National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

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

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	CSL Behring	It is appropriate to refer etranacogene dezaparvovec for a NICE appraisal. However, the assessment needs to take into account that haemophilia B is a very rare condition and the expected eligible population for treatment with etranacogene dezaparvovec is small. Routing etranacogene dezaparvovec through the STA process could result in an unsuitable evaluation, which is likely to prevent access to patients and the NHS to a treatment option for haemophilia B that has the potential to reduce the need for life-long prophylaxis therapy (please see “Additional comments on the draft scope” section below).	Comment noted. This topic and considerations raised by the company were discussed at the Topic Selection Oversight Panel. A decision was made to route this to the single technology appraisal process.
	Cochrane	Yes [it would be appropriate to refer this topic to NICE for appraisal]	No action needed.
	Genetic Alliance	-	No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	Haemophilia Society	Yes [it would be appropriate to refer this topic to NICE for appraisal]	No action needed.
Wording	CSL Behring	The wording of the remit is not appropriate because the expected license for etranacogene dezaparvovec has been updated to the treatment [redacted] PharmaScan has been updated to reflect the updated proposed licensed indication and the NICE project manager has been informed. The remit should be amended to reflect that, to: 'To appraise the clinical and cost effectiveness of etranacogene dezaparvovec within its marketing authorisation for treating adults with haemophilia B who currently use FIX prophylaxis.'	Comment noted. Because marketing authorisation wording is confidential and may be subject to change, it is appropriate to keep the remit broad. No action needed.
	Cochrane	Yes [the wording of the remit reflects the issue(s) of clinical and cost effectiveness about this technology]	No action needed.
	Genetic Alliance	-	No action needed.
	Haemophilia Society	Yes [the wording of the remit reflects the issue(s) of clinical and cost effectiveness about this technology]	No action needed.
Timing Issues	CSL Behring	Currently there is substantial unmet need and scope to improve standard of care. Timely reimbursement of etranacogene dezaparvovec is important and	Comment noted. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		urgent because current treatments for haemophilia B present multiple negative impacts to the patient and their quality of life. These include the requirement for frequent intravenous infusions which put patients at risk of infection, injection site reactions, allergic reactions, patients developing inhibitors, and poor adherence leading to low FIX activity and higher risk of bleeds. These bleeds can cause severe disability and, in some cases, can even be life threatening. Etranacogene dezaparvovec has shown the ability to provide sustained and durable expression of endogenous FIX from a single administration, has the potential to eliminate the requirement for continuous prophylaxis, reduce bleeds and improve quality of life. If the technology is not evaluated in a timely manner, this would lead to delays in treatment, resulting in poorer, and sometimes irreversible, outcomes for people with haemophilia B.	
	Cochrane	Not urgent. There is currently highly effective (but inconvenient as it involves intravenous injections) treatment for the condition.	Comment noted. No action needed.
	Genetic Alliance	-	No action needed.
	Haemophilia Society	The Haemophilia community has been following developments in gene therapy for many years and expects that licensed treatments of this novel approach to bleeding disorder treatments will be efficiently reviewed and approved by NICE and NHS England.	Comment noted. No action needed.
Additional comments on the draft remit	CSL Behring	No further comments.	No action needed.
	Cochrane	-	No action needed.
	Genetic Alliance	-	No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	Haemophilia Society	-	No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	CSL Behring	1. Please re-word the following section: Current wording: “Haemophilia is a rare genetic condition that affects the ability of blood to clot. This is caused by the inability or reduced ability of the body to produce substances called clotting factors which are needed for clotting. In haemophilia B, the factor affected is called factor IX (nine). Haemophilia B is normally an inherited condition found in males, but some people can have haemophilia B without family history of the disease. Instances of moderately severe or severe haemophilia B in females are rare.” CSL Behring have just made a few minor changes to the wording for additional clarity. In particular, the last sentence has been amended to reflect the appropriate patient population. <u>Proposed wording:</u> Haemophilia is a rare, lifelong inherited genetic condition that affects the ability of blood to clot, which can lead to frequent spontaneous bleeding episodes. In haemophilia B one of the clotting factor proteins important for	Comment noted. The NICE technical team has reviewed the proposed wording changes. The aim of the background section is to provide an overview of the disease area. In some cases, the suggested change has not been accepted to keep the background broad and accessible to audiences.

Section	Consultee/ Commentator	Comments [sic]	Action
		blood clotting is either partly or completely missing. In people with haemophilia B, it takes longer than normal for bleeding to stop. In haemophilia B, the factor affected is called factor IX (FIX). The disease is caused by changes in the FIX gene, which is found on the X chromosome, meaning that haemophilia B predominantly affects males. 2. <u>Please re-word the following section:</u> Current wording “The main symptom of haemophilia is prolonged bleeding but other complications include joint and muscle damage from internal bleeding and bruising.” CSL Behring feel that prolonged bleeding and joint/muscle damage are equal in their impact on the patient so have reworded appropriately. We’ve added a sentence onto the end which explains the link between the two symptoms/complications. Proposed wording: In addition to prolonged bleeding, other complications include bleeding into joints and muscles without having had an injury. To prevent or reduce the number of bleeding episodes that can result in chronic, debilitating disease, treatment is aimed at reducing spontaneous bleeding.	This sentence has been updated to add ‘other complications include bleeding into joints and muscles without having had an injury’.

Section	Consultee/ Commentator	Comments [sic]	Action
		3. Please reword the following section to reflect the numbers of people who were treated for haemophilia B in England instead of the UK and to correct the population estimate for the moderately severe group. Current wording: "Registry data suggests that in 2019/2020 there were 369 people with severe haemophilia B and 344 people with moderately severe haemophilia B in the UK." The numbers in this section are incorrect and the 2020/2021 report is now available, so the numbers need to be updated. The expected license has also been modified to: [redacted] Therefore, the population discussed should reflect those patients currently using FIX prophylaxis which we have calculated as follows: In the UKHCDO 2020/2021 annual report[xxi] there are 247 adult patients reported with severe haemophilia B and 271 with moderate haemophilia B	This sentence has been updated to reflect the numbers of people with haemophilia B as reported in the 2021 UKHCDO publication. Marketing authorisation is in progress and subject to change. Because of this, numbers of the overall haemophilia B population have been included within the background section.

Section	Consultee/ Commentator	Comments [sic]	Action
		(518 patients in total). Using assumptions from the CHESS EU study[i] (55% of severe haemophilia B adult patients using FIX prophylaxis in the UK) and Fischer et al. study conducted in the Netherlands (12-29% of adult patients reported with moderate haemophilia B using FIX prophylaxis, 29% assumed here), CSL Behring have estimated 214 adult patients to be on FIX prophylaxis. No patients with mild haemophilia B are expected to be using FIX prophylaxis.[vi] Proposed wording: Registry data suggest that in 2020/2021 in England there were 214 adults with haemophilia B using FIX prophylaxis.[4] Please reword the following section to reflect the administration route of FIX as by intravenous infusion or injection. [ii] Current wording: "Current clinical management involves replacing the missing clotting factor IX in the blood through an intravenous infusion of clotting factor concentrate. For more severe haemophilia, this involves regular injections of clotting factor (recommended twice weekly) that are used to prevent bleeding (known as prophylaxis). On-demand injections of clotting factor can also be used in less severe haemophilia as an immediate response to bleeding (known as episodic treatment)."	'Episodic' treatment has been replaced by 'on-demand'.

Section	Consultee/ Commentator	Comments [sic]	Action
		FIX dosing frequency has been updated and 'episodic' amended to the clinically recognised term 'on-demand'. Proposed wording: 'Current clinical management involves replacing the missing clotting FIX in the blood through an intravenous infusion or injection of clotting factor concentrate. Replacement could involve regular intravenous infusion or injection (administration frequency dependent on prescribed treatment – as administered every 3 to 14 days with possibility of extension up to 21 days for well controlled patients aged ≥18 years old) of FIX that are used to prevent bleeding (known as prophylaxis) or as an immediate response to bleeding (known as on-demand treatment).'	The aim of the background section of the scope is to provide a broad overview. Because of this, detailed information of dosing and administration of current treatment options are not included within this section. Following discussions with clinicians at the scoping workshop, the dose of regular injections of clotting factor has been updated to "once or twice weekly".

Section	Consultee/ Commentator	Comments [sic]	Action
	Cochrane	The background states that prophylactic treatment is with twice weekly injections. This is incorrect because this is based on the old type of prophylaxis with standard half life products. The current standard for treatment of the condition is with once weekly prophylaxis with extended half life FIX concentrate.	Following discussions with clinicians at the scoping workshop, the dose of regular injections of clotting factor has been updated to “once or twice weekly”.
	Genetic Alliance	-	No action needed.
	Haemophilia Society	Since this was written a new UKHCDO and NHD annual report has been published which includes updates figures for people with Haemophilia B. The report with figures as of March 2021 are available here: http://www.ukhcdo.org/wp-content/uploads/2021/12/2021-UKHCDO-Annual-Report-2020-21-Data.pdf	Comment noted. This sentence has been updated to reflect the numbers of people with haemophilia B reported in the 2021 UKHCDO publication.

Section	Consultee/ Commentator	Comments [sic]	Action
		The latest UK-wide figures are 370 severe (123 under 18 and 247 18 or older) and 346 moderate (75 under 18 and 271 18 or older). Included in the 271 moderate adults are 6 women. Moderately severe is a subset of the moderate numbers reported by the UKHCDO.	
The technology/ intervention	CSL Behring	Suggest rewording this section to take into account that the viral vector is inactivated, as 'harmless' may present an inaccurate description. Current wording: "Etranacogene dezaparvovec (brand name unknown, CSL Behring) is a gene therapy that works by using a harmless viral vector" Added additional clarity to the wording and changed 'harmless viral vector' to 'inactivated' Proposed wording: 'Etranacogene dezaparvovec (brand name unknown, CSL Behring) is a gene therapy that works by using an inactivated, non-integrating viral vector to insert a highly active copy of the FIX gene into a patient's hepatocytes.'	Comment noted. The scope has been updated to the latest scoping template, which does not provide details on technology mechanism of action or method of administration. This sentence has been removed.
	Cochrane	Yes [the description of the technology is accurate]	No action needed.
	Genetic Alliance	-	No action needed.
	Haemophilia Society	Describing the AAV vector as "harmless" may be inaccurate as the viral vector is regarded as a foreign invader and leads to the activation of innate and adaptive immune responses. Most gene therapy trials have shown elevated liver transaminases as a common adverse event often needed to be treated with immune suppression.	Comment noted. The scope has been updated to the latest scoping template, which does not provide details on technology

Section	Consultee/ Commentator	Comments [sic]	Action
		Due to the dosing levels AAV vectors can lead to liver toxicity, toxicity in the in the dorsal root ganglia and may increase the risk of Hepatocellular Carcinoma. (ref: https://pubmed.ncbi.nlm.nih.gov/34758292/)	mechanism of action or method of administration. This sentence has been removed.
Population	CSL Behring	The population defined in the scope is not appropriate because the expected license has been updated to account for all patients with haemophilia B currently receiving FIX prophylaxis, rather than moderately severe to severe patients. However, we anticipate the number of eligible patients to be very similar between these two populations, as only a subset of patients in the UK are offered prophylactic FIX therapy. The population should be amended to: • Adults with haemophilia B who are currently receiving FIX prophylaxis	Comment noted. Because marketing authorisation wording is confidential and may be subject to change, it is appropriate to keep the remit broad. No action needed.
	Cochrane	No. It should be adult males aged over 18 years since the clinical trial excluded children and women.	Comment noted. The population has been kept broad for all adults, regardless of gender. No action needed.
	Genetic Alliance	-	No action needed.
	Haemophilia Society	While the total number of people with severe and moderate haemophilia B in the UK is 641. Trials of the treatment have only included people with haemophilia B on prophylaxis and have excluded people with ongoing or historic inhibitors (21), children (198) and women (6).	Comment noted. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		The Hope-B trial definition of moderately severe refers to people with Factor IX levels of between 1-2%. This is not a category that is usually reported on separately in UK data. However, UKHCDO using the NHD should be able to estimate the proportion of the eligible population who are on prophylaxis and may be able to advise on the break-down in factor levels among people with moderate haemophilia B in the UK.	
Comparators	CSL Behring	The term 'episodic treatment' is not used in clinical practice, the term 'on-demand treatment' is used for patients that are not on prophylaxis or who experience breakthrough bleeding episodes whilst on prophylaxis. Please amend the comparators to: 'Established clinical management including FIX replacement prophylaxis with or without on-demand treatment.'	Comment noted. 'Episodic treatment' has been replaced with 'on-demand' treatment.
	Cochrane	Yes [the comparators are the standard treatments currently used in the NHS with which the technology should be compared].	Comment noted. No action needed.
	Genetic Alliance	-	No action needed.
	Haemophilia Society	This is all correct.	Comment noted. No action needed.
Outcomes	CSL Behring	Please change 'bleeding' to 'annualised bleeding rate' to reflect the outcomes in the HOPE-B clinical trial. Please change 'need for further treatment with FIX injections' to 'need for further treatment with FIX injections for spontaneous bleeds'. Please change the outcome 'complications of the disease (e.g. joint problems)' to reflect the outcomes in the clinical trial to 'complications of the disease (e.g. joint bleeds and joint surgeries)'.	Comment noted. 'Bleeding' has been changed to 'annualised bleeding rate'. 'Joint surgeries' has been added as an example of disease complication.

Section	Consultee/ Commentator	Comments [sic]	Action
			Based on comments at the scoping workshop, 'need for further treatment with factor IX injections' is unchanged. Outcomes included within the scope are kept broad. Consultees can provide data for additional outcomes within their submission. No action needed.
	Cochrane	There are 2-3 additional outcomes to be considered a) You should capture the adverse events of the treatments used to treat the adverse events of the treatment ie although the adverse event may be a rise in ALT, this is treated with high dose steroids for many months. The main adverse event of a patient having gene therapy is often not directly due to the gene therapy but rather due to the steroids. Steroid side-effects should be integral to the assessment. b) I hope the HRQOL will include the psychological impact on the patients and their families c) Unlike other treatments the adverse effects (eg malignancy risk) may not become obvious for 10-20 years. The psychological impact of this uncertainty needs to be considered.	Comment noted. Outcomes included within the scope are kept broad. Consultees can provide data for additional outcomes within their submission. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	Genetic Alliance	-	No action needed.
	Haemophilia Society	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	Comment noted. Outcomes included within the scope have been kept broad. Data on additional outcomes can be provided by consultees at submission, if relevant. No action needed.
Economic analysis	CSL Behring	NICE has recognised the key challenges in assessing advanced therapy medicinal products (ATMPs) like etranacogene dezaparvovec in the CHTE methods review – technology specific issues, task and finish group report, September 2020. The key challenges highlighted included the sensitivity of the ICERs to the discounting rate applied, identifying a relevant comparator, lack of comparative data and high cost of treatment. Please include the following in the economic analysis section to acknowledge the challenges of assessing ATMPs: 'A non-reference case discount rate of 1.5% for health and cost effects will be considered.'	Comment noted. The company is able to include a scenario analysis with a 1.5% discount rate within their submission. The committee will assess the suitability of this against the criteria set out in section 4.5.3 in the 2022 NICE health technology evaluations manual. No action needed.
	Cochrane	Yes.	No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	Genetic Alliance	-	No action needed.
	Haemophilia Society	The benefits of gene therapy for haemophilia B could last for the lifetime of the patient. This could mean that benefits are seen over 50 years or more.	Comment noted. No action needed.
Equality and Diversity	CSL Behring	No equalities issues relating to recommendations on the use of etranacogene dezaparvovec that could have a differential impact on people protected by the equality legislation or any adverse impact on people with a particular disability or disabilities have been identified.	Comment noted. No action needed.
	Cochrane	No issues.	No action needed.
	Genetic Alliance	-	No action needed.
	Haemophilia Society	There are 6 women in the UK with moderate 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.	Comment noted. No action needed.
Other considerations	CSL Behring	None.	No action needed.
	Cochrane	Cost of investigation of every malignancy which occurs in the future. Two components: a) Psychological impact of the long term uncertainty b) Every malignancy will need to be investigated in detail for signs of DNA integration and such studies will be expensive to so and interpret.	Comment noted. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
	Genetic Alliance	-	No action needed.
	Haemophilia Society	-	No action needed.
Innovation	CSL Behring	Etranacogene dezaparvovec is innovative and represents a step-change in the management of haemophilia B and has been recognised as a breakthrough therapy by international agencies. People with haemophilia B currently rely on lifelong treatment to manage the risk of a spontaneous bleed, which can involve regular prophylaxis of FIX. Etranacogene dezaparvovec has the potential to be the first gene therapy licensed for use in patients with haemophilia B, providing sustained increase of endogenous FIX activity levels to within the mild to normal range from a single dose. In the pivotal phase III, open label, single-dose, single arm HOPE-B trial, etranacogene dezaparvovec has demonstrated the ability to reduce annualised bleeding rate compared to baseline FIX prophylactic therapy and after a single infusion participants maintained stable FIX activity over the 18-month study period. Further, patients in the HOPE-B trial experienced an improvement in quality of life, measured with the haemophilia quality-of-life questionnaire. Patients experienced a 21.5% improvement in mean patient quality-of-life score in the post-treatment period, as measured by the Haem-A-QoL score compared to the lead-in period ($p<0.0001$). All participants in the HOPE-B trial were receiving prophylactic FIX therapy at baseline and 98% of patients treated with a full dose of etranacogene dezaparvovec discontinued use of prophylaxis treatment (from lead-in period to months 13 to 18). Etranacogene dezaparvovec has been granted Breakthrough Therapy Designation by the U.S. Food and Drug Administration and access to the Priority Medicines (PRIME) regulatory initiative by the European Medicines Agency.[iv][v]	Comment noted. The innovative nature of the technology will be appraised by the evaluation committee.

Section	Consultee/ Commentator	Comments [sic]	Action
	Cochrane	Yes [the technology is considered innovative in its potential to make a significant and substantial impact on health-related benefits]	Comment noted. The innovative nature of the technology will be appraised by the evaluation committee.
	Genetic Alliance	Yes, we do consider this technology as innovative in its potential to make a significant and substantial impact on health-related benefits.	Comment noted. The innovative nature of the technology will be appraised by the evaluation committee.
	Haemophilia Society	The treatment has the potential to remove the need for prophylaxis and greatly reduce the need for factor infusion in people with haemophilia B. Protecting them from painful and damaging bleeds without the need for regular treatment and retreatment. A one-off treatment would vastly reduce the burden of treatment and revolutionise the management of haemophilia B for those people. Some of this benefit will be captured by an analysis that take into account the outcomes mentioned above. However, the reduction in burden of treatment and the ability to take part in life without worrying about adherence to treatment may not be fully captured. A study of the impact of living with haemophilia on ability to take part in everyday life and achieve career, educational and social goals was analysed in the CHESS 2 study: https://ashpublications.org/blood/article/136/Supplement%201/1/473118/An-Insight-into-the-Impact-of-Hemophilia-a-on.	Comment noted. The innovative nature of the technology will be appraised by the evaluation committee.

<table>
<tr><th>Section</th><th>Consultee/ Commentator</th><th>Comments [sic]</th><th>Action</th></tr>
<tr><td>Questions for consultation</td><td>CSL Behring</td><td>Have the relevant comparators for etranacogene dezaparvovec been included in the scope?

See ‘comparators’ section above

How are the severity criteria used in clinical practice?
The severity criteria for haemophilia B are defined as factor IX activity levels (IU/dL) of: [i]
Severe: <1
Moderate: 1 to 5
Mild: > 5 to < 40
Normative: ≥ 40
<table><tr><th>Phenotype</th><th>Spontaneous bleeding</th><th>Prophylaxis recommended</th><th>FIX activity, IU/dL</th></tr><tr><td>Severe</td><td>Frequent</td><td>Yes</td><td><1</td></tr><tr><td>Moderate</td><td>Rare</td><td>Variable</td><td>1 to 5</td></tr><tr><td>Mild</td><td>Very rare</td><td>No</td><td>5 to <40</td></tr><tr><td>Normative</td><td>No</td><td>No</td><td>≥40</td></tr></table>Which treatments are considered to be established clinical practice in the NHS for haemophilia B?</td><td>Comment noted. No action needed.</td></tr>
</table>

Section	Consultee/ Commentator	Comments [sic]	Action
		There are two main methods of treatment for haemophilia B, preventative treatment (prophylactic) and on-demand treatment. Preventative treatment aims to prevent bleeding and subsequent joint and muscle damage by replacing the missing or reduced factor IX (FIX) with a man-made substitute. This is given regularly, usually as an intravenous injection the frequency of treatment varies from every 3 days to every 21 days. Intravenous injections can be given at home, which is less disruptive to family life than intravenous infusion given in hospital. People with mild Haemophilia B, that is they FIX levels of 5% to less than 40%, may not need preventative treatment. On-demand treatment is given to treat prolonged bleeding, for example after an injury or as part of planning surgery. It is used temporarily to reduce the side effects of bleeding. Physiotherapy will usually be needed after a bleed, this may involve stretches, exercises or splints to maintain the full range of joint movement.ii The primary aim of treatment for haemophilia B is to prevent bleeding and to preserve musculoskeletal function, usually through prophylaxis treatment. In the UK prophylaxis is initiated at an increasingly young age to preserve musculoskeletal function.ii Outcomes for patients receiving prophylaxis treatment differs depending on when treatment is initiated. The International Society of Thrombosis and Haemostasis defined the aims of prophylaxis into three categories depending on joint health at onset: primary prophylaxis, secondary prophylaxis and tertiary prophylaxis. ○ Primary prophylaxis is defined as prophylaxis given in early childhood before the second joint bleed or before the age of 3 years, with the aim that the child reaches maturity with normal	

Section	Consultee/ Commentator	Comments [sic]	Action
		joints. The expected outcome is that, with optimised prophylaxis, a child with haemophilia will reach adulthood with normal joints and live a full and active life, in the absence of bleeds. ○ Secondary prophylaxis is defined as prophylaxis given after two or more joint bleeds, but before the onset of joint disease. These bleeds may have caused irreversible joint disease. Prophylaxis aims to preventing further bleeding and limit the consequence of this damage. ○ Tertiary prophylaxis is defined as prophylaxis given after the onset of clinically/radiologically apparent joint disease and aims to slow down progression of joint disease, reducing pain and maintaining quality of life. It cannot reverse established joint disease.[ii] FIX products themselves are categorised by standard-acting half life FIX (SHLs) and extended half life FIX (EHL), dependant on their dosing frequencies. What proportions of people would be expected to be treated with prophylaxis and on-demand treatment? Of the 518 adult patients with moderate to severe haemophilia B, ~ 214 (41%) are estimated to be on prophylaxis vs 304 (59%) on-demand. We would assume 0% of mild patients are using FIX prophylaxis.[i vi xiii xxi] What proportion of people develop factor IX inhibitors? What is current clinical	

Section	Consultee/ Commentator	Comments [sic]	Action
		management for factor IX inhibitors in haemophilia B? Would it be expected that patients with factor IX inhibitors could be treated with etranacogene dezaparvovec? It is estimated that 3% of patients with haemophilia B develop inhibitors.[iii] If patients developed inhibitors while on FIX prophylaxis, they receive treatment including high-dose clotting factor concentrates, bypassing agents, and immune tolerance induction therapy. These patients would not be eligible for etranacogene dezaparvovec. Are the outcomes listed appropriate? **See 'outcomes' section above.** Are there any subgroups of people in whom etranacogene dezaparvovec is expected to be more clinically effective and cost effective or other groups that should be examined separately (e.g. severity or presence of inhibitors)? No subgroups in which etranacogene dezaparvovec is expected to be more clinically and cost effective have been identified. 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 proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:	

Section	Consultee/ Commentator	Comments [sic]	Action
		• could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which etranacogene dezaparvovec will be licensed; • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. 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 tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. **No equalities issues have been identified.** Do you consider etranacogene dezaparvovec to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? **Please see 'innovation' section above.** Do you consider that the use of etranacogene dezaparvovec can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? The use of etranacogene dezaparvovec is likely to result in health-related benefits that are unlikely to be included in the QALY	Comment noted. The committee will consider any significant and substantial health-related benefits that are unlikely to be included in the QALY calculation

Section	Consultee/ Commentator	Comments [sic]	Action
		calculation. Capturing the benefits beyond the QALY has been recognised as a challenge for assessing gene therapies for haemophilia B, in particular the benefits that are derived from the reduction of treatment burden expected with etranacogene dezaparvovec.[iv] That is, improvement in mental health, freedom of choice and peace of mind. Further, etranacogene dezaparvovec has the potential to alleviate challenges caused by current treatment that impair patients' quality of life, including frequent intravenous injections needed for prophylactic treatment, which is particularly challenging for patients with difficult venous access.[v] Etranacogene dezaparvovec has the potential to be the first gene therapy licensed for use in patients with haemophilia B, providing sustained mild to normal endogenous FIX activity levels, therefore it is likely to provide hope to haemophilia B patients. This is not likely to be captured in the QALY calculations and therefore, this should be taken into account in the committee's decision making. Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. The HOPE-B trial collected data on patients quality of life using the haemophilia quality of life questionnaire for Adults (Haem-A-QoL) which includes domains specific to the treatment of haemophilia including; feelings, work/ school, future and treatment.[iii] This data can be used to support the impact of etranacogene dezaparvovec on quality of life for patients with haemophilia that may not be captured in the model.	within their decision-making. Comment noted. Because the use of etranacogene

Section	Consultee/ Commentator	Comments [sic]	Action
		To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. It is likely that an [redacted] test will be required prior to use of etranacogene dezaparvovec, as the expected license is restricted to those [redacted]. This test is not carried out as part of current routine clinical practice, therefore, has the potential to present a barrier to adoption of this technology. NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction). **Etranacogene dezaparvovec should be assessed via the HST route, please see 'Additional comments on the draft scope' section below.**	dezaparvovec is expected to be conditional on the presence a specific biomarker, the economic modelling should include the costs associated with diagnostic testing in people with haemophilia B who would not otherwise have been tested. More information on this has been included within the 'economic analysis' section of the scope.
	Cochrane	The risk of inhibitors in severe haemophilia B is 10%. Patients with an inhibitor to FIX need to be excluded from the intervention.	Comment noted. No action needed.
	Genetic Alliance	-	No action needed.
	Haemophilia Society	With a total eligible adult patient population of less than 250 across the UK and hence a prevalence of less than 1 in 250,000 NICE may want to consider if the HST process is better suited for this treatment.	Comment noted. This topic was discussed at the Topic Selection Oversight Panel. A

Section	Consultee/ Commentator	Comments [sic]	Action
		Is this treatment and the timetable for its consideration likely to make it eligible for the Innovative Medicines Fund if there is remaining uncertainty regarding its clinical or cost effectiveness?	decision was made to route this to the single technology appraisal process. Eligibility for the innovative medicines fund can be considered during the evaluation process. No action needed.
Additional comments on the draft scope	CSL Behring	Please add the following to the 'related national policy' section: Department of Health and Social Care (2021). UK Rare Diseases Framework HM Government (2021). Life Sciences Vision. HM Government (2017). Life Sciences Sector Deal Office for Life Sciences (2017). Life Sciences Industrial Strategy Department of Health and Social Care Outcome Delivery Plan: 2021 to 2022 (2021) **CSL Behring Comments for NICE's Recommended Review under STA vs. HST**	Comment noted. The related national policy section is not intended to be exhaustive. No action needed. Comment noted. This topic was discussed at the Topic Selection Oversight Panel. A decision was made to route this to the single technology appraisal process.

Section	Consultee/ Commentator	Comments [sic]	Action
		Etranacogene dezaparvovec is currently routed to STA, however it is our belief that etranacogene dezaparvovec is more suitable for assessment via the HST process. For people with haemophilia B currently using FIX prophylaxis and [redacted] etranacogene dezaparvovec meets the routing criteria for assessment under the HST programme. **Criterion 1: The disease is very rare (defined as a prevalence in England lower than 1 in 50,000 people or about 1,100 people).** Haemophilia B is a rare genetic disorder, in 2020/2021 there were approximately 1,270 adults in England with haemophilia B according to the UK national haemophilia database.[viii] Etranacogene dezaparvovec is anticipated to be indicated for the [redacted] Therefore, the population expected to receive treatment with etranacogene dezaparvovec are a sub-group of patients with haemophilia B that require FIX prophylaxis therapy. Only some patients with severe and moderate haemophilia B, and typically no patients with mild haemophilia B are prescribed FIX prophylaxis therapy.[vi] In the UKHCDO 2020/2021 annual report[xxi] there are 247 adult patients reported with severe haemophilia B and 271 with moderate haemophilia B (518 patients in total). Using assumptions from the CHESS EU study[i] (55% of severe haemophilia B adult patients using FIX prophylaxis in the UK) and Fischer *et al.* study conducted in the Netherlands[vi] (12-29% of adult patients reported with moderate haemophilia B	

Section	Consultee/ Commentator	Comments [sic]	Action
		using FIX prophylaxis, 29% assumed here), CSL Behring have estimated 214 adult patients to be using FIX prophylaxis. Of these, a further 7% are estimated to be ineligible based on [redacted] (214*0.93 = 199).[vii viii ix x xi] To ensure this number is representative of the English population, rather than UK, we used a multiplier of 0.84*, resulting in 167 patients. *84% of the UK population resides in England.[xii] Etranacogene dezaparvovec represents a step change in current treatment for a very rare condition and it is likely to face similar challenges to gene therapies that have been assessed via the HST route previously. • **Step change:** People with moderate or severe haemophilia B need lifelong treatment, which usually involves prophylaxis treatment with factor IX (FIX) on a weekly basis, to reduce their risk of spontaneous bleeds and associated morbidities. Etranacogene dezaparvovec has the potential to provide sustained endogenous FIX activity levels, increased to within the mild to normal range from a single infusion. The phase III HOPE-B trial showed that participants experienced a stable and durable increase in mean FIX activity and 98% of patients treated with a full dose of etranacogene dezaparvovec discontinued use of prophylaxis treatment (from lead-in period to months 13 to 18). **Similar challenge:** Etranacogene dezaparvovec has been developed for the treatment of [redacted]	

Section	Consultee/ Commentator	Comments [sic]	Action
		[redacted] Etranacogene dezaparvovec addresses a very rare condition. The NICE topic selection proposal consultation document (2021) states that the HST process is designed to take into account the difficulty in generating evidence in very small populations (see Criterion 2) and the inability for developers to develop these products under normal market conditions, as the conditions occur so infrequently that the cost of bringing them to market may not be recovered by the expected sales.[xiii] Etranacogene dezaparvovec has been developed for a small population and has faced similar challenges to other gene therapies that have been routed to the HST programme previously, that is: • Onasemnogene abeparvovec for treating spinal muscular atrophy (HST15) • Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations (HST11) • Strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency (HST7) **Criterion 2: Normally, no more than 300 people in England are eligible for the technology in its licensed indication, and no more than 500 across all its indications.** The expected license for etranacogene dezaparvovec is for the treatment of [redacted]	

Section	Consultee/ Commentator	Comments [sic]	Action
		[redacted] In the UKHCDO 2020/2021 annual report[xxi] there are 247 adult patients reported with severe haemophilia B and 271 with moderate haemophilia B (518 patients in total).[xiv] Using assumptions from the CHESS EU study[i] (55% of severe haemophilia B adult patients using FIX prophylaxis in the UK) and Fischer *et al.* study conducted in the Netherlands (12-29% of adult patients reported with moderate haemophilia using FIX prophylaxis, 29% assumed here), CSL Behring have estimated 214 adult patients to be using FIX prophylaxis. Of these, a further 7% are estimated to be ineligible based on [redacted](214*0.93 = 199).[xiv - xvii] To ensure this number is representative of the English population, rather than UK, we used a multiplier of 0.84*, resulting in 167 patients. This number falls well below the HST Criterion 2 threshold. *84% of the UK population resides in England.[xix] **Criterion 3: The very rare disease for which the technology is indicated significantly shortens life or severely impairs quality of life.**	

		Haemophilia B is a congenital, genetic X-linked deficiency in blood clotting factor IX characterised by bleeding episodes and joint conditions.[i] [xv] [xvi] The extent of bleeding events depends on the disease severity, i.e. plasma FIX trough activity level in blood. Bleeds within joints are common and affect mobility and patient independence. Untreated patients with severe disease severity (FIX trough activity level <1%) can be hospitalised due to uncontrolled bleeding events. In rare cases, sub-cranial bleeds can occur and cause death or severe disability;[xvii] the incidence of intracranial haemorrhage is 10 to 20 times higher in people with haemophilia compared with the general male population.[xviii] [xix] Current treatment to reduce prevalence of these outcomes are either regular preventative prophylaxis of FIX (administration frequency dependent on prescribed treatment – as administered every 3 to 21 days) or on demand treatment in the occurrence of a bleed event. A study of young adults in the US aged 18 to 34 years (N=141) found that, compared with the general US adult population, people with haemophilia experienced significant health and social burdens, with more liver disease, joint damage, and joint pain. Joint pain affected 90% of the cohort.[xx] Increased pain is associated with disease severity and reduced joint range of motion.[xxi] The HERO study (N=675) showed that 42% of respondents with haemophilia B experienced chronic pain relating to haemophilia, and the majority of people with haemophilia (89% in haemophilia A and B) experienced pain that had interfered with activities in the past 4 weeks. Joint damage leads to functional impairment, with patients frequently suffering from arthropathy/arthritis.[xxii] [xxiii] Life expectancy is lower for people with haemophilia B than the general population. A Dutch survey found that median life expectancy for patients with	

Section	Consultee/ Commentator	Comments [sic]	Action
		haemophilia was 6 years lower than the life expectancy of the general Dutch male population.[xxiv] A study of the UK registry found that, even when excluding patients with HIV, patients with severe haemophilia are nearly three times as likely to die compared with the general population. Life expectancy was 15 years lower than in the general male population.[xxv] **Criterion 4: There are no other satisfactory treatment options, or the technology is likely to offer significant additional benefit over existing treatment options.** Etranacogene dezaparvovec is expected to offer significant additional benefit over existing treatment options. People with haemophilia B require a lifelong treatment to manage the risk of a life-threatening bleed, which usually involves prophylaxis treatment with FIX on a weekly basis. Etranacogene dezaparvovec has the potential to provide functionally normal FIX activity levels for patients with haemophilia B, through a sustained increase in plasma FIX activity levels. In the HOPE-B trial etranacogene dezaparvovec has demonstrated the ability to reduce annualised bleeding rate compared to baseline FIX prophylactic therapy and, after a single infusion, participants maintained stable FIX activity over the 18-month study period.	
	Cochrane	Consideration should be given as to whether the evidence from the regulatory approval of the intervention is good enough to recommend it also for patients with cirrhosis or extensive fibrosis. This is a very real issue in patients with haemophilia because those born before 1985 have an almost 100% chance of hepatitis C infection. By now almost all have had their hepatitis C eliminated but this was around 30 years post infection, and some patients developed cirrhosis in the meantime. The risk of liver cancer is 0.8 per 100	Comment noted. The technology will be evaluated within its marketing authorisation. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		patient years in patients with previous hepatitis C and 1.8 per 100 patient years for those with cirrhosis.	
	Genetic Alliance	We maintain a cautious attitude to the routing of gene therapy treatments through STA as we believe gene therapies in general create a form of uncertainty that the STA appraisal process struggles to accommodate.	Comment noted. This topic was discussed at the Topic Selection Oversight Panel. A decision was made to route this to the single technology appraisal process.
	Haemophilia Society	-	No action needed.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

- Pfizer
- Novo Nordisk

[i] Srivastava A, Santagostino E, Dougall, et al. WFH guidelines for the management of Hemophilia, 3rd edition. Haemophilia 2020;26(Suppl 6):1–158

[ii] 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

[iii] The haemophilia society. Bleeding disorders – inhibitors. Online available at: https://haemophilia.org.uk/bleeding-disorders/inhibitors/ Accessed: 18.02.22

[iv] O'Hara J and Neumann P J. Health technology assessment for gene therapies in haemophilia. Haemophilia 2022:1-8.

[v] Okaygoun D, Oliveira D D, Soman S, et al. Advances in the management of haemophilia: emerging treatments and their mechanisms. Journal of Biomedical Science. 2021;28:64.

[vi] Fischer K. Prophylaxis for adults with haemophilia: one size does not fit all. Blood Transfusion. 2012;10:169-73.

[vii] Boutine S, Monteilhet V, Veron P, et al. Prevalence of Serum IgG and neutralising factors against adeno-associated virus (AAV) types 1, 2, 5, 6, 8, and 9 in the healthy population: implications for gene therapy using AAV vectors. Human gene therapy 2010;21:704-712.

[viii] Calcedo R, Hiroki M, Wang L, et al. Adeno-associated virus antibody profiles in newborns, children, and adolescents. Clinical and vaccine immunology 2011;18(9):1586-1588.

[ix] Kruzik A, Fetahagic D, Hertlieb B, et al. Prevalence of anti-adeno-associated virus immune responses in international cohorts of healthy donors. Molecular therapy 2019;14:126-133.

[x] Li C, Narkbunnam N, Samulski, et al. Neutralising antibodies against adeno-associated virus examined prospectively in pediatric patients with haemophilia. Gene therapy 2012;19:288-294.

[xi] Majowicz A, van Waes F, Timmer N, et al. Prevalence and affinity/avidity assessment of pre-existing NABs against AAV2, 5 and 8 analysed in the serum of 300 healthy donors. Poster presented at: The 13th annual congress of the European association for haemophilia and allied disorders, EAHAD 2020, The Hague, 5th to 6th February 2020.

[xii] ONS. England population mid-year estimate. 2021. Online available at: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/timeseries/enpop/pop Accessed: 21.02.22

[xiii] NICE. Review of the topic selection approach for health technology evaluation. Online available at: https://www.nice.org.uk/Media/Default/About/what-we-do/our-programmes/nice-guidance/chte-methods-and-processes-consultation/topic-selection-proposal-paper.docx Accessed: 17.02.22.

[xiv] UKHCDO. Annual report 2021 & bleeding disorder statistic for the financial year 2020/21. Online available at: http://www.ukhcdo.org/wp-content/uploads/2021/12/2021-UKHCDO-Annual-Report-2020-21-Data.pdf Accessed: 16.02.22.

[xv] Liras A, Segovia C, Gabán AS. Advanced therapies for the treatment of hemophilia: future perspectives. Orphanet J Rare Dis. 2012;7:97.

[xvi] Mannucci PM. Hemophilia therapy: the future has begun. Haematologica. 2020;105(3):545-553.

[xvii] Zanon E, Pasca S. Intracranial haemorrhage in children and adults with haemophilia A and B: a literature review of the last 20 years. Blood Transfus. 2019;17(5):378-384.

[xviii] Stieltjes N, Calvez T, Demiguel V, et al. Intracranial haemorrhage in French haemophilia patients (1991–2001): clinical presentation, management and prognosis factors for death. Haemophilia. 2005;11:452–8.

[xix] Giroud M, Milan C, Beuriat P, et al. incidence and survival rates during a two-year period of intracerebral and subarachnoid haemorrhages, cortical infarcts, lacunes and transient ischaemic stroke. The Stroke registry of Dijon: 1985–1989. Int J Epidemiol. 1991;20:892–9.

[xx] Curtis R, Baker J, Riske B, et al. Young adults with hemophilia in the U.S.: demographics, comorbidities, and health status. Am J Hematol. 2015;90 Suppl 2:S11-16.

[xxi] Knobe K and Berntorp. Haemophilia and joint disease: pathophysiology, evaluation, and management. Journal of comorbidity. 2011;1:51-59.

[xxii] Forsyth AL, Gregory M, Nugent D, et al. Haemophilia Experiences, Results and Opportunities (HERO) Study: survey methodology and population demographics. Haemophilia. 2014;20(1):44-51.

[xxiii] Forsyth AL, Witkop M, Lambing A, et al. Associations of quality of life, pain, and self-reported arthritis with age, employment, bleed rate, and utilization of hemophilia treatment center and health care provider services: results in adults with hemophilia in the HERO study. Patient Prefer Adherence. 2015;9:1549-1560.

[xxiv] Hassan S, Monahan RC, Mauser-Bunschoten EP, et al. Mortality, life expectancy, and causes of death of persons with hemophilia in the Netherlands 2001-2018. J Thromb Haemost. 2021;19(3):645-653.

[xxv] Darby SC, Kan SW, Spooner RJ, et al. Mortality rates, life expectancy, and causes of death in people with hemophilia A or B in the United Kingdom who were not infected with HIV. Blood. 2007;110(3):815-825.