NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

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

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using marstacimab in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation 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 recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: December 2024

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using marstacimab in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 06 February 2025
- Second evaluation committee meeting: 12 March 2025
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Marstacimab is not recommended, within its marketing authorisation, for preventing bleeding episodes (prophylaxis) caused by severe haemophilia A (congenital factor VIII [8] deficiency) or severe haemophilia B (congenital factor IX [9] deficiency) in people 12 years and over, weighing at least 35 kg, without factor inhibitors (anti-factor antibodies).

1.2 This recommendation is not intended to affect treatment with marstacimab that was started in the NHS before this guidance was published. People having treatment outside this may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop. For children or young people, this decision should be made jointly by the healthcare professional, the child or young person, and their parents or carers.

Why the committee made this recommendation

People with severe haemophilia A usually have prophylaxis with factor 8 replacement therapy or emicizumab to prevent bleeding episodes. People with severe haemophilia B have prophylaxis with factor 9 replacement therapy.

Evidence from a clinical trial shows marstacimab reduces the number of bleeding episodes a person has compared with factor 8 or 9 prophylaxis. There is no trial directly comparing marstacimab with emicizumab. An indirect comparison suggests marstacimab reduces bleeding episodes by a similar number as emicizumab. But the evidence for this is highly uncertain.

There are also important uncertainties in the economic model and it is not possible to determine the most likely cost effectiveness estimates for marstacimab. So, marstacimab is not recommended.

2 Information about marstacimab

Anticipated marketing authorisation indication

2.1 Marstacimab (Hympavzi, Pfizer) does not yet have a marketing authorisation in Great Britain. It received a marketing authorisation by The European Commission "for routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with: severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors or severe haemophilia B (congenital factor IX deficiency, FIX < 1%) without factor VIX inhibitors.

Dosage in the marketing authorisation

2.2 The dosage schedule will be available in the summary of product characteristics for marstacimab.

Price

2.3 The list price of marstacimab is confidential until published by the Department for Health and Social Care.

2.4 The company has a commercial arrangement, which would have applied if marstacimab had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by Pfizer, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

3.1 Haemophilia A and B are caused by gene mutations that result in the inability or reduced ability to produce factor VIII for haemophilia A and factor IX for haemophilia B, which are vital for blood clotting. This leads to prolonged bleeding after injury and, when severe, bleeding into joints and muscles without any injury. Haemophilia A and B are inherited disorders

that mostly occur in men and boys. Women and girls who carry the haemophilia gene mutation may have mild, or rarely, moderate to severe symptoms of bleeding. For this evaluation, the company presented evidence of clinical and cost effectiveness for marstacimab in severe haemophilia A and B only in people who do not have anti-factor antibodies. The severity of haemophilia A and B is classed according to the amount of clotting factor remaining compared with expected levels. Severe haemophilia is defined as having less than 1% of clotting factor present. The clinical experts explained that severe haemophilia A and B usually present in the first few years of life with joint or muscle bleeds. Occasionally, this may cause spontaneous and potentially fatal bleeds. The clinical experts explained that subclinical bleeds are also associated with the condition. These bleeds can cause chronic pain and damage joints, potentially affecting mobility and, over time, needing surgery. The patient experts explained that the risk of bleeding can limit jobs, sports and other activities. They explained that factor prophylaxis treatment for severe haemophilia often requires intravenous injection, self-administered or by carers, as often as every 2 to 3 days, which is a substantial treatment burden. It is also associated with a substantial negative psychological effect on people with the condition, and is associated with a worsened quality of life of carers of children with the condition. Because haemophilia A and B are inherited there may be several siblings with the condition in the same family, increasing its impact on carers. The committee recognised that severe haemophilia A and B are chronic conditions that substantially affect people's lives.

Clinical management

Treatment pathway

3.2 The clinical experts explained that the main aim of treatment for severe haemophilia A and B is to prevent bleeding and long-term damage, especially to joints. This is achieved through prophylaxis to prevent bleeds and on-demand treatment for bleeding episodes when needed. The

available treatment options for haemophilia A for long-term prophylaxis are factor VIII replacement therapy, through intravenous injection, to replenish missing clotting factor in the blood, and emicizumab through subcutaneous injection. Emicizumab, a non-factor VIII treatment, is commissioned through an NHS England clinical commissioning policy as prophylaxis for severe congenital haemophilia A in people of all ages without anti-factor antibodies. Emicizumab is a monoclonal antibody administered every 1 to 4 weeks and mimics the activity of factor VIII to restore clotting function. The available treatment option for haemophilia B for long-term prophylaxis is factor IX replacement therapy, through intravenous injection. For both severe haemophilia A and B, standard and extended half-life factor replacement therapies are available and extra on-demand factor replacement therapy can also be used for treating bleeds. The committee noted that NICE's technology appraisal guidance on etranacogene dezaparvovec for treating moderately severe or severe haemophilia B (TA989) recommended it through a managed access programme. But etranacogene dezaparvovec is not a relevant comparator in this evaluation. The committee concluded that treatment for severe haemophilia A includes prophylaxis with factor VIII replacement therapy or emicizumab, and treatment for severe haemophilia B includes prophylaxis with factor IX replacement therapy.

Limitations of the current treatment options

3.3 The clinical and patient experts explained that current treatment options do not always prevent bleeding and are associated with administration challenges. Frequent injections for factor replacement therapy can damage veins, resulting in pain on administration and increasing the chance of 'vein collapse'. The frequency of injections is especially challenging in older people and young children who may have poor venous access. The patient experts stated that as they have become older they are limited on which veins they can use because of scar tissue. This can make treatment more painful and difficult to administer. Also, about 5% to 7% of people with haemophilia A develop antibodies

(inhibitors) to factor VIII and about 5% of people with haemophilia B develop antibodies to factor IX. Anti-factor antibodies make factor replacement therapies less effective. The committee heard that people with anti-factor antibodies, particularly those with severe haemophilia B, have limited treatment options. The clinical experts explained that the outcomes for these individuals are worse compared with people who do not develop antibodies. They may be wheelchair bound by their second decade because of worsened bleed control and increased bleeds in the joints. The committee noted that because of the anticipated marketing authorisation, people with anti-factor antibodies are outside the scope of this appraisal (see section 2.1). In the NHS, most people with severe haemophilia A are offered emicizumab, an alternative to factor replacement therapy, which is administered subcutaneously. The patient experts explained that there is no single best treatment option for everybody; different people will value aspects of treatment options differently. For example, some people will value a subcutaneous option, while others value an intravenous option. People who participate in sports, for example, may prefer intravenous options so they can have flexibility in adjusting their required dose. The committee acknowledged there are no subcutaneous treatment options available for severe haemophilia B. It concluded that new treatment options for severe haemophilia A and B would be welcomed.

Clinical evidence

BASIS trial

3.4 The clinical evidence for marstacimab came from BASIS, an unpublished phase 3 open-label non-randomised one-way non-inferiority cross-over trial. This enrolled people 12 years and over with severe haemophilia A or severe haemophilia B who had no antibodies to factor VIII or IX. The observational phase enrolled 128 people who previously had either:

- factor VIII or factor IX prophylaxis and who had at least 80% adherence with the scheduled prophylaxis regimen during the 6 months before enrolment (n=91), or
- on-demand treatment with 6 or more acute bleeding episodes that required coagulation factor infusion during the 6 months before enrolment and would be willing to continue on-demand treatment during the observational phase (n=37).

The active treatment phase included 83 people who had used factor VIII or IX prophylaxis in the observational phase. They had 300 mg of marstacimab as a loading dose followed by 150 mg once weekly, self-administered by subcutaneous prefilled syringe injection. After 6 months, people could have their dose increased to 300 mg once weekly. This was decided by a clinician based on the dose escalation criteria:

- body weight at least 50 kg
- at least 2 spontaneous bleeds in a 6-month period treated with on-demand factor VIII or IX.

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 bleeds per year. The committee understood that if non-inferiority of marstacimab compared with factor prophylaxis was shown, then superiority was tested. Key secondary outcomes included annualised joint bleeding rate, spontaneous bleeds, target joint bleeds and total bleeds (treated and untreated) at 12 months after starting marstacimab. The number of people with no treated bleeds was recorded. 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 committee noted that the BASIS trial design was not aligned with UK practice. The committee concluded that the relevant evidence for marstacimab came from BASIS and its open-label extension study. But it noted the following limitations with the trial design:

- no randomisation within the trial
- being open label, there could be a differential reporting of bleeds
- no UK trial sites (see section 3.6)
- emicizumab was not permitted in the observational phase of the trial, but this is a relevant comparator for people with severe haemophilia A in the NHS
- for people who had routine factor replacement prophylaxis, the proportion who had standard half-life or extended half-life was not reflective of the proportions used in the NHS (see section 3.6).

The committee considered these limitations led to important uncertainties including: the trial results (see section 3.5), generalisability (see section 3.6) and the use of ABR data in the model (see section 3.9).

Trial results

3.5 The company presented results from the 6-month observational phase and 12-month active treatment phase of BASIS, and results for a data cut from the open-label extension study. The EAG advised that dose escalation occurred after 6 months of the active treatment phase and the 12-month results presented by the company for the active treatment phase were censored for dose escalations. The EAG requested additional data at 6 months to view results before any dose escalation happened. The BASIS trial demonstrated an improvement with marstacimab over factor prophylaxis, as measured by the ABR of treated bleeds. The mean model-derived ABR for treated bleeds was 5.08 (95% confidence interval [CI] 3.40 to 6.77) for marstacimab during the 12-month active treatment phase compared with 7.85 (95% CI 5.09 to 10.61) for routine prophylaxis during the 6-month observational phase. This represented a reduction in

estimated ABR for treated bleeds of 2.77 (95% CI -5.37 to -0.16). The mean ABR for treated bleeds in haemophilia A was 5.30 for marstacimab during the 12-month active treatment phase compared with 9.16 for routine prophylaxis during the 6-month observational phase. For haemophilia B, the mean ABR for treated bleeds was 4.71 for marstacimab during the 12-month active treatment phase compared with 3.26 for routine prophylaxis during the 6-month observational phase. Six people with haemophilia B increased their dose of marstacimab during the active treatment phase. The mean ABR for treated bleeds for all 18 people with haemophilia B was 3.88 for marstacimab. People having marstacimab had a reduction in ABR for treated joint bleeds from baseline.

Generalisability

3.6 BASIS and its open-label extension were multicentre studies across 19 countries and included sites in Europe. The EAG raised concerns that no UK sites were included. The committee considered the impact of non-UK sites on factor prophylaxis usage in BASIS. The clinical experts advised that in other countries people may have a different history of prophylaxis treatment compared with the UK, which could mean much higher baseline bleed rates. They noted that people with higher background bleed rates who have experienced joint bleeds are more likely to bleed into that joint again, compared with those who have never had a joint bleed. The patient experts noted that people in the UK have optimal factor prophylaxis from a young age. This typically results in a very low bleeding frequency and fewer target joint bleeds. The committee noted several countries were included in the trial, and some may not manage bleeds as optimally. The EAG noted that data was not available to identify countries in BASIS that may have a similar treatment approach to the NHS. It also noted that BASIS included different proportions of people having standard half-life and extended half-life treatment compared with data from the UK Haemophilia Centre Doctors' Organisation (UKHCDO) and the exact results were considered confidential. The clinical experts

stated people in BASIS were not on factor prophylaxis that is comparable to standard of care in the NHS. The EAG also noted that baseline ABRs were higher during the observational phase compared with in the NHS. The committee concluded that there are substantial concerns about trial generalisability and that bleed rates were likely to be higher than in UK practice. The committee further concluded that the effect of marstacimab may have been overestimated compared to its potential effect in UK clinical practice. It also concluded that the trial generalisability may have implications for the results used in the model.

Indirect treatment comparison

Comparison with emicizumab

3.7 There were no trials directly comparing marstacimab with emicizumab, so the company did an indirect treatment comparison (ITC) to establish the relative efficacy. The clinical-effectiveness data for emicizumab came from HAVEN-3. HAVEN-3 was an open-label study including 152 people 12 years and over with severe haemophilia A and no anti-factor antibodies. It had 4 arms including people who:

- had on-demand regimens (instead of factor prophylaxis), randomised to have 1.5 mg/kg emicizumab weekly (arm A), 3 mg/kg every 2 weeks (arm B) or no prophylaxis (arm C)
- had prophylaxis regimens, who had 1.5 mg/kg emicizumab weekly (arm D).

Only arm D was included in the ITC because this group had previously used factor VIII prophylaxis. The company did not have access to individual patient data from HAVEN-3, so it did an unanchored simulated treatment comparison (STC). The STC analysis was based on bleed rates for all participants and did not distinguish between people who did and did not experience bleeds. The analysis accounted for effect modifiers and prognostic variables of previous ABRs (total rate), target joints (yes or no), age (years), body mass index (BMI) and ethnicity. The EAG advised that

these differed from a published study from Astermark et al. 2023; a study which identified medically relevant covariates from HAVEN-3 that included covariates for age, ethnicity, BMI, baseline ABR, proportion of people with less than 9 bleeds in the previous 24 weeks and proportion having standard half-life factor VIII replacement therapy. The company did another STC analysis using these covariates and included target joints in the STC adjustment. These analyses used only the first 33 weeks of follow up from BASIS for consistency with the reported follow-up data available for HAVEN-3. The EAG did its own network meta-analysis (NMA) using data from BASIS and HAVEN-3, in which the follow-up data for the observation and active treatment phases are limited to 6 months. This produced similar results to the STC. The results of the unanchored STC, using the company's preferred assumptions, suggested there were no statistical differences between marstacimab and emicizumab for total ABR. Using the STC covariates from Astermark et al. (2023), bleed rate ratios were closer to 1. The EAG's NMA had similar results. Exact results cannot be reported because the company marked them as confidential. The EAG advised that neither BASIS nor HAVEN-3 were designed to be compared in this way, and it is possible that differences in treatment effect may exist that have not been detected in these analyses. The committee concluded that the indirect comparisons were highly uncertain. It considered that the available evidence did not suggest that marstacimab's effectiveness is markedly different to emicizumab, but the results are highly uncertain.

Economic model

Company's economic model

3.8 The company developed a 3-state Markov model to determine the cost effectiveness of marstacimab. The health states were 'no bleeds', 'bleeds' and 'death'. Patients could transition between the 'bleeds' and 'no bleeds' health states. All people entering the model were distributed among the 'no bleeds' and 'bleeds' health states. People having factor prophylaxis or

marstacimab were distributed based on the BASIS observational and active treatment phase results, respectively, for the proportion of people with zero treated bleeding events. Within the 'bleeds' health state both joint and non-joint bleeds were considered. The company estimated ABR for treated bleeds and annualised joint bleed rate for treated joint bleeds were estimated from a post-hoc analysis of BASIS data for factor prophylaxis and marstacimab, and evidence from the company's ITC for the ABR for emicizumab. In the factor prophylaxis and emicizumab arms, distribution across the 'no bleeds' and 'bleeds' health states was unchanged across the model time horizon. People were assumed to remain on treatment. In the marstacimab arm of the model, the company assumed that the distribution of people in each health state remained constant over time while on treatment, and also assumed that people later redistributed across these health states to model stopping treatment. The company chose a cycle length of 1 year with a half-cycle correction and a time horizon of 64 years. Some people transitioned to death, aligned with general population mortality. That is, no mortality benefit was assumed for marstacimab and people with severe haemophilia A or B were assumed to have the same mortality as the general population. Treated bleeds were associated with a utility decrement per joint and non-joint bleed, and each bleed was associated with a cost. The company modelled a utility decrement per administration for subcutaneous treatments, marstacimab and emicizumab, and for intravenous treatments, factor VIII and factor IX replacement therapies. The committee concluded that the company's model structure was appropriate for decision making.

Treatment effectiveness in the model

3.9 The company base case used the BASIS data to inform the ABRs of marstacimab and factor prophylaxis treatments and the ITC to inform the bleeding rates of emicizumab compared with marstacimab. The EAG advised that prophylaxis treatments used in BASIS did not reflect NHS standard of care (see section 3.6) and the results of the ITC were highly uncertain (see section 3.7). The EAG decided that the UKHCDO data was

the best source to inform the ABRs of factor prophylaxis and emicizumab. It calculated estimates of bleed rates across adult and 12 years and over age groups using weighted averages. The results using the UKHCDO data are confidential and cannot be reported. The UKHCDO uses Haemtrack, a database used by people with haemophilia to record when they experience a bleed. The EAG calculated baseline ABRs for treated bleeds by combining the reported ABR from the UKHCDO report with the balance of standard half-life and extended half-life factor prophylaxis used in BASIS. It then derived a real-world UK-specific baseline ABR estimate for the BASIS population. Bleeding rates for marstacimab were calculated by applying relative effectiveness estimates from BASIS to the real-world UK-specific baseline ABR estimate. This estimate was used when applying the relative effects as estimated from BASIS to derive the efficacy of marstacimab. The committee considered whether the UKHCDO dataset is reliable because it relies on people self-reporting. The clinical experts confirmed that the UKHCDO data is broadly reflective of bleed rates in the NHS. The patient experts stated that recording bleeding episodes on Haemtrack has become easier because it can now be done through an app on a mobile device. So people are more likely to record bleeds compared with previous methods of recording. The committee noted the limitations associated with BASIS and the uncertainty in the company ITC. It accepted the views of the clinical and patient experts that UKHCDO is a reliable source of self-reported bleed rates. The committee concluded that using the UKHCDO baseline ABR for factor prophylaxis and emicizumab is preferable compared to those obtained from BASIS and the ITC. This is because it is more reflective of NHS practice.

Dose escalation of marstacimab

3.10 The BASIS trial protocol allowed dose escalation after 6 months in the active treatment phase and dose escalation could continue in the open-label extension study. People who dose escalated had their dose of marstacimab increased from 150 mg to 300 mg. A clinician decided

whether a person dose escalated once they met the dose escalation criteria defined in the trial; not everybody who met the criteria did dose escalate. The company's base case included dose escalation only in the first year of the model, and this was modelled as 13.25%. The model captured a clinical benefit of dose escalation, but people could not revert to the original dose because ABR for treated bleeds is modelled as constant thereafter. The EAG adjusted the percentage of dose escalation to reflect that nobody who dose escalated stopped treatment, so this figure is higher than the company's estimate. The EAG noted that people were able to dose escalate during the open-label extension study, which is beyond year 1 and therefore not captured in the model. So, the EAG's base case modelled dose escalation for year 2 of the model. The patient experts explained that, in the NHS, dose escalation may take more than a year to implement because people would have a conversation with their clinician and choices around dose escalation are complex. The committee noted that decisions about dose escalation may depend on bleeding rates. It acknowledged that the modelled ABRs were lower using the UKHCDO data (see section 3.6) and that using this data may lead to a lower rate of dose escalation compared with the rate used in the company model. Clinical experts confirmed that some NHS clinical settings have zero tolerance for bleeding episodes, therefore dose escalation could be higher with this practice. If a person had 2 spontaneous bleeds in a 6-month period on a treatment they could either dose escalate, or stop treatment and have factor prophylaxis. The company stated that dose escalation varied between sites in the trial, but this data was not available for the committee. The patient experts explained that in the case of emicizumab, people accept a lower treatment efficacy compared with factor prophylaxis because they value the ease of subcutaneous administration compared with factor VIII administration. So, people may be willing to dose escalate rather than switch treatments to have the benefit of subcutaneous injections. The committee concluded that there is uncertainty about the proportion of people who would dose escalate in the

NHS. It noted that the dose escalation rate could be higher or lower than the rate assumed by the company. It recognised that dose escalation may occur beyond year 1, so preferred the EAG's base-case assumption of including dose escalation in the second year of the model to reflect the trial evidence.

Treatment discontinuation

3.11 In its model, the company assumed that people could stop marstacimab and switch to factor prophylaxis. The company applied a one-off discontinuation rate for marstacimab of 6.02% in the first cycle based on the rates of discontinuation in BASIS. The company stated it did not apply a discontinuation rate for emicizumab because of a lack of data availability. The EAG advised that this is a source of uncertainty and probable bias. The EAG retained this assumption in its base case, but presented a scenario that removed the discontinuation rate for marstacimab so neither treatment was stopped. This increased the incremental cost-effectiveness ratio (ICER) for marstacimab. The clinical expert confirmed that about 10% of people stop using emicizumab. The committee concluded that this is a source of uncertainty in the company's modelling, and that some people on emicizumab would also likely stop treatment. The committee requested further analyses from the company to model a plausible scenario, matching UK practice, that is coherent between the discontinuation of marstacimab and emicizumab. This should include a scenario of applying a treatment discontinuation rate of 10% for emicizumab.

Dosing of factor prophylaxis

3.12 The company did not use the BASIS data to estimate the dosage of factor prophylaxis in its base case. The company took the summaries of product characteristics (SmPCs)-recommended dosage and weighted it by market shares estimated by iQVIA, a global healthcare company providing real-world data. The company also assumed drug wastage and dosing and rounded up these figures. The EAG advised that the dosing figures for

factor prophylaxis in the company's base case were 18% higher compared with the mean total prophylaxis dose in the BASIS trial. The EAG did an analysis using the proportion of people having standard half-life and extended half-life factor prophylaxis in BASIS split by haemophilia A and B and applied these weights using iQVIA market share data. This showed a mean total prophylaxis dose 21% higher than the value in BASIS. The EAG suggests this result is either because dosing during BASIS was lower than in the NHS (which may imply suboptimal treatment during the observational phase) or routine prophylaxis dosing in the model is too high. The EAG explored the second option by reducing the total factor prophylaxis dosing to 75% of the company's estimates. The clinical experts confirmed that they use SmPC recommendations for factor dosing because they want to aim for zero bleeds, so dosing is at the higher end of the recommendations. The company stated that their methods of using SmPC dosing aligned with TA989. The EAG noted that the total factor VIII issued per person per year in the model was higher compared with figures in the UKHCDO annual report. The EAG also noted that UKHCDO included factor VIII used for both routine prophylaxis and treating bleeds, but the company's estimates only included factor VIII used for routine prophylaxis. The committee considered both the company's and EAG's approaches. It noted that the company may have overestimated dosing of factor prophylaxis compared with the UKHCDO data, which it considered was representative of NHS practice. It concluded that the EAG's base-case assumption of reducing the factor dosing to 75% of the company base case was preferred.

Separate or pooled modelling

3.13 The company applied no haemophilia-specific ABR estimates or dose escalation for haemophilia A and B. The company stated that the BASIS trial and open-label extension was not powered to detect differences in ABRs of marstacimab between haemophilia A or B (which were subgroups of the trial population). Marstacimab had a smaller treatment effect for severe haemophilia B compared with severe haemophilia A (see

section 3.5). The company and EAG both provided scenario analyses using the separate estimates of clinical effectiveness for haemophilia A and B. The clinical experts at the meeting noted that there is likely no biological reason why marstacimab would be less effective for severe haemophilia B. The committee noted that the confidence intervals for haemophilia B crossed the boundary of non-inferiority, which was set by the company as an ABR of 2.5. The committee acknowledged that the haemophilia B population in the trial was small (n=18) and evidence generation in this group is difficult because haemophilia B is less common than haemophilia A. The committee considered whether the model captured different pathway parameters for haemophilia A and B. It noted that the company model may not accurately reflect treatment discontinuation because the same discontinuation rate was applied to both haemophilia A and B. The committee accepted the analyses that included the use of pooled ABR data from people with haemophilia A and B. But it remained concerned that the model had not captured other differences in haemophilia A and B, for example, discontinuation of treatments. The committee requested the company provide further clarity on whether the model captured different treatment pathways and parameters for haemophilia A and B.

Health-related quality of life

Bleed-related utility decrements

3.14 In its base case, the company derived differences in quality of life between the 'bleeds' and 'no bleeds' health states through utility decrements applied to acute joint and non-joint bleed events, which only occur in the 'bleeds' state. The company decided it was unfeasible to use EQ-5D scores collected in BASIS because they may not have reflected changes in health-related quality of life related to acute bleed events. The company applied 2 types of utility decrements from the literature dependent upon the type of bleed experienced in the 'bleeds' health state:

- joint bleeds had a utility decrement of 0.28, taken from O'Hara et al. (2018)
- non-joint bleeds had a utility decrement of 0.16, taken from Neufeld et al. (2012).

The company's model assumed these utility decrements applied for 4.5 days. The EAG had concerns about the quality of evidence presented by the company. O'Hara et al. (2018), which was funded by Novo Nordisk, explored the effect of target joints on quality of life in 515 people with severe haemophilia in Europe. The general linear model in the study estimated the effect of the presence of one or more target joints, defined as chronic synovitis. The EAG noted this study was based on target joints and not joint bleeds. It acknowledged these will be linked but the relationship between the number of joint bleeds and the number of joints with chronic synovitis is unknown. The EAG could not source the utility decrement of 0.28 from O'Hara et al. (2018). Neufeld et al. (2012) surveyed 52 people with haemophilia and all participants had anti-factor antibodies. In this study, participants were asked to complete diary entries and complete an EQ-5D for 90 days or until they had experienced 4 bleeds. The EQ-5D index on non-bleed days was 0.82 and on bleed days was 0.66, yielding a net effect of 0.16. The EAG raised concerns that the Neufeld et al. (2012) study was not limited to non-joint bleeds. The EAG's base case applied the same utility decrement of 0.16 for non-joint bleeds and joint bleeds, obtained from Neufeld et al. (2012), because this study encompassed both types of bleed. The EAG applied the 0.16 utility decrement for 2.5 days because this was implied in Neufeld et al. (2012). The committee acknowledged that joint and non-joint bleeds may not have the same decrements but they had not been presented with any evidence that measured these together. It acknowledged the concerns raised by the EAG and requested that the company provide further information and justification for using separate joint and non-joint bleed decrements. The committee concluded that there was uncertainty around the correct values to use for the utility decrements for bleeding events. In

the absence of further evidence, it preferred the EAG's assumption of a single utility decrement of 0.16 applied for a period of 2.5 days.

Treatment disutility per administration

3.15 The company's model applied treatment administration-related utility decrements. It applied a utility decrement of 0.0003 for each intravenous injection for factor prophylaxis, and a utility decrement of 0.0002 for each subcutaneous injection for marstacimab and emicizumab. These values were taken from Johnson et al. (2021). The EAG noted this paper was sponsored by Hoffman-La Roche, the manufacturer of emicizumab which is administered subcutaneously. Johnson et al. (2021) did a time trade off by presenting scenarios for 6 health states. The EAG was concerned that the vignettes did not represent factor prophylaxis administration in the NHS because most people self-administer factor prophylaxis at home, but the vignettes placed more emphasis that factor prophylaxis would be administered in a clinic or hospital. The EAG was also concerned that the disutility estimates for treatment administration were provided at 4 decimal places. So, the actual mean disutility for intravenous administration could be in the range of 0.00025 to 0.00035 and the mean disutility for subcutaneous administration could be in the range of 0.00015 to 0.00025. The EAG noted that because of rounding there may be little to no difference between the 2 central estimates. Also, there were no reported confidence intervals for these values. There is uncertainty whether these confidence intervals would overlap. The EAG's base case provided scenarios for halving utility decrement for treatment administration or applying no utility decrement. The committee was concerned that the time trade off was capturing not only different treatment administration but also different treatment effects, because the bleeding rates were higher in treatments that had to be administered intravenously. The differences may have been exaggerated. The committee noted these 2 issues were not separated out for each health state. The patient experts stated that they could self-administer factor prophylaxis by intravenous injection quickly but noted that as they have become older it is becoming more

difficult to find a vein because scar tissue has formed. The patient experts, in their submission, said that there is a high treatment burden associated with frequent intravenous infusions, and that patients and carers value ease of administration and a reduction in treatment burden. The committee concluded that the evidence presented by the company had serious limitations and lacked adequate explanation but acknowledged there would be some benefit for a subcutaneous treatment option. The committee requested that the company provide further evidence and modelling for the effect of administration method on health-related quality of life, including a full explanation and justification for the approaches taken. The committee concluded there is likely to be a difference in utility decrements between treatment administration methods, but this remains a source of uncertainty and the company's approach may have overestimated the benefits of marstacimab. It further concluded that there was insufficient evidence to justify the treatment administration utility decrements used in the company's model.

Severity

3.16 NICE's methods for conditions with a high degree of severity did not apply to this evaluation.

Cost-effectiveness estimates

Committee's preferred assumptions

3.17 The committee concluded that the cost-effectiveness estimates were uncertain and further justifications for assumptions are needed (see sections 3.14 and 3.15). It agreed the company's overall model structure was acceptable for decision making (see section 3.8). It concluded that its preferred assumptions were:

- using UKHCDO data to model treatment effectiveness for baseline ABR for factor prophylaxis and emicizumab (see section 3.9)
- including dose escalation in year 2 of the model (see section 3.10)

- reducing the factor VIII and factor IX prophylaxis doses to 75% of the company's base case (see section 3.12)
- using the pooled clinical-effectiveness estimates for haemophilia A and B (see section 3.13)
- using a single utility decrement for bleed events of 0.16 applied for a period of 2.5 days (see section 3.14).

The committee also identified further preferred assumptions:

- fixing model errors identified by the EAG
- using the UKHCDO data to inform factor VIII and factor IX administration for bleeds to better reflect NHS practice
- capping the emicizumab dose at 100 kg body weight to reflect NHS practice
- assuming only 20% of bleeds incur hospital resource use to better reflect clinical practice
- using the UKHCDO data to estimate usage of factor prophylaxis in the basket of comparators for consistency with NHS practice.

Uncertainty in the cost-effectiveness estimates

3.18 The committee acknowledged there was uncertainty in the evidence about stopping emicizumab and for the treatment-related and bleed rate utility decrements. It would like to see the following analyses and further evidence to enable it to decide on the cost effectiveness of marstacimab:

- analyses to plausibly model discontinuation of treatments including emicizumab, including scenarios in which 10% of people stop emicizumab (see section 3.11)
- exploration and justification for the evidence on bleed rate utility decrements (see section 3.14)
- further evidence and justification to model treatment-related utility decrements (see section 3.15)

- further exploration of the pathway and parameters of haemophilia A and B captured in the model.

Cost-effectiveness estimates

3.19 Because of confidential commercial arrangements for marstacimab, the comparators and other treatments in the model, the exact cost-effectiveness estimates are confidential and cannot be reported here. Using the committee's preferred assumptions the results showed:

- For haemophilia A, marstacimab was dominated by emicizumab (that is marstacimab is more expensive and less effective than emicizumab) and against a factor VIII basket of weighted comparators the ICER exceeded £1 million per quality-adjusted life-year (QALY) gained.
- For haemophilia B, the ICER for marstacimab against a factor IX basket of weighted comparators exceeded £1 million per QALY gained.

The committee noted that these analyses did not address key uncertainties, including the uncertainty of dose escalation rates, discontinuation rates and utility decrements for treatment administration. The committee concluded that the cost-effectiveness estimates were highly uncertain, and that further evidence was needed to establish plausible ICERs.

Other factors

Equality

3.20 The committee noted that a recommendation in severe haemophilia A or B would not be affected by biological sex. Stakeholders advised that some of the treatments for haemophilia A are derived from human blood or human or animal cells. This may not be considered acceptable by people with some religious beliefs. In haemophilia A, the committee noted there are several treatment options. These include emicizumab, which is not derived from human blood products. The committee did not identify this as an equalities issue that would affect its recommendations. Stakeholders

and clinical experts explained that some people may have difficulty self-administering an intravenous factor treatment if they have joint damage or a separate disability in addition to haemophilia. The committee noted for haemophilia A there are alternative treatments to intravenous administration, such as emicizumab. The committee concluded that all equalities issues for marstacimab had been considered in its decision making.

Uncaptured benefits

3.21 The committee considered whether there were any uncaptured benefits of marstacimab. It did not identify additional benefits of marstacimab not captured in the economic modelling. So, the committee concluded that all additional benefits of marstacimab had already been taken into account.

Conclusion

Marstacimab is not recommended

3.22 The committee noted the important uncertainties in the modelling, including utility decrements and treatment discontinuation. The committee could not conclude that marstacimab would represent a cost-effective use of NHS resources. So, marstacimab is not recommended.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D. Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation. The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Raju Reddy

Chair, technology appraisal committee D

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager and an associate director.

Alice Pritchard

Technical lead

Victoria Kelly

Technical adviser

Greg O'Toole

Project manager

Ian Watson

Associate director

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