National Institute for Health and Care Excellence

Health Technology Evaluation
Denecimig (Mim8) for preventing bleeding episodes in haemophilia A in people of any age [ID6400]

Response to stakeholder organisation comments on the draft remit and draft scope

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 and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Novo Nordisk (Company)	Novo Nordisk agrees that a single technology appraisal is the most appropriate route of evaluation for denecimig (Mim8). Denecimig, a next-generation activated Factor VIII (FVIIIa) mimetic bispecific antibody, provides a prophylactic treatment option for people with haemophilia A (HA) across all severities and with or without FVIII inhibitors in all age groups. The clinical value of denecimig across the above population is supported by the comprehensive FRONTIER clinical trial programme	Thank you for your comment. No action required.
	Roche (Comparator)	No comment	No action required.
	Genetic Alliance UK (patient)	In preparation for this consultation, Genetic Alliance UK spoke with one of its member organisations, the Haemophilia Society. Based on this discussion, we agree that this the routing of denecimig (MIM8) for haemophilia A (HA) via STA is appropriate.	Thank you for your comment. No action required.

Section	Stakeholder	Comments [sic]	Action
	The Haemophilia Society (patient)	We agree this is an appropriate evaluation route.	Thank you for your comment. No action required.
	United Kingdom Haemophilia Centre Doctors Organisation (UKHCDO, professional)	The previous products have undergone a similar process, and we welcome the continuation of this approach.	Thank you for your comment. No action required.
Wording	Novo Nordisk (Company)	The wording of the draft remit should be corrected to align with the anticipated marketing authorisation (as per Medicines & Healthcare products Regulatory Agency [MHRA]), which covers all age groups. [redacted] This indication, covering all age groups, is supported by the Paediatric Investigation Plan (PIP) MHRA-101319-PIP01-23-M02, which has been agreed upon with the Medicines and Healthcare products Regulatory Agency (MHRA). Data from pharmacometric modelling substantiating the use of denecimig in patients of all ages was submitted to the MHRA as part of the PIP full compliance check application and will also be included in the forthcoming marketing authorisation application submission. The model demonstrates that younger population (less than 2 years of age) achieves clinical protection and exposure levels comparable to those seen in older children and adults. The MHRA has issued a decision (MHRA-101319-PIP01-23-M02-C) confirming compliance with the agreed PIP.[7] Novo Nordisk proposes the draft remit wording be amended to the following:	Thank you for your comment. We have updated the title and remit.

Section	Stakeholder	Comments [sic]	Action
		"To appraise the clinical and cost effectiveness of denecimig (Mim8) within its marketing authorisation for preventing bleeding episodes in haemophilia A with or without inhibitors."	
	Roche (Comparator)	No comment	No action required.
	Genetic Alliance UK (patient)	No comment	No action required.
	The Haemophilia Society (patient)	We would suggest that the age range from 1 year is removed. Denecimig has not yet been given marketing authorisation in the UK or in jurisdictions outside the UK. Therefore to state that the appraisal should be for the marketing authorisation in people within haemophilia A 1 year and over is not accurate. There is a need, as explored further under the population section, for children with haemophilia A from birth to have access to this treatment.	Thank you for your comment. We have updated the title and remit.
	United Kingdom Haemophilia Centre Doctors Organisation (UKHCDO, professional)	Children with severe haemophilia are now commenced on treatment from the first month of life, with the current standard of care in the UK being to initiate treatment within the first week to first month of life. This shift in practice reflects the aim of preventing intracranial haemorrhage, the risk of which is highest during the first year of life, and has been enabled by the practicality of emicizumab, which is administered subcutaneously. We propose the following wording 'To appraise the clinical and cost effectiveness of denecimig (Mim8) within its marketing authorisation for preventing bleeding episodes in haemophilia A'	Thank you for your comment. We have updated the title and remit.

Section	Stakeholder	Comments [sic]	Action
Additional comments on the draft remit	Novo Nordisk (Company)	**Timing issue:** The evaluation of denecimig holds relative urgency for the NHS due to the persistent clinical unmet need for prophylactic treatment options with reduced treatment burden among people with HA with or without inhibitors. The urgency is heightened for people with HA who have developed inhibitors, as they face a highly severe bleeding phenotype, compared to people with HA without inhibitors.[8,9] The only available and current standard non-factor prophylaxis for HA with or without inhibitors in the UK is emicizumab, a FVIIIa mimetic bispecific antibody.[10-12] Denecimig, as a next-generation FVIIIa mimetic bispecific antibody, offers potential for consistent bleed protection across all ages, severities and inhibitor statuses, coupled with advantages due to its, low-volume, pre-filled pen and flexible tiered dosing options.[2] Therefore, a prompt evaluation is justified to ensure that this treatment, anticipated for UK regulatory approval [redacted] is available to people with HA with or without inhibitors.	Thank you for your comment.
	Roche (Comparator)	No comment	No action required.
	Genetic Alliance UK (patient)	**Timing issue:** We recognise the importance of timely access to effective treatments like MIM8 for people living with HA and consider this evaluation to be a priority for the NHS. HA is a lifelong condition characterised by recurrent spontaneous and traumatic bleeding, including joint and muscle bleeds that can result in chronic pain, irreversible joint damage, reduced mobility and long term disability. In this context, evolving standards emphasise early and sustained bleed control to preserve joint health and support quality of life for people living with this rare condition.	Thank you for your comment.

Section	Stakeholder	Comments [sic]	Action
	The Haemophilia Society (patient)	No comment	No action required.
	United Kingdom Haemophilia Centre Doctors Organisation (UKHCDO, professional)	**Timing issue:** This is not an immediate area of unmet need; however, there are potential advantages associated with the new molecule.	Thank you for your comment. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Novo Nordisk (Company)	**Epidemiology** Novo Nordisk notes that the epidemiological information for HA should be updated to reflect the most recent data from the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) annual report covering the financial year 2024/2025.[13] This report registers a total of 9,999 people with HA and carriers in the UK. The registered population breakdown is 2,404 people with severe HA (FVIII <1 IU/dL), 800 people with moderate HA (FVIII 1–5 IU/dL) and 2,400 people with mild HA (FVIII >5 IU/dL).[13] Background on epidemiology regarding people with HA with inhibitors is also crucial for completeness and should be added to this section, as HA is further complicated by the development of inhibitors against FVIII.[14] The overall prevalence of people with HA with any inhibitor history across all severities of HA stands at 703 individuals (7.0%). This history is heavily concentrated in	Thank you for your comment. We have updated the epidemiological statistics to reflect 2024/25 data.

Section	Consultee/ Commentator	Comments [sic]	Action
		the most severe group, with 554 people having a history of inhibitors among those with severe HA (23%).[13] **HA with inhibitors** Novo Nordisk emphasises that the clinical impact of FVIII inhibitors must be clearly noted as it impacts people with HA across all severities. Novo Nordisk proposes that the "Background" section of the draft scope be updated to include the following wording: "HA is further complicated by the development of FVIII inhibitors. People with inhibitors experience a highly recurrent and severe bleeding phenotype, regardless of their original baseline severity classification.[9,14,15] This complication results in a significantly increased clinical burden, including more than double the mean annualised bleeding rate and joint bleed rate, greater mortality risk, worse QoL and substantially higher healthcare costs than people with HA without inhibitors.[9,16]" **Current clinical management** It is essential to clarify that FVIII replacement products are ineffective for routine prophylaxis in people with HA with inhibitors because the neutralising antibodies inactivate the therapeutic FVIII.[17,18] Novo Nordisk proposes that the current clinical management within the "Background" section of the draft scope be amended to include the following additional text: "FVIII replacement products are ineffective for routine prophylaxis in people with HA with inhibitors because the neutralising antibodies inactivate the therapeutic FVIII.[17,18] For acute bleeds in this population, bypassing agents (BPA) like recombinant activated FVII must be used.[17]"	The background section has been updated to further emphasise the increased risk of complications for those with inhibitors. The use of bypassing agents has been included in the Background section.

Section	Consultee/ Commentator	Comments [sic]	Action
		The commissioning status of emicizumab should be updated within the draft scope to reflect recent developments, as NHS England has ratified and implemented a commissioning policy and funding agreement for the use of emicizumab for prophylaxis in people with moderate HA without inhibitors.[12] This expands its established use for congenital HA with FVIII inhibitors and severe congenital HA without FVIII inhibitors.[10-12] Novo Nordisk proposes that the current clinical management within the "Background" section of the draft scope be amended to include the following revised text: "NHS England has clinical commissioning policies for emicizumab as a prophylactic treatment option in people with HA with inhibitors, those with severe HA without inhibitors and people with moderate HA without inhibitors.[10-12]"	The commissioning status of emicizumab has been updated in line with NHS England policy in the scope.
	Roche (Comparator)	It's mentioned here: “NHS England has a clinical commissioning policy for emicizumab as a further prophylactic treatment option in people with haemophilia A with inhibitors and in people with severe haemophilia A without inhibitors.” The corresponding reference is for the 2019 clinical commissioning policy only. There is also the 2018 with inhibitors clinical commissioning policy: https://www.england.nhs.uk/wp-content/uploads/2018/07/1717-emicizumab.pdf. The text mentions this policy but does not include the reference. There is also an updated clinical commissioning policy (July 2025) which should also be referenced and included for emicizumab, which now includes the prophylactic treatment for moderate heamophilia A without inhibitors. See	Thank you for your comments. These updates have been made to the scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		link here: https://www.england.nhs.uk/wp-content/uploads/2025/07/2333-emicizumab-mod-haem-a-policy-proposition-1.pdf The definition of mild haemophilia is incorrect; it should be having between 5-40% of normal clotting factor.	
	Genetic Alliance UK (patient)	No comment	No action required.
	The Haemophilia Society (patient)	Clotting factors could be described as “proteins” rather than “substances” Haemophilia A is normally inherited but around a third of new cases have no known family history of the disease and may be due to random mutations. Although much rarer, females can have severe and moderate haemophilia A requiring prophylaxis or regular treatment, not just moderate to severe symptoms of bleeding symptoms. We would suggest that the population data be revised to include the latest data from the UKHCDO report 24/25. The total number of people quoted from the 23/24 report to be 9,662 includes those people with identified low levels of factor VIII levels (>40IU/dl) which would not be categorised as severe, moderate or mild haemophilia and therefore would be out of scope. We suggest this consideration is applied to the 24/25 figures. In the final paragraph of the background section there is a comment in brackets that says that prophylactic treatment is administered 2-3 times a week. The actual situation is more complex than that; Treatment frequency will vary based on bleeding phenotype, individual pharmacokinetic (PK) response and product used.	Thank you for your comment. The aim of the background and technology sections are to provide a very brief summary of the disease area. Further data and information can be provided at the submission stage of the appraisal. We have updated the scope to include the latest data from the UKHCDO report.

Section	Consultee/ Commentator	Comments [sic]	Action
		The use of on demand for people with severe haemophilia A and moderate haemophilia A with a high bleeding phenotypes is now not considered the standard of care and the majority will be on prophylaxis.	
	United Kingdom Haemophilia Centre Doctors Organisation (UKHCDO, professional)	The management of haemophilia, at a minimum, includes on-demand treatment of bleeding episodes and peri-operative haemostatic cover. The majority of patients with severe haemophilia A, and a substantial proportion of those with moderate disease, are also receiving prophylactic treatment to prevent bleeding, in addition to on-demand therapy. Only a small number of patients continue to rely solely on on-demand treatment.	Thank you for your comment. The aim of the background section is to provide a very brief summary of the disease area. Further data and information can be provided by the company at the submission stage of the appraisal.
Population	Novo Nordisk (Company)	In line with the amendment to the draft remit, the population should be amended to the following wording: People with haemophilia A (congenital coagulation factor VIII [FVIII] deficiency) with or without FVIII inhibitors.	Thank you for your comment. The population has been updated.
	Roche (Comparator)	The definition of mild haemophilia is incorrect; it should be having between 5-40% of normal clotting factor.	Thank you for your comment. This has been updated in the scope.
	Genetic Alliance UK (patient)	The draft scope for MIM8 defines the population from the age of 1 year to reflect the criteria used in clinical trials. However, this threshold may not fully reflect current or emerging clinical practice - HA is often diagnosed earlier	Thank you for your comment. The

Section	Consultee/ Commentator	Comments [sic]	Action
		and there is increasing clinical focus on initiating prophylaxis at a young age to prevent early bleeding episodes and joint damage, including as children begin to crawl and become more active. Given that MIM8 does not require regular intravenous access, there may be clinical circumstances in which earlier use could be considered appropriate. We would therefore encourage flexibility in the population definition to ensure that access to MIM8 is not unintentionally limited.	population has been updated.
	The Haemophilia Society (patient)	We would argue that the standard of practice now is to treat children with haemophilia A from birth rather than from 12 months. As an inherited bleeding disorder it is often possible for a significant proportion of children to be diagnosed with haemophilia A from birth. With the onset of subcutaneous treatment, venous access for babies is no longer an issue. It is no longer appropriate to wait for bleeds to happen and risk causing joint damage and then start prophylaxis in young children. It should be a preventive measure from birth. Treating very young children with injections can be traumatic for the parents and children. Having an option that may reduce the frequency of injections required, with potentially monthly injections being as option (Part 2 of the Frontier 3 – Safety and Efficacy of Mim8 in Prophylaxis in Paediatric Patients with Haemophilia A) could reduce the anxiety a family might experience at an early stage of managing this condition and be a positive step. The product delivery system could potentially offer a more user-friendly experience that would be of significant benefit for this population. (Data from poster: Evaluating pen-injector handling and PROs in patients switching from Emicuzimab to Mim8 in FRONTIER5). Therefore we suggest that the treatment be available from birth rather than from 1 year, as defined in the draft scope. This would give clinicians more	Thank you for your comment. The population has been updated.

Section	Consultee/ Commentator	Comments [sic]	Action
		choice when it comes to treating children under 1 year and preventing early bleeds.	
	United Kingdom Haemophilia Centre Doctors Organisation (UKHCDO, professional)	As treatment is now initiated from the first day of life, the lower age limit should be removed.	Thank you for your comment. The population has been updated.
Subgroups	Novo Nordisk (Company)	Novo Nordisk would like to clarify that this submission covers the full expected marketing authorisation of denecimig. The FRONTIER clinical trial programme was intentionally designed to evaluate the efficacy and safety of denecimig across a diverse population, including participants with HA with or without FVIII inhibitors and across all severities, consistently demonstrating efficacy regardless of FVIII inhibitor status or HA severity. Novo Nordisk proposes that the only subgroup appropriate to be considered separately is the presence of inhibitors. This is because individuals with inhibitors face a disproportionately severe bleeding phenotype, greater mortality risk, worse QoL and substantially higher healthcare costs than people with HA without inhibitors. Furthermore, because standard FVIII replacement is rendered ineffective by inhibitors, people with inhibitors require different on-demand treatments, specifically BPAs such as recombinant activated FVII to manage acute bleeds.	Thank you for your comment. Where possible, analysis of subgroups noted in the scope should be provided. The company will have the opportunity to justify any exclusion of these subgroups or inclusion of additional subgroups in their submission.
	Roche (Comparator)	No comment	No action required
	Genetic Alliance UK (patient)	We consider it important that the scope explicitly includes all individuals with HA who have a clinical requirement for routine prophylaxis, including specific subgroups that have historically been under-represented in both trials and	Thank you for your comment. The population in the scope

Section	Consultee/ Commentator	Comments [sic]	Action
		commissioning decisions. For example, females living with HA also require prophylaxis. Although the number is small, females with HA can experience significant bleeding symptoms and have traditionally been excluded from research and treatment pathways. The inclusion of females in MIM8 clinical trials should therefore be reflected in the scope. We also emphasise the inclusion of people with moderate HA who require routine prophylaxis. Moderate HA is defined by endogenous factor VIII levels of 1-5%, but it is our understanding that factor level alone may not reliably predict bleeding phenotype or clinical need. This is because many people living with moderate HA experience bleeding patterns that are comparable to those with a more severe form of the condition, and that they also require prophylactic treatment to manage symptoms and prevent long term complications. Exclusion of this group from access to MIM8 would therefore risk reinforcing existing inequities in access to treatment for rare conditions. Further, we agree with the inclusion of people with inhibitors, for whom additional effective treatment options remain a significant unmet need.	covers all individuals with haemophilia A and does not exclude females. The subgroups included in the scope are considered to be clinically relevant, and people with moderate haemophilia A should be considered within the analysis by severity of haemophilia. Further details on subgroups may be provided in submissions.
	The Haemophilia Society (patient)	It is important that people living with, what is defined as moderate haemophilia A, but require routine prophylaxis are included within this scope. Moderate haemophilia is defined by factor VIII levels between 1-5%. Most severe haemophilia A patients are now treated to a factor trough level above 5% or a non-factor replacement treatment that replicates living above 5%. In the commissioning of some new treatments for haemophilia A, moderate haemophilia A patients requiring routine prophylaxis treatment have been excluded from the commissioning policy. This has caused anxiety and confusion as to why they have been excluded from advances in medical treatment and in some cases anger and distress for both themselves and their children. In some cases it has been years before they have been able to access the same benefits of modern treatment advances. We believe this is an inequity that should not be repeated.	Thank you for your comment. The population in the scope covers all individuals with haemophilia A and includes people with moderate haemophilia and females. People with moderate haemophilia A should be considered as a subgroups within the analysis by severity of

Section	Consultee/ Commentator	Comments [sic]	Action
		We also wanted to highlight the inclusion of females within some of the trials (FRONTIER 2 study) and welcome this addition as females are often excluded from trials. We agree with the inclusion of people with inhibitors as the need for an alternative treatment option would be a valuable addition for this subgroup of patients.	haemophilia. Further details on subgroups may be provided in submissions.
	United Kingdom Haemophilia Centre Doctors Organisation (UKHCDO, professional)	We propose including children and adults as an additional subgroup. The proposed subgroups are appropriate, and we also suggest age (<12, 12 to 18 and > 18 yrs) as another criteria for new subgroup analysis.	Thank you for your comment. NICE avoids making recommendations by age because it is a protected characteristic. If it is appropriate to assess the technology by age, there will be the opportunity to justify this subgroup in the submissions.
Comparators	Novo Nordisk (Company)	Emicizumab, another FVIIIa mimetic bispecific antibody , is the only prophylactic treatment option for people with HA with or without inhibitors in the UK. Therefore, Novo Nordisk proposes that emicizumab should be the only relevant comparator for this appraisal. Since its commissioning in 2019, emicizumab has effectively replaced FVIII replacement therapy for prophylaxis in the majority of people with HA. The UKHCDO data from the 2024/25 financial year confirms that the majority of treated patients received emicizumab.	Thank you for your comment. The comparators have been retained, as those listed in the scope are intended to be broad and cover the relevant comparators for the full population in the scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		This uptake is most pronounced in the severe HA population compared to the moderate HA population as emicizumab was only ratified for routine commissioning in moderate HA without inhibitors in 2025, and the current UKHCDO report (ending March 2025) does not yet reflect the impact of this policy change. Within the specific cohort of previously untreated people (PUPs) with severe HA under the age of 2 years old emicizumab's share as the first treatment rose from 13.5% in 2019/20 to 76.3% in 2024/25. Given this profound market shift, where FVIII prophylaxis is no longer the predominant standard of care, emicizumab (a non-factor replacement therapy) should be considered the only relevant comparator for denecimig. UK clinicians consider emicizumab the standard prophylactic care for people with severe HA, both with and without inhibitors. As denecimig is a FVIIIa mimetic bispecific antibody, mimicking the function of activated FVIII, like emicizumab, it is a non-factor therapy, making it the most appropriate and comparable technology for evaluation. Both treatments offer subcutaneous administration and flexible, less frequent dosing schedules. Denecimig offers dosing options for once every month, once every 2 weeks or once every week, comparable to emicizumab’s dosing options of once every 4 weeks, once every 2 weeks or once every week. UK clinicians view denecimig as a treatment option within the prophylactic treatment pathway alongside emicizumab. It is also important to acknowledge that efanesoctocog alfa is structurally an extended half-life (EHL) FVIII product. While efanesoctocog alfa has been recommended by NICE for people aged 2 years and over with severe HA, it	The most appropriate comparator(s) will be discussed in more detail during the appraisal and by the committee, with input from the company submission and clinical experts.

Section	Consultee/ Commentator	Comments [sic]	Action
		can be considered within the FVIII replacement therapy class and should be subsumed within the broader comparison against FVIII replacement therapies, rather than listed as a separate comparator. Novo Nordisk would also like to clarify that on-demand treatment is not a suitable comparator for prophylactic treatment and on-demand treatment will be captured as resource use and clinical burden associated with managing breakthrough bleeding episodes rather than as a comparator.	Efanesoctocog alfa has been retained as a separate comparator in the scope as it is available for a specific population.
	Roche (Comparator)	Emicizumab should be considered as a comparator for severe, moderate and inhibitor patients, as there are 3 NHS England clinical commissioning policies in place (see the references listed in the 'Background Information' comments box). Currently, the document only references the severe clinical commissioning policy.	Thank you for your comment. The scope has been updated to include all three clinical commissioning policies and to specify the populations eligible under these policies.
	Genetic Alliance UK (patient)	From our understanding, 'on demand' treatment with factor VIII is unlikely to reflect current best practice for those eligible for MIM8, as routine prophylaxis is now standard care in the NHS. We also query the inclusion of standard half-life factor VIII products as comparators. These are no longer routinely used for prophylaxis in most patients, and the majority of people requiring prophylaxis in the UK are now treated with extended half-life factor VIII or non-factor replacement therapies, so comparator selection needs to reflect current clinical pathways.	Thank you for your comment. The comparators have been retained as those listed in the scope are intended to be broad. The most appropriate comparator(s) will be discussed in more detail during the appraisal and by the committee, with

Section	Consultee/ Commentator	Comments [sic]	Action
			input from the company submission and clinical experts.
	The Haemophilia Society (patient)	We do not agree that on demand treatment with factor VIII is a suitable comparator. The standard of best practice is that people receive routine prophylaxis. This comparator may only be suitable for patients with mild and some moderate patients with low bleeding phenotypes. We also do not think that standard half-life products (SHLs) should be considered as a comparator. The majority of people with haemophilia requiring prophylaxis are now routinely treated with extended half-life products (EHLs), ultra extended half-life factor VIII (efanesoctocog alfa) or non-factor replacement products (emicuzimab, marstacimab). From UKHCDO data the use of SHLs has declined over the last 10 years (use for severe haemophilia reduced by 84% since 2015/16 – NHD report 24/25) and continues to decline whilst a marked increase in the use of EHLs and non-factor replacement treatment.	Thank you for your comment. The comparators have been retained as those listed in the scope are intended to be broad. The most appropriate comparator(s) will be discussed in more detail during the appraisal and by the committee, with input from the company submission and clinical experts.
	United Kingdom Haemophilia Centre Doctors Organisation (UKHCDO, professional)	All patients required occasional on-demand treatment, using factor VIII for bleeding episodes in the absence of inhibitors and activated factor VIIa in the presence of inhibitors. Current prophylactic options include: • Prophylaxis with emicizumab • Prophylaxis with efanesoctocog alfa (ultra-long-half-life factor VIII) Comparison with standard or extended half-life factor VIII is no longer appropriate, as these are no longer considered standard of care. Their use	Thank you for your comment. The comparators have been retained as those listed in the scope are intended to be broad. The most appropriate comparator(s) will be discussed in more detail during the appraisal and by the committee, with

Section	Consultee/ Commentator	Comments [sic]	Action
		continues to decline, particularly following the introduction of ultra-long-half-life factor VIII. From a clinical perspective, this therapy is best considered an alternative to emicizumab, as it is within a similar therapeutic class and is administered subcutaneously, in contrast to factor VIII products, which require intravenous administration.	input from the company submission and clinical experts.
Outcomes	Novo Nordisk (Company)	Novo Nordisk proposes that certain outcomes listed in the draft scope warrant refinement or exclusion based on the drug's mechanism of action and the nature of the evaluation: • Change in FVIII levels is an arbitrary outcome measure because denecimig is a FVIIIa mimetic bispecific antibody, mimicking the function of FVIII without being FVIII itself.1,21 Denecimig operates independently of functional FVIII, binding and bridging activated Factor IX (FIX) and Factor X (FX) to promote coagulation. Consequently, standard FVIII assays (which rely on FVIII activity) are affected by the presence of denecimig, leading to an overestimation of coagulation in assays like Activated Partial Thromboplastin Time (aPTT)-based tests. Interpreting a 'change' in FVIII, activity is non-physiological and not central to denecimig's clinical efficacy.1,21 Although FVIII levels can be measured using specific bovine chromogenic assays, interpreting a 'change' in FVIII, activity is non-physiological and not central to denecimig's clinical efficacy.1 Change in FVIII levels should therefore be removed from the list of outcomes in the scope, consistent with the final scope of marstacimab, the only other non-factor treatment evaluated by NICE.22 • Duration of response to treatment is an outcome measure more pertinent to one-time interventions, where the decline of sustained endogenous FVIII production is a key concern. Since denecimig is a regularly administered prophylactic therapy with dosing options spanning once weekly,	Thank you for your comments. Change in factor VIII levels has been removed from the scope. The outcome duration of response to treatment has been retained as the scope is intentionally kept broad. The outcome relating to need for further treatment has been expanded to include bypassing agents.

Section	Consultee/ Commentator	Comments [sic]	Action
		once every two weeks or once every month, and demonstrating a long half-life of around 30 days, the continuity of protection is measured accurately through ABR and the proportion of participants achieving zero bleeds. Duration of response to treatment should therefore be removed from the list of outcomes in the scope. • The outcome relating to the need for further treatment with FVIII injections must be expanded to include the need for further treatment with BPAs to stratify breakthrough bleed management by inhibitor status. This inclusion is critical, especially for people with HA with inhibitors, for whom denecimig offers prophylaxis but whose potential acute bleed management often requires BPAs like recombinant activated Factor VII.17	
	Roche (Comparator)	The outcome: 'change in factor VIII levels' is an unsuitable outcome measure for denecimig, as it is a non-factor replacement therapy and therefore will have no effect on FVIII levels. Will 'adverse effects of treatment' include the development of anti-drug antibodies?	Thank you for your comments. Change in factor VIII levels has been removed from the scope. For clarity, development of anti-drug antibodies has been included in the scope.
	Genetic Alliance UK (patient)	Change in factor VIII levels is not an appropriate efficacy outcome for MIM8, as it is not a factor VIII replacement therapy and would not be expected to increase circulating factor VIII levels. MIM8 acts by mimicking the function of activated factor VIII within the clotting cascade, and outcomes should align with this mechanism of action. Assessment of health related quality of life (QoL) should prioritise haemophilia specific patient reported outcome measures (PROMs) alongside	Thank you for your comments. Change in factor VIII levels has been removed from the scope. The committee will assess the technology

Section	Consultee/ Commentator	Comments [sic]	Action
		generic instruments. While we understand that this is an area of ongoing work by NICE, we feel it is important to note that for haemophilia A, generic measures alone may underestimate the burden of the condition due to long term adaptation to pain, mobility limitations and functional impairment.	in line with the NICE manual. A strong and clear rationale and evidence should be provided for any deviance from the specified methods. Considerations of any uncaptured benefits should also be presented in submissions.
	The Haemophilia Society (patient)	We don't think that a change in factor VIII levels for this assessment of this efficacy of this product is appropriate. It is not a factor VIII replacement product therefore it should not be expected to raise the factor VIII levels. This product impacts the clotting cascade by binding activated factor IX to factor X therefore effectively mimicking the action of activated factor VIII. In the section looking at health-related quality of life it is vital that the data from the specific PROMs related to this condition should be considered. It is widely accepted that people living with haemophilia overestimate their QOL in comparison to 'normal' population data. They routinely demonstrate a stoic acceptance of living with pain and mobility issues, a trend identified as the disability paradox.	Thank you for your comments. Change in factor VIII levels has been removed from the scope. A strong and clear rationale and evidence should be provided for any deviance from the specified methods. Considerations of any uncaptured benefits should also be

Section	Consultee/ Commentator	Comments [sic]	Action
			presented in submissions.
	United Kingdom Haemophilia Centre Doctors Organisation (UKHCDO, professional)	Factor VIII activity levels are not relevant for either emicizumab or denecimig, as both are bispecific antibodies that mimic factor VIII function but cannot be measured in the same way as endogenous or infused factor VIII. We agree with the following outcome measures: • Annualised bleeding rate • Need for additional treatment with factor VIII injections • Mortality • Adverse effects of treatment • Health-related quality of life We are less clear about the relevance of: • Duration of response to treatment In this context, treatment response is largely determined by the pharmacokinetic half-life of the medication, and it is unclear whether this is what is intended by this outcome. This contrasts with gene therapy, where treatment effects can be assessed over several years. Similarly, outcomes such as: • Complications of the disease (for example, joint problems and joint surgeries)	Thank you for your comments. Change in factor VIII levels has been removed from the scope. The outcome duration of response to treatment has been retained as the scope is intentionally kept broad. The outcome complications of the disease has been

Section	Consultee/ Commentator	Comments [sic]	Action
		reflect the cumulative lifetime burden of haemophilia rather than short- to medium-term treatment efficacy. Instead, we suggest that resolution of target joints and improvements in pain and mobility would be more appropriate and sensitive markers of joint health and treatment effectiveness.	expanded to include resolution.
Equality	Novo Nordisk (Company)	Novo Nordisk does not believe that the draft remit or scope will exclude people protected by equality legislation.	Thank you for your comment. No action required.
	Roche (Comparator)	No comment	No action required
	Genetic Alliance UK (patient)	We would highlight the importance of ensuring that access to MIM8 is not determined solely by rigid factor VIII thresholds in practice, and that individuals with similar factor VIII levels may have markedly different bleeding phenotypes and clinical needs, so treatment decisions should reflect this variability. We also note the importance of consideration of women and girls with HA within the evaluation, recognising that they have historically experienced barriers to equitable care for their condition. On this point, we would like to signpost a recent report launched by the Haemophilia Society '*Underserved – Overlooked: How our health systems are failing women and girls with a bleeding disorder'* available on their website: https://haemophilia.org.uk/underserved-overlooked/ The Society's 'Initial diagnosis' report (2018) also covers some of the challenges outlined above and is available to read here: Initial Diagnosis Report | The Haemophilia Society	Thank you for your comment. Equality issues relating to women and girls has been noted in the equality impact assessment. The committee will assess the technology in line with its marketing authorisation.

Section	Consultee/ Commentator	Comments [sic]	Action
	The Haemophilia Society (patient)	Referring to the comments made in the subgroups section that those with moderate haemophilia A requiring routine should not be excluded from receiving this product. To expand upon this point, people with the same clinically determined factor VIII levels can have very different symptoms and bleed rates and what we commonly refer to as a bleeding phenotype. As an example someone with a factor VIII level of 1.5% and therefore categorised as moderate, could experience a similar bleed rate and lived experience as someone with a factor VIII level of 0.8% who is categorised as severe. To exclude some people from this treatment whose lived experience is the same as those eligible for it would be unfair and would cause anxiety for those living with moderate haemophilia A and those who care for them. Again we emphasis the inclusion of females with haemophilia A requiring prophylaxis. Women and girls with bleeding disorders are often underserved and overlooked in treatment for their bleeding disorder, as highlighted in a report we launched last year. Underserved – Overlooked: How our health systems are failing women and girls with a bleeding disorder | The Haemophilia Society Although the cohort of women with haemophilia A within the moderate and severe categories are small (NHD report 24/25 there are 39 identified females with in the severe and moderate haemophilia A group) their needs for effective treatment should not be dismissed. There is a need to have effective	Thank you for your comment. Equality issues relating to women and girls has been noted in the equality impact assessment. The committee will assess the technology in line with its marketing authorisation.

Section	Consultee/ Commentator	Comments [sic]	Action
		products for this population as this may also have an impact on the need for hormonal therapy to control Heavy Menstrual Bleeding (HMB). As a subcutaneous injection this product may be particularly useful for people with venous access issues due to joint mobility or damage to veins. These people may not currently be on effective prophylaxis, so particular care should be given to considering the benefits in this group of people.	
	United Kingdom Haemophilia Centre Doctors Organisation (UKHCDO, professional)	The exclusion of children under one year of age is likely to have a significant and lasting adverse impact on treatment choice and long-term outcomes, as it withholds protection at the period of greatest vulnerability, when effective prophylaxis is most critically needed. In this age group, bispecific antibodies are the only feasible treatment option, and their exclusion therefore directly limits access to appropriate and effective care.	Thank you for your comment. The population has been updated to include children from birth. .
Other considerations	Novo Nordisk (Company)	• The economic analyses section of the draft scope table mentions that the use of denecimig may be conditional on the presence of anti-factor antibodies in the economic analysis section, implying potential additional diagnostic costs. However, testing for FVIII inhibitors is already a routine part of standard HA management, mandated by protocols such as testing FVIII inhibitor levels every 12 months for people with HA receiving emicizumab prophylaxis. Denecimig is positioned for people with HA with and without inhibitors and treatment with denecimig will not increase FVIII inhibitor levels. Therefore, there is no requirement to introduce additional routine FVIII inhibitor testing specifically for patients starting denecimig. FVIII inhibitor testing remains standard clinical practice in UK haemophilia centres and would continue as normal regardless of whether people with HA are treated with denecimig. The	Thank you for your comments. The section relating to the costs associated with diagnostic testing has been removed from the scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		monitoring burden is not expected to be greater than that for comparable therapies. FVIII inhibitor testing can be done in the presence of denicimig using bovine chromogenic assays. These assays are routinely used in clinical practice in the UK to measure FVIII inhibitors. Therefore,diagnostic testing costs specifically conditional on denecimig use would be unnecessary. Splitting the economic analysis into two distinct base cases, HA without inhibitors and HA with inhibitors remains appropriate. It is robustly supported by the clinical reality that the people with HA with inhibitors experience a disproportionately severe and recurrent bleeding phenotype, substantially greater clinical burden, notably worse QoL and markedly higher healthcare costs compared to those without inhibitors. • Regarding national policy, it is essential that the evaluation incorporate the expanded scope of commissioning for emicizumab. Related national policy must explicitly include the NHS England Clinical Commissioning Policy for "Emicizumab for prophylaxis of bleeding episodes in people with moderate HA without inhibitors (all ages)". This policy extends routine commissioning of emicizumab prophylaxis to people with moderate HA (FVIII levels ≥ 1% and ≤ 5%) who present with a severe bleeding phenotype (e.g., joint damage or more than three treated bleeds in 12 months)	The scope has been updated to include all three NHSE clinical commissioning policies.
	Roche (Comparator)	No comment	No action required
	Genetic Alliance UK (patient)	No comment	No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	The Haemophilia Society (patient)	No comment	No action required.
	United Kingdom Haemophilia Centre Doctors Organisation (UKHCDO, professional)	We would strongly welcome the inclusion of an evaluation of treatment burden and ease of use as part of the assessment.	The committee will assess the technology in line with the NICE manual, including consideration of any uncaptured benefits.
Questions for consultation	Novo Nordisk (Company)	**Intended positioning of denecimig in the therapeutic pathway** Denecimig is intended to fit into the existing care pathway as another subcutaneous non-factor treatment option for prophylaxis in people with HA with or without FVIII inhibitors, across all severities and ages. Denecimig is intended to be prescribed in specialist secondary care with follow-up routinely managed by local haemophilia centres (answer C). The setting for prescribing and routine follow-up for comparator (emicizumab) is the same as that for denecimig. **Managed Access** Denecimig is not considered a candidate for managed access, as there are no anticipated uncertainties regarding its clinical efficacy or safety profile that would necessitate further data collection to inform the standard technology appraisal process. **Patient reported outcomes**	Thank you for your comment. The committee will assess the technology

Section	Consultee/ Commentator	Comments [sic]	Action
		Denecimig may deliver benefits unlikely to be fully captured by the standard Quality-Adjusted Life Year (QALY) calculation, primarily related to reduced treatment burden and enhanced QoL associated with administration convenience. The nature of the available data to enable the committee to account for these benefits includes patient-reported outcomes (PROs) collected across the FRONTIER clinical trial programme. Specifically, the key instruments used demonstrate improvements or maintenance of health-related quality of life and reduced treatment burden, including (Hemo-TEM), the Child Hemo-TEM, the Paediatric Quality of Life Inventory (PedsQL), the Haemophilia Patient Preference Questionnaire (H-PPQ), the Joint Pain Rating Scale (JPRS) and the Patient Global Impression of Change (PGIC).3-6 The FRONTIER5 switching study specifically provides data on participants preference for the denecimig pen-injector compared with their previous administration device (emicizumab vial and syringe).	in line with the NICE manual. A strong and clear rationale and evidence should be provided for any deviance from the specified methods. Considerations of any uncaptured benefits should also be presented in submissions.
	Roche (Comparator)	Response to question: *"Where do you consider denecimig (Mim8) will fit into the existing care pathway for preventing bleeding episodes in haemophilia A?"* C. Prescribed in secondary care with routine follow-up in secondary care, which is the same for comparator emicizumab and efanesoctacog alfa.	Thank you for your comment. No action required.
	Genetic Alliance UK (patient)	No comment	No action required.
	The Haemophilia Society (patient)	We want to comment on the statement within the economic analysis which references the use of denecimig for those with inhibitors. There is a section talking about the need to include economic modelling for costs to include the testing for anti-factor [VIII] antibodies which would not otherwise be tested.	Thank you for your comments. The section relating to the costs associated with diagnostic testing of

Section	Consultee/ Commentator	Comments [sic]	Action
		The testing for inhibitors would be a routine procedure regardless of the product a person is on and therefore we do not see why this should be included in this economic modelling for this particular product. We do acknowledge that there is a need for a consideration of the development of neutralising antibodies to denecimig. Although this risk seems to be low, in some trials 0 in the studied population (FRONTIER 1 and 3) there remains a risk and therefore the appropriate assays should be available and the costs considered in the modelling. **Related NICE technology appraisals in development.** Valoctocogene roxaparvovec for treating severe haemophilia A. NICE technology appraisal guidance [ID3806] Publication date to be confirmed. This should not be considered and has been withdrawn. We are not aware of any plans to bring this product to the UK currently. Concizumab for treating haemophilia A or B in people 12 years and over with inhibitors. NICE technology appraisal guidance [ID6665] Publication date to be confirmed. Marstacimab for treating severe haemophilia A or B in people 12 years and over with inhibitors to factor-replacement therapy. NICE technology appraisal guidance [TSID12143] Publication date to be confirmed In reality the two appraisals above would only be products used with the haemophilia B inhibitor population. As emicuzimab, which is available from birth, is widely used for the haemophilia A inhibitor population, in practical terms we suspect that both	anti-factor antibodies has been removed. Inclusion of the costs of potential testing for anti-drug antibodies (antibodies for denecimig) has been added to the scope. The related NICE technology appraisals in development have been retained as the scope is intended to be broad. This section of the scope provides relevant context for related NICE products in the disease area, but will not necessarily be used within the evaluation.

Section	Consultee/ Commentator	Comments [sic]	Action
		conzizumab and marstacimab may only be used in haemophilia B inhibitor patients. Therefore we would suggest they should not be considered within this evaluation.	
Additional comments on the draft scope	Novo Nordisk (Company)	Novo Nordisk notes that the current draft scope references the previous UKHCDO annual report. This reference should be updated to the most recent annual report covering the financial year 2024/2025.13 This report is publicly available	Thank you for your comment. The scope has been updated.
	Roche (Comparator)	The July 2025 clinical commissioning policy for emicizumab for prophylaxis in moderate haemophilia A without inhibitors should be added to 'Related National Policy' if appropriate: https://www.england.nhs.uk/wp-content/uploads/2025/07/2333-emicizumab-mod-haem-a-policy-proposition-1.pdf. Suggestion to include Haemophilia Chartered Physiotherapists Association as part of the healthcare organisations under provisional consultees. Suggestion to include Haemophilia Northern Ireland patient group, as the other devolved nation patient groups have been included (i.e. Haemophilia Scotland and Haemophilia Wales) under the provisional commentators.	Thank you for your comment. The scope has been updated to include the new clinical commissioning policy. The Haemophilia Chartered Physiotherapists Association and Haemophilia Northern Ireland patient group have been added to the stakeholder list.
	Genetic Alliance UK (patient)	We note that under the section on related NICE technology appraisals, valoctocogene roxaparvovec is referenced. To our knowledge, this technology has been withdrawn and there are currently no plans for its introduction in the UK. In the absence of any ongoing appraisal activity, we do not consider it necessary for inclusion alongside MIM8 within this evaluation.	Thank you for your comment. The related NICE technology appraisals in development have been

Section	Consultee/ Commentator	Comments [sic]	Action
		We also note the references to concizumab for treating haemophilia A/B with/without inhibitors (ID5099 and ID6665) and to marstacimab for treating haemophilia A/B with inhibitors (TSID12143). While these appraisals are listed as in development, Genetic Alliance UK or the Haemophilia Society have not seen draft scope consultations for these. However, since we are aware that the populations potentially eligible for these treatments, particularly for people with inhibitors, are expected to be very small (i.e. perhaps 5-10 individuals for some groups) perhaps it may be helpful to clarify the current status of these appraisals and how they relate to the evaluation of MIM8.	retained as the scope is intended to be broad. This section of the scope provides relevant context for related NICE products in the disease area, but will not necessarily be used within the evaluation.
	The Haemophilia Society (patient)	We would also want the evaluation to consider some wider aspects of the lived experience of the patient and some potential cost savings to both individuals and potentially the wider NHS that are harder to demonstrate within the constraints of the evidence gathered within clinical trials. The CHESS and CHESS II studies give an evaluation of the impact on lived experience. “This retrospective analysis of the CHESS population studies has quantified the substantial humanistic and economic burden of patient-identified joint-related morbidity among children, adolescents and adults with moderate and severe haemophilia A without inhibitors.” The humanistic and economic burden of problem joints for children and adults with moderate or severe haemophilia A: Analysis of the CHESS population studies - Chowdary - 2023 - Haemophilia - Wiley Online Library Analysis from the PROBE study (https://probestudy.org/headlines/) showed that “Haemophilia has a significant negative impact on work life. [People with severe haemophilia] report a higher rate of retiring early or working part-time	Thank you for your comment. The committee will assess the technology in line with the NICE manual. Considerations of any uncaptured benefits should be presented in submissions.

Section	Consultee/ Commentator	Comments [sic]	Action
		due to health than age-matched controls. Use of mobility aids, acute / chronic pain, difficulty with ADL and history of joint surgery are associated with retiring early or working part-time." And it concluded that "The lifetime impact of haemophilia on employment should be more fully considered within health technology assessments." The frequency of dosing has a direct impact on work, education, family life and social integration. For an older population, less frequent injections may require less support from family or external caregivers. Therefore this should be an element of the lived experience of patients to be considered with in the evaluation. People with damaged joints who may struggle with age to self-infuse or inject will benefit from the delivery mechanism and ease of use of this product. This may be useful in care environments where a medical professional may not available to administer infusions but may be able to assist with a pen injector device. This may lead to a reduction in care requirements and NHS support for the individual.	