NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Marstacimab for treating severe haemophilia A or B in people 12 years and over without anti-factor antibodies [ID6342]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Marstacimab for treating severe haemophilia A or B in people 12 years and over without anti-factor antibodies [ID6342]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from Pfizer**

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. CSL Behring
   b. Novo Nordisk

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 **Comments on the Draft Guidance received through the NICE website**

4. **External Assessment Group critique of company comments on the Draft Guidance**

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

NICE National Institute for Health and Care Excellence

Marstacimab for treating severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Thursday 06 February 2025. Please submit via NICE Docs.

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

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A – Submitting Company
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted], [redacted], Pfizer Ltd.

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Summary	The company would like to thank the Committee for their time and consideration during the appraisal committee meeting (ACM). The company welcomes the National Institute for Health and Care Excellence's (NICE) position that current treatment options for severe haemophilia A and B are associated with challenges and that new treatment options would be welcomed. The company is disappointed by the draft guidance which does not recommend marstacimab for the prevention of bleeding episodes (prophylaxis) caused by severe haemophilia A (congenital factor VIII [FVIII] deficiency) or severe haemophilia B (congenital factor IX [FIX] deficiency) in people 12 years and over weighing at least 35 kg. Marstacimab is an alternative prophylaxis therapy which offers patients a simpler subcutaneous (SC), self-administered treatment, removing the burden of intravenous (IV)

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	factor infusions. The patient experts at the committee meeting clearly communicated the individualised nature of haemophilia treatment for each patient's personal circumstances, and the importance of patient choice through having access to a variety of treatment options. The company strongly believe that the introduction of marstacimab would fulfil an important unmet need as the first SC treatment option for people living with severe haemophilia B, and the first pre-filled SC option for those living with severe haemophilia A, thereby offering a choice of SC treatment options for patients with severe haemophilia A. The company are grateful for the opportunity to provide comments for the consultation of the Draft Guidance Document (DGD) to address the Committee's key areas of uncertainty. In this response, the company have aligned with 8 out of 10 of the Committee's preferred assumptions and incorporated these into a revised base case. For the remaining assumptions, the company have presented additional evidence for the Committee's consideration. The company consider most of the key issues to now be resolved. Additionally, the company have provided an updated patient access scheme (PAS) which provides marstacimab at a reduced net price. **Updated Patient Access Scheme (PAS):** The company have submitted a revised PAS that has reduced the net price of marstacimab by [redacted] and would provide marstacimab at a fixed net price of [redacted] per 150 mg pack. This represents an approximate [redacted] discount from the list price of [redacted] per 150 mg pack. This revised PAS is included in the updated model results and scenario analyses discussed throughout this response document. **Revised company base case:** Alongside these responses, the company have also provided a revised base case incorporating most of the Committee's preferred assumptions. A summary of the changes made to the base case cost-effectiveness analyses is presented in Appendix 1. The revised deterministic base case results demonstrate that marstacimab remains cost-effective versus comparators, with a net health benefit (NHB) of [redacted], [redacted] and [redacted] versus FVIII prophylaxis, emicizumab and FIX prophylaxis respectively, at a willingness-to-pay (WTP) threshold of £30,000. **Blended haemophilia A and haemophilia B analysis:** Alongside the company's revised base case, the company have updated the EAGs blended comparator across haemophilia A and haemophilia B. In this analysis, the haemophilia A and haemophilia B comparators are weighted based on the expected uptake of marstacimab in UK clinical practice (see company Comment 11), derived from NHS England's budget impact analysis submission (Table 3, Appendix 1). This analysis provides a comparison of marstacimab with one single comparator and is intended to reflect the anticipated opportunity cost of introducing marstacimab within UK clinical practice. The

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deterministic base case results from this new analysis demonstrates that marstacimab also remains cost-effective versus a blended haemophilia A and B comparator, with a NHB of [redacted].

Key issues:

The company now consider most of the key issues to be resolved.

Key Issue	Revised company base case aligned with Committee preference?
1. Generalisability of BASIS trial	**Yes**
2. Source of baseline annualised bleed rates	**Yes**
3. Dose escalation of marstacimab	**Yes**
4. Discontinuation	**Yes**
5. Dosing of factor prophylaxis	**No**
6. Modelling of haemophilia types	**Yes**
7. Treatment disutility per administration	**Yes**

Summary of company comments in this document:

In this response to the draft guidance document, the company have provided detailed comments on each of the following topics:

1. Generalisability of BASIS trial and baseline ABRs (Key Issue 1 and 2)
    - In line with the Committee's preferences, the company's revised base case uses the baseline annualised bleed rate (ABR) data from the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO)
2. Dose escalation rates (Key Issue 3)
    - In line with the Committee's preferences, dose escalation rates presented in the company's revised base case include dose escalation in Year 2 of the model based on the open-label extension (OLE) data
3. Treatment discontinuation (Key Issue 4)

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	○ In line with the Committee's preferences, discontinuation rates for emicizumab have been incorporated into the company's revised base case to better reflect clinical practice in the UK 4. Dosing of factor prophylaxis (Key Issue 5) ○ The company base case has adjusted the dosing of factor prophylaxis to be 85% of the recommended mid-point dose in the Summary of Product Characteristics (SmPC) of each factor product 5. Appropriate modelling of both haemophilia A and haemophilia B (Key Issue 6) ○ The economic model adequately captures relevant differences between patients with severe haemophilia A and severe haemophilia B 6. Bleed-related utility decrements (Key Issue 7) ○ Aligned with the Committee's preference, the company's updated base case uses a single utility decrement for both joint and non-joint bleeds 7. Treatment disutility per administration (Key Issue 7) ○ Further support for the difference in disutility experienced with SC versus IV administration 8. Market share of factor prophylaxis treatments ○ The updated base case uses the latest available market share data from the November 2023–November 2024 IQVIA market share analysis to inform the baskets of FVIII and FIX products. 9. Additional base case changes to align to the External Assessment Group's (EAG) updates to the cost-effectiveness model ○ Minor base case cost effectiveness model updates to align with the Committee's preferred assumptions 10. Uncaptured benefits not reflected in the incremental cost-effectiveness ratio (ICER) ○ The company proposes that there are uncaptured benefits of marstacimab not reflected in the economic modelling related to the potential benefit of SC treatment on parents, siblings and caregivers who have the responsibility of administering or supporting adolescent patients 11. Blended haemophilia A and haemophilia B analysis ○ The company has updated the EAG's blended haemophilia A and B comparator based on the anticipated uptake of marstacimab within NHS clinical practice; because there is the greatest unmet need in haemophilia B, both the company and NHS England consider the usage of marstacimab will be highest in haemophilia B. In haemophilia A, given the high usage of emicizumab in the

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	NHS, this is the key comparator for the relatively smaller proportion of patients expected to receive marstacimab in haemophilia A. 12. Rationale for presenting net health benefit (NHB) values ○ The company proposes that NHB may be a more informative measure of cost-effectiveness to consider alongside the ICER in this appraisal **Scenario analyses:** In addition to the revised base case, the company have carried out the following scenario analyses to address the Committee's preferred assumptions: • Discontinuation of emicizumab, including scenarios in which 10% of patients discontinue emicizumab (see company Comment 3) • Exploration and justification for the evidence on bleed rate utility decrements (see company Comment 6) • Further evidence and justification to model treatment-related utility decrements (see company Comment 7) Each of these scenario analyses have a relatively small impact on the cost-effectiveness of treatment with marstacimab, with the NHB remaining positive in all scenarios. These economic model inputs therefore should not be considered key areas of uncertainty when establishing a plausible ICER. Finally, a factual inaccuracy identified within the DGD is detailed in Appendix 2.
1	**Key Issue 1 and 2: The company's revised base case uses the baseline ABR data from the UKHCDO, in line with the Committee's preferences. Resultingly, the company now consider Key Issues 1 and 2 to be resolved.** The company considers the BASIS trial to represent the most robust comparative evidence base for marstacimab versus factor prophylaxis. The company conducted additional interviews after the ACM with four UK clinicians to further clarify points of uncertainty raised in the DGD (please note these interviews will hereafter be referred to as consultancy calls).[1] During these consultancy calls, clinical experts also confirmed that the results of the BASIS trial remain applicable to the UK patient population with severe haemophilia A and B.[1] One clinician stated that *"you actually might expect better efficacy in a lower risk population (lower joint score), like in the UK population, so the treatment effect from BASIS is certainly still applicable*." However, the company acknowledge that there are differences between the baseline population in BASIS and the UKHCDO data. Therefore, the company consider that it is appropriate to use UKHCDO data to inform the baseline ABR for the comparators. The ABR for patients receiving marstacimab is calculated using the comparative efficacy results

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	from BASIS applied to the UKHCDO baseline ABR, in line with the Committee's preference as modelled in the EAG's base case. The company's base case has therefore been updated, with UKHCDO data informing the baseline ABR (full results from the updated base case cost-effectiveness analysis are presented in Appendix 1). Based on this change, the company therefore considers Key Issues 1 and 2 presented at the ACM to be resolved.
2	**Key Issue 3: Dose escalation rates presented in the updated cost-effectiveness model base case include dose escalation rates in Year 2 of the model based on OLE trial data, which presents an evidence-based estimate of the cost-effectiveness of marstacimab. This is in line with the Committee's preferred assumption to model dose escalation for two years following treatment initiation. As a result, the company now consider Key Issue 3 to be resolved.** The Committee acknowledged during the discussion of Key Issue 3 that there is uncertainty about the proportion of people receiving marstacimab who would dose escalate from 150 mg once a week (QW) to 300 mg QW in the NHS, as patient and physician decisions about dose escalation are complex. Dose escalation depends on several factors including patient preference and bleed rates, with physicians ultimately deciding whether escalation is appropriate for the patient in question. The Committee further noted that dose escalation rates could be higher or lower in UK clinical practice than the rate used by the company, which was based on the rates of dose escalation observed in the BASIS trial. The company's base case originally modelled dose escalation within Year 1 of the economic model, as informed by the data in the BASIS trial. Dose escalation rates in the BASIS trial (12 months) were chosen to be used in the model to align with the clinical inputs which were also informed by the BASIS pivotal trial. This ensured consistency between dose escalation and treatment effect (bleeding rates). During the clarification questions, additional data were provided from the October 2023 data cut of the BASIS OLE trial. These data were incorporated into the EAG's base case to model dose escalation in Year 2 of the economic model. The Committee considered this latter approach to be the most appropriate for modelling dose escalation rates in the UK, as dose escalation may happen after one year of treatment with marstacimab. In the absence of real-world data on dose escalation of marstacimab within the UK, the company acknowledge that the observed data from the OLE trial represents an appropriate source of data. The company's cost-effectiveness model base case has been updated accordingly to align with the Committee's preference and now includes dose escalation in Year 2, based on data from the OLE trial (full results from the updated base case cost-effectiveness analysis are presented in Appendix 1). However, the company would like to acknowledge that, although the revised company base case now aligns to the Committee's preference, it is clinically plausible for the rate of dose

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	escalation in the UK to be lower than observed in the BASIS trial. For example, the company has also aligned with the Committee's preference to use baseline ABRs from the UKHCDO data as the base case (see company Comment 1) and the UKHCDO ABRs are lower than those generated by the BASIS trial. The decision to dose escalate is dependent on bleeding control, and it is assumed that UK patients are expected to have better bleeding control compared with patients in the BASIS trial at baseline. This perspective was supported in recent consultancy calls where clinical experts noted that dose escalation is likely to be in line with that seen in the BASIS trial, but that it could potentially be lower in UK clinical practice due to the lower observed baseline ABR in the UK.[1] This is because the bleeding rate is the most important factor when considering whether to escalate a patient's dose. The experts also highlighted that there are various considerations which lead to choosing whether to escalate a patient's dose, with some tolerance for bleeding depending on patient age, the bleed type or bleed location.[1] Additionally, UK clinicians also suggested that dose escalation is likely to happen early following initiation of a new SC treatment.[1] In summary, the company consider that utilising the dose escalation rates from the OLE trial data is appropriate but that the rate of dose escalation in the UK could plausibly be lower than that currently assumed in the economic analysis. Therefore, the company considers that the updated cost-effectiveness model may provide a conservative estimate of the cost-effectiveness of marstacimab.
3	**Key Issue 4: Discontinuation rates for emicizumab have been incorporated into the economic model, in both the base case with a 6.02% discontinuation rate and as a scenario with a 10% discontinuation rate, to better reflect clinical practice in the UK.** In the original submission of the company's base case cost-effectiveness model, no discontinuation was modelled for patients receiving emicizumab because of a lack of data availability. During the discussion of Key Issue 4, the Committee acknowledged that there is a small proportion of patients with severe haemophilia A who will discontinue treatment with emicizumab in UK clinical practice. Clinical experts clarified during the committee meeting that they expected a discontinuation rate of approximately 10% in patients treated with emicizumab. To research this further, the company conducted consultancy calls with haemophilia clinicians who confirmed the likely discontinuation rate for emicizumab in UK clinical practice ranges from 2–10%.[1] To create a clinically realistic scenario, a discontinuation rate of 6.02% for emicizumab was utilised in the base case of the cost-effectiveness model (full results from the updated base case cost-effectiveness analysis are presented in Appendix 1), matching the base case discontinuation rate of marstacimab as there is no clinical reason to expect discontinuation

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	rates to differ between the two treatments. This was supported by consultancy calls where clinicians suggested that discontinuation can be due to intolerance, but more commonly is due to the individual's perspective of efficacy and preference to revert to a factor-based prophylaxis.[1] Therefore, there is not expected to be a difference in discontinuation rates between marstacimab and emicizumab. Furthermore, the company have modelled a 10% discontinuation rate for emicizumab in a scenario where marstacimab discontinuation is also 10% (full results from the updated base case cost-effectiveness analysis are presented in Appendix 1) to reflect the discussions and requested scenario from the Committee. Whilst the true rate of discontinuation of emicizumab within UK clinical practice is unknown, this input only has a small influence on the overall cost-effectiveness of marstacimab. The NHB for marstacimab versus emicizumab in the base case, where discontinuation is modelled at 6.02% per year, is [redacted], whereas the NHB is [redacted] when discontinuation is modelled at 10% per year (Table 4). Additionally, modelling emicizumab discontinuation at 10% decreases the NHB of marstacimab versus the blended haemophilia A and B comparator from [redacted] (in the base case) to [redacted], at a WTP threshold of £30,000.
4	**Key Issue 5: The company base case has adjusted the dosing of factor prophylaxis to be 85% of the recommended mid-point dose in the SmPC, which is supported by clinician consensus of dosing regimens in UK clinical practice.** During the discussion of Key Issue 5, the Committee acknowledged there is uncertainty around the dosing regimens used in UK clinical practice for factor prophylaxis products. The company's original base case utilised the SmPC recommended mid-point dosing for each factor product. For example, the company's model utilised a dose of 30 international units (IU)/kilogram (kg) for short half-life FVIII products which represents the mid-point of the SmPC recommendations of 20 to 40 IU per kg body weight. This was supported by expert clinicians feedback during the consultancy calls with one clinician stating that they prescribe 30 IU/kg for short half-life FVIII products from which they would expect a dose of 2,000–3,000 IU, 2–3 times a week. This matches the SmPC dosing used for short half-life FVIII products (e.g., Advate) and the dosing inputs for the company's cost-effectiveness model.[1] Furthermore, UK clinicians who provided consultancy opinions to the company during the submission and following the ACM noted that, in order to achieve a zero bleed rate, UK physicians will tend to dose at the upper limit of SmPC recommendations.[1] Additionally, one clinician stated that it is not uncommon for them to prescribe more than SmPC recommendations.[1] To reflect clinician variation, the company's original base case utilised the mid-point of the doses reported in the SmPC's for each factor product. In summary, this

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	may be considered a conservative approach if UK prescribing is towards the upper end of SmPC recommendations. However, data from the UKHCDO suggest that in UK clinical practice a lower average dose of factor prophylaxis is given, compared with the SmPC recommended dose.[2] Therefore, in their base-case, the EAG assumed a reduction of factor dosing to 75% of the company base case (from SmPC mid-point recommended dosing), to align with the UKHCDO dosing data. The company notes that there are limitations to the UKHCDO data, as it does not only represent patients receiving factor therapy as prophylaxis treatment for haemophilia. For example, the data includes a proportion of patients receiving an on-demand treatment regimen, which is likely to significantly bring down the average annual dose, even if the patient numbers are small. This is because a patient receiving an on-demand treatment regimen only receives factor when they bleed; therefore, their annual factor consumption is anticipated to be only a fraction of the annual factor consumption of a patient receiving a regular prophylactic treatment regimen. The exact proportion of patients receiving an on-demand treatment regimen or who are non-compliant with a prophylactic regimen is currently unknown and would require further analysis by the UKHCDO. To obtain more representative data on patients receiving factor prophylaxis, clinicians consulted by the company recommended that patients receiving an on-demand regimen should be removed from the UKHCDO data tables; however, these data are not available from the UKHCDO. Whilst the original company base case already conservatively utilises the mid-point of the doses reported in the SmPC's for each factor product (100% of the mid-point), the company proposes to apply 85% of this mid-point within the updated base case analysis. This 85% is aligned with the level of dosing observed in the BASIS trial, and also represents an appropriate mid-point between the UKHCDO data (75% of the mid-point), noting its limitations, and UK clinician feedback on their preferred use of full SmPC dosing (100% of the mid-point). Full results from the updated base case cost-effectiveness analysis are presented in Appendix 1). A scenario analysis has also been presented where factor prophylaxis dosing is set to 100% of the mid-point of the recommended SmPC dose, in line with the original company base case. In this scenario, the NHB for marstacimab versus FVIII prophylaxis increases from [redacted] to [redacted], and for marstacimab versus FIX prophylaxis the NHB increases from [redacted] to [redacted], at a WTP threshold of £30,000. This scenario analysis does not change the NHB for marstacimab versus emicizumab ([redacted]). Additionally, in this scenario the NHB for marstacimab versus the blended haemophilia A and B comparator increases from [redacted] to [redacted], at a WTP threshold of £30,000.

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5	**Key Issue 6: The economic model presented by the company adequately captures relevant differences between patients with severe haemophilia A and severe haemophilia B, including treatment costs, bleed rates, cost of administration and disutilities.** The company would like to reassure the Committee that the model appropriately considers any relevant differences. Specifically, the model accounts for the specific treatments, and their costs, dosing, and method of administration that are available for severe haemophilia A and B. For example, this includes the impact that the frequency and route of dosing of each product has on the overall QALYs, the ongoing prophylactic cost of each product and the cost of treating an acute bleeding event with different factor products, which are all modelled separately for severe haemophilia A and B. Additionally, the Committee previously noted that the model may not have captured potential differences in the rate of treatment discontinuation; the company have now provided updated scenarios for discontinuation, including a scenario with 10% discontinuation for emicizumab within haemophilia A. Changing this input only has a small influence on the overall cost-effectiveness of marstacimab (see company Comment 3). No other differences between severe haemophilia A and B are modelled. However, this is considered clinically appropriate, with clinical experts confirming during consultancy calls with the company that, besides the different treatments used, both severe haemophilia A and B are managed and monitored identically in UK clinical practice.[1, 3] For example, healthcare resource use and bleed disutilities are modelled to be the same across severe haemophilia A and B; this is clinically appropriate as patients with severe haemophilia A and B are considered to be equivalent in these contexts. Overall, the model captures all relevant key differences between severe haemophilia A and B.
6	**The company's updated base case uses a single utility decrement for both joint and non-joint bleeds, in line with the Committee's preferences. The company suggests that this is a conservative approach to calculating the cost-effectiveness of marstacimab.** The Committee noted the uncertainty surrounding different utility decrements for joint bleeds and non-joint bleeds. They therefore summarised in the DGD that their preferred assumption was the EAG's approach of a single utility decrement of 0.16 applied over 2.5 days, compared with the company's base-case approach of separate utility decrements for joint bleeds (0.28 taken from O'Hara et al. [2018]) and non-joint bleeds (0.16 taken from Neufeld et al. [2012]) applied over 4.5 days.[4, 5] The separation of utility decrements for joint bleeds and non-joint bleeds was consistent with the approach used in TA989 where the EAG considered that the method of modelling bleed disutility was appropriate.[6] However, the company acknowledge that Neufeld et al.

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	2012 was not limited to non-joint bleeds.[4] In the original cost effectiveness model, a scenario analysis was conducted where non-joint and joint bleeds had the same disutility per bleed event. This scenario had a minor impact on the cost-effectiveness of marstacimab. The company have aligned their model base case with the EAG's approach of a single utility decrement of 0.16 applied over 2.5 days, acknowledging that there are uncertainties within the data provided. These changes have minimal impact on the cost-effectiveness results, as shown in Table 1, demonstrating the utility decrement for bleeds has a limited impact on the cost effectiveness of marstacimab (full results from the updated base case cost-effectiveness analysis are presented in Appendix 1). Furthermore, a scenario analysis was presented using the differential utility approach (0.28 for joint bleeds and 0.16 for non-joint bleeds) applied over 4.5 days, in line with the company's original base-case model. The NHB for marstacimab versus FVIII prophylaxis and FIX prophylaxis increases from [redacted] to [redacted] and [redacted] to [redacted] respectively, at a WTP threshold of £30,000. This scenario analysis does not change the NHB for marstacimab versus emicizumab ([redacted]). Additionally, in this scenario the NHB for marstacimab versus the blended haemophilia A and B comparator increases from [redacted] to [redacted], at a WTP threshold of £30,000.
7	**Key Issue 7: Additional evidence from a discrete choice experiment provides further support for a difference in quality of life experienced with a SC method of administration compared with an IV method of administration.** The discussion of Key Issue 7 raised whether differences in utility values due to treatment administration (SC versus IV) have a large effect on the ICER. Importantly, the company proposes that NHB may be a more informative measure of cost-effectiveness to consider alongside the ICER in this appraisal because, although treatment disutilities may have a large impact on the ICER, they actually have a very small impact on the NHB (see company Comment 12). Although disutilities have a minor impact on the NHB results, the Committee mentioned in the DGD that there is uncertainty surrounding the source for the utility decrements for IV injection compared with SC injection. In the company's original base case, a disutility was applied for each individual treatment administration (0.0002 for SC administration and 0.0003 for IV administration), as reported in the Johnson et al. (2021) study.[7] The company acknowledges that the Johnson et al. (2021) study has limitations which lead to uncertainties surrounding the decrement values presented.[7] These limitations include the vignette design of the study placing greater emphasis on factor prophylaxis administered in secondary care settings and differences in bleeding rates between the vignettes, as noted in the DGD. However, the company would like to emphasise that SC and IV methods of

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	treatment administration do have differing impacts on patient's treatment and quality of life experiences, as evidenced by patient expert testimonies during the appraisal committee meeting. Since the company submission, results from a patient-preference study conducted by the company have been presented at the American Society of Haematology (ASH) annual meeting 2024, which further strengthen the evidence base supporting the benefit of SC administration compared with IV administration. The Lu et al., 2024 ASH abstract reports on a cross-sectional, web-based survey including a discrete choice experiment in 194 people living with haemophilia A and B, of which 44 were from the UK. The discrete choice experiment aimed to identify patient preference regarding prophylaxis treatment and administration. Treatment frequency was determined as the most important attribute for prophylaxis treatment (relative attribute importance: 31.3%), with method of administration changing from IV to SC injection via pre-filled pen having a relative attribute importance of 12.1% ($p<0.001$). The study concluded that patients value reduced treatment frequency of prophylaxis via a pre-filled pen instead of IV infusion.[8] During consultancy calls with the company, clinicians overwhelmingly expressed that type of administration and frequency of administration is very important for patients, who strongly prefer a SC option.[1] For example, one clinician highlighted the psychological impact of putting a needle into one's own vein, quoting a patient who told them "it's taking me longer and longer to take the injections" because of the time required to psychologically prepare themselves for the injection. This strong patient preference for a SC treatment option has been demonstrated by the rapid uptake of emicizumab in patients with severe haemophilia A. Furthermore, the clinicians noted that the availability of a SC treatment option additionally relieved burden on families and caregivers, particularly for paediatric patients (see company Comment 10).[1] In the draft guidance of efanesoctocog alfa for treating and preventing bleeding episodes in haemophilia A (ID6170), the Committee concluded that scenarios should be included that measure the impact of method and frequency of treatment administration on utility values.[9] Therefore, the company conclude there is value in capturing the impact of administration on utility values. In line with the additional evidence presented above, the company's base case maintains a utility decrement of 0.0003 for each IV injection for factor prophylaxis, and a utility decrement of 0.0002 for each SC injection for marstacimab and emicizumab. Scenario analyses have also been conducted in line with the EAG's scenarios of halving the utility decrement or removing the utility decrement. In both scenarios, the overall impact on the NHB of marstacimab is minimal, as shown in Table 4, Table 5 and Table 6. In the scenario analysis where the administration based disutilities are halved, the NHB for marstacimab versus FVIII prophylaxis and FIX prophylaxis decreases from [redacted] to [redacted] and [redacted] to [redacted], respectively, at a WTP threshold of £30,000. In this scenario the NHB

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	for marstacimab versus emicizumab increases from [redacted] to [redacted]. Additionally, in this scenario the NHB for marstacimab versus the blended haemophilia A and B comparator decreases from [redacted] to [redacted], at a WTP threshold of £30,000. The same trend is observed in the scenario analysis where the administration based utilities are removed. The NHB for marstacimab versus FVIII prophylaxis and FIX prophylaxis decreases from [redacted] to [redacted] and [redacted] to [redacted], respectively, at a WTP threshold of £30,000. In this scenario the NHB for marstacimab versus emicizumab increases from [redacted] to [redacted]. Additionally, in this scenario the NHB for marstacimab versus the blended haemophilia A and B comparator decreases from [redacted] to [redacted], at a WTP threshold of £30,000. Therefore, utility decrement for method of administration should be considered a source of minimal impact on the cost-effectiveness of marstacimab. The company consider these scenarios to be conservative, and not the most accurate representation of patient experience in the UK.
8	**The company's updated base case uses the latest available market share data from the November 2023–November 2024 IQVIA market share analysis to inform the relative market share of factor prophylaxis treatments.** The Committee stated in the DGD that their preferred assumption for estimating the usage of factor prophylaxis in the basket of comparators was to use the 2023 UKHCDO data as this was consistent with UK clinical practice. The company note that the market share data from the bespoke IQVIA report, used in the base case for the original submission, was specific to the UK and provided more up to date data than the 2023 UKHCDO report.[2, 10] The IQVIA report data covered a period from July 2023 to July 2024, whereas the 2023 UKHCDO report covered a period from April 2022 to March 2023. Since the submission, IQVIA market share data from November 2023 to November 2024, as well as the 2024 UKHCDO report which covers data from April 2023 to March 2024 have been released.[11] To align with the previous approach of using the most recently available data, the company have used the 2024 IQVIA data to inform the product market shares in the updated cost effectiveness model. Market share data from the 2024 UKHCDO report has been used to inform a scenario analysis, as per committee preference.[11, 12] In this scenario analysis, the NHB for marstacimab versus factor FVIII prophylaxis and FIX prophylaxis changed from [redacted] to [redacted] and [redacted] to [redacted], respectively, at a WTP threshold of £30,000. This scenario analysis does not change the NHB for marstacimab versus emicizumab ([redacted]). Additionally, in this scenario the NHB for marstacimab versus the blended haemophilia A and B comparator decreases from [redacted] to [redacted], at a WTP threshold of £30,000.

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	Full results from the updated base case and cost-effectiveness scenario analyses are presented in Appendix 1.
9	**Miscellaneous base case cost effectiveness model updates** Beyond the changes to the base case outlined in the responses above, a few additional minor updates to the cost effectiveness model were applied to align the updated company base case with the preferred modelling approaches from the EAG. These included: • Emicizumab dosing has been capped at 100 kg body weight for the base case to align with EAG expert opinion (EAG model update 5) • The dosing of factor products following a bleed has been increased to align with UKHCDO data; the factor product used for the bleed is the same factor product that a patient is receiving for prophylaxis treatment (EAG model update 4) • The model assumes that 20% of bleeds incur the hospital resource use benefit to align with EAG preference (EAG model update 6)
10	**There are uncaptured benefits of marstacimab not reflected in the economic modelling.** In the Draft Guidance Section 3.21 'Uncaptured benefits', the committee concluded that all additional benefits of marstacimab had been taken into account within the economic modelling presented. However, as noted in company Comment 7, the availability of a SC treatment option in severe haemophilia A and B does have a positive impact on caregivers, which is not captured in the economic model. During consultancy calls with UK clinicians, it was noted by multiple clinicians that there is an improvement in quality of life for the family members and caregivers of patients with severe haemophilia A and B following the introduction of a SC treatment option, particularly for adolescents (12 years old and above). A clinician noted that a SC treatment could benefit parents, siblings and caregivers who have the responsibility of administering or supporting a patient who needs an IV injection.[1] This quality of life improvement for family members and caregivers is not captured in the utility decrements of the cost effectiveness model and represents a potentially uncaptured benefit of marstacimab treatment, especially for carers of patients with severe haemophilia B, who do not currently have a SC treatment option. Therefore, the company concludes that there are additional, yet uncaptured, benefits of treatment with marstacimab.
11	**The company has presented an updated analysis of the EAGs blended haemophilia A and B comparator analysis based on the anticipated uptake of marstacimab within**

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	NHS clinical practice and the current uptake of emicizumab within UK clinical practice. Alongside the pairwise base case cost-effectiveness analyses, the company have presented an updated analysis of a blended comparator across haemophilia A and haemophilia B, that was previously presented by the EAG in their report. The original analysis by the EAG presented a blended comparator that was weighted by the prevalence of haemophilia A (83%) and B (17%) in the UK. However, this does not reflect the anticipated update of marstacimab in the UK; NHS England's budget impact analysis submission predicted that most patients receiving marstacimab in the NHS will have haemophilia B. As such, in this revised analysis presented by the company, the weighting of haemophilia A and haemophilia B is based on the expected uptake of marstacimab in patients with haemophilia A or haemophilia B in UK clinical practice from NHS England's estimates (Table 3, Appendix 1). There is a large unmet need for patients with haemophilia B who currently do not have any subcutaneous treatment options. Therefore, most haemophilia treatments displaced by the introduction of marstacimab are anticipated to be FIX products for haemophilia B. Additionally, within the blended comparator, the haemophilia A subgroup considers that 70% of patients receive emicizumab. This market share reflects recent data from the UKHCDO. Figure 1 below is adapted from the 2024 UKHCDO Annual Report which shows continued increasing uptake of emicizumab since its launch, with 59% of patients with severe haemophilia A being treated with emicizumab in 2023/24 (data up to March 2024).[11] Emicizumab increasingly remains the most relevant comparator for patients with severe haemophilia A. This was supported by clinicians interviewed during the consultancy calls, who all stated that emicizumab is the most commonly used treatment for patients with severe haemophilia A, and that they expect the uptake of emicizumab to continue increasing.[1] The 2024 UKHCDO Annual Report includes data up to March 2024. However, a recent presentation at the November 2024 UKHCDO Annual Meeting revealed that the current percentage uptake of emicizumab has continued to rise and is now estimated to be between 60% and 70% of patients with severe haemophilia A.[13]

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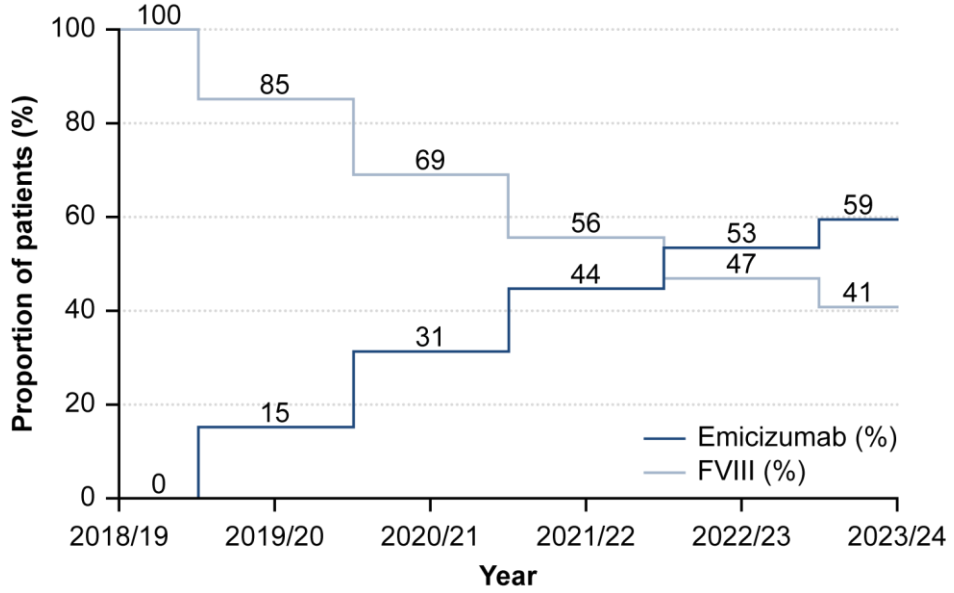
	Figure 1: The proportion of patients with severe congenital haemophilia A and no inhibitor issued treatment by primary treatment 2019 Q2 – 2024 Q1  **Abbreviations:** FVIII: Factor VIII. **Source:** UKHCDO Annual Report, 2024.[11] In summary, this analysis intends to reflect the anticipated opportunity cost of introducing marstacimab within UK clinical practice and provides an alternative way of considering the cost-effectiveness impact of the introduction of marstacimab. In this analysis, marstacimab is highly cost-effective versus the blended haemophilia A and B comparator, with a NHB of [redacted], at a WTP threshold of £30,000. Results from this analysis are presented in Table 2, Appendix 1.
12	**The company proposes that NHB may be a more informative measure of cost-effectiveness to consider alongside the ICER in this appraisal**. Whilst ICER values are typically the most commonly presented outputs of cost-effectiveness analysis, the company suggest that NHB may be a more informative measure to consider alongside the ICER in this appraisal. The ICER values and the impact of varying assumptions on the ICER are difficult to interpret due to the small differences in QALYs in the analyses. Given the small differences in QALYs, the incremental costs are divided by a very small denominator which can result in extremely volatile ICERs, making it hard to identify key drivers of cost-effectiveness. In these circumstances, the NICE manual (Section 4.2.16) states that NHB can be an informative measure and should be considered alongside the ICER value.[14] This aligns with the approach taken by the company and the EAG. As an example of the importance of this, in the 'Key Issues' slides in the committee's presentation (slide 9) it is stated that Key Issue 7 'treatment disutility per administration' has a large

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	impact on the ICER but this actually has a very small impact on the NHB as demonstrated in the EAG's scenario analyses, and in the scenario analyses presented in this response (see Appendix 1).

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Appendices

Appendix 1. Updated cost effectiveness model results

Updated DGD response base case results

The updated base case results of the economic evaluation of marstacimab, which address much of the uncertainty discussed by the Committee, show marstacimab to be a cost-effective alternative versus all three comparator therapies, with NHBs of [redacted], [redacted] and [redacted], versus FVIII prophylaxis, emicizumab and FIX prophylaxis, respectively, at a WTP threshold of £30,000. In the comparison versus FVIII and FIX prophylaxis (in patients with haemophilia A and B, respectively), marstacimab was dominant, being associated with both lower costs and greater health benefits (i.e., higher total QALYs). In the comparison versus emicizumab, marstacimab resulted in fewer overall QALYs, however resulted in cost savings large enough to be considered cost-effective at a WTP threshold of £30,000 saved per QALY forgone.

Table 1 presents the incremental changes in the NHB (see company Comment 12) following each update of the company's cost-effectiveness model detailed in the responses above.

Table 2 presents the company's overall updated base-case results for marstacimab versus comparators, demonstrating that following the changes to the model described in the DGD response, marstacimab remains cost-effective. Additionally, the company have also presented an alternative analysis to illustrate the cost-effectiveness of marstacimab versus a blended haemophilia A and B comparator (see company Comment 11). This blended comparator is similar to that presented by the EAG in their report, and weights haemophilia A and haemophilia B based on the expected uptake of marstacimab in patients with severe haemophilia A and B in the UK (Table 3). In this analysis, marstacimab remains cost-effective versus the blended haemophilia A and B comparator, with an NHB of [redacted], at a WTP threshold of £30,000. This alternative analysis reflects the impact of introducing marstacimab into UK clinical practice, and highlights the large unmet need in patients with severe haemophilia B which will be addressed by treatment with marstacimab.

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Table 1: Cumulative changes to the company's cost-effectiveness estimates (deterministic results; PAS price)

	Vs FVIII NHB (£30,000 WTP)	Vs emicizumab NHB (£30,000 WTP)	Vs FIX NHB (£30,000 WTP)	Vs blended haemophilia A and B comparator NHB (£30,000 WTP)
Company's base case (at clarification questions)	[redacted]	[redacted]	[redacted]	[redacted]
Minor model error corrections following EAG report	[redacted]	[redacted]	[redacted]	[redacted]
Minor model updates: emicizumab dosing capped at 100kg body weight, increased factor dosing per acute bleed in line with UKHCDO data, and bleed related resource use costs applied to 20% of bleeds	[redacted]	[redacted]	[redacted]	[redacted]
Response 1 (Key Issues 1 & 2): Use of UKHCDO data for baseline bleed rates. Relative treatment effect from BASIS used to inform marstacimab treated patients bleed rate	[redacted]	[redacted]	[redacted]	[redacted]
Response 2 (Key Issue 3): Dose escalation rates for patients receiving marstacimab include dose escalation in Year 2 of the model to reflect OLE data	[redacted]	[redacted]	[redacted]	[redacted]
Response 3 (Key Issue 4): An annual discontinuation rate of 6.02% is applied to patients receiving marstacimab and emicizumab	[redacted]	[redacted]	[redacted]	[redacted]
Response 4 (Key Issue 5): Factor prophylaxis dosing is set at 85% of the recommended SmPC dose	[redacted]	[redacted]	[redacted]	[redacted]

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	Vs FVIII NHB (£30,000 WTP)	Vs emicizumab NHB (£30,000 WTP)	Vs FIX NHB (£30,000 WTP)	Vs blended haemophilia A and B comparator NHB (£30,000 WTP)
Response 6: the same disutility is applied for both joint and non-joint bleeds	[redacted]	[redacted]	[redacted]	[redacted]
Response 8: IQVIA analysis from Nov 2023 – Nov 2024 has been used to inform treatment market share data	[redacted]	[redacted]	[redacted]	[redacted]
Updated base case following DGD response	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: FIX: Factor IX; FVIII: factor VIII; NHB: net health benefit; OLE: open label extension; PAS: patient access scheme; SmPC: summary of product characteristics; UKHCDO: United Kingdom Haemophilia Centre Doctors' Organisation.

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Table 2: Deterministic DGD response base-case results for marstacimab versus comparators (with PAS)

Intervention	Total Costs	Total LYs	Total QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)	NHB at £20,000	NHB at £30,000
Marstacimab versus haemophilia A comparators									
Marstacimab	[redacted]	21.52	[redacted]	-	-	-	-	-	-
FVIII prophylaxis	[redacted]	21.52	[redacted]	[redacted]	-	[redacted]	Marstacimab is dominant	[redacted]	[redacted]
Emicizumab	[redacted]	21.52	[redacted]	[redacted]	-	[redacted]	£55,655,075[a] (SW)	[redacted]	[redacted]
Marstacimab versus haemophilia B comparator									
Marstacimab	[redacted]	21.52	[redacted]	-	-	-	-	-	-
FIX prophylaxis	[redacted]	21.52	[redacted]	[redacted]	-	[redacted]	Marstacimab is dominant	[redacted]	[redacted]
Marstacimab versus blended haemophilia A and B comparator									
Marstacimab	[redacted]	21.52	[redacted]	-	-	-	-	-	-
Blended haemophilia A and B comparator	[redacted]	21.52	[redacted]	[redacted]	-	[redacted]	Marstacimab is dominant	[redacted]	[redacted]

[a]ICER in the south west quadrant of the cost-effectiveness plane – cost saved per QALY forgone.
Abbreviations: FIX: Factor IX; FVIII: factor VIII; ICER: incremental cost-effectiveness ratio; LY: life years; NHB: net health benefit; PAS: patient access scheme; QALYs: quality-adjusted life years.

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Displacement weightings

Displacement weightings used in the blended haemophilia A and haemophilia B comparison are presented in Table 3.

Table 3: Blended haemophilia A and haemophilia B comparator displacement weightings

Distribution of population expected to receive marstacimab		
Severe haemophilia A[1]		Severe haemophilia B[1]
[redacted]%		[redacted]%
FVIII prophylaxis[2]	Emicizumab[2]	FIX prophylaxis[1]
[redacted]%	[redacted]%	[redacted]%

Abbreviations: UKHCDO: The United Kingdom Haemophilia Centre Doctors' Organisation: NHS: National Health Service.
Sources: [1]NHS England Budget Impact Analysis Submission for Marstacimab [ID6342], [2]UKHCDO Annual Meeting, 2024.[13]

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Scenario analyses

Several deterministic scenario analyses were conducted to assess the impact of the uncertainty associated with key inputs and assumptions in the updated economic model. Results of these scenario analyses in both haemophilia A and B are presented in Table 4 and Table 5, respectively. Additionally, results of the scenario analyses applied to the comparison of marstacimab versus the blended haemophilia A and B comparator are presented in Table 6. In all scenario analyses marstacimab remained dominant versus factor prophylaxis comparators.

Table 4: Results of the scenario analyses for patients with haemophilia A (with PAS; deterministic)

Scenario		Marstacimab vs FVIII prophylaxis				Marstacimab vs emicizumab			
		Incremental costs	Incremental QALYs	ICER (£/QALY)	NHB (£30,000)	Incremental costs	Incremental QALYs	ICER (£/QALY)	NHB (£30,000)
Base case		[redacted]	[redacted]	Dominant	[redacted]	[redacted]	[redacted]	£55,655,075[a] (SW)	[redacted]
1	Use of UKHCDO 2024 report to inform factor prophylaxis market shares	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] (SW)	[redacted]
2	Factor prophylaxis dosing is set to the recommended SmPC dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] (SW)	[redacted]
3	Marstacimab and emicizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] (SW)	[redacted]

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	discontinuation rate set at 10% in the first year								
4	Original base case bleed disutilities applied: −0.28 for joint bleeds and −0.16 for non-joint bleeds lasting 4.5 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted](SW)	[redacted]
5	Administration based disutilities are halved: 0.00015 for IV administration and 0.0001 for SC administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted](SW)	[redacted]
6	Administration based disutilities are removed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted](SW)	[redacted]

Some variation may exist in the interpretation of these results relative to the base case results due to the probabilistic nature of the analyses.
[a]ICER in the south west quadrant of the cost-effectiveness plane – cost saved per QALY forgone.
Abbreviations: FVIII: factor VIII; ICER: incremental cost-effectiveness ratio; IV: intravenous; NHB: net health benefit; PAS: patient access scheme; QALY: quality-adjusted life year; SC: subcutaneous; SmPC: summary of product characteristics; UKHCDO: United Kingdom Haemophilia Centre Doctors' Organisation.

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Table 5: Results of the scenario analyses for patients with haemophilia B (with PAS; deterministic)

Scenario		Marstacimab vs FIX prophylaxis			
		Incremental costs	Incremental QALYs	ICER (£/QALY)	NHB (£30,000)
Base case		[redacted]	[redacted]	Dominant	[redacted]
1	Use of UKHCDO 2024 report to inform factor prophylaxis market shares	[redacted]	[redacted]	[redacted]	[redacted]
2	Factor prophylaxis dosing is set to the recommended SmPC dose	[redacted]	[redacted]	[redacted]	[redacted]
3	Marstacimab and emicizumab discontinuation rate set at 10% in the first year	[redacted]	[redacted]	[redacted]	[redacted]
4	Original base case bleed disutilities applied: −0.28 for joint bleeds and −0.16 for non-joint bleeds lasting 4.5 days	[redacted]	[redacted]	[redacted]	[redacted]
5	Administration based disutilities are halved: 0.00015 for IV administration and 0.0001 for SC administration	[redacted]	[redacted]	[redacted]	[redacted]
6	Administration based disutilities are removed	[redacted]	[redacted]	[redacted]	[redacted]

Some variation may exist in the interpretation of these results relative to the base case results due to the probabilistic nature of the analyses.
Abbreviations: FIX: Factor IX; ICER: incremental cost-effectiveness ratio; IV: intravenous; NHB: net health benefit; PAS: patient access scheme; QALY: quality-adjusted life year; SC: subcutaneous; SmPC: summary of product characteristics; UKHCDO: United Kingdom Haemophilia Centre Doctors' Organisation.

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Table 6: Results of the scenario analyses versus the blended haemophilia A and B comparator (with PAS; deterministic)

Scenario		Marstacimab vs Blended haemophilia A and B comparator			
		Incremental costs	Incremental QALYs	ICER (£/QALY)	NHB (£30,000)
Base case		[redacted]	[redacted]	Dominant	[redacted]
1	Use of UKHCDO 2024 report to inform factor prophylaxis market shares	[redacted]	[redacted]	[redacted]	[redacted]
2	Factor prophylaxis dosing is set to the recommended SmPC dose	[redacted]	[redacted]	[redacted]	[redacted]
3	Marstacimab and emicizumab discontinuation rate set at 10% in the first year	[redacted]	[redacted]	[redacted]	[redacted]
4	Original base case bleed disutilities applied: −0.28 for joint bleeds and −0.16 for non-joint bleeds lasting 4.5 days	[redacted]	[redacted]	[redacted]	[redacted]
5	Administration based disutilities are halved: 0.00015 for IV administration and 0.0001 for SC administration	[redacted]	[redacted]	[redacted]	[redacted]
6	Administration based disutilities are removed	[redacted]	[redacted]	[redacted]	[redacted]

Some variation may exist in the interpretation of these results relative to the base case results due to the probabilistic nature of the analyses.
Abbreviations: FIX: Factor IX; ICER: incremental cost-effectiveness ratio; IV: intravenous; NHB: net health benefit; PAS: patient access scheme; QALY: quality-adjusted life year; SC: subcutaneous; SmPC: summary of product characteristics; UKHCDO: United Kingdom Haemophilia Centre Doctors' Organisation.

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Appendix 2. Factual inaccuracies

Page number	Quote from the DGD	Factual inaccuracy identified and rationale for requested correction	Correction requested
8	*"The company also included data from an open-label extension study of 88 people who had prophylaxis for 6 months before BASIS and continued to have factor prophylaxis during the observational phase."*	The figure of 88 includes on-demand patients in the OLE. The number of patients who had prophylaxis prior to the BASIS study and included in the OLE data sets were n=58 and n=75 for the March 2023 and October 2023 data cuts, respectively. Please see page 68 of the company submission for further details.	*"The company also included data from an open-label extension study of 75 people who had prophylaxis for 6 months before BASIS and continued to have factor prophylaxis during the observational phase, as of October 2023."*

Abbreviations: OLE: open-label extension.

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

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Marstacimab for treating severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Draft guidance comments form

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	CSL Behring is a comparator company, marketing Idelvion (a comparator) and Hemgenix (non-comparator, but reimbursed for Haemophilia B) in the UK.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	In the "why NICE made this recommendation" subsection, the conclusion is clear for haemophilia A with the comparison to emicizumab but there is no clear conclusion for haemophilia B. We suggest the final paragraph should be rephrased to make clear that there are uncertainties in the cost-effectiveness estimates for marstacimab in both haemophilia A and haemophilia B, hence leading to the recommendation.

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2	In section 2.1, final sentence, the copy states "factor VIX inhibitors" for haemophilia B instead of "factor IX inhibitors"
3	In 3.1, the copy states "requires intravenous injection, self-administered or by carers, as often as every 2 to 3 days, which is a substantial treatment burden", however the standard of care nowadays is the use of extended half-life (EHL) factor concentrates enabling injections every 7 to 21 days, or the use of emicizumab for haemophilia A which requires weekly, biweekly or monthly injections. Please consider adding a dosing frequency range here, rather than only quoting the highest dosing frequency, which could be misleading.
4	We agree with the committee conclusion that the ABRs in the BASIS trial population for patients on FIX treatment is significantly higher than those seen in other trials targeting the same patient groups and not representative of the same population in the UK, and that National Haemophilia Database data should be used as the reference source. CSLB agree with the concerns raised that the incremental benefit of marstacimab compared to comparators could be overestimated for the UK population.
5	In 3.13, and in other sections of the Draft Guidance, it has been suggested that there is no clinical reason why there would be a difference in effectiveness of marstacimab between Haemophilia A and B, and that the lower efficacy results in Haemophilia B may just be a result of the small trial size. It cannot be assumed that there are identical relationships of the tenase complex/Tissue Factor Pathway Inhibitor (TFPI) in persons with Haemophilia A v Haemophilia B. Published studies are available which summarise the molecular and clinical differences between Haemophilia A and B[1]. Comparator therapies have conducted studies with extensive patient sample sizes, particularly within the Haemophilia B population. It is therefore unclear why similar considerations were not included in the study design for marstacimab. The submitting company should provide more evidence specific to the Haemophilia B population. When assessing cost-effectiveness, data specific to each studied population should be taken into account. [1] Castaman G, Matino D. Hemophilia A and B: molecular and clinical similarities and differences. Haematologica. 2019 Sep;104(9):1702-1709. doi: 10.3324/haematol.2019.221093. Epub 2019 Aug 8. PMID: 31399527; PMCID: PMC6717582.

Insert extra rows as needed

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- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
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comments form with that information replaced with asterixis and highlighted in black.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Marstacimab for treating severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

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

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NICE National Institute for Health and Care Excellence

Marstacimab for treating severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

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

Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**Evidence on treatment administration disutility (section 3.15)** In light of NICE's preference for additional evidence on treatment-related disutilities, Novo Nordisk (NN) would like to reference the Okkels 2024 time trade-off (TTO) publication, which provides UK-specific evidence on haemophilia treatment. The study underscores the treatment burden in haemophilia, citing multiple publications, and estimates UK utilities associated with treatment

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	device and dosing frequency. The study offers both point estimates and confidence intervals for both patients with haemophilia and caregivers. Given that the EAG was concerned that the Johnson et al study design might be biased due to potential efficacy differences being captured in the treatment utility estimates, we would like to highlight that the Okkels 2024 TTO study attempted to limit this by describing the efficacy component of all treatment health states identically as 'treatments that keep the disease under control' (see Supplementary information document of Okkels 2024).
2	**BASIS trial population haemophilia B severity (section 3.4)** Current wording: *"This enrolled people 12 years and over with severe haemophilia A or **severe haemophilia B** who had no antibodies to factor VIII or IX."* Proposed wording: "This enrolled people 12 years and over with severe haemophilia A or **moderately severe to severe** haemophilia B who had no antibodies to factor VIII or IX." Rationale: The draft guidance states that the BASIS trial enrolled patients with severe haemophilia B (HB) however according to Document B and Matino 2023 the study included participants with moderately severe to severe (FIX ≤2%) HB.
3	**Emicizumab use within the NHS (section 3.2)** Current wording: *"Emicizumab, a non-factor VIII treatment, is commissioned through an NHS England commissioning policy as prophylaxis for **severe** congenital haemophilia A in people of all ages **without anti-factor antibodies**."* Proposed wording: "Emicizumab, a non-factor VIII treatment, is commissioned through an NHS England commissioning policy as prophylaxis for congenital haemophilia A in people of all ages" Rationale: According to NHS England commissioning policy, emicizumab is available for routine commissioning to people with and without inhibitors. The same policy document states that emicizumab can be used by people with HA with inhibitors of all severities. Additionally, the NICE topic selection web page for emicizumab clarifies that "Because emicizumab is covered by an existing NHS England clinical commissioning policy, NHS England have confirmed that this indication [mild or moderate haemophilia A without inhibitors] may be considered for routine commissioning.
4	**Other comments** - Page 3: *"Evidence from clinical trial shows marstacimab reduces the number of bleeding episodes a person has compared with factor 8 or 9 prophylaxis"* Comment: The sentence can result in misunderstanding. It requires a clarification stating that the evidence come from a non-randomised cross-over clinical trial and that the conclusion is based on pooled HA/HB data. - Page 8: *The primary outcome in BASIS was the annualised bleeding rate (ABR) for treated bleeds through the observational phase and active treatment phase. The non-inferiority margin was 2.5 years per bleed.* Comment: As mentioned in Matino 2023, this text refers to 2.5 **treated** bleeds per year based on the upper bound of the confidence interval in difference in bleeds with marstacimab vs previous prophylaxis. There is a need to specify these details to avoid confusion.

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	- Page 8: *"The company also included data from an open-label extension study of **88** people who had prophylaxis for 6 months before BASIS and continued to have factor prophylaxis during the observational phase."* Comment: According to the Document B, the open label extension enrolled 58 and not 88 people - Page 10: *"The mean ABR for treated bleeds for all 18 people with haemophilia B was 3.88 for marstacimab. "* The same paragraph states that "For haemophilia B the mean ABR for treated bleeds was 4.71 for marstacimab during the 12-month active treatment phase". There is a need to clarify which sentence is correct or whether the two sentences refer to different endpoints.

Insert extra rows as needed

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Single Technology Appraisal

Marstacimab for treating severe haemophilia A or severe haemophilia B in people 12 years and over [ID6342]

Comments on the draft guidance received through the NICE website

Name	[redacted]
Role	Not specified
Other role	Not specified
Organisation	Haemophilia NI
Location	Not specified
Conflict	No
Notes	N/A

Comments on the DG:

Has all of the relevant evidence been taken into account?

The Haemophilia NI Board has reviewed the documents relating to NICE's appraisal of Marstacimab and wishes to make the following comments:

1) HNI acknowledges the decision of NICE to not to approve Marstacimab within the marketing authorisation for prophylaxis in cases of severe haemophilia A and B. HNI agrees that there is a need for robust clinical trial design which incorporates blinding, randomisation, appropriate comparator and UK data where possible. Given the nature of haemophilia as a lifelong condition, HNI also feels having long term data where possible is highly preferable. In light of the infected blood scandal – safety must be a priority.

2) HNI would like to highlight significant areas of unmet need for people with bleeding disorders that still exist despite substantial progress in therapeutics over the past 20 years. Presently, there is only one subcutaneous treatment option for severe haemophilia A and no subcutaneous treatment option for people with severe haemophilia B. In addition, people with haemophilia B and inhibitors do not have any treatment options other than ITI, which has lower response rates than in severe haemophilia A, and bypassing agents with which prophylaxis is difficult to achieve. People with ultra rare inherited coagulation disorders such as Factor V deficiency and prothrombin deficiency also have no specific treatment agents.

3) HNI appreciates that the manufacturer did not seek a license for haemophilia with inhibitors or rare factor disorders, however we feel it is important to underline the potential role that rebalancing agents have in these circumstances and how underserved these patients presently are. We hope NICE will see fit to acknowledge these unmet needs and the potential role for rebalancing agents in these settings. We also request that NICE continue to remember the enormous heterogeneity which exists amongst patients with bleeding disorders (for example phenotype, lifestyle and vascular access issues) and the need to ensure patients have access to treatment options which suit them as individuals.

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

We believe the summaries of clinical and and cost effectiveness presented by Pfizer are a fair interpretation of submitted evidence.

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

HNI believes the recommendations form a suitable basis for NHS guidance, however we would be keen that learning takes place related to the aforementioned comments.

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

Within the limits of the small number of patients included in the BASIS trial we do not believe an unlawful discrimination has occurred in the interpretation of available evidence.

External Assessment Group's Critique of Company Comments on Draft Guidance following AC1 [ID6342]

Produced by	*Warwick Evidence/Birmingham Centre for Evidence and Implementation Science*
Authors	*Ewen Cummins, Health Economist, McMDC Ltd* *Daniel Gallacher, Assistant Professor, University of Birmingham*
Correspondence to **Date completed**	*Dr Daniel Gallacher: d.c.gallacher@bham.ac.uk* *13/02/2025*

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number 16/82/32.

Declared competing interests of the authors
None

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Please note that: Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue. Depersonalised Data (DPD) is highlighted in pink.

1 Committee draft recommendations and consultation responses

This section summarises elements of the Committee draft recommendation together with responses from one or more consultees:

- the company Pfizer,
- CSL Behring, the manufacturer of Idelvion EHL FIX, and
- the Haemophilia NI board as represented by William McKeown.

Where relevant these are followed by an EAG response.

Comments were also received from Novo Nordisk but these relate mainly to the wording of the draft guidance and are of limited relevance to what follows.

1.1 *Section 1: Recommendations*

Committee: Marstacimab is not recommended.

1.2 *Section 3.2: Treatment pathway*

Committee: Current treatments do not always prevent bleeds and are associated with administration challenges, particularly among the young and the elderly.

1.3 *Section 3.6: Generalisability of trial results*

Committee: The marstacimab trial, BASIS, had no UK sites. Patients in other countries may have a different prophylaxis history than UK patients which could mean much higher background bleed rates. UK patients typically have very low bleed rates.

Haemophilia NI: There is a need for robust trial design incorporating blinding, randomisation, appropriate comparator(s) and UK data where possible. Long term data is highly preferable. In the light of the infected blood scandal safety must be a priority.

1.4 *Section 3.7: Comparison with emicizumab*

Committee: The indirect comparison with emicizumab was highly uncertain but the available evidence did not suggest that the effectiveness of marstacimab is markedly different from that of emicizumab.

1.5 *Section 3.9: Modelled baseline bleed rates*

Committee: UKHCDO bleed rates for factor prophylaxis and for emicizumab are preferable to those of BASIS and the indirect treatment comparison with emicizumab.

Pfizer: The company revised base cases apply the UKHCDO bleed rates for factor prophylaxis and for emicizumab.

CSL Behring: Bleed rates among BASIS FIX patients are significantly higher than in other trials targeting the same patient groups and do not represent UK experience. UKHCDO bleed rates should be used for modelling.

1.6 *Section 3.10: Marstacimab dose escalation*

Committee: The proportion of marstacimab patients who will dose escalate from 150mg to 300mg is uncertain and could be higher or lower than that assumed by the company. Dose escalation may occur after the first year. The base case should include the EAG's year 2 dose escalation.

Pfizer: The company revised base cases apply the BASIS ATP (Active Treatment Phase) and OLE (Open Label Extension) dose escalation rates, in line with the EAG's year 1 and year 2 dose escalation. Company experts suggest that dose escalation is likely to be in line with BASIS but could be lower due to UKHCDO bleed rates for factor prophylaxis being lower than during the BASIS OP (Observation Phase).

EAG: The ATP saw [redacted] dose escalation among those remaining on marstacimab treatment. During the OLE a further [redacted] dose escalated. The OLE proportion eligible for dose escalation was [redacted] Over time dose escalation may exceed that observed during the BASIS ATP and OLE October 2023 Data Cut.

1.7 *Section 3.11: Treatment discontinuation*

Committee: Clinical experts suggest that around 10% of emicizumab patients discontinue their emicizumab. The company should submit UK relevant scenarios that explore discontinuations from emicizumab, including 10% discontinuing.

Pfizer: The company ACD base case applies the marstacimab 6.02% discontinuation rate to emicizumab as there is no reason for discontinuation rates to

differ. The company also provides a scenario of a 10% emicizumab discontinuation rate. The effect is relatively minor at list prices.

EAG: Committee views the relative effectiveness of marstacimab and emicizumab as uncertain but there was no evidence of a marked difference, as per section 1.4 above. In the light of this assuming the same discontinuation rate for emicizumab and marstacimab seems most reasonable for the base case. The effect may be larger when FVIII cPAS discounts are included.

1.8 *Section 3.12: Factor prophylaxis dosing*

Committee: The company method may have overestimated factor prophylaxis dosing compared to UKHCDO data, which is representative of NHS practice. The EAG base case that applies 75% of the company factor prophylaxis dosing is appropriate.

Pfizer: The original company base case applied the mid-point of the SmPC dose range per kg. In practice there is wide variation and some clinicians prescribe in excess of SmPC recommendations. UKHCDO data includes patients receiving on-demand regimens which will reduce the average dose. Dosing during BASIS was around 85% of the original company base case, so the company applies a 85% adjustment factor in its revised base case.

EAG: The data is reviewed in more detail in section 5.3.2 of the original EAG report.

The UKHCDO dosing data may include patients receiving on-demand treatment. As outlined in section 2.2.1 of the original EAG report it seems that some patients in BASIS may also have been receiving on-demand treatment.

The original EAG report noted that the original company base case dosing for FVIII was around [redacted] more than UKHCDO data. The proportion of adolescents in the UKHCDO data may have been too high, but even among adults the assumed dosing was [redacted] and [redacted] higher than UKHCDO data for SHL and EHL respectively. Given that there are adolescent patients, the EAG base case of a 75% adjustment factor may be too optimistic for FVIII. The EAG report notes that for FIX based upon UKHCDO data an adjustment factor of [redacted] may be more reasonable.

Given the above the EAG retains its base case 75% adjustment factor, also supplying scenarios of 70% and 80%.

1.9 *Section 3.13: Separate or pooled modelling of Type A and Type B*

Committee: Pooling bleed rates across Type A and Type B is acceptable. But there may be other differences between Type A and Type B, such as discontinuation rates. The company should provide further clarity on whether the model captures different treatment pathways and parameters for haemophilia A and B.

Pfizer: Other than the different types of treatment Type A and Type B are managed and monitored identically in the UK. The company revised base case differentiates treatment costs, administration disutilities and bleed treatment costs between Type A and Type B.

CSL Behring: Studies are available that summarise the molecular and clinical differences between Type A and Type B. Comparator therapies have conducted studies with extensive patient sample sizes, notably among Type B patients. It is unclear why similar considerations were not applied in BASIS. Pfizer should submit more evidence specific to Type B. When assessing cost effectiveness data specific to Type A and to Type B should be taken into account.

EAG: The model has the facility to differentiate all clinical effects between Type A and Type B, such as discontinuation rates, baseline bleed rates, bleed relative risks and dose escalation rates. If pooling baseline bleed rates for FVIII and FIX is acceptable to Committee it is unclear what other clinical parameters Committee thinks should or could be differentiated between Type A and Type B. The EAG will present results that differentiate baseline bleed rates and relative effectiveness between Type A and Type B.

1.10 *Section 3.14: Bleed disutilities*

Committee: Joint and non-joint bleeds may have different disutilities. No evidence was presented that measured these together. The company should provide further information and justification for their assumed disutilities. In the absence of further evidence, the EAG preference for a common disutility of 0.16 lasting 2.5 days should be applied.

Pfizer: The original company approach was aligned with TA989. But the company acknowledges the data uncertainties and aligns its revised base case with the original EAG base case.

EAG: The effects become relatively minor due to the low UKHCDO baseline bleed rates meaning that reducing bleeds further has only a small effect upon QALYs.

1.11 *Section 3.15: Administration disutilities*

Committee: There are patient benefits from subcutaneous administrations compared to intravenous infusions. The company evidence had limitations and may have overestimated these benefits. There was insufficient evidence to justify the company treatment administration disutilities.

Pfizer: The modelled QALY gains are small while the differences in treatment costs and to a lesser extent bleed costs are large. This means that the net health benefits are little affected by changes to the QALY gains and are driven by the differences in treatment costs. The company cites an additional paper as ranking the preferences of haemophiliacs for injection frequency and subcutaneous over intravenous infusion, frequency being more important than route of administration. The company retains its original treatment disutilities as sourced from Johnston et al.

EAG: The EAG has a preference for reporting net health benefits when a technology is estimated to dominate another, but reverts to the more usual ICER when this is not the case.

The EAG accepts that patients have a preference for fewer administrations and for subcutaneous over intravenous infusions. The company appears to suggest that there is a stronger preference for fewer administrations than for subcutaneous over intravenous infusions.

As reviewed in greater detail in section 5.2.2 of the original EAG report the EAG thinks that the vignettes of Johnston et al., funded by the manufacturer of emicizumab, are biased against intravenous infusion. Intravenous infusion is described as having "*significant risks of complications including injury, infections and internal bleeding*". The infusion time of "*up to 30 minutes*" may be too high. In time patients "*may be able to*" self-administer, when in practice it is highly probably. These appear designed to bias the analysis against intravenous infusion, and it should be borne in mind that the study was conducted among members of the general public who would not be expected to have any experience of factor infusions.

The EAG presents a brief literature review of relevant quality of life papers in Appendix 1 below. The EAG thinks that the studies with utility estimates provide some support to the values of Johnston et al., despite the vignettes of Johnston et al. being biased. Some caution needs to be exercised due to the quality of life values being estimated from the general population rather than haemophiliacs. The discrete choice experiments suggest that administration frequency is not as important as other treatment attributes in determining patient preferences between treatments, and may be relatively unimportant.

1.12 *Section 3.17: Committee preferred modelling assumptions*

Committee: The base case should apply the following:

1. UKHCDO bleed rates for factor and for emicizumab
2. Year 2 dose escalations for marstacimab
3. Factor prophylaxis dosing 75% of company base case
4. Pooled clinical effectiveness estimates for Type A and Type B
5. A common bleed disutility of 0.16 for 2.5 days
6. Fix model errors identified by EAG
7. UKHCDO factor use for bleeds
8. Cap emicizumab dosing at that for a patient weight of 100kg
9. Only 20% of bleeds incur hospital resource use
10. Apply UKHCDO market share data for factor prophylaxis

Pfizer: The company revised base case applies 1, 2, 4, 5, 6, 7, 8 and 9. Under 3 it applies 85% factor prophylaxis dosing compared to its previous base case. Under 10 it updates the market share data to be from the IQVIA 2024 data, and further increases emicizumab use to 70% through extrapolation. When combining Type A and Type B the company assumes [redacted] Type A and [redacted] Type B.

Committee: The following analyses should be presented by the company:

1. Emicizumab discontinuations, including a 10% discontinuation rate

2. Further justify the evidence on bleed disutilities
3. Further justify the evidence on administration disutilities
4. Further explore the treatment pathways and model parameters split by Type A and Type B.

Pfizer:

1. Emicizumab discontinuations are modelled, in the revised base case assuming them to be equal to those of marstacimab.
2. The company adopts the EAG approach.
3. An additional paper is summarised as showing a patient preference for fewer administrations and for subcutaneous over intravenous infusion, the former being the more important.
4. Clinical parameters are not differentiated by Type A and Type B.

1.13 *Section 3.21: Uncaptured benefits*

Committee: No uncaptured benefits were identified in the economic modelling.

Pfizer: Subcutaneous administration compared to intravenous infusions also has a carer benefit.

Haemophilia NI: There is no subcutaneous option for haemophilia type B. Haemophilia NI also expresses concerns about those with inhibitors and rare factor disorders but since these are outside the license the EAG has not presented them.

EAG: The 2022 NICE methods guide section 4.3.17 states that "*Evaluations should consider all health effects for patients, and, when relevant, carers. When presenting health effects for carers, evidence should be provided to show that the condition is associated with a* ***substantial effect*** [EAG emphasis] *on carer's health-related quality of life and how the technology affects carers*." How substantial the carer effect needs to be is not defined.

The company base case estimates lifetime patient gains due to administrative disutilities of [redacted] QALYs for FVIII, [redacted] QALYs for FIX and a loss of [redacted] QALYs compared to emicizumab. Annual gains are estimated to be [redacted] QALYs for FVIII, [redacted] QALYs for FIX and a loss of [redacted] QALYs compared to emicizumab. These need to be read alongside the EAG concerns about the source of the administrative

disutilities as summarised in section 1.11 above. EAG expert opinion suggests that the vast majority, 90% to 95%, of adult patients self-administer, and that children begin training in aspects of self-administration from a very early age. The proportion of patients requiring carer assistance is likely to be low.

2 Additional Pfizer model revisions

The company has made a number of minor revisions to the EAG base case clinical effect estimates. The EAG broadly accepts these with the exception of the FIX/FVIII ABR for the BASIS OP which is used to calculate the relative effectiveness of marstacimab. The company prefers the all patient value while the EAG prefers the value for the subset who entered the BASIS OLE, this being the more relevant figure for extrapolation. More detail is provided in Appendix 2 below. The effects of these changes are minor, as outlined in Table 7 below.

The company has updated the market share data to be from 2024 sources.

Table 1: Company revised market shares: FIX

	2023		2024	
	IQVIA	UKHCDO	IQVIA	UKHCDO
Advate	[redacted]	28%	[redacted]	25%
Refacto AF	[redacted]	16%	[redacted]	14%
NovoEight	[redacted]	8%	[redacted]	5%
Nuwiq	[redacted]	3%	[redacted]	2%
Esperoct	[redacted]	23%	[redacted]	28%
Elocta	[redacted]	20%	[redacted]	23%
Adynovi	[redacted]	2%	[redacted]	2%

Table 2: Company revised market shares: FIX

	2023		2024	
	IQVIA	UKHCDO	IQVIA	UKHCDO
BeneFix	[redacted]	23%	[redacted]	19%
Alprolix	[redacted]	47%	[redacted]	51%
Idelvion	[redacted]	15%	[redacted]	14%
Refixia	[redacted]	15%	[redacted]	15%

The company further argues that the emicizumab market share among those with severe type A haemophilia continues to increase. The UKHCDO 2024 report shows it increasing to 59%[1], with the company citing an additional presentation at the November 2024 UKHCDO annual meeting as estimating it to be between 60% and 70%. The company applies a 70% market share for emicizumab.

The EAG thinks that the extrapolation to 70% is unreasonable. The absolute rate of increase is slowing over time and only increased by 6% between 2022/23 and 2023/24. The EAG does not have access to the November 2024 data so applies the 2023/24 59% market share, also providing a scenario of a 64% market share.

When pooling Type A and Type B results, the company assumes [redacted]% Type A and [redacted]% Type B. The EAG has previously pooled assuming all patient switch to marstacimab, so 83% Type A and 17% Type B, which is also consistent with the company approach which pools emicizumab and FVIII. The EAG retains this approach. This does highlight that pooling results across Type A and Type B is questionable and it may be better to consider their cost effectiveness estimates separately. A further argument for considering their cost effectiveness estimates separately is that they are wildly different.

3 COST EFFECTIVENESS RESULTS

3.1 *Cost basis*

The results of this report only include the marstacimab PAS. This has been increased from [redacted] to [redacted] resulting in annual costs of [redacted] for 150mg and [redacted] for 300mg. First year dose escalation results in a weighted average annual cost of [redacted] while second year dose escalation results in a weighted average annual cost of [redacted] It should be borne in mind that during the BASIS OLE considerably more patients were eligible for dose escalation than escalated during the OLE, around [redacted] of those who remained on 150mg at the start of the OLE. Should [redacted] of all marstacimab patients dose escalate over time the weighted average annual cost increases to [redacted]

There are commercial agreements in place for all comparators with the exception of Novo Eight which is no longer part of the MPSC framework. Other treatments are

[1] Figure 7, Page 41

costed using list prices and where appropriate the publicly available CMU EMIT prices. A confidential cPAS appendix that summarises and applies the comparator price discounts has been supplied.

3.2 *Company base case cost effectiveness results*

The revised company base case results in the following costs and benefits for haemophilia type A.

Table 3: Company base case: Costs and QALYs: Type A

Treatment	Tx Cost	Cost	QALY
Marstacimab	[redacted]	[redacted]	[redacted]
Advate	[redacted]	[redacted]	[redacted]
Refacto AF	[redacted]	[redacted]	[redacted]
NovoEight	[redacted]	[redacted]	[redacted]
Nuwiq	[redacted]	[redacted]	[redacted]
Esperoct	[redacted]	[redacted]	[redacted]
Elocta	[redacted]	[redacted]	[redacted]
Adynovi	[redacted]	[redacted]	[redacted]
FVIII Basket	[redacted]	[redacted]	[redacted]
Hemlibra	[redacted]	[redacted]	[redacted]

Net costs, net QALYs and cost effectiveness estimates are presented in Table 4.

Table 4: Company base case: Net Costs, net QALYs and cost effectiveness: Type A

				NHB at WTP of:	
Treatment	Δ Cost	Δ QALY	ICER	£20k	£30k
Marstacimab	..	..	..	..	..
Advate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refacto AF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NovoEight	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nuwiq	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Esperoct	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Elocta	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adynovi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FVIII Basket	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hemlibra	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The revised company base case for haemophilia type B is presented below.

Table 5: Company base case: Costs and QALYs: Type B

Treatment	Tx Cost	Cost	QALY
Marstacimab	[redacted]	[redacted]	[redacted]
BeneFIX	[redacted]	[redacted]	[redacted]
Alprolix	[redacted]	[redacted]	[redacted]
Idelvion	[redacted]	[redacted]	[redacted]
Refixia	[redacted]	[redacted]	[redacted]
FIX Basket	[redacted]	[redacted]	[redacted]

Net costs, net QALYs and cost effectiveness estimates are presented in Table 6.

Table 6: Company base case: Net Costs, net QALYs and cost effectiveness: Type B

				NHB at WTP of:	
Treatment	Δ Cost	Δ QALY	ICER	£20k	£30k
Marstacimab	..	..	..	..	..
BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FIX Basket	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Pooling results assuming 70% emicizumab among Type A and [redacted] Type A and [redacted] Type B results in net health benefits of [redacted] QALYs at a willingness to pay of £20,000 and [redacted] QALYs at a willingness to pay of £30,000.

A variety of scenario analyses are presented in Appendix 1 of the company consultation response.

4 EXTERNAL ASSESSMENT GROUP'S ADDITIONAL ANALYSES

4.1.1 EAG model revisions

The EAG revised base case differs from the company revised base case in the following.

- EAG01: 75% FVIII/FIX dose adjustment rather than 85%
- EAG02: UKHCDO market share data rather than IQVIA
- EAG03: Minor revisions to clinical inputs

Table 7: EAG model changes effects upon NHB of marstacimab: WTP £20,000

Comparator	Section	Emicizumab	FVIII	FIX
Company BC	3.2	[redacted]	[redacted]	[redacted]
EAG01	1.8	[redacted]	[redacted]	[redacted]
EAG02	2	[redacted]	[redacted]	[redacted]
EAG03	2	[redacted]	[redacted]	[redacted]
EAG01-EAG03		[redacted]	[redacted]	[redacted]

The revised EAG base case results in the following costs and benefits for haemophilia type A.

Table 8: EAG base case: Costs and QALYs: Type A

Treatment	Tx Cost	Cost	QALY
Marstacimab	[redacted]	[redacted]	[redacted]
Advate	[redacted]	[redacted]	[redacted]
Refacto AF	[redacted]	[redacted]	[redacted]
NovoEight	[redacted]	[redacted]	[redacted]
Nuwiq	[redacted]	[redacted]	[redacted]
Esperoct	[redacted]	[redacted]	[redacted]
Elocta	[redacted]	[redacted]	[redacted]
Adynovi	[redacted]	[redacted]	[redacted]
FVIII Basket	[redacted]	[redacted]	[redacted]
Hemlibra	[redacted]	[redacted]	[redacted]

Net costs, net QALYs and cost effectiveness estimates are presented in Table 9.

Table 9: EAG base case: Net Costs, net QALYs and cost effectiveness: Type A

				NHB at WTP of:	
Treatment	Δ Cost	Δ QALY	ICER	£20k	£30k
Marstacimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Advate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refacto AF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NovoEight	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nuwiq	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Esperoct	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Elocta	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adynovi	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FVIII Basket	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hemlibra	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Pooling across emicizumab and FVIII results in estimates of net health benefits of [redacted] QALYs at a willingness to pay of £20,000 and [redacted] QALYs at a willingness to pay of £30,000.

The revised EAG base case for haemophilia type B is presented below.

Table 10: EAG base case: Costs and QALYs: Type B

Treatment	Tx Cost	Cost	QALY
Marstacimab	[redacted]	[redacted]	[redacted]
BeneFIX	[redacted]	[redacted]	[redacted]
Alprolix	[redacted]	[redacted]	[redacted]
Idelvion	[redacted]	[redacted]	[redacted]
Refixia	[redacted]	[redacted]	[redacted]
FIX Basket	[redacted]	[redacted]	[redacted]

Net costs, net QALYs and cost effectiveness estimates are presented in Table 11.

Table 11: EAG base case: Net Costs, net QALYs and cost effectiveness: Type B

				NHB at WTP of:	
Treatment	Δ Cost	Δ QALY	ICER	£20k	£30k
Marstacimab	-	-	-	-	-
BeneFIX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alprolix	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Idelvion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Refixia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FIX Basket	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Pooling across Type A and Type B results in estimates of net health benefits of [redacted] QALYs at a willingness to pay of £20,000 and [redacted] QALYs at a willingness to pay of £30,000.

4.1.2 EAG scenario analyses

The EAG supplies the following scenario analyses:

- SA01: Reducing the administration disutilities to 50% and 0% of their base case values.
- SA02: Varying the FVIII/FIX dose adjustment from 75% to 70% and 80%.
- SA03: Applying the year 2 dose escalation percentage to subsequent years until 50% of marstacimab patients have dose escalated.
- SA04: 10% emicizumab discontinuation rate
- SA05: emicizumab 64% Type A market share
- SA06: Type A and Type B specific bleed rates, treatment effectiveness and dose escalation.

Table 12: EAG scenarios: NHB for WTP £20,000: QALY gains

Comparator	Emic.	FVIII	Type A	Type B	All
EAG BC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA01a: Admin disutility 50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA01b: Admin disutility 0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SA02a: FVIII/FIX 70% adjust	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA02b: FVIII/FIX 80% adjust	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA03: Dose escalation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA04: 10% emic. disc.	[redacted]	..	[redacted]	..	[redacted]
SA05: 64% emic. market	..	..	[redacted]	..	[redacted]
SA06: Type specific	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 13: EAG scenarios: NHB for WTP £30,000: QALY gains

Comparator	Emic.	FVIII	Type A	Type B	All
EAG BC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA01a: Admin disutility 50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA01b: Admin disutility 0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA02a: FVIII/FIX 70% adjust	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA02b: FVIII/FIX 80% adjust	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA03: Dose escalation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SA04: 10% emic. disc.	[redacted]	..	[redacted]	..	[redacted]
SA05: 64% emic. market	..	..	[redacted]	..	[redacted]
SA06: Type specific	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

5 Appendix 1: Literature review of quantitative studies of administrative quality of life values.

The EAG has provided an extensive review of the estimates of the disutilities of subcutaneous administration and intravenous infusion of Johnston et al. in section 5.2.2 of its original report. It views the health state vignettes as biased against intravenous infusion. There are also concerns around the poor reporting of the statistical analyses and the disutility estimates only being reported to one significant figure.

Okkels et al. (2024), sponsored by Novo Nordisk, undertook a time trade off exercise through an online survey among members of the UK, Canadian and USA male general public. Long form health state descriptors were initially presented to participants but for most of the survey short form summaries were presented. Unfortunately, the short form summaries are largely not presented. Haemophilia was not mentioned.

Respondents who would not trade off any survival or all their future survival were asked why. Respondents who stated that ethical or religious beliefs led to their trading behaviour or that they did not understand the question were excluded from the analysis. The reason for excluding those with ethical or religious reasons is unclear. Excluding those who said they did not understand the question appears to exclude noise from a particular direction so may bias the analysis. Around a fifth of respondents were excluded though not solely for these reasons.

Within one block of the three blocks of surveys treatments could be characterised as having no injections site reactions or always having an injection site reaction within 48 hours, this being mild rash, redness, bruising, itching or discomfort. It is unclear how or to which health states the injection site reactions were associated with. Most vignettes appear to have assumed no injection site reactions.

The prefilled pen for subcutaneous injection is described as taking 1 minute, the vial with single use syringe for subcutaneous injection is described as taking 5 minutes while single use syringe for intravenous infusion is described as taking 10 minutes.

The EAG thinks that the vignettes of Okkels et al. are both reasonable and superior to those of Johnston et al.

The utility gains of Okkels et al. can be compared with those implied by the estimates of Johnston et al., assuming that prefilled and single use syringe for subcutaneous injection involve the same disutility of -0.0002. For monthly prefilled subcutaneous versus weekly prefilled subcutaneous Okkels et al. estimate a utility gain of 0.012 compared to 0.008 for Johnston et al. For monthly prefilled subcutaneous versus weekly intravenous Okkels et al. estimate a utility gain of 0.049 compared to 0.013 for Johnston et al.

Okkels et al. also raise the possibility of prefilled subcutaneous resulting in gains compared to single use syringe subcutaneous. While not entirely unambiguous it appears that monthly prefilled subcutaneous compared to monthly single use syringe subcutaneous resulted in a utility gain of 0.031.

It is tempting to assume a constant disutility per administration to infer disutilities per administration for use in the modelling. But this results in estimates that are inconsistent with one another, suggesting that a constant disutility per administration is invalid.

Despite the apparent bias in the vignettes of Johnston et al. the estimates of Okkels et al. provide some support to the estimates of Johnston et al. They also suggest that there could be additional gains from prefilled subcutaneous such as marstacimab compared single use syringe subcutaneous such as emicizumab.

Carlsson et al. (2017), funded by Sobi Swedish Orphan Biovitrium AB, performed a time trade off study among 184 Swedish haemophiliacs and 1,233 members of the Swedish general population. This rated four health states:

1. injection frequency every other day, can participate in physical activity, 1 – 2 bleeds per year
2. injection frequency every other day, cannot participate in physical activity, 1 – 2 bleeds per year
3. injection frequency every fifth day, can participate in physical activity, 1 – 2 bleed per year
4. injection frequency every fifth day, can participate in physical activity, 5 - 6 bleed per year

Injections are described as taking 20-30 minutes including preparation. EAG expert opinion suggests that 10-25 minutes might be a more usual average for FVIII/FIX plus an additional 5 minutes for Haemtrack recording. Haemophiliac respondents rated each of the four health states considerably higher than members of the general public, with an increment of around 0.15. The differences between mean health states were more consistent, haemophiliac respondents suggesting a differences between (1) and (3) of 0.3 while the general public suggested a difference of 0.4. Assuming a constant disutility per intravenous injection, further regression results of Carlsson et al. suggests a haemophiliac estimates of a -0.00026 decrement and -0.00036 from the general public, which are broadly aligned with the estimate of Johnston et al.

Turning to discrete choice experiments, Furlan et al. (2015), sponsored by Biogen, conduct what appears to be a similar survey of patient preferences as that of the Lu et al. (2024) abstract cited by Pfizer in its consultation response. Haemophilia patients, 89 type A and 32 type B, were asked about their likelihood of switching between different treatment scenarios, these varying by administration frequency, number of bleeds, vials per infusion, diluent volume, whether the device did or did not premix and manufacturer. The manufacturer could be either new to haemophilia and unfamiliar to the patient, or one the patient was familiar with both it and its haemophilia products. Frequency of infusion was the most important attribute, 47%, followed by breakthrough bleeds, 25%, and manufacturer, 19%. Whether the device premixed was relatively unimportant at around 3% which contrast with the results of Okkels et al.

Chiou et al. (2025) in a series of discrete choice experiments among 51 Taiwanese haemophiliacs found type of treatment, Factor VIII vs non-Factor VIII, and risk of thromboembolic events to be the most important determinants of preferences. This was followed by whether treatment was subcutaneous or intravenous. Administration frequency and bleed rates followed, then long term evidence on safety being available and monitoring requirements.

Fifer et al. (2020), sponsored by Roche Products, also conducted discrete choice experiments among 56 haemophilia patients, treatment attributes including time per administration, < 5 minutes, 5-15 minutes and > 5 minutes, and administration frequency, daily, weekly, fortnightly and monthly. Other attributes were bleed

frequency, whether the treatment could be used as rescue treatment, risk of developing inhibitors, side effects, severe side effects, injection site reactions, storage requirements and prescription collection/delivery options. In contrast to Furlan et al. the frequency of administration and time taken for administration are of 0% relative importance. Bleeds, side effects, injection site reactions, use as rescue therapy and storage determining patient choices.

Naraine et al. (2002) in an unsponsored study used the standard gamble to estimate quality of life values for haemophilia health states among 30 health adults, 30 parents of children with haemophilia and 28 adults with haemophilia. The health state vignettes encompassed bleeds which varied with the treatment received: on demand therapy, FVIII weekly, FVIII twice weekly and FVIII every other day. Median utilities for each health state are presented rather than means, with those of the general population being the lowest. In contrast to parents of children with haemophilia and adults with haemophilia, the median responses from the general population were non-monotonic; i.e. they did not steadily decline over the health states. The difference between the best and the worst health state for the general population was 60% higher than that of parents of children with haemophilia and of adults with haemophilia.

Naraine et al. in their conclusions note that subjects with experience of haemophilia generated higher median scores and that this mirrors other results such as those of Boyd et al. This also mirrors the results of Carlsson et al. reviewed above. Naraine et al. suggest that parents of children with haemophilia and adults with haemophilia have experienced some elements of the scenarios involved and so were less willing to take the risk of death within the standard gamble; i.e. having experience of haemophilia health states including varying treatment frequencies meant they viewed them less negatively than the general population. This may give some pause for thought about estimates from members of the general population, such as those of Johnston et al. and Okkels et al.

The EAG thinks that the studies that provide utility estimates provide some support to the values of Johnston et al., despite the vignettes of Johnston et al. being biased. The discrete choice experiments in general suggest that administration frequency is not as important as other treatment attributes and may be relatively unimportant.

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6 Appendix 2: EAG review of company changes to clinical inputs

	Company	EAG	Description
AJBR Proportion (Cell B6)	[redacted]	[redacted]	When cell F98 is corrected to [redacted] company aligns with EAG of [redacted]
Year 1 Rate Ratio (Cell B13)	[redacted]	[redacted]	Company estimate comes from raw data rather than EAG estimates from a combining different sources and rounded numbers. Company estimate likely correct.
Year 2 Rate Ratio (Cell C13)	[redacted]	[redacted]	EAG calculation of long term rate based on OLE population only, excluding those who drop out, whilst use pre-OLE estimate for all people, including those who do not reach OLE. As estimate is relevant for OLE period and population, EAG maintain their preference.