National Institute for Health and Care Excellence

Single Technology Appraisal

Fidanacogene elaparvovec for treating moderately severe to severe haemophilia B [ID4032]
Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	The Haemophilia Society	Another gene therapy for haemophilia B, Etranacogene Dezaparvovec (Hemgenix) was considered as a potential candidate for an HST evaluation but was ultimately rejected and routed to an STA. The arguments in this case are similar and the target population identical.	Thank you for your comment. The technology will be evaluated as a single technology appraisal. No further action needed.
	Pfizer	Yes, it is appropriate to refer fidanacogene elaparvovec for a NICE appraisal. It is important to note that haemophilia B is a very rare condition and the expected eligible population for treatment with fidanacogene elaparvovec is small. Furthermore, the 2022 NICE manual advises that in circumstances where evidence generation is difficult such as for rare diseases and innovative and complex technologies, the committee may be able to make recommendations accepting a higher degree of uncertainty. If fidanacogene elaparvovec is evaluated through the STA process rather than the HST process, this greater flexibility is likely to be appropriate.	Thank you for your comment. The committee will take this issue into account when appraising the evidence.

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	Royal college of Pathologists	Single technology appraisal	Thank you for your comment. The technology will be evaluated as a single technology appraisal. No further action needed.
Wording	The Haemophilia Society	Yes	Thank you for your comment. No further action needed.
	Pfizer	Yes, the wording is appropriate as it is Pfizer's understanding that the remit is meant to be kept broad at this stage in the appraisal.	Thank you for your comment. No further action needed.
	Royal college of Pathologists	Yes	Thank you for your comment. No further action needed.

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Timing issues	The Haemophilia Society	A policy on a similar treatment, Etranacogene Dezaparvovec is expected in September 2023 and this product will be a direct alternative to that treatment.	Thank you for your comment. No further action needed.
	Pfizer	It is expected that NICE will schedule committee discussions such that the gap between Marketing Authorisation and final guidance is as short as possible. Timely NICE guidance is crucial to ensure this innovative technology reaches NHS patients quickly.	Thank you for your comment. No further action needed.
	Royal college of Pathologists	Routine. New gene therapy treatment for haemophilia B which has recently been approved by FDA-would benefit patients with Haemophilia B.	Thank you for your comment. No further action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Genetic alliance UK	It is important to note that living with a chronic, life long condition that currently requires daily injections to manage symptoms can have significant impacts on a person's quality of life. The burden of an individual's treatment may mean that planning outings and overnight trips become more complicated, may prevent some individuals from doing certain activities or they may struggle to adhere to their treatment regime resulting in further complications.	Thank you for your comment. The background section is meant to provide a brief introduction to the disease area and is not exhaustive. The committee will discuss issues surrounding the

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		As this technology is a gene therapy, we understand that one of the main advantages is that it is likely to decrease the burden of treatment. Therefore it is important to consider the burden of current treatment options as part of this appraisal.	burden of treatment during the appraisal process.
	The Haemophilia Society	The introduction falsely conflates the proportion of women and men in severe haemophilia B with the proportion in haemophilia B in general. I would suggest the sentence be amended to “Haemophilia B is normally an inherited condition but some people can have haemophilia B without family history of the disease. Instances of moderately severe or severe haemophilia B in women are rare.” The registry data numbers quoted are wrong in that they are for all ages not just adults. The correct figures for 21/22 are: 242 Severe adults and 271 moderate adults. Moderately severe is a subset of the 271 figure. There are 7-8 women included in those figures, at least one of whom is severe. (https://www.ukhcdo.org/wp-content/uploads/2022/12/UKHCDO-Annual-Report-2022-2021-22-Data.pdf - Table 10, page 49)	Thank you for your comment, the introduction has been amended accordingly.
	Pfizer	Registry data figures are incorrect The registry data prevalence figures are incorrect. The current wording states: “Registry data suggests that in 2021/2022 there were 372 adults with severe haemophilia B and 350 adults with moderate haemophilia B in the UK”.	Thank you for your comment, the introduction has been amended accordingly.

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		However, these figures represent the total number of individuals, including both adults and children. Please reword to reflect only adults with haemophilia B. Proposed wording is as follows: “Registry data suggests that in 2021/2022 there were 242 adults with severe haemophilia B and 271 adults with moderate haemophilia B in the UK”. The technology This section is currently quite brief. Additional detail may be helpful and suggested wording is provided below: “It has been studied in open label clinical trials in adult males with moderately severe to severe haemophilia B (defined as less than or equal to 2% of normal factor IX activity) who do not have current or historic factor IX inhibitors and are negative for neutralising antibodies to variant adeno-associated viruses (AAV) serotype Rh74.”	
	Royal college of Pathologists	Clear and concise	Thank you for your comment. No further action needed.
Population	The Haemophilia Society	Yes	Thank you for your comment. No further action needed.

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	Pfizer	It is Pfizer's understanding that the population is meant to be kept broad at this stage in the appraisal. However, it might be helpful to add 'adults' to this wording. Suggested wording is provided below: "Adults with moderately severe to severe haemophilia B". Additionally, NICE's 'questions for consultation' asked where fidanacogene elaparvovec will fit into the existing care pathway for haemophilia B. Fidanacogene elaparvovec is predominantly intended to displace routine prophylaxis, eliminating the need for patients to have frequent intravenous injections. This reflects the Phase 3 clinical trial inclusion criteria.	Thank you for your comment, 'adults' has been added to the population.
	Royal college of Pathologists	Yes	Thank you for your comment. No further action needed.
Subgroups	Pfizer	Currently, no subgroups have been identified in which fidanacogene elapravovec is expected to be more or less clinically and cost effective.	Thank you for your comment. No further action needed.
	Royal college of Pathologists	Patients with severe haemophilia B and moderately severely haemophilia B who are still having a significant number of bleeds on current standard replacement therapy with standard half-life or extended half-life factor IX concentrates.	Thank you for letting us know this group of people has the highest unmet

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			need. No further action needed.
Comparators	Genetic alliance UK	One of the comparators stated in the draft scope is Etranacogene dezaparvovec. As it is subject to a NICE evaluation, it is therefore not widely available and as far as we understand, the definition of a comparator is a technology that is routinely used in the NHS, therefore we have concerns that this comparator appears to be outside of the usual definition of a comparator. We understand that there may be circumstances that are appropriate to use technologies that are currently being assessed by NICE as a comparator but we would appreciate an overview of how decisions about expanding the definition of a comparator are made, and a discussion with the patient community as to the potential risks and benefits of using comparators outside of the definition and when it may be appropriate to do so. Otherwise, we fear this may lead to an inconsistency and inequality between appraisals.	Thank you for your comment. You are correct that comparator technologies should be routinely used in the NHS when committee meets to appraise the cost-effectiveness evidence of a new technology. This is currently scheduled for June 2024 for fidanacogene elaparvovec. Etranacogene dezaparvovec has the potential to be routinely used in the NHS (subject to NICE evaluation) before then, with guidance

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			currently expected to be published on September 2023. Therefore, it has been tentatively included.
	The Haemophilia Society	You may wish to be more specific in differentiating between factor replacement products. Some products have longer half-lives and so are infused less often and/or have higher trough levels. Also, the processes to extend the half-lives of these products varies so they may have different patient preference or safety profiles	Thank you for your comment. Differences between treatments in terms of frequency of administration, safety profiles and patient preferences will be explored during the appraisal process.
	Pfizer	Prophylactic factor IX (FIX) replacement is the most relevant comparator as an established clinical management for the target population, i.e. adults with moderately severe to severe haemophilia B.[1] A small number of patients who are eligible for prophylaxis may continue to use on-demand treatment (i.e. factor treatment only at the time of a bleeding event) due to personal preference and clinical challenges with administration of prophylactic treatment.[2] Fidanacogene elaparvovec is intended to displace predominately routine factor prophylaxis, as it reflects the trial population who had been on factor replacement therapy for at least 50 days before screening, and then received at least 6 months of standard of care factor replacement prophylaxis in the lead-in study before the administration of fidanacogene elaparvovec.[3] Therefore, it is proposed to remove 'on-demand' treatment as an appropriate comparator. Suggested wording for established clinical management:	Thank you for your comment. The comparators have been kept broad to include all potentially relevant comparators. The committee will discuss relevant comparators as part of its deliberations, based on available evidence and clinical opinion on current standard care in the NHS. Etranacogene dezaparvovec has the

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		"Established clinical management (factor IX prophylaxis)" The NICE STA process for etranacogene dezaparvovec is currently in progress.[4] Therefore, etranacogene dezaparvovec is not currently considered as established clinical practice in the NHS. Although etranacogene dezaparvovec may in future provide an option for NHS patients, established clinical management (factor IX prophylaxis) should be considered to be the most appropriate comparator. 1. Rayment R, Chalmers E, Forsyth K et al. Guidelines on the use of prophylactic factor replacement for children and adults with Haemophilia A and B. 2020;190:684-695. 2. Pfizer Ltd. Treatment patterns and outcomes in haemophilia B produced by National Haemophilia Database. 2023 (data on file). 3. ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT03587116 (Access June 2023). 4. Etranacogene dezaparvovec for treating moderately severe or severe haemophilia B' NICE technology appraisal [ID3812].	potential to be routinely used in the NHS (subject to NICE evaluation; expected guidance publication on September 2023) prior to the committee meeting for the present appraisal, currently scheduled for June 2024.
	Royal college of Pathologists	Yes	Thank you for your comment. No further action needed.
Outcomes	The Haemophilia Society	Change in factor IX levels should specify that the baseline is endogenous factor IX levels (which will be negligible for the eligible patients). It may be	Thank you for your comment. The outcomes are kept broad at this

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		simpler to use the outcome measure of factor level achieved as this is how data is normally published. Durability of response to treatment needs to be considered in relation to factor levels achieved and so the outcome might be better expressed as mean/median factor level after X years. Or percentage of patients above a certain level after X years. There is a large grey area of levels which are above treatment failure but are below levels achievable with the current standard of care. In addition to the outcomes mentioned NICE should consider pain, mental health impact, joint health score, ability to take part in work, education and social activities, time off work, cost savings in NHS care and social care as well as the burden of treatment. A core-outcome set for haemophilia gene therapy trials agreed as part of the coreHem panel of stakeholders (including NICE representatives) is available here: https://onlinelibrary.wiley.com/doi/full/10.1111/hae.13504	stage of the process with the intention of being later refined based on availability of data and economic modelling choices. The outcomes listed in the penultimate paragraph will be included within health-related quality of life and/or explored during the appraisal process The economic evaluation will capture the impact of disease and treatment on patient's quality of life, including impact on mobility, self-care, usual activities, pain/discomfort and anxiety/depression; as well as burden of treatment and cost-savings to the NHS. Additionally, patient perspectives and experiences will be explored during the appraisal process.

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	Pfizer	It is Pfizer's understanding that outcomes within the scope are kept broad. Therefore, the outcomes listed here are generally considered appropriate. Please note that joint surgeries were not included as an outcome in the BeneGene-2 Phase 3 clinical trial. Therefore, to more accurately reflect the outcomes of this trial, please change "complications of the disease (e.g. joint problems and joint surgeries)" to "complications of the disease (e.g. joint problems)". Health-related quality of life is an important outcome and encapsulates a range of physical, psychological, and social domains. It will be important for this appraisal to consider outcomes beyond just the disutility associated with acute bleeding. For example, current routine prophylaxis is associated with repetitive intravenous infusions that can negatively impact the ability of individuals to fully engage in social and sporting activities, travel, education, and employment. Additionally, anxiety and worrying about bleeding and frequent infusions can have significant psychological impacts.[1] The impact of fidanacogene elaparvovec on these quality of life domains is important to consider. Finally, NICE may also wish to consider indirect outcomes related to the considerable economic burden of haemophilia such as the societal cost of impaired work productivity and time off work.[2] The NICE manual states that productivity costs can be presented separately as additional information for the committee.[3] 1. Buckner TW, et al. Impact of hemophilia B on quality of life in affected men, women, and caregivers—Assessment of patient-reported outcomes in the B-HERO-S study. Eur J Haematol. 2018;100(6):592-602.	Thank you for your comment. The scope aims to list all outcomes potentially relevant to the appraisal, regardless of whether they are captured in the pivotal trials. The submission should describe the impact of disease and treatment on patients' quality of life. The submission can also describe additional benefits associated with the treatment (such as reducing impaired work productivity) for committee consideration, but these should not be included in the base case analysis.

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		2. O'Hara, J., et al. The cost of severe haemophilia in Europe: the CHESS study. Orphanet J Rare Dis. 2017;106:12. 3. NICE health technology evaluations: the manual. NICE. January 31, 2022. Introduction to health technology evaluation | NICE health technology evaluations: the manual | Guidance | NICE	
	Royal college of Pathologists	Yes	Thank you for your comment. No further action needed.
Equality	The Haemophilia Society	There are 6 women in the UK with moderate haemophilia B and at least one with severe haemophilia B who potentially meet the criteria for access to this treatment. It should be ensured that they are covered by this policy if possible. NICE should ensure its recommendations do not discriminate against people with HIV or historical Hep B or C infection in accessing this treatment.	Thank you for your comment. The committee will bear this in mind when making decisions and ensure that recommendations do no discriminate based on any protected characteristics.
	Pfizer	The Phase 3 trial did not include females with haemophilia B and very few females meet the criteria for moderately to severe haemophilia B. NICE should aim to ensure that recommendations do not discriminate based on sex.	Thank you for your comment. The committee will bear this in mind when making decisions.

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		Additionally, NICE should aim to ensure that recommendations do not discriminate against people with HIV or historical hepatitis B or C infection.	
	Royal college of Pathologists	appropriate	Thank you for your comment. No further action needed.
	United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO)	Appropriate	Thank you for your comment. No further action needed.
Other considerations	CSL Behring	The economic modelling should include the costs associated with diagnostic testing for biomarkers in people with haemophilia B who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. This should be taken into account in the description of the technology section of the scope.	Thank you for your comment. We have added to the scope to clarify that the costs of diagnostic testing should be included in the economic analysis
	Pfizer	The innovative nature of fidanacogene elaparvovec should be considered. Fidanacogene elaparvovec is an innovative gene therapy that was designed to bring about therapeutic plasma level of FIX expression from hepatocytes, the natural site of synthesis of FIX. The components of	Thank you for your comments, the committee will discuss innovative nature of fidanacogene elaparvovec during the appraisal.

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		fidanacogene elaparvovec, which included a novel bioengineered capsid and a high specific activity hFIX transgene, were optimised to improve efficacy and safety by maximising specificity for the liver, transcription in the hepatocytes and translation of the FIX gene product.1 Fidanacogene elaparvovec being a one-time treatment addresses an important unmet medical need for haemophilia B patients. It offers the benefits of prophylaxis regimen without the need for frequent intravenous (IV) access and infusions, reducing the burden of FIX administration on patients and improves treatment outcomes. In the Phase 3 study, fidanacogene elaparvovec has demonstrated haemostatic efficacy with a low annualised bleeding rate that was superior compared with standard of care prophylaxis at the primary analysis timepoint of 15 months post-infusion. It also achieved FIX activity in the mild range in over 80% of participants and low rate of infusions along with significant improvements in quality-of-life assessments.2 Durability over time has also been demonstrated with patient follow-up data up to 6.3 years.3 The robust efficacy results have been associated with an acceptable safety profile with no new safety signals emerging in Phase 3 and the overall safety profile being consistent with what would be expected with a hepatotropic AAV vector-based gene transfer vector. 1. George LA, et al. Hemophilia B Gene Therapy with a High-Specific-Activity Factor IX Variant. N Engl J Med. 2017;377(23):2215-2227. 2. Kavakli, et al. Presented at the 16th Annual Conference of the European Association for Haemophilia and Allied Disorders (EAHAD); February 7-10, 2023	

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		3. Rasko JEJ, et al. Presented at the 16th Annual Conference of the European Association for Haemophilia and Allied Disorders (EAHAD); February 7-10, 2023	
Questions for consultation	Pfizer	**Where do you consider fidanacogene elaparvovec will fit into the existing care pathway for haemophilia B?** Please see comments on 'Population' section above. **Are there any subgroups of people in whom fidanacogene elaparvovec is expected to be more clinically effective and cost effective or other groups that should be examined separately?** Please see comments on 'Subgroups' section above. **Would fidanacogene elaparvovec be a candidate for managed access?** Due to the innovative nature of fidanacogene elaparvovec, there is likely to be uncertainty regarding long-term outcomes. During submission development, it will be considered whether a managed access proposal could help to resolve such uncertainties.	Thank you for your comment, your answers have been noted. No further action needed at this stage.

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		Do you consider that the use of fidanacogene elaparvovec can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Please see comments on 'Outcomes' section above. Additionally, haemophilia patients take on a burden of disease management that requires routine and frequent infusions of FIX to prevent bleeding risk[1]. The patients' life is impacted by the need to plan the type of work, exercise and leisure activities around infusions, storage and transport of their factor replacement products. Those who choose to be less active to manage bleeding risk may be less socially engaged which can be associated with increased anxiety and depression, combined with the negative implications of a more sedentary lifestyle.[2] Despite prophylaxis, insufficient trough FIX activity level (e.g. prior to the next dose of factor prophylactic infusions) causes occasional clinical and subclinical bleeds, resulting in gradual progression of joint disease over a lifespan.[3] Frequent and repeated venipuncture required for IV administration of FIX is also problematic in patients with needle phobia or limited venous access. Fidanacogene elaparvovec, a gene therapy, provides a one-time treatment that may reduce these burdens on patients by restoring haemostasis to a level that minimises or eliminates spontaneous bleeds and limits progression of joint damage in the long term without the burden for frequent IV injections of current standard of care prophylaxis regimens. This opens up patients' life choices and improve mental wellbeing. Such health-related benefits may not be able to be captured in the QALY calculations but should be taken into consideration in the committee's decision making. 1. Brod M.,et al. Understanding treatment burden in hemophilia: development and validation of the Hemophilia Treatment Experience Measure (Hemo-TEM). J Patient Rep Outcomes 2023;7:17	

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		2. Pinto PR, et al. Emotional distress in haemophilia: Factors associated with the presence of anxiety and depression symptoms among adults. Haemophilia. 2018;24(5):e344-e353. 3. Oldenburg J. Optimal treatment strategies for hemophilia: achievements and limitations of current prophylactic regimens. Blood. 2015;125(13):2038-2044. **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** The BENEGENE-2 Phase 3 clinical trial collected data on patient-reported outcomes including the Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) and Haemophilia Activities List (HAL). These are disease specific health-related quality of life measures that assess the impact of haemophilia on patients' physical health and wellbeing as well as functional abilities. This data may not be included in the QALY calculation but can be used to support the benefits of fidanacogene elaparvovec on patients' quality of life. The BENEGENE-2 Phase 2 clinical trial collected data on Haemophilia Joint Health Score (HJHS), annualised joint bleeding rates as well as number of target joints. This data may not be captured in the QALY calculation but should be taken into account when considering the potential benefits of fidanacogene elaparvovec on avoiding or reducing long-term, progressive joint damage. **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**	

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		know if you think that the proposed remit and scope may need changing in order to meet these aims. Please see comments on 'Equality' section above.	
	UKHCDO	***Where do you consider fidanacogene elaparvovec will fit into the existing care pathway for haemophilia B?*** **Response:** This is the second gene therapy for Haemophilia B to be considered by NICE and will be offered to people with severe and moderate Haemophilia B. People with pre-existing antibodies to the AAV serotype used in a gene therapy vector will not be eligible for its use so there is a need for gene therapy vectors developed from different AAV serotypes to be available to provide greater access to gene therapy. ***Are there any subgroups of people in whom fidanacogene elaparvovec is expected to be more clinically effective and cost-effective or other groups that should be examined separately?*** Response: All patients on regular prophylaxis should be eligible for gene therapy, but it is particularly beneficial in patients with poor venous access. ***Would fidanacogene elaparvovec be a candidate for managed access?*** **Response:** yes ***Do you consider that the use of fidanacogene elaparvovec can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?*** Response: The treatment burden in Haemophilia is underestimated. We draw attention to the long-established concept of the 'disability paradox', where patients typically report greater happiness and QoL across a wide range of health conditions than healthy people under similar circumstances	Thank you for your comment, your answers have been noted. No further action needed at this stage.

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		(Albrecht and Devlieger 1999). This phenomenon is more marked in patients with inherited disorders because they do not have a normal baseline for comparison. It has been particularly challenging to assess the change in treatment burden, as no validated tool exists for this. Patients with chronic health conditions often undertake risk-benefit analyses about their treatment adherence. They can actively decide not to follow the recommendations because of time and other considerations, i.e. rationalised or reasoned non-adherence (Demain, Goncalves et al. 2015). Quality of life instruments are not particularly sensitive, and clinical experience suggests that they fail to capture significant benefits to patients that derive from reduced treatment burden and changes towards a new and more active life relatively unburdened by disease. ***Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.*** Structured Interviews with people with Haemophilia B who have had gene therapy will be most beneficial.	
Additional comments on the draft scope			

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