial could provide further data to address some of the uncertainty about the treatment's long-term durability.

Outcome data and data sources

To reiterate, we believe routine access is most appropriate. The uncertainty with durability, even if the phase 1–3 patients (summarised below) are included will not be resolved within the 5 years covered by managed access.

The data available in the clinical trial programme for etranacogene dezaparvovec to date is listed in Table 2.

Table 2. List of uncertainties and the data that could be collected to resolve them.

Clinical uncertainty	Outcome data	Data source	Likelihood data collection could sufficiently resolve key uncertainties.
Long-term durability	CT-AMT-060-01 with OLE (AMT-060)	CSL Behring clinical trial programme* Last patient OLE visit expected Q2 2026	AMT-060 is a gene therapy product with the same vector and cassette design as etranacogene dezaparvovec but using a wildtype Factor IX transgene, which differs from Padua Factor IX transgene in etranacogene dezaparvovec. Outcomes from phase 1/2 trial are not used in the economic model. Moreover, the committee considered that the AMT-060 sample size was too small to support robust conclusions on the long-term durability of etranacogene dezaparvovec. This makes it unlikely that additional data collection from patients treated with AMT-060 would sufficiently resolve the key durability uncertainty.
Long-term durability	CT-AMT-061-01 (Phase 2b) with OLE	CSL Behring clinical trial programme Last patient visit expected in September 2023, with data available approximately May 2024. Patients will then enrol into OLE for 5 years, with last patient visit expected in Q3/Q4 2028.	The phase 2b trial included 3 patients, which, given the committee's comment on the size of CT-AMT-060-01, would suggest that the committee may also consider the sample size of the phase 2b trial to be too small to support robust conclusions on the long-term durability of etranacogene dezaparvovec. While additional follow-up time during the MAA may support modelling, the likelihood that the additional data collection could *sufficiently* resolve the key uncertainties in the 5 years maximum allowable length of managed access data collection is small.

Clinical uncertainty	Outcome data	Data source	Likelihood data collection could sufficiently resolve key uncertainties.
			During the appraisal process, United Kingdom Haemophilia Centre Doctors Organisation (UKHCDO) stated "*A single infusion with etranacogene dezaparvovec has potential benefits for up to 10 years.*". Moreover, the EAG presented a strategy during Technical Engagement in which etranacogene dezaparvovec became the most cost-effective at a durability of approximately 9.2 years. This was largely insensitive to whether the threshold was £20,000 or £30,000. Even if the managed access would run for the maximum period of 5 years, the data would not be mature enough to reach the 10 years discussed by committee and sufficiently resolve the key uncertainty of durability.
Long-term durability	**CT-AMT-061-02 (HOPE-B, Phase 3) with OLE**	CSL Behring clinical trial programme Phase 3: Latest data cut-off is at 36-month post-treatment, as provided in Appendix C of the draft guidance company response. Last patient visit is expected approximately Q2 2025. Patients will then enter into an OLE for 5 years, with last patient visit expected Q2 2030	As described above, while additional follow-up time during the MAA may support modelling, the likelihood that the additional data collection could *sufficiently* resolve the key uncertainties in the 5 years maximum allowable length of managed access data collection is small.

Clinical uncertainty	Outcome data	Data source	Likelihood data collection could sufficiently resolve key uncertainties.
			During the appraisal process, United Kingdom Haemophilia Centre Doctors Organisation (UKHCDO) stated "*A single infusion with etranacogene dezaparvovec has potential benefits for up to 10 years.*". Moreover, the EAG presented a strategy during Technical Engagement in which etranacogene dezaparvovec became the most cost-effective at a durability of approximately 9.2 years. This was largely insensitive to whether the threshold was £20,000 or £30,000. Even if the managed access would run for the maximum period of 5 years, the data would not be mature enough to reach the 10 years discussed by committee and the clinical experts, and sufficiently resolve the key uncertainty of durability.
Long-term durability	Observational post-authorisation long-term follow-up study	CSL Behring post- authorisation development plan with patients treated with commercial product. Data to be entered into National Haemophilia Database (NHD)	This long-term observational study includes only patients treated with commercial product (dependent on a NICE recommendation). These patients would be treatment-naïve at the start of the study and so, after a maximum of 5 years managed access, the patients would be a maximum of 5 years post-treatment.[25] This data would not be sufficient to resolve the durability issue.

Phase 1/2 (AMT-060)

- Open-label, uncontrolled, single-dose, dose-ascending designed study enrolled subjects (n=10) with haemophilia B. Eligible subjects were allocated to 2 consecutive dose cohorts and received a single intravenous dose of AMT-060; Cohort 1 (n=5) received the low dose of 5.0×10^{12} gc/kg and Cohort 2 (n=5) received the high dose of 2.0×10^{13} gc/kg
- AMT-060 is a gene therapy product with the same vector and cassette design as etranacogene dezaparvovec but using a wildtype Factor IX transgene, which differs from Padua Factor IX transgene in etranacogene dezaparvovec.
- AMT-060 was administered as a single dose and subjects were followed for 5 years for safety and efficacy.
- Currently, patients have enrolled in an open label extension (OLE) study, which is planned to run for 5 years.
- 9/10 patients have completed 6 years follow up (July 2023), with 8/9 patients stopping previous Factor IX prophylaxis.
- At study entry, 5/5 patients in Cohort 1 and 4/5 patients in Cohort 2 were on a prophylactic Factor IX regimen, while 1/5 subject in Cohort 2 used an on-demand Factor IX regimen.
- Of the 5/5 patients in Cohort 1 who were on a prophylactic Factor IX regimen, 1 subject received on-demand Factor IX replacement therapy until 2015 and then switched to prophylactic replacement therapy thereafter.
- One death, which was confirmed to not be treatment-related, was reported in a patient following study completion and clinical database lock.
- The anticipated completion date for this study (with OLE) is Q2 2026.
- Since this trial did not include the use of etranacogene dezaparvovec, the outcomes were not and will not be used to inform the economic model for etranacogene dezaparvovec.

Please note that there were no UK patients included in the phase 1/2 study. Protocols for the OLE have been confirmed and CSL Behring will only have access to predefined data points, which cannot be tailored to meet UK-specific needs.

Phase 2b

- Open-label, single-dose, single-arm, multicentre trial was initiated to confirm the Factor IX activity level of AAV5-hFIXco-Padua in adults (n=3) with severe or moderately severe haemophilia B.
- Single dose of 2.0×10^{13} gc/kg
- This trial was supported by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to address the change of transgene product and to inform the dose choice for etranacogene dezaparvovec in a phase 3 trial.
- 3 patients have completed 4 years follow up (July 2023) and none have returned to prophylaxis.
- Patients will enter an OLE study after 5 years.
- The anticipated completion date for this study (with OLE) is Q3/Q4 2028

Please note that there were no UK patients included in the 2b study. Protocols for the OLE have been confirmed and CSL Behring will only have access to predefined data points, which cannot be tailored to meet UK-specific needs.

Phase 3 (HOPE-B trial)

- Open-label, single-dose, multicentre trial to evaluate safety and efficacy of etranacogene dezaparvovec
- Single dose of 2.0×10^{13} gc/kg
- 54 patients enrolled in HOPE-B.
- 53 patients have completed 36 months follow-up (July 2023) with 51 patients remaining off prophylaxis.
    - One patient had a high NAb titre and did not achieve Factor IX expression post treatment. This patient remained on prophylaxis since study initiation.
    - One patient received 10% dose and remained on prophylaxis since study initiation.
    - One patient lost Factor IX expression at month 30 and returned to prophylaxis.
- Patients will enter an OLE study after 5 years.
- The anticipated completion date for this study (with OLE) is Q2 2030

Please note that only 5 UK patients were included in the phase 3 HOPE-B trial. Protocols for the OLE have been confirmed and we will only have access to predefined data points, which cannot be tailored to meet UK specific needs. Outcome data from the 5 UK patients was not captured in the National Haemophilia Database (NHD), as per trial protocol.

Additional data analyses and economic modelling

This managed access proposal would not change the approach to economic modelling but could inform updates to the long-term durability statistical modelling used within it in the case of the phase 2b/3 data. However, the likelihood that the additional data collection could sufficiently resolve the key uncertainties in the 5 years maximum allowable length of managed access data collection is small.

Since the phase 1/2 trial did not include the use of etranacogene dezaparvovec, the outcomes are not used in the economic model and the approach to the economic modelling would not change. Moreover, the committee considered that the AMT-060 sample size was too small to support robust conclusions on the long-term durability of etranacogene dezaparvovec.

Overview of clinical studies/registries within the suitability of managed access

Each of the phase 1/2, 2b and 3 studies within the clinical trial program will complete after 5 years. Patients will then enrol in an open label extension (OLE) study for each of these programs which will be coordinated by CSL Behring.

Patients in phase 1/2 are already enrolled in OLE, see the trial protocol Table 3 below.

Table 3. Overview of data source – CT-AMT-060-01 OLE

Study	Phase 1/2 extension study assessing the long-term safety and efficacy of an adeno-associated viral vector containing a codon-optimised human factor IX gene (AAV5-hFIX) previously administered to adult patients with severe or moderately severe haemophilia B during the CT-AMT-060-01 phase 1/2 study.
Study design	Open-label, extension study enrolling patients who have successfully completed all assessments in Study CT-AMT-060-01 (Years 1–5).
Population	Male patients, who previously received an infusion of AMT-060, with severe haemophilia B or moderately severe haemophilia B with a severe bleeding phenotype and who completed all assessments in Study CT-AMT-060-01.
Intervention(s)	Not applicable; all patients enrolled will have been previously administered a single dose of AMT-060 (5×10^{12} gc/kg or 2×10^{13} gc/kg) during Study CT-AMT-060-01.
Comparator(s)	Not applicable

Outcomes (Mark in bold the outcomes listed as a primary source within the 'suitability for managed access' section)	Primary safety endpoints include the following: - Adverse events possibly or probably related to previous AAV5-hFIX administration. - Neutralising Factor IX antibodies (Factor IX inhibitors) - ALT/AST levels - Liver pathology (assessed by ultrasound) - Alpha-fetoprotein (AFP) Secondary efficacy endpoints include the following: - Endogenous Factor IX activity - Utilisation of Factor IX-replacement therapy - Annualised bleeding rate (Factor IX-requiring); including the following: • All bleeds • Spontaneous bleeds • Traumatic bleeds • Joint bleeds - Procedures (including major and minor surgeries) - Short form (SF-36) and EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) QoL scores - Haemophilia Joint Health Score (HJHS) Exploratory endpoint: - Anti-AAV5 antibodies (total [IgM and Ig], neutralising antibodies) - Factor IX protein concentration (FIX:Ag)
Indicate if study used in the NICE economic model	No
Trial start date	Q3 2020 for OLE
Data cut submitted to NICE (complete as 'Not applicable' for trial data not presented within the NICE submission)	Not applicable
Anticipated data cut after a period of managed access	Q2 2026 (last subject visit)

The trial protocol for CT-AMT-061-01 (phase 2b) and HOPE-B (phase 3) are shown in and Table 4 and Table 5, respectively.

Table 4. Overview of data source – CT-AMT-061-01

Study	Phase IIb, open-label, single-dose, single-arm, multi-center trial to confirm the factor IX activity level of the serotype 5 adeno-associated viral vector containing the Padua variant of a codon-optimized human factor IX gene (AAV5-hFIXco-Padua, AMT-061) administered to adult subjects with severe or moderately severe hemophilia B
Study design	Open-label, single-dose, single-arm multi-centre study
Population	Male, aged ≥18 years, with congenital haemophilia B classified as severe (<1% of normal circulation FIX) or moderately severe FIX deficiency (1-2% of normal circulating FIX, inclusive)
Intervention(s)	Etranacogene dezaparvovec (previously AMT-060)
Comparator(s)	Not applicable
Outcomes	*Primary endpoint* • Endogenous FIX activity level at Week 6 post-AMT-061 dose *Secondary endpoints:* • Endogenous FIX activity level at Week 52 post-AMT-061 dose • Remaining free of previous continuous prophylaxis during 52 weeks following AMT-061 dosing • Total usage of FIX replacement therapy until 52 weeks following AMT-061 dosing, excluding ad hoc prophylaxis for invasive procedures • ABR after 52 weeks of AMT-061 dosing (including a further break down of the frequency and percentage of spontaneous, traumatic, and joint bleeding events) *Exploratory endpoints:* • Joint health and quality of life (QoL) scores • Correlation between AAV5 NAb titers and FIX activity levels • Factor IX-protein-to-activity ratio in subjects without residual expression of nonfunctional FIX protein (analysed as activity divided by protein) *Safety endpoints* included AEs, haematology and serum chemistry parameters, observed ALT/AST levels and corticosteroid use for any elevations, antibody formation to AAV5 and human FIX, AAV5 capsid-specific T-cell response, inflammatory markers, vector DNA in semen and blood, and AFP. An additional endpoint in the long-term follow-up is abnormal findings on the abdominal ultrasound
Indicate if study used in the NICE economic model	Yes
Trial start date	July 2018 (First subject's informed consent date)

Data cut submitted to NICE	N/A as data was not presented within NICE submission. For completeness, please note that the 30 Month post-treatment data-cut was included in the Shah extrapolation, and this was used to inform the economic model.
Anticipated data cut after a period of managed access	Last patient visit in clinical trial September 2023. Patients will then enrol into OLE for 5 years, with last patient visit expected in Q3/Q4 2028.

Table 5. Overview of data source – HOPE-B

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 (AMT-061)
Comparator(s)	Not applicable
Outcomes	**Primary outcome** **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)
	  o interleukin-2 (IL-2)
	  o interleukin-6 (IL-6)
	  o interferon gamma (IFNγ)
	  o monocyte chemotactic protein-1 (MCP-1)
	  o AST and ALT level increases and use of corticosteroids for AST/ALT increases
	• Alpha-fetoprotein

Indicate if study used in the NICE economic model	Yes
Trial start date	June 2018 (First subject's informed consent date)
Data cut submitted to NICE	24-months post-treatment, data of the most recent cut-off (36-months post-treatment) is included in Appendix C of the draft consultation guidance response.
Anticipated data cut after a period of managed access	Last subject visit is Q2 2025, therefore anticipated OLE end would be Q2 2030

Patients treated with commercial product will enter the post-authorisation development plan with an observational post-authorisation long-term follow-up study. The protocol has been developed by CSL Behring. Patients will be enrolled for 15 years, and data will be entered onto UK NHD. See Table 6.

Table 6. Overview of data source – registry

Registry	National Haemophilia Database (NHD) managed by the UK Haemophilia Centre Doctors'
Type of registry	The UK NHD is a register of people in the UK with all types of bleeding disorders started in 1969. Set up at the request of the Department of Health. All Haemophilia Centres in the UK are required (and recently contracted) to report to NHD on all patients with bleeding disorders The database is held within the NHS and managed by the UK Haemophilia Centre Doctors' Organisation (UKHCDO) UKHCDO is the data controller and processor and determines the purpose and means of processing the personal data collected.
Population	People in the UK with all types of bleeding disorders
Relevant data items collected (Mark in bold the outcomes listed as a primary source within the 'suitability for managed access' section)	Safety endpoints - Serious adverse events (SAEs) - Adverse events of special interest (AESIs) Effectiveness endpoints - Bleeding - Factor IX activity - Annualised bleed rate - Annualised consumption of Factor IX replacement therapy - Number of patients remaining free of previous continuous routine prophylaxis - Target joints - PROs (EQ-5D-5L and Haem-A-QoL)
Data analysis	The company will not have access to the NHS Digital patient data, but will receive de-personalised summary data
Governance	All necessary governance arrangements through NHD, and other datasets brought together by NHS Digital, have been established with NHS Trusts and NHSE.
Indicate if registry previously used within a NICE managed access	No

Proposed registry

Discussions are ongoing with NHD/UKHCDO for collection/analysis/sharing of data for the observational post-authorisation study, however NHD/UKHCDO have no prior experience with managed access and additional time and resource will be required for NHD to set this study up.

Proposed eligibility criteria for a MAA

In order to provide guidance on the appropriate eligibility of patients treated with etranacogene dezaparvovec, CSL Behring have developed proposed eligibility criteria for the managed access proposal.

Patient eligibility

Etranacogene dezaparvovec is indicated for the treatment of severe and moderately severe haemophilia B (congenital Factor IX deficiency) in adult patients without a history of Factor IX inhibitors.[24]

Key eligibility criteria for the use of etranacogene dezaparvovec include:[24]

- 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.
- Patients without a history of Factor IX inhibitors
- Prior to the treatment with etranacogene dezaparvovec, patients should be assessed for the titre of pre-existing neutralising anti-AAV5 antibodies.
    - Pre-existing neutralising anti-AAV5 antibodies above a titre of 1:678 may impede transgene expression at desired therapeutic levels and thus reduce the efficacy of etranacogene dezaparvovec therapy.
- 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.
- Etranacogene dezaparvovec will be otherwise used as set out in its Summary of Product Characteristics (SmPC).[24]

Anticipated time frame

The anticipated time frames for data collection to address the durability uncertainty are outlined in Table 7. However, it is unlikely that the maximum timeframe of managed access (5 years) would sufficiently resolve this key uncertainty.

Table 7. Ongoing and planned clinical trials

Product	Trial	Phase	Number of patients	Duration	Anticipated timeframe of data collection	Additional comments
AMT-060	CT-AMT-060-01	Phase 1/2	9 patients	6 years data cut-off (July 2023)	Last patient OLE visit expected Q2 2026	AMT-060 is a gene therapy product with the same vector and cassette design as etranacogene dezaparvovec but using a wild-type Factor IX transgene, which differs from the Padua Factor IX transgene in etranacogene dezaparvovec. Since the phase 1/2 trial did not include the use of etranacogene dezaparvovec, the outcomes are not used in the economic model. Moreover, the committee considered that the AMT-060 sample size was too small to support robust conclusions on the long-term durability of etranacogene dezaparvovec.

Etranacogene dezaparvovec	CT-AMT-061-01	Phase 2b	3 patients	4 years data cut-off	Last patient visit expected in September 2023, with data available approximately May 2024. Patients will then enrol into OLE for 5 years, with last patient visit expected in Q3/Q4 2028.	In the anticipated timeframe of managed access, the phase 2b trial would provide data on the 3 patients currently enrolled in CT-AMT-061-01. Given the committee's comment on the size of CT-AMT-060-01, the committee may also consider the sample size of the phase 2b trial to be too small to support robust conclusions on the long-term durability of etranacogene dezaparvovec. After the maximum duration of managed access (5 years), the three patients in the phase 2b trial would be at 9 years post-treatment. Particularly when taking into account the population size of the study (n=3) and the committee's comments provided above, this may be too short to provide robust and meaningful evidence to address the uncertainty of durability.

Etranacogene dezaparvovec	CT-AMT-061-02 (HOPE-B)	Phase 3	53 patients	3 years data cut-off	Phase 3: Latest data cut-off is at 36 months post-treatment, as provided in Appendix C of the draft guidance company response. Last patient visit is expected approximately Q2 2025. Patients will then enter into an OLE for 5 years, with last patient visit expected Q2 2030	The latest data-cut of the OLE falls beyond the maximum duration of 5 years allowed within the managed access programme. During the appraisal process, United Kingdom Haemophilia Centre Doctors Organisation (UKHCDO) stated "*A single infusion with etranacogene dezaparvovec has potential benefits for up to 10 years.*". Moreover, the EAG presented a strategy during Technical Engagement in which etranacogene dezaparvovec became the most cost-effective at a durability of approximately 9.2 years. This was largely insensitive to whether the threshold was £20,000 or £30,000. This means that, even if the managed access would run for the maximum period of 5 years, the data would not be mature enough to reach the 10 years discussed by committee and sufficiently resolve the key uncertainty of durability.

		Observational post-authorisation long-term follow-up	Collection of real-world data for patients treated with commercially available product	15 years	CSL Behring post-authorisation development plan with patients treated with commercial product. Data to be entered into National Haemophilia Database (NHD)	Since this long-term observational study includes only patients treated with commercial product (dependent on a NICE recommendation). These patients would be treatment-naïve at the start of the study and so, after a maximum of 5 years managed access, the patients would be a maximum of 5 years post-treatment. Additionally, the study is anticipated to have read-outs in 3-yearly intervals, meaning that the latest data within the MAA would be from 3-years post-treatment.[25] This data would not be sufficient to resolve the durability issue.

Additional considerations

Several additional considerations that may impact feasibility of data collection within managed access are listed below.

A managed access may cause additional burdens to patients, clinicians or the NHS, including:

- Data currently collected within the phase 2b and phase 3 studies is managed (i.e., collected, analysed, interpreted) by CSL Behring's clinical development team, with predefined protocols, which cannot be amended post regulatory approvals.
- Outcome data from the 5 UK patients enrolled in HOPE-B were not captured in the NHD, as per trial protocol.
- Clinical teams input limited outcome data into the NHD. The data is currently only summarised once a year for publication in the UKHCDO annual report. Any further sub-analyses, data points or more frequent data cut will place additional burden on clinicians and the NHD team.
- NHD/UKHCDO have no prior experience with managed access and additional time and resource will be required for NHD to set this study up.

There may be potential barriers to agreeing to or implementing a managed access, including:

- The primary source of evidence generation is the phase 3 clinical trial (CT-AMT-061-02, HOPE-B) that is anticipated to include 53 patients who have received treatment. The maximum 5-year timeframe of managed access may not be sufficient to address the long-term durability uncertainty, as is outlined in Table 2 and Table 7.
- CSL Behring would have to seek consent to input clinical trial data into the UK NHD database (registry). This may be possible for the 5 UK patients enrolled in the HOPE-B but will be challenging from a data sharing perspective for non-UK patients.

Any ethical, equality, or patient safety concerns with the proposed data collection and analysis?

There are not expected to be any equality issues or patient safety concerns from a recommendation for use with managed access compared to a recommendation for routine use.

To improve the feasibility of a managed access, CSL Behring:

- has held discussions with NHD to understand how the existent registry can help with data collection.
- is open to discussing any infrastructure requirements to deliver the MAA with NHS England, if required.

Commercial access proposal

CSL Behring is open to discussing a commercial access proposal with NHS England to support initiation of a MAA and patient access to etranacogene dezaparvovec if an MAA is required.

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 23 August 2023. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	The Haemophilia Society

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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 • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	The Haemophilia Society receives funding from companies involved in the development, manufacture, marketing and distribution of treatments for haemophilia and other bleeding disorders. I have included the companies, total amounts and projects funded for the financial year 22/23 below: CSL Behring £60,000 – Communications, Core Funding LFB £10,000 – Women's Project Novo Nordisk £16,000 – Conference Attendance, Member Magazine, Information Days Octapharma £10,000 – Women's Project Pfizer £20,000 – Youth Ambassador Project, Publications Roche/Chugai £15,000 – Transition Project, Newly Diagnosed Weekends Sobi £25,000 – Publications, Conference Attendance, Information Days Takeda £19,000 Women's Project, Publications
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	In section 3.5 the committee discusses how it might compare factor levels between prophylaxis and Etranacogene Dezaparvovec. This is confused as prophylaxis does not have set doses and

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	frequencies and instead can be tailored on a per patient basis to ensure suitably high troughs and for peaks to coincide with days of particular activity. If a patient has troughs that are too low, insufficient coverage at certain times of the week or uses up factor quicker (the factor has a shorter half-life for that individual due to their physiology) this can be improved with higher doses or more frequent dosing or both. Different products also have differing half-lives and the half-life of a product will vary from individual to individual. The required trough level and the required levels over time will also vary by individual based on lifestyle, physiology and bleeding phenotype. For patients on prophylaxis, levels over time, trough levels (and as a result outcomes) could be improved by changing product, dosing frequency and/or size of dose. This would of course increase cost of treatment, but it is for this reason that the trial is unable to provide a comparison between levels achieved on factor prophylaxis and on Etranacogene Dezaparvovec.
2	In section 3.1 the conclusion is that severe and moderately severe haemophilia B substantially affect quality of life. However, there is no clear consideration of how substantial this effect is and the committee does not appear to have quantified the value that they assign to this evidence. 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. It is therefore plausible that the treatment could lead to fewer hospital visits, better joint health and lower rates of disability over time. From the published data at the end of year 1 (https://www.ema.europa.eu/en/documents/assessment-report/hemgenix-epar-public-assessment-report_en.pdf page 72) there was already a minimal improvement to Haemophilia Joint Health Score (HJHS) which may be an indicator of continuing improvements to quality of life and joint health over time. The committee should consider whether they have fully valued the benefits of improved outcomes such as a lower annual bleed rate and the reduced burden of treatment that Etranacogene Dezaparvovec and other gene therapies for haemophilia B can provide.
3	Management of haemophilia B with factor replacement therapy has a high burden of treatment due to the required frequency of intravenous infusions, the importance of adherence to treatment to improve outcomes and the difficulties some face with venous access and self-infusion. Living with haemophilia managed with prophylaxis involves planning when you will have your intravenous infusions to ensure your peaks and troughs occur at the most relevant times, or least inopportune times. This means planning your life around your haemophilia and your treatment plans.
4	There is a potential equality issue implied by the guidance in that the treatment is generally discussed as an alternative to prophylaxis. However, some people may not be on prophylaxis due to psychological issues, venous access issues or disability making it difficult for them to be given factor infusions or to self-infuse. This group may benefit disproportionally from the treatment as they are unable to manage their condition well with the currently available treatments.
5	Section 3.1 does not adequately consider the range of other benefits this treatment may provide to people with severe and moderately severe haemophilia over the longer term beyond a reduction in annual bleed rate and reduced burden of treatment. Many people with haemophilia are or feel they are restricted in the jobs and leisure activities they can engage in. They plan their day-to-day life and their holidays and other plans around their haemophilia. A long-term treatment for haemophilia B offers the chance to escape that.
6	

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Insert extra rows as needed

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- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	UKHCDO

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[Insert disclosure here]
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	The committee discussed, at length, the most valid parameter with which to compare gene therapy to standard prophylaxis, arguing that gene therapy efficacy should not be expressed in terms of difference in factor IX level on treatment compared to baseline, as presented by the manufacturer,

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	preferring comparison with factor IX level on standard factor IX prophylaxis. The manufacturers present factor IX at baseline compared to factor IX after gene therapy. This demonstrates the pharmacokinetic efficacy of the product and is a valid comparison. Comparison with factor IX level on standard prophylaxis is difficult or impossible because the factor IX levels vary from 70% to 3% during the interval between doses. Further, many of the products in use are fusion proteins and unlike wild type factor IX have different volume of distribution of FIX and affinity to collagen. As such any comparison of factor IX levels is not meaningful and incorrect. Clinical efficacy may be compared by comparing clinical parameters i.e. bleed rates rather than factor levels. Clinical efficacy of gene therapy is partly a function of the factor IX levels achieved and partly a function of those levels being sustained, without the low trough levels observed when using standard factor IX prophylaxis.
2	In the indirect treatment comparisons, the committee commented that the degree of improvement in bleeding outcomes above and beyond that of factor IX prophylaxis was unclear. The committee has remarked that HB has a substantial effect on health-related quality of life. However, the patient's perspective on the value of gene therapy in comparison to other treatment choices has not been considered. An analogy could be drawn between the process of travelling weekly from London to Glasgow and the relocation of the organisation to London, which eliminates the need to travel. Further, skilled and attentive care is necessary for successful intravenous infusions. There is no respite during holidays or illness or any other life situations. Indeed, some of our patients suffer from needle phobia. Comparison of bleed outcomes alone ignores one of the most important benefit of gene therapy, which is the substantial reduction in treatment burden. It has also been our observation that during times of stress, it is not uncommon for prophylaxis to be de-prioritised to address other life personal and professional challenges.
3	Modelling can be requested for a trough factor IX level of 3%, but based on our experience, patients rarely resume prophylaxis unless there are bleeds. We do not believe that prophylaxis should be offered based solely on FIX levels. In our opinion, most patients will likely start experiencing bleeds when their levels are between 1 and 2%.
4	Long term durability of liver directed gene therapy (etranacogene dezaparvovec) is area of intense research. Generically, 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. The differential decline across the different indications and the rate of decline with time does not support the simple concept of cell turnover as cause of loss of expression with time. Loss can occur through apoptosis, which is programmed cell death, and other proposed mechanisms. We do not have information about the impact of fatty liver on the durability of expression. However, our concern lies in identifying the risk factors that contribute to the potential for liver cancer in patients.
5	Patients with significant antibodies to vector would be screened out and not offered gene therapy. The application of an intention to treat analysis to the trial data to include such patients and those offered only a tenth of the intended dose, therefore appears counterintuitive and inappropriate.
6	We would accept that there is a degree of uncertainty to be applied to any treatment intended to have a long-term effect but with relatively short follow up. However, this uncertainty may be costed in but adopting the payment system, which is being applied to this therapy in other countries. This envisages an annual payment of say a tenth of the overall cost, until either treatment fails or a financial break-even point is reached, when payment would stop. This does not eliminate uncertainty but shifts the cost of that uncertainty to the manufacturer and away from the NHS for whom it would be cost-neutral compared with current standard prophylaxis.

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.

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NICE National Institute for Health and Care Excellence

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

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 23 August 2023. Please submit via NICE Docs.

- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations 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.

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Single Technology Appraisal

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

Comments on the draft guidance received through the NICE website

Name	[redacted]
Role	
Other role	
Organisation	[redacted]
Location	London
Conflict	
Notes	
Comments on the DG:	

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

The EAG have assumed that the treatment effect durability of etranacogene dezaparvovec is 6-8 years and this is based on clinician advice. CGTC acknowledges that this parameter is highly uncertain and that factors such as hepatocyte turnover could plausibly reduce the effectiveness of the product over time. CGTC also consider that the Shah et al. analysis that informed the company submission has limitations, is subject to uncertainty and that in practice etranacogene dezaparvovec may not be able to achieve FIX activity levels up to 25.5 years, however the treatment effect duration assumed by the EAG may be overly conservative.

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”, this study has a small sample size but nevertheless suggests that longer treatment effect durations are plausible. Overly conservative assumptions around treatment effect duration risk undervaluing the health and cost displacement benefits offered by etranacogene dezaparvovec.

*Nathwani, Amit C., et al. "Adeno-associated mediated gene transfer for hemophilia B: 8 year follow up and impact of removing “empty viral particles” on safety and efficacy of gene transfer." Blood 132 (2018): 491

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

As previously mentioned in the appraisal documentation it is important to ensure that patients who were excluded from the trial due to HIV or hepatitis status but would otherwise be eligible for treatment will be able to access the therapy if approved by NICE. The same applies to women with haemophilia B.

Are the recommendations sound and a suitable basis for guidance to the NHS?

Gene therapies such as etranacogene dezaparvovec are considered to be highly innovative by CGTC and are potentially transformative. This is supported by the UK government who have invested significantly in cell and gene therapies through the Cell and Gene Therapy Catapult and Innovate UK.

CGTC recommend that the innovative nature of etranacogene dezaparvovec is considered qualitatively by the committee

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

A Single Technology Appraisal

EAG review of company's response to ACD

September, 2023

Produced by

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Source of funding This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR135784.

Declared competing interests of the authors None

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 addendum is linked to ERG report Farmer C, Nikram E, Trigg L, Robinson S, Coppell J, Muthukumar M, Melendez-Torres, G.J., Wilson ECF.Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B [ID3812]. Peninsula Technology Assessment Group (PenTAG), 2023.

1. INTRODUCTION

In their appraisal consultation document (ACD), the committee raised a number of concerns regarding the clinical and economic evidence presented by the company for the appraisal of etranacogene dezaparvovec for the treatment of moderately severe or severe haemophilia B. In this document, the external appraisal group (EAG) review additional evidence presented by the company to address these concerns in advance of a second committee meeting and present modification to their base case as well as additional sensitivity analyses exploring durability of etranacogene. In an addendum to this document, the EAG provide results from the company's revised model and additional sensitivity analyses incorporating confidential prices for comparator treatments.

2. EAG APPRAISAL OF POINTS RAISED AND EVIDENCE PRESENTED BY THE COMPANY

2.1. Benefits of etranacogene not included in the economic model

The EAG notes the company response (section 1) cited the ACD (draft guidance section 3.17) that the economic model excluded the benefit of avoidance of long-term joint damage and mortality benefits. The EAG's clinical experts were of the opinion that the introduction of prophylactic IV FIX has resulted in reduced incidence of joint damage, meaning that the younger cohort of people with haemophilia in the NHS are unlikely to experience the same levels of joint damage as the older population. As joint damage is irreversible, the introduction of etranacogene would not be expected to affect existing joint damage in the population. In addition, since the introduction of prophylactic IV FIX, people with haemophilia B are expected to enjoy a near normal life expectancy. Therefore, the benefit of etranacogene over and above that already provided by IV FIX is likely to be minimal.

2.2. Annualised bleeding rate and change in FIX levels

The company agreed with the conclusion of the committee regarding bleeding rates (section 3.4 of the draft guidance) but queried the specific figures referred to in the guidance. The EAG has reviewed the data and can confirm that the data in the draft guidance are correct and refer to the average number of bleeds experienced during the 6-month lead-in phase (=total bleeds/number of participants who experienced bleeds) while the company refer to the annualised rates of bleeds (extrapolated to 12-months based on total bleeds/time at risk).

2.3. Results of the indirect treatment comparison

The EAG notes the company has adopted the EAG's preferred base case assumption of a gradual improvement in bleed rates over the first 24 months post administration of ED.

2.4. Shah et al. (2022) durability extrapolation and additional scenario analyses including previously excluded observations

As per the committee's request (section 3.14 of the draft guidance), the company presented a re-analysis of the Shah durability analysis based on a 3% threshold for reintroduction of IV FIX and inclusion of data from the participant receiving the partial dose as well as a second scenario including data from both previously excluded participants. The company stated that its preferred analysis would include data from just the participant receiving the partial dose and exclude the

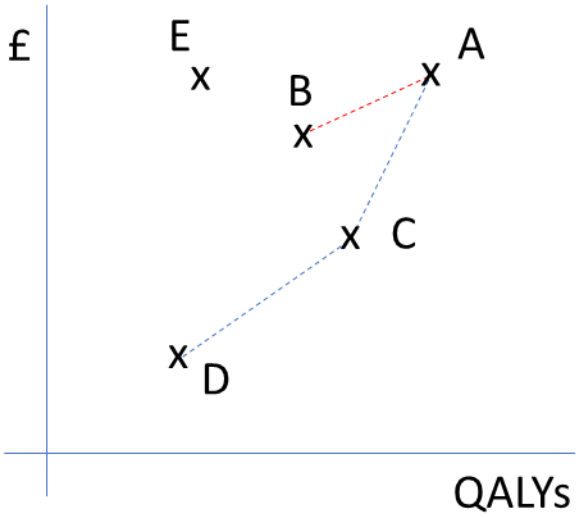
high NAb count as according to their clinical expert such patients would not be deemed suitable for etranacogene. However, the EAG notes that high NAb titre is not a contra-indication and that the SmPC states that "antibodies above a titre of 1:678 may… reduce the efficacy of Hemgenix [etranacogene] therapy". [1] Thus patients with a high titre are not prevented from being offered etranacogene in routine clinical practice.

The company presents revised analyses in Appendices A and B of its response. These are reproduced in Section 3 below (with some presentational modifications for consistency). The EAG notes that whilst the results of the list price analysis are insensitive to inclusion of one or both of the two observations, the estimated ICERs are sensitive to these when including confidential discounts to the comparators (see confidential appendix), although all are substantially above what would normally be considered a cost-effective use of NHS resources.

2.5. Further scenario analysis using a 'basket of comparators' weighted by market share in the NHS.

The EAG notes the committee's preference for a 'basket of comparators' (section 3.9 of draft guidance). The company states that this is "…on average a better reflection wholistically [sic], of the choices that the clinicians face in treating patients…" (company response, point 3.9). Whilst in one sense this is true, in reality the decision faced by the clinician is which one of the eight discrete strategies to follow, not a binary choice between a basket of 'all other treatments' or etranacogene. This approach can result in misleading conclusions, and incorrect application of incremental analysis. For example, in Figure 1 below, treatment strategy A may appear cost-effective compared with B (basket of other treatments) simply because B is itself not cost-effective: the true opportunity cost of A is only revealed in comparison with C which lies on the 'efficient frontier'.

Figure 1: Fully incremental analysis



In the above, treatments A, C, D and E are alternative treatment strategies for a hypothetical disease. B represents a weighted average 'basket' of C, D and E. Comparing A with B (as per the basket approach) yields an ICER equal to the gradient of line AB. However, B is not on the efficient frontier (it is dominated by C), thus the correct comparison is with C, which has a much higher ICER (the gradient of line AC is steeper than AB).

Furthermore, the use of a weighted basket means that the data used to inform appropriate market shares of each treatment are highly influential. Such data are typically challenging to determine accurately, as treatment uptake data can vary over time and across settings and populations, even within the same healthcare system. The company did not provide a reference for the market share data used in its 'basket of comparators' analysis and did not provide any information about the methodology used. In the company Excel model, the market share data are labelled as data from NHS England ('data store' tab), and so the EAG assumed that data were provided on actual uptake of prophylactic FIX replacement treatments received by people with severe and moderately severe patients within the NHS, though over an unclear period of time and from an unknown sample selection.

The company did not provide a rationale for their use of these data in preference to the market share data provided in their reference pack at technical engagement, which appears to be based on a larger evaluation of market uptake in the UK commissioned by the company. [2] Estimates of treatment uptake in this report vary from those in the NHS England data (see **Error! Reference source not found.**). The EAG note that the NHS England data are based on a small number of patients overall (N=[redacted]). Whilst the EAG notes the rarity of the disease limits sample size, it's unclear whether the sample is the total number of people included in the data

set, or whether this is the number of people receiving alprolix, idelvion, refixia or beneFIX and thus other treatments were received by a minority of people not represented (which would also affect the weighting of market share).

Without detail about the methods used to derive the NHS England data, the EAG cannot make an informed decision about whether these data are more reliable than those in the company's commissioned report. The EAG was also unclear which data points in the original data would be the most relevant to use in the analysis, given that the market share has changed markedly over time for some treatments (for BeneFIX, which took a [redacted]% share in 2018 (Q3) compared to [redacted]% in 2020 (Q3)). This may reflect a trend in patient preferences for treatment that would mean that the latest data would be the most appropriate, or it may reflect a temporary move away from the short-acting treatments during the COVID-19 pandemic that may reverse over time. As market share estimates vary between data sources and over time, and the EAG was unable to determine the most appropriate selection of estimates to inform a basket analysis, the EAG considered this to be a further limitation of the basket analysis approach. Overall, for these reasons and those discussed in this section above, the EAG retained its preference for a fully incremental analysis of each discrete strategy.

Table 1: UK market share data for prophylactic FIX replacement therapies

	Data in the company's commissioned report (Q3 2020)	NHS England data
Alprolix	[redacted]	[redacted]
Idelvion	[redacted]	[redacted]
Refixia	[redacted]	[redacted]
BeneFIX	[redacted]	[redacted]
Alphanine	[redacted]	[redacted]
Replenine	[redacted]	[redacted]

3. COMPANY'S REVISED MODEL FOLLOWING THE ACD

The EAG noted the following changes made to the company's Excel model:

- Revision of the Shah projection based on a FIX activity level at which prophylactic IV FIX is reintroduced of 3%
- Revision of Shah projection including data from a participant who received a partial dose (which the company labels the ITT analysis), and a second analysis including both the previously excluded participants
- Introduction of a 'market share' comparator
- Modification of IV FIX received during a bleeding event and post ED failure to reflect the market share of IV FIX for the market share analyses
- An increase in the PAS discount to [redacted]

The EAG was able to reverse engineer the changes and recreate the previous analysis so believed the changes to be correctly implemented.

The company presented a number of scenarios:

1. Deterministic pairwise analysis of ED vs basket of comparators at 3% durability threshold
2. Deterministic pairwise analysis of ED vs basket of comparators at 3% durability threshold, including data from one participant who received a partial dose previously excluded from the analysis (which the company labels ITT approach)
3. Deterministic pairwise analysis of ED vs basket of comparators at 3% durability threshold including data from both previously excluded participants
4. Deterministic, fully incremental analysis of ED vs each IV FIX at 3% durability threshold
5. Deterministic, fully incremental analysis of ED vs each IV FIX at 3% durability threshold including one of the two excluded patients (labelled 'ITT')
6. Deterministic, fully incremental analysis of ED vs each IV FIX at 3% durability threshold including both excluded patients.
7. Probabilistic analysis of scenario 1
8. Probabilistic analysis of scenario 2

Probabilistic analyses were conducted with 10,000 simulations. Scenario results are reproduced in Table 2 to Table 9 below. The EAG also conducted an additional PSA on

scenario 3 (reported in Table 10). In its ACD response, the company presented net benefit in its probabilistic analyses rather than ICERs. Mathematically these present the same information so the EAG has reverted these to ICERs for consistency with the deterministic results. Furthermore, the company defines the ITT analysis as including data from the participant who received a partial dose, but excluding the patient with the high NAb titre. To avoid potential confusion the EAG avoids 'ITT' terminology. Analogous tables including PAS discounts for all comparators are provided in the confidential appendix.

In all analyses (based on the PAS discount offered by the company and list prices for comparators), strategies including etranacogene dominate other treatment options. Specifically, etranacogene followed by BeneFIX is the most cost-effective of all treatment options.

The EAG's duplication of these analyses with PAS discounts included for all comparators yields ICERs considerably in excess of those normally considered cost-effective in the fully incremental analysis, and etranacogene dominating the 'basket of comparators' pairwise analysis.

Table 2. Pairwise incremental analysis of etranacogene dezaparvovec followed by a basket of comparators, against a basket of comparators, for the Shah 3% durability threshold

Technology	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Etranacogene dezaparvovec (Basket of comparators)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Basket of comparators	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 3. Pairwise incremental analysis of etranacogene dezaparvovec followed by a basket of comparators, against a basket of comparators, for the Shah 3% durability threshold, including participant receiving partial dose

Technology	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Etranacogene dezaparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

(Basket of comparators)					
Basket of comparators	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 4. Pairwise incremental analysis of etranacogene dezaparvovec followed by a basket of comparators, against a basket of comparators, for the Shah 3% durability threshold including all participant data

Technology	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
Etranacogene dezaparvovec (Basket of comparators)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Basket of comparators	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 5. Fully incremental analysis of all non-blended comparators, for the Shah 3% durability threshold

Technology	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
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]

Table 6. Fully incremental analysis of all non-blended comparators, for the Shah 3% durability threshold, including participant receiving partial dose

Technology	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
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]

Table 7. Fully incremental analysis of all non-blended comparators, for the Shah 3% durability threshold, including all participant data

Technology	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
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]

Table 8. Probabilistic analysis for the pairwise incremental analysis of etranacogene dezaparvovec followed by a basket of comparators, against a basket of comparators, for the Shah 3% durability threshold, including participant receiving partial dose

Technology	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs	ICER	% of Cost-effectiveness @ £30,000/QALY
Etranacogene dezaparvovec (Basket of comparators)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Basket of comparators	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 9. Probabilistic analysis for the fully incremental analysis of all non-blended comparators, for the Shah 3% durability threshold, including participant receiving partial dose

Technology	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs	ICER	% of Cost-effectiveness @ £30,000/QALY
Etranacogene dezaparvovec (Benefix)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etranacogene dezaparvovec (Alprolix)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etranacogene 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 10. Probabilistic sensitivity analysis for the fully incremental analysis of all non-blended comparators, for the Shah 3%, including all participant data

Technology	Total Costs (£)	Total QALYs	Inc. Costs (£)	Inc. QALYs	ICER	% of Cost-effectiveness @ £30,000/QALY
Etranacogene dezaparvovec	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etranacogene dezaparvovec (Alprolix)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Etranacogene 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]

4. REVISED EAG BASE CASE

Following publication of the ACD and revised company submission the EAG changed its base case to reflect the committee's preferred 3% durability threshold and believes the EAG and company are now mostly aligned in their base cases, with the notable exceptions of exploring uncertainty around the durability function and inclusion of one or both of the excluded patients from the Shah analysis.

The EAG notes the committee's desire (section 3.14 of the draft guidance) for a scenario including data from one of the two previously excluded participants from the Shah analysis (receiving an incomplete dose) and another scenario including both (incomplete dose and high NAb titre). The EAG also notes the company's point regarding inclusion of the patient with high antibody count (company response, point 3.11), but also notes that high NAb titre is not a contra-indication to receiving etranacogene.

Based on this the EAG's preferred analyses match the company's analyses presented in Table 6 and Table 7 (deterministic analysis), and in Table 9 and Table 10 (probabilistic analyses) above. Additionally, the EAG conducted a one-way sensitivity analysis on the durability function as described below.

4.1. Durability sensitivity analysis

To explore the uncertainty intrinsic in the small sample size informing the Shah extrapolations (durability function), in its initial critique of the company submission, the EAG replaced it with a step function to conduct a one-way sensitivity analysis, varying the durability from 0 to 60 years (Figure 2, dotted red line). This was a pragmatic approach to explore different durability assumptions, but was less useful for decision making as due to the extreme timing of costs in this analysis (large upfront cost followed by minimal cost followed by large continuing cost following ED failure) and the interaction with discounting, the *shape* of the durability function was a key determinant of cost-effectiveness.

The EAG therefore conducted additional sensitivity analyses following the Shah function but truncating it at various time points. Whilst a formal rescaling of the Shah function would be preferable, resources did not permit development of a more sophisticated analysis. The EAG notes that truncating the existing Shah function represents an optimistic scenario for durability compared with a 'smoothed' function.

Figure 2 Sensitivity analysis on durability function

Figure shows Shah extrapolation (blue solid line), which is truncated at 60 years. The 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).

Figure 3 and Figure 4 (and Data behind Figure 3 to Figure 6 are in Table 11 to Table 14 respectively.

Table 11 & Table 12) show the net monetary benefit of each comparator as a function of durability using the Shah function including data from the participant who received a partial dose. Figure 5 and Figure 6 (plus Table 13 and Table 14) show the same information but including both previously excluded participants.

In all cases a strategy with etranacogene becomes the most cost-effective (associated with the highest net monetary benefit) when durability is truncated at 9 or 10 years (equating to a *mean* durability of around 8.5 or 9 years). In other words, etranacogene is cost-effective as long as the mean durability is at least 8.5 or 9 years. This result is largely insensitive to both inclusion or exclusion of the patient with high NaB titre and to the threshold adopted (£20,000 or £30,000).

Equivalent analyses including cPAS discounts for all comparator products (see confidential appendix) suggest that there are no scenarios where a strategy including etranacogene is the most cost-effective.

Figure 3 Net Monetary benefit as a function of durability (durability function at 3% threshold, original sample + px receiving partial dose, NMB calculated at £20,000/QALY)

Figure 4: Net Monetary benefit as a function of durability (durability function at 3% threshold, original sample + px receiving partial dose, NMB calculated at £30,000/QALY)

Figure 5 Net Monetary benefit as a function of durability (durability function at 3% threshold, original sample + both excluded patients, NMB calculated at £20,000/QALY)

Figure 6 Net Monetary benefit as a function of durability (durability function at 3% threshold, original sample + both excluded patients, NMB calculated at £30,000/QALY)

5. CONCLUSION

The key uncertainties remaining are:

1. whether data from one or both the previously excluded participants from the Shah analysis should be included.
2. whether the Shah durability function is a plausible estimate of the long-term effect of etranacogene

The EAG is of the opinion that on methodological grounds data from the participant receiving only a partial dose should be included in the durability function. Furthermore it is highly likely that data from the second participant with high NAb titre should be included given that this is not a contra-indication and thus patients with such a titre may be offered etranacogene therapy in routine practice.

In the EAG's preferred analyses including the PAS discount for etranacogene alone (and list prices for comparators), treatment strategies including etranacogene represent the most cost-effective strategies.

However, when PAS discounts for comparators are included (see confidential appendix), strategies including etranacogene are associated with ICERs substantially above what is normally considered a cost-effective use of NHS resources.

6. APPENDIX. DATA RELATING TO DURABILITY ONE-WAY SENSITIVITY ANALYSES

Data behind Figure 3 to Figure 6 are in Table 11 to Table 14 respectively.

Table 11 Durability threshold analysis, (durability function at 3% threshold, original sample + px receiving partial dose, NMB calculated at £20,000/QALY)

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

Years	NMB ED+benefix	ED+alprolix	ED+idelvion	ED+refixia	Benefix	Alprolix	Idelvion	Refixia	Winner
36	[redacted]								ED+Benefix
37									ED+Benefix
38									ED+Benefix
39									ED+Benefix
40									ED+Benefix
41									ED+Benefix
42									ED+Benefix
43									ED+Benefix
44									ED+Benefix
45									ED+Benefix
46									ED+Benefix
47									ED+Benefix
48									ED+Benefix
49									ED+Benefix
50									ED+Benefix

Table 12 Durability threshold analysis, (durability function at 3% threshold, original sample + px receiving partial dose, NMB calculated at £30,000/QALY)

Years	NMB ED+benefix	ED+alprolix	ED+idelvion	ED+refixia	Benefix	Alprolix	Idelvion	Refixia	Winner
1	[redacted]								Benefix
2									Benefix
3									Benefix
4									Benefix
5									Benefix
6									Benefix
7									Benefix
8									Benefix
9									Benefix
10									ED+Benefix
11									ED+Benefix
12									ED+Benefix
13									ED+Benefix
14									ED+Benefix
15									ED+Benefix
16									ED+Benefix
17									ED+Benefix
18									ED+Benefix
19									ED+Benefix
20									ED+Benefix
21									ED+Benefix
22									ED+Benefix

Years	NMB ED+benefix	ED+alprolix	ED+idelvion	ED+refixia	Benefix	Alprolix	Idelvion	Refixia	Winner
23	[redacted]								ED+Benefix
24									ED+Benefix
25									ED+Benefix
26									ED+Benefix
27									ED+Benefix
28									ED+Benefix
29									ED+Benefix
30									ED+Benefix
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41									ED+Benefix
42									ED+Benefix
43									ED+Benefix
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47									ED+Benefix
48									ED+Benefix
49									ED+Benefix
50									ED+Benefix

Table 13 Durability threshold analysis, (durability function at 3% threshold, original sample + both excluded patients, NMB calculated at £20,000/QALY)

Years	NMB ED+benefix	ED+alprolix	ED+idelvion	ED+refixia	Benefix	Alprolix	Idelvion	Refixia	Winner
1	[redacted]								Benefix
2									Benefix
3									Benefix
4									Benefix
5									Benefix
6									Benefix
7									Benefix
8									Benefix
9									Benefix

Years	NMB ED+benefix	ED+alprolix	ED+idelvion	ED+refixia	Benefix	Alprolix	Idelvion	Refixia	Winner
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
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 14 Durability threshold analysis, (durability function at 3% threshold, original sample + both excluded patients, NMB calculated at £30,000/QALY)

Years	NMB ED+benefix	ED+alprolix	ED+idelvion	ED+refixia	Benefix	Alprolix	Idelvion	Refixia	Winner
1	[redacted]								Benefix
2									Benefix
3									Benefix
4									Benefix
5									Benefix
6									Benefix
7									Benefix
8									Benefix
9									Benefix
10									ED+Benefix
11									ED+Benefix
12									ED+Benefix
13									ED+Benefix
14									ED+Benefix
15									ED+Benefix
16									ED+Benefix
17									ED+Benefix
18									ED+Benefix
19									ED+Benefix
20									ED+Benefix
21									ED+Benefix
22									ED+Benefix
23									ED+Benefix
24									ED+Benefix
25									ED+Benefix
26									ED+Benefix
27									ED+Benefix
28									ED+Benefix
29									ED+Benefix
30									ED+Benefix
31									ED+Benefix
32									ED+Benefix
33									ED+Benefix
34									ED+Benefix
35									ED+Benefix
36									ED+Benefix
37									ED+Benefix
38									ED+Benefix
39									ED+Benefix
40									ED+Benefix
41									ED+Benefix
42									ED+Benefix

Years	NMB ED+benefix	ED+alprolix	ED+idelvion	ED+refixia	Benefix	Alprolix	Idelvion	Refixia	Winner
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

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2. Adivo. FIX Market Tracking: United Kingdom Q3 2020. 2021.

Memo to: Vicky Kelly, Mohammed Towhasir and colleagues, NICE

From: Ed Wilson, PenTAG

Date: 8th September 2023

This memo summarises the EAG's response to Company's email to NICE dated Tuesday 15th August 2023 1339.

Deterministic & probabilistic differences and utility methodology

The company notes that the difference in deterministic and probabilistic results amount to a 1% difference in QALYs accrued in the IV FIX arms. However, this equates to approximately [redacted], and as stated in the EAG's report, has a substantial impact on the ICER when all cPAS prices are included. It is the absolute impact on the ICER that is of greater importance than the relative difference in QALYs accrued. As this difference is observed to a much lesser extent in the ED arms, it is worthy of further investigation.

The EAG thanks the company for providing an explanation as to why the differences in QALYs accrued for IV FIX patients vary between the two analyses. The EAG notes that as per its previous assertion, the coding does indeed model utility inputs as independent beta distributions, but the company clarifies that a correlation is induced by not allowing the utility of IV FIX to exceed that of ED (using a 'min() function in Excel).

The EAG considers this an inappropriate approach to modelling health state utilities as it does not sample from the full uncertainty distribution of IV FIX health state utility. Specifically, it biases the health state utility estimate for IV FIX downwards, leading to an underestimate of the QALYs accrued in the IV FIX arms, and a lower ICER for ED.

The EAG reiterates its previous stance that a baseline health state utility modified by a difference in utility is the appropriate approach for modelling utilities, and that the method chosen by the company biases the results in favour of ED.

Hernandez Alva mapping function & EAG data request

The EAG thanks the company for indicating that the utility difference was located in the papers it received and apologises for the oversight. The company submitted several hundred pages of additional information in its response to Technical Engagement, and the EAG kindly requests that in future such critical data are highlighted in a summary document, or else adequately referenced in the Excel model, so as to avoid any oversight. The EAG notes that the difference in health state utility is not statistically significant, with a 95% confidence interval [redacted] This 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.

Conclusion and recommendation

Within the remaining timeframe for this appraisal, it would not be possible to re-run all probabilistic analyses, which the EAG considers would be necessary to produce reliable estimates given the issues discussed above. The EAG therefore suggests that despite the known limitations of deterministic analyses, in this case the deterministic results provide a more plausible (less biased) estimate of the ICER than the probabilistic.

Managed Access Agreement

Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B (ID3812)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Innovative Medicines Fund – Data Collection Arrangement

Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B (ID3812)

Company name: CSL Behring UK Ltd (the company)

Primary source(s) of data collection: CT-AMT-061-02 (HOPE-B, Phase 3) with Open-label extension trial (OLE)

NICE Agreement Manager	[redacted], Associate Director, Managed Access
NHSE Agreement Manager	[redacted], NHSE Clinical Advisor (Non-oncology)
CSL Behring UK Ltd Agreement Manager	[redacted]

1 Purpose of data collection arrangement

- The purpose of the agreement is to describe the arrangements and responsibilities for further data collection for etranacogene dezaparvovec for treating moderately severe or severe haemophilia B (ID3812) (to be updated with TA number after final guidance has been published). A positive recommendation within the context of a managed access agreement (MAA) has been decided by the appraisal committee.

2 Commencement and period of agreement

- This data collection arrangement shall take effect on publication of the MAA.

- Estimated dates for data collection, reporting and submission for a guidance update are:

End of data collection (primary source)	Q1 2030, last patient visit for PhIII HOPE-B trial. [redacted]
Data available for development of company submission	[redacted]
Anticipated company submission to NICE for a guidance update	[redacted]

[redacted]

- CSL Behring anticipates the results from the additional data collected during the Innovative Medicines Fund period will be incorporated into an evidence submission and the updated economic model by November 2027.
- CSL Behring acknowledges their responsibility to adhere as closely as possible to the timelines presented in this document.
- NICE will, as far as is practicable, schedule the guidance update into the technology appraisal work programme to align with the estimated dates for the end of data collection.
- The NICE guidance update will follow the process and methods applicable to guidance updates that are in place at the time the invitation to participate in the guidance update is issued. These

may be different from the process and methods applicable to guidance updates when this technology entered into the managed access agreement.

- At the appropriate time NICE will explore and discuss with the company and NHSE if a proportionate approach can be applied to the exit from Managed Access as per NICE Methods.
- As part of the managed access agreement, the technology will continue to be available through the Innovative Medicines Fund after the end of data collection and while the guidance is being updated. This assumes that the data collection period ends as planned and the guidance update follows the standard timelines.
- The company is responsible for paying all associated charges for a guidance update. Further information is available on the NICE website.
- The company must inform NICE and NHS England (NHSE) in writing of any anticipated changes to the estimated dates for data collection and reporting at the earliest opportunity.
- Any changes to the terms or duration of any part of the data collection arrangement must be approved by NICE and NHSE.
- If data collection is anticipated to conclude earlier than the estimated dates for data collection, for example due to earlier than anticipated reporting of an ongoing clinical trial, the company should note:
- Where capacity allows, NICE will explore options to reschedule the guidance update date to align with the earlier reporting timelines.

- It may be necessary to amend the content of the final real-world data report (for example if planned outputs will no longer provide meaningful data).

- If data collection is anticipated to conclude later than the estimated dates for data collection, the company should note:

  - The company must submit a written request to NICE and NHSE, with details of the extension requested, including an explanation of the factors contributing to the request.
  - It may be necessary for the company to mitigate the impact of any delay and reduce any risks of further delays.

- CSL Behring acknowledge their responsibility to provide an evidence submission for this technology to NICE under all circumstances following a period of managed access.

- In the event that CSL Behring does not make a submission to NICE for the purpose of updating the guidance, NICE and NHSE will require the company to agree to submit the clinical evidence collected during the managed access period, and to participate in an engagement meeting convened by NICE with attendance from NHSE, patient and professional group stakeholders, with the company presenting the clinical evidence collected during the managed access period and an explanation of the decision to proceed with withdrawal of the guidance.

- NICE and NHSE may consider the data collection arrangement no longer valid, and withdraw the technology from the Innovative Medicines Fund for the following, non-exhaustive, grounds:

  - The primary sources of data are delayed, without reasonable justification.

- The primary sources of data are unlikely to report outcome data that could resolve the uncertainties identified by the technology appraisal committee.
- Amendments are made to the marketing authorisation.

3 Monitoring arrangements

- NICE will convene a Managed Access Oversight Group (MAOG) with representation from NICE, NHSE, and the company.
- The MAOG exists to oversee the operation of all aspects of the MAA and to address issues that may arise throughout the MAA term. The MAOG is responsible for monitoring the implementation of the MAA and for recommending actions to support its operation and will meet regularly throughout the data collection period.
- A detailed description of the MAOG function will be available in a Terms of Reference document produced by NICE.

4 Patient eligibility

- Key patient eligibility criteria for the use of etranacogene dezaparvovec in the Innovative Medicines Fund include:
  - Aged 18 years or older
  - Moderately severe or severe haemophilia B
  - Demonstrated absence of Factor IX inhibitors and no previous history of Factor IX inhibitors
  - A pre-existing neutralising antibody titre has been performed and that the patient does not have neutralising anti-AAV5 antibodies above a titre of 1:678 (7-point assay) or 1:898 (9-point assay)

- Baseline hepatic function has been assessed
- The treatment will be delivered by a commissioned haemophilia ATMP treatment hub
- Use is in accordance with the SmPC

o The estimated patient numbers per year for this technology within the Innovative Medicines Fund are:

As estimated by the company	[redacted]
As estimated by NICE Resource Impact Assessment team	Year 1: 10 Year 2: 11 Year 3: 16

5 Patient safety

o The company and NHSE have a responsibility to monitor the safety profile of the technology and must provide an overview of

any new or updated safety concerns to NICE. If any new safety concerns are confirmed, NICE and NHSE will take steps, as appropriate, to mitigate the risk including but not limited to updating the eligibility criteria or recommending that the managed access agreement be suspended.

6 Area(s) of clinical uncertainty

- The appraisal committee identified the following key areas of uncertainty during the course of the appraisal process:
  - Long-term treatment durability of etranacogene dezaparvovec
  - Proportion of people that require Factor IX prophylaxis after etranacogene dezaparvovec.
  - The committee concluded that further data collection within the Innovative Medicines Fund could resolve these uncertainties. For further details of the committee's discussion see section 3 of the Final Appraisal Document.

7 Sources of data collection

Primary and secondary sources of data collection

Primary source(s)	○ **CT-AMT-061-02 (HOPE-B, Phase 3) with Open-label extension trial (OLE)**
Secondary	○ CT-AMT-060-01 (Phase 1-2) with OLE. [redacted] ○ CT-AMT-061-01 (Phase 2b) with OLE. [redacted]

Description of sources

- Primary Source: Phase 3 clinical trial (HOPE-B). Open-label, single-dose, multicentre trial to evaluate safety and efficacy of etranacogene dezaparvovec. N=54 patients dosed. The latest data cut-off is at 36-month post-treatment, as provided in Appendix C of the draft guidance company response. [redacted]

- Secondary data source - CT-AMT-060-01: Open-label, uncontrolled, single-dose, dose-ascending designed study enrolled subjects (n=10) with haemophilia B. [redacted]. Eligible subjects were allocated to 2 consecutive dose cohorts and received a single intravenous dose of AMT-060; Cohort 1 (n=5) received the low dose of 5.0×10^{12} centigram/Kilogram (gc/kg) and Cohort 2 (n=5) received the high dose of 2.0×10^{13} gc/kg. [redacted]

- Secondary data source - CT-AMT-061-01 (Phase 2b) with OLE. Open-label, single-dose, single-arm, a multicentre trial was initiated to confirm the Factor IX activity level of AAV5-hFIXco-Padua in adults (n=3) with severe or moderately severe haemophilia B. 3 patients have completed 4 years follow up (July 2023) and none have returned to prophylaxis. [redacted]

8 Outcome data

Clinical trial

Outcome data	Data source	Outcomes measured	Likelihood data collection could sufficiently resolve key uncertainties
CT-AMT-060-01 with OLE (AMT-060) Currently patients are enrolled in an open label extension (OLE) study, [redacted]	Open-label, uncontrolled, single-dose, dose-ascending designed study enrolled subjects (n=10) with haemophilia B. Eligible subjects were allocated to 2 consecutive dose cohorts and received a single intravenous dose of AMT-060; Cohort 1 (n=5) received the low dose of 5.0×10^{12} gc/kg and Cohort 2 (n=5) received the high dose of 2.0×10^{13} gc/kg	***Efficacy*** **Endogenous Factor IX activity** **Utilisation of Factor IX-replacement therapy** **Annualised bleeding rate (Factor IX-requiring); including the following:** • **All bleeds Spontaneous bleeds Traumatic bleeds** • **Joint bleeds** Short form (SF-36) and EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) QoL scores Haemophilia Joint Health Score (HJHS) ***Safety*** Factor IX inhibitors ALT/AST levels Liver pathology (assessed by ultrasound) Alpha-fetoprotein (AFP)	[redacted]
CT-AMT-061-01 (Phase 2b) with OLE Last patient visit expected in September 2023, with data available approximately May 2024.	Open-label, single-dose, single-arm, multicentre trial was initiated to confirm the Factor IX activity level of AAV5-hFIXco-Padua in adults (n=3) with severe or	***Efficacy*** **Endogenous FIX activity** **Total usage of FIX replacement therapy** **ABR (including a further break down**	[redacted]

Patients will then enrol into OLE [redacted]	moderately severe haemophilia B. Single dose of 2.0 x 10^{13} gc/kg	**of the frequency and percentage of spontaneous, traumatic, and joint bleeding events)** Joint health and quality of life (QoL) scores ***Safety*** Observed ALT/AST levels and corticosteroid use for any elevations Antibody formation to AAV5 and human FIX AFP Abnormal findings on the abdominal ultrasound	[redacted]
CT-AMT-061-02 (HOPE-B, Phase 3) with OLE Last patient visit is expected approximately Q2 2025 with final data available after 6 months Patients will then enter into an OLE [redacted]	Open-label, single-dose, multicentre trial to evaluate safety and efficacy of etranacogene dezaparvovec Single dose of 2.0 X 10^{13} gc/kg 54 patients were dosed in HOPE-B. 53 patients have completed 36 months follow-up (July 2023) with 51 patients remaining off prophylaxis.	***Efficacy*** **Endogenous Factor IX expression** **Proportion free from Factor IX prophylaxis** **Annualised consumption of Factor IX replacement therapy** **Estimated ABR** Correlation of pre -IMP anti -AAV5 antibody titres on Factor IX activity levels after dosing Occurrence and resolution of target joints **Proportion of subjects with zero bleeding episodes** Patient reported outcomes: International Physical Activity Questionnaire (iPAQ), EuroQol-5	[redacted]

		dimensions-5 levels (EQ-5D-5L) Visual Analog Scale (VAS), Work Productivity and Activity Impairment Questionnaire (WPAI), Brief Pain Inventory (BPI), Haemophilia Activities List (HAL), and Haemophilia Quality of Life Questionnaire for Adults (Haem - A - QoL) Haemophilia Joint Health Score (HJHS) scores ***Safety*** Changes in abdominal ultrasound Formation of Factor IX inhibitors and recovery Liver enzyme: AST, ALT and proportion requiring corticosteroid use if increases noted Alpha-fetoprotein	
Outcomes in bold will be used to address uncertainty			

Summary of data currently available and data to be available at the end of the managed access period:

Clinical trial	Latest data cut off	Data available at end of managed access period (assuming start in Q2 2024)
CT-AMT-060-01	[redacted]	[redacted]
CT-AMT-061-01 (Phase 2b)	[redacted]	[redacted]
CT-AMT-061-02 (HOPE-B)	[redacted]	[redacted]

Data analysis plan

Clinical trials

Outcome data	Data analysis plan
OLE (AMT-060)	Data will be summarized using descriptive statistics. No formal statistical comparisons are planned. *Analysis populations* The Full Analysis Set (FAS) will consist of all patients previously administered AMT-060 (Study CT-AMT-060- 01) and who enrolled in this study. If applicable, further analysis sets will be defined, such as a Per Protocol Analysis set. *Sample Size* No formal sample size calculation is made. The choice of 10 patients total is based on the total number of patients enrolled in Study CT-AMT-060-01. *Statistical Methods Sko* Primary safety analysis Adverse events, possibly or probably related to previous AAV5-hFIX administration, will be summarized by system organ class and preferred term within each dosing cohort from Study CT-AMT-060-01. *Secondary efficacy analysis* Endogenous FIX activity and FIX replacement therapy will be summarized individually and overall. Annualized bleeding rates will be summarized individually and overall. Quality of life and HJHS will be described at each time point and overall change from Baseline in Study CT-AMT-060-01. Summaries will be done by each dosing cohort from Study CT-AMT-060-01
CT-AMT-061-01 (Phase 2b) with OLE	Given the small sample size (N = 3), no formal, inferential statistical analyses will be performed, and no analysis populations will be defined. Data will be presented descriptively in plots and tabular displays to visualize individual effects for selected efficacy and safety measures and/or in subject data listings. If applicable, continuous variables will be summarized with descriptive statistics including: the number of non-missing values, mean, SD, median, minimum, and maximum. In some cases, the standard error of the mean and/or confidence intervals were optionally to be provided. Categorical variables will be summarized by number, percent of subjects and, if applicable, the number of events.
CT-AMT-061-02 (HOPE-B, Phase 3) with OLE	**CT-AMT-061-02 (HOPE-B, Phase 3)** *Selection of subjects to be included in the analyses* The FAS (Full Analysis Set) will include all subjects who are enrolled, entered the lead-in phase, were dosed with AMT-061, and provide at least one efficacy endpoint. The FAS population will be the primary population considered in the primary analysis. The PP population (PP) will include all subjects from the FAS population, for whom efficacy data are available until and including Week 52, and who adhere to a stable and adequate prophylaxis use during the lead-in phase. The PP population will be the primary population considered in the ABR analysis. The safety population will consist of all subjects who receive AMT-061, irrespective of any protocol deviations

	Subject disposition Subjects in each analysis set, as well as subjects who complete the trial, and subjects who prematurely discontinue from the trial will be summarized using descriptive statistics. In addition, for subjects who prematurely discontinue from the trial, the reasons for discontinuation will be summarized *Demographic and baseline characteristics* Descriptive summaries of demographic and baseline characteristics will be presented for the FAS, PP, and safety populations. Descriptive statistics will be number of observations, mean, standard deviation, median, minimum, and maximum for quantitative data. For qualitative data, frequency counts and percentage will be determined. A full description of demographic variables will be included in the SAP. Individual subject demographics and baseline information will be provided in data listings. *Efficacy analyses* All efficacy analyses will be performed for the FAS and PP populations. Statistical analysis will be performed and plots and tabular displays will be created, visualizing individual effects for the selected efficacy measures as specified in the following sections. The primary efficacy analysis will be completed using the FAS population. The analysis using the PP population is considered to be a sensitivity analysis. Subjects in the FAS population that have not been treated with AMT-061 will be included using a missing imputation method The primary aim of the trial is to demonstrate the effect of AMT-061 on endogenous FIX activity 6 months after a single AMT-061 treatment (reported already: Pipe SW, et al. Gene Therapy with Etranacogene Dezaparvovec for Hemophilia B. N Engl J Med. 2023 Feb 23;388(8):706-718. doi: 10.1056/NEJMoa2211644. PMID: 36812434) The non-inferiority of a single AMT-061 treatment as compared to FIX prophylaxis treatment, with respect to ABR will be assessed as a secondary endpoint. Other secondary endpoints of the trial will focus on investigating the effect of 2 x 10^{13} gc/kg AMT 061 on assessment of trough FIX activity, discontinuation of previous continuous routine prophylaxis, total consumption of FIX replacement therapy, bleeding events, occurrence and resolution of target joints, correlation of FIX activity levels and observed anti-AAV5 antibody titers using the luciferase based NAB assay after AMT-061 dosing, endogenous FIX activity after AMT-061 dosing, and safety **OLE** Statistical analyses plan will be finalised at entry to study

Ownership of the data

- For all clinical trial data listed above, CSL Behring will be the owner.

Publication

- Publications regarding the implementation or managed access process are permitted as long as no data collected in clinical practice is included (e.g. patient leaflets, NICE presentations about operational aspects of MAAs).
- Any draft abstracts or manuscripts related to this DCA must be shared with the MAOG prior to submission to conferences, journals or any other publicly available site.
- The contribution of all relevant individuals must be acknowledged in any publications related to this DCA. Authors will need to contact the NICE Managed Access Team for the full list of relevant individuals.

Patient Safety

- The company, and clinical MAOG members if applicable, have a responsibility to report any suspected unexpected serious adverse reactions (SUSARs) to the MAOG. The MAOG will assess any SUSARs and if there are safety concerns will take steps, as appropriate, to mitigate the risk including but not limited to updating the eligibility criteria or recommending that the managed access be halted.

Data protection

- Patient data collected as part of this Data Collection Arrangement will be managed in accordance with all applicable data protection legislation, including but not limited to the Data Protection Act 2018 and the UK General Data Protection Regulation.

- The terms of the Managed Access Agreement relating to data protection, as apply between NHSE and the company, shall also apply between the parties to this Data Collection Arrangement in relation to the performance of their obligations under this Data Collection Arrangement.

Equality considerations

- Do you think there are any equality issues raised in data collection?

☐ Yes ☐ No

- Due to the male-only clinical trial populations for this product, data collected within the managed access agreement will not obtain any data for female patients. However, given that there are no female patients with severe haemophilia B in the UK, we perceive this to have minimal impact. Moreover, real-world data will also be collected via the Phase IV, observational post-authorisation long-term follow-up study. Data pertaining to any female patients receiving etranacogene dezaparvovec will be collected within this.

Commercial Access Agreement

Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B (ID3812)

The contents of this document have been redacted as they are confidential

- A glossary of terms relating to managed access agreements in the Cancer Drugs Fund is available here.