# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Appraisal consultation document

# Avatrombopag for treating primary chronic immune thrombocytopenia

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

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

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 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 race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy, and maternity?



Issue date: June 2022

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

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 27 July 2022

Second appraisal committee meeting: 10 August 2022

Details of membership of the appraisal committee are given in section 5

# 1 Recommendations

1.1 The committee was minded not to recommend avatrombopag as an option for treating primary chronic immune thrombocytopenia refractory to other treatments (for example, corticosteroids, immunoglobulins) in adults.

1.2 The committee recommends that NICE requests further clarification and analyses from the company, which should be made available for the second appraisal committee meeting, and should include:

- a network meta-analysis with the mean platelet count as a continuous outcome that, together with a distributional assumption, can be used to derive response probabilities
- scenario analyses for comparison with the company's model assumptions that estimate treatment duration or stopping rates based on the:
  - patient-level data from Study 302
  - empirical data from the extension of Study 302
- details on the:
  - methods of the company's market research that informed the costs in the model
  - how the bleed-related unit costs were derived
- a probabilistic sensitivity analysis, including probabilistic incremental cost-effectiveness ratios, cost-effectiveness scatter plots and cost-effectiveness acceptability curves for £20,000 and £30,000 per quality-adjusted life year gained.

### Why the committee made these recommendations

Current treatment for newly diagnosed primary chronic immune thrombocytopenia usually includes corticosteroids and immunoglobulins. This is followed by thrombopoietin receptor agonists (TPO-RAs). Avatrombopag is another TPO-RA.

Clinical trial evidence suggests that avatrombopag is more effective than placebo at increasing the number of platelets in the blood (cells that help the blood to clot) to a

level that meaningfully reduces the risk of bleeding. But avatrombopag's clinical effectiveness compared with other TPO-RAs is unclear because of uncertainties in the company's indirect treatment comparison.

Whether avatrombopag is cost effective is unknown because of uncertainties in the clinical evidence and the economic model. So, no recommendations could be made, and the company is invited to provide more analyses for consideration at the second appraisal committee meeting.

# 2 Information about avatrombopag

## Marketing authorisation indication

2.1 Avatrombopag (Doptelet, Swedish Orphan Biovitrum) is 'indicated for the treatment of primary chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g., corticosteroids or immunoglobulins)'.

## Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for avatrombopag.

## Price

2.3 The list price of a 10-tablet pack of avatrombopag 20 mg is £640.00 (excluding VAT; BNF online, accessed June 2022).

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

# 3 Committee discussion

The appraisal committee considered evidence submitted by Swedish Orphan Biovitrum, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

# The condition

## Immune thrombocytopenia (ITP) is an autoimmune condition that is chronic in most affected adults

3.1 ITP is characterised by a platelet count less than $100x10^9$ per litre. This reduced platelet count is caused by abnormally high platelet destruction and reduced platelet production. ITP is a rare condition. About 3,000 to 4,000 adults in the UK are estimated to have ITP at any one time. To make a diagnosis, any other possible causes of thrombocytopenia, including impaired bone marrow need to be excluded. Most diagnosed cases in adults progress to chronic ITP that may be difficult to control. Symptoms include fatigue, spontaneous bruising and regular bleeding episodes. The patient experts highlighted that the fatigue can be debilitating, reducing cognitive function and making it difficult to focus. The fatigue also often contributes towards increased bruising. This is because reduced coordination related to the fatigue may cause people to bump into things more often. Bleeding episodes can range from minor bleeds to severe, life-threatening haemorrhages. The patient experts emphasised the effect ITP has on mental as well as physical health. This is because many people with ITP worry about maintaining high enough platelet levels to prevent bleeding episodes. Treatment for ITP is usually introduced when the platelet count drops below $30x10^9$ per litre. Current treatments include corticosteroids, immunoglobulins, thrombopoietin receptor agonists (TPO-RAs) and immunosuppressants such as rituximab. The patient and clinical experts highlighted that the current treatments have disadvantages, including unpleasant and potentially harmful side effects, and the need for dietary changes. They emphasised a need for another treatment option that offered more normality for those affected by ITP. The committee concluded that ITP is a chronic condition that significantly affects the lives of those affected by it.

## People with chronic ITP would welcome new treatment options that maintain platelet counts at a level that prevents bleeds

3.2 ITP is a burden to people with the condition, as well as their families and carers. This burden is often linked to the unpredictable nature of the condition and the side effects of treatment. Also, some people with ITP need to inject some treatments themselves, so need to plan their life around injection dates, and ensure safe storage and administration of these treatments. The patient experts highlighted that this could affect everyday life. Self-injecting can also cause increased anxiety. One patient expert described how they still had stress about injecting 5 years into treatment. Also, soreness and bruising can occur at the injection site, particularly in people whose platelet counts are low. There is an oral TPO-RA, but this can cause side effects including chronic gastrointestinal issues and increased risk of blood clots. It can also be affected by diet, and people taking it may need to restrict what foods they eat, and when they eat them. Both the patient and clinical experts highlighted that this has a large effect on everyday life, adherence to treatment and effectiveness. Some treatments for ITP also cause immunosuppression, which increases the risk of infection. One patient expert explained that they had had 22 infections in an 18-month period when taking an immunosuppressant for ITP. Infections can cause a drop in platelet count, which may need hospitalisation and rescue therapy if uncontrolled. Both the patient and clinical experts agreed that avatrombopag, an oral treatment with no dietary restrictions and no immunosuppression would be an advance in ITP treatment in the UK. They also agreed it could improve quality of life for people with ITP by increasing platelet count without being a difficult treatment to take. The committee agreed that a new treatment option for maintaining platelet counts would be welcomed by people with ITP.

## Treatment pathway and comparators

### The company's positioning of avatrombopag in the treatment pathway is appropriate

3.3 The company's positioning of avatrombopag was aligned with avatrombopag's marketing authorisation, that is, for treating primary chronic ITP in adults refractory to other treatments. When someone is diagnosed with ITP, they are given an 'initial' treatment that includes corticosteroids, immunoglobulins or both. The clinical experts explained that TPO-RAs would not be used before corticosteroids and immunoglobulins but would be used if this initial treatment failed. The committee concluded that avatrombopag is likely to be used after initial treatment of newly diagnosed chronic ITP. It agreed that the company's positioning of avatrombopag in the treatment pathway was appropriate.

### The relevant comparators for avatrombopag are other TPO-RAs

3.4 In its submission, the company considered other TPO-RAs (eltrombopag and romiplostim) to be the only appropriate comparators for avatrombopag. The company's rationale for this was that:

- TPO-RAs are considered to be well-established standard care for ITP
- it would be inappropriate to consider rituximab or surgical splenectomy as the comparators given the availability 2 other TPO-RAs.

The ERG agreed that the company's positioning of avatrombopag was reasonable. But it highlighted uncertainty around the variations in rituximab use in clinical practice. The committee queried at what point in the treatment pathway TPO-RAs are prescribed in the NHS. The clinical experts explained that, while care is individualised to people with ITP, clinicians generally use TPO-RAs before rituximab. They also explained that, before the COVID-19 pandemic, rituximab's use varied across the UK. But international guidance changes have caused a shift in practice to use TPO-RAs first after initial treatment has failed. This is because

rituximab can suppress the immune system. They also confirmed that clinicians rarely offer splenectomy in the first year of diagnosis and do not consider it as an alternative to TPO-RAs. The committee concluded that eltrombopag and romiplostim were the appropriate comparators for avatrombopag.

## Clinical effectiveness

### The population of Study 302 may represent the likely NHS population but there are uncertainties

3.5 The key clinical evidence for avatrombopag came from 1 clinical trial, Study 302, and its 72-week open-label extension. Study 302 was a 26-week, phase 3, multicentre, randomised, double-blind, parallel-group trial of avatrombopag compared with placebo. The company also submitted clinical evidence from 2 open-label clinical trials:

- Study 305, a discontinued phase 3, multicentre, randomised, double-blind, parallel-group trial of avatrombopag compared with eltrombopag
- CL-003, a 28-day, phase 2, double-blind, randomised, controlled trial of avatrombopag compared with placebo, and CL-004, a 6-month rollover study for people who completed CL-003.

The company only included Study 302 data in the economic model because it considered that it contained robust comparative data on key efficacy and safety outcomes. It stated that the results of the other studies largely supported the safety and efficacy profile of avatrombopag. But it did not think it was appropriate to include the data from these studies in the economic model. The ERG noted that, although Study 302 did not have a UK site, the baseline characteristics of its population would likely be applicable and relevant to an NHS population. But the committee noted that the trial's population may have been younger than the NHS population. The clinical experts explained that they would not expect the response to avatrombopag to be age specific. However, more fatal bleeds and infection events may happen in older people, which the clinical

experts thought may not have been fully captured in the trial. The committee also noted that 72% of the avatrombopag group were women compared with 47% in the placebo group. There were also people in the trial who had had a splenectomy, which would normally be done after treatment with avatrombopag. Neither the ERG nor the clinical experts thought that this would have had a meaningful effect on the trial results. The committee concluded that the population in Study 302 may represent the NHS population but that there were uncertainties in the study population's baseline characteristics. It took this into account in its decision making.

## The clinical trials of avatrombopag had recruitment and attrition issues, resulting in a limited evidence base

3.6 There were 49 people in Study 302, 32 in the avatrombopag group and 17 in the placebo group. Twenty two people on avatrombopag completed the trial, while 7 stopped because of inadequate treatment effects and 3 stopped for other reasons. One person on placebo completed the trial, while 15 stopped because of inadequate treatment effects and 1 stopped for other reasons. The clinical experts explained that it is difficult to have a true 'placebo' group for chronic ITP treatments. This is because people in a placebo group would not be expected to stay in a trial if they had extremely low platelets and bleeding episodes. This led to limitations when estimating the durable platelet response rate in the placebo group over the course of Study 302. The ERG was concerned with the robustness of the efficacy and safety data from Study 302 because of the imbalanced drop-out between the avatrombopag and placebo groups. It highlighted that this also affected the results of the network meta-analysis (NMA) indirectly comparing avatrombopag with other TPO-RAs done by the company (see section 3.9). This was because the durable platelet response rate was a key outcome assessed in the NMA. The committee was aware that Study 305 was stopped early, and that the results of this study were not included in the economic model. It questioned why it was stopped early. The company explained that the trial protocol for Study 305

mandated unpleasant screening and monitoring procedures for people in the trial, and this contributed to recruitment challenges. It also commented that the trial started when eltrombopag was approved and became commercially available. It thought that people may have been reluctant to enrol and be randomised to avatrombopag, a non-approved treatment. So, the trial was stopped before durable platelet response rate could be measured. But the company thought that data from the study could have been used to provide information on other outcomes, including bleeding episodes. The committee understood that there was a limited evidence base for the clinical efficacy of avatrombopag because of recruitment and attrition issues in the clinical trials.

## Avatrombopag may improve cumulative platelet response and durable platelet response rate, but the clinical evidence is highly uncertain

3.7 The primary outcome of Study 302 was the median cumulative number of weeks of platelet response, measured over 26 weeks. A platelet response was defined as $50\times10^9$ per litre or more. Evidence suggested that the median cumulative number of weeks of platelet response was 12.4 weeks with avatrombopag and 0 weeks with placebo ($p<0.0001$). Other outcomes measured included:

- secondary:
  - proportion of people with a platelet response without rescue therapy at day 8 (avatrombopag 65.6%, placebo 0%; $p<0.0001$)
  - proportion of people with a reduction in concomitant ITP medication (avatrombopag 33.3%, placebo 0%; $p=0.13$)
- exploratory:
  - durable platelet response rate, that is, the proportion of people who had a platelet response for 6 or more of the last 8 weeks of treatment (avatrombopag 34.4%, placebo 0%; $p=0.009$)
  - incidence of any grade of bleeding (avatrombopag 43.8%, placebo 52.9%; $p=0.54$)

- use of rescue therapy (avatrombopag 21.9%, placebo 11.8%; p=0.47).

The ERG noted that the evidence suggested that avatrombopag improved the median cumulative number of weeks of platelet response over 26 weeks and the durable platelet response rate. But it highlighted that the interpretation of the evidence was difficult because of the high drop-out in the placebo group. The committee commented that a platelet response without any form of treatment is improbable. It noted the statistically significant difference in proportion of people with a platelet response without rescue therapy at day 8 between avatrombopag and placebo. It contrasted this with the relatively smaller difference between the 2 groups for the outcome of incidence of bleeds. It questioned what the most clinically meaningful outcomes for assessing clinical effectiveness would be. The clinical experts explained that time spent above a platelet count threshold is a clinically meaningful outcome, but this can be difficult to reach because ITP is variable. They thought that a platelet count of $30\times10^9$ per litre or more could usually be taken as a response in practice. But they added that a platelet count of $50\times10^9$ per litre or more indicates a clinically meaningful response. The company explained that sometimes a platelet count of $20\times10^9$ per litre or more reduces bleeding risk and that there could be bleeding with a count of $50\times10^9$ per litre or more. So, the company thought that the proportion of people with a platelet count of $50\times10^9$ per litre or more without rescue therapy at day 8 could not be a reliable indicator for incidence of bleeds. It thought this was particularly so, given the imbalanced drop-out and follow-up times of the 2 groups in Study 302. The results from Study 305 are confidential so cannot be discussed here. Also, long-term outcomes such as durable platelet response rate were not recorded because Study 305 was stopped before they could be measured. The committee concluded that the evidence from Study 302 suggested that avatrombopag improved cumulative platelet response and the durable platelet response rate, but that this was highly uncertain.

### The frequency of adverse reactions is broadly similar between avatrombopag and placebo

3.8 In Study 302, the incidence of adverse reactions was compared between the avatrombopag and placebo groups at 26 weeks. Because of the imbalanced treatment durations between these groups (mean 22.8 weeks for avatrombopag compared with mean 8.9 weeks for placebo), the ERG adjusted the treatment duration times to allow a fair comparison. The adjusted analysis suggested that the frequencies of adverse reactions were broadly similar (avatrombopag 6.6%, placebo 4.3%; p value not reported). The ERG noted that higher adverse-reaction incidence rates were seen in Study 305 and CL-003/004. However, the incidence rates for the avatrombopag and comparator groups in these studies were largely similar. The committee highlighted that the small number of people in Study 302 meant that only adverse reactions occurring in more than 10% to 20% would have been identified. It concluded that, within the limitations of the data, the frequency of adverse reactions was broadly similar between avatrombopag and placebo.

## NMA

### The ERG's continuity correction method proportional to sample size may be appropriate, but there are uncertainties

3.9 The company did a series of NMAs comparing avatrombopag's efficacy and safety with other TPO-RAs (eltrombopag and romiplostim), fostamatinib and placebo. This was because there was no direct comparison available. The company originally used a Bayesian approach for the NMAs but aligned its NMA to the ERG's frequentist approach after the technical engagement stage. The ERG also highlighted that fostamatinib was included unnecessarily because it was not included in the final scope as a comparator and is not recommended by NICE. So, the ERG did not consider it in its own analysis. Fixed effect models were considered appropriate and the NMAs were done for 6 outcomes, including:

- 2 binary outcomes, reported as odds ratios (ORs):
  - proportion of people with a durable platelet response (durable platelet response rate)
  - proportion of people with reduced concomitant ITP medications
- 4 incidence rate ratio outcomes:
  - any bleeding episodes
  - bleeding episodes with World Health Organization bleeding assessment score grades 2 to 4
  - need for rescue therapy
  - any adverse events.

The NMA for durable platelet response rate was done despite it not being the primary outcome of Study 302. The company stated that this was because it was the only platelet response outcome that could provide comparative effectiveness data between avatrombopag, and eltrombopag and romiplostim. The committee's discussion focused on the durable platelet response rate NMA because it was the only outcome that informed the company's model. It noted that 2 other trials included in the NMA for this outcome had zero event or response in its placebo group because of early drop-out or no response. So, the company adjusted the zero events or response in placebo groups to calculate the ORs. Its first continuity correction attempt resulted in an OR of 102.80 (95% credible interval [CrI] 3.87 to 2,796,448) for avatrombopag compared with placebo. The ERG pointed out that this estimate lacked face validity compared with the evidence from Study 302. It also noted that the company did not provide any detail on how it had corrected for zero events in placebo groups. The ERG preferred another continuity correction method. This involved adding 0.5 to both event and non-event cells in each treatment group to OR. It resulted in an OR of 18.72 (95% CrI 1.02 to 340) for avatrombopag compared with placebo using Study 302 as an example. During technical engagement, the company argued that this approach by the ERG was not appropriate. This was because people were randomised into placebo (n=17) and treatment groups (n=32) in a 1 to 2 proportion in

Study 302. The company considered that the ERG's approach introduced directional bias and made the OR highly uncertain.

3.10 In response to the ERG's response at technical engagement, the company revised its correction method. It did this by adding an adjustment value to each treatment group proportional to the sample size of the trial, but only to event cells. The company stated that this method was based on Sweeting et al. (2004). When there was a zero event or response cell in the placebo group, an adjustment value of 0.35 (17 of 49) was added to the placebo events cell but subtracted from placebo no-events cell. Also, an adjustment value of 0.65 (32 of 49) was added to any avatrombopag events cell but subtracted from an avatrombopag no-events cell. This was done to maintain the original number of people in each treatment group (17 in the placebo group and 32 in the avatrombopag group). This correction method resulted in an OR of 27.49 (95% confidence interval [CI] 0.88 to 855.90) for avatrombopag compared with placebo. The ERG acknowledged that Sweeting et al. suggested an option of correcting zero events or response by adding adjustment values proportional to the sample size to the cells. But it thought that the company had implemented the method incorrectly. This was because, according to Sweeting et al., any adjustments must be applied to both event and no-event cells. This then increases the total number of people in each group as well. So, the ERG did a study-specific sensitivity analysis that correctly implemented the adjustment method suggested by Sweeting et al. As a result, when there was a zero events or response cell in the placebo group, an adjustment value of 0.35 (17 of 49) was added to both events and no-events cells for the placebo group. Also, an adjustment value of 0.65 (32 of 49) was added to both events and no-events cells in the avatrombopag group. This resulted in an OR of 26.91 (95% CI 0.87 to 835.27). During the committee meeting, the company stated that it agreed with the ERG's sensitivity analysis. The committee considered that any correction should have been done across both events and no events and would ideally have been weighted according to sample size. It concluded

that the proportional to sample size approach used in the ERG's sensitivity analysis may have been appropriate for correcting zero events in placebo groups. But it considered that any correction methods would have been associated with high uncertainties for assessing avatrombopag's clinical effectiveness relative to other TPO-RAs. The committee took this into account in its decision making.

## An alternative NMA with mean platelet count as a continuous outcome should be explored

3.11 The committee recalled the uncertainties associated with the clinical evidence from Study 302 because of the:

- high attrition in the placebo group (see section 3.6)
- uncertainties associated with the correction of zero events involved in the NMA analysis on durable platelet response rate (see sections 3.9 and 3.10).

The committee was aware that a durable platelet response would be unlikely with placebo. This would have made it challenging to compare treatments that had been compared with placebo for this outcome, regardless of the approach taken to adjust for the zero events. It was aware that the company's NMA results on the outcome of 'any bleeding events' suggested that avatrombopag may be associated with a lower risk of bleeding compared with placebo (OR 0.32, 95% CI 0.16 to 0.61), eltrombopag (OR 0.43, 95% CI 0.22 to 0.84) or romiplostim (OR 0.39, 95% CI 0.18 to 0.85). But durable platelet response rate was the only outcome that informed the model. The committee was aware that there is an alternative way of exploring avatrombopag's clinical effectiveness relative to other TPO-RAs, while avoiding the issue of zero events or response in placebo groups. This was used to assess mean platelet count as a continuous outcome and transform the resulting estimates into response probabilities for the economic model using an appropriate distributional assumption. Given the uncertainties in the NMA for durable

platelet response rate, the committee concluded that it would have preferred to see the results of an NMA with mean platelet count as a continuous outcome.

## Economic model

### The company's economic model structure is appropriate for decision making

3.12 The economic model was a Markov cohort model consisting of 4 mutually exclusive health states: 'active treatment' (up to 24 weeks waiting for a response), 'responder', 'no treatment no response' (watch and wait) and 'death'. People began in the 'active treatment' state with a platelet count of less than $30x10^9$ per litre and remained there until their response status was determined. People moved to the 'responder' state if their platelet count increased to more than $50x10^9$ per litre. There, they continued active treatment. People stopped active treatment and moved to the 'no treatment no response' state if their platelet count did not increase above $50x10^9$ per litre while on active treatment. 'Responders' could also stop treatment and move to the 'no treatment no response' state if relapse occurred. People in the 'no treatment no response' state restarted active treatment if a bleeding episode occurred, or if there was a need for rescue therapy. At this point, they had an alternative active treatment from their first-line treatment option. People could move into the 'death' state from any of the other model states. Each model cycle lasted 4 weeks, with a time horizon of 56 years representing a lifetime horizon. The ERG considered the model structure to be broadly representative of ITP, and appropriate for modelling the effect of TPO-RAs. The clinical experts noted that people with a low platelet count would typically have active treatment. But they explained that this is not the only factor considered when determining treatment. However, the platelet response threshold of $50x10^9$ per litre is widely used to define treatment response and has been used in previous NICE technology appraisals for ITP. The committee

concluded that the economic model structure was appropriate for decision making.

### The 24-week timeframe for assessing non-response does not represent clinical practice and leads to uncertainty in the model

3.13 The company used durable platelet response rate to measure the clinical effectiveness of avatrombopag. This was because it was the only platelet response measure that provided comparative effectiveness data between avatrombopag, and eltrombopag and romiplostim (see section 3.9). The company took a pragmatic approach and assumed a 24-week timeframe to assess response to TPO-RA treatments in the model based on Study-302. The ERG considered an 8-week timeframe to be appropriate for assessing response to treatments. It highlighted that, according to the summaries of product characteristics for TPO-RAs, treatment should be stopped if there is no response within 4 weeks of prescribing the maximum dose. The clinical experts explained that they would expect to assess response over a period of 8 to 12 weeks rather than 24 weeks. They anticipated that the time taken to titrate an oral treatment would be 4 to 8 weeks, followed by 4 weeks at maximum dose to determine response. They also noted that choice of TPO-RA could affect this. For example, romiplostim has 10 dosing levels so it can take longer to titrate and to determine response to its maximum dose. The committee queried the effect on the cost-effectiveness analysis of changing this timeframe. The ERG explained that the 24-week was a relatively short timeframe because the model considered a lifetime horizon. It thought that this may have been the reason why its scenario analysis with an 8-week timeframe had a small effect on the cost-effectiveness results. The committee concluded that the 24-week timeframe to assess response did not reflect clinical practice. Although it had a small effect on the cost-effectiveness results, the committee concluded that it led to uncertainty in the model and took it into account in its decision making.

## The company's approach to modelling subsequent treatments is acceptable

3.14 The company used a mixed treatment approach to model subsequent lines of treatment in the model. These included other TPO-RAs and non-TPO-RAs, and did not consider treatment sequencing of TPO-RAs. As a result, response rates for subsequent lines may have been higher than for first-line treatment in the company's model (see section 3.15). The company did not consider that assessing treatment sequencing in the model was plausible from a clinical perspective. This was because it considered that avatrombopag and other TPO-RAs had similar efficacy, safety and long-term treatment durations. Also, avatrombopag would be considered for use in people who are suitable for other TPO-RAs. The ERG disagreed with the company. It stated that a comprehensive assessment of fixed treatment sequences, weighted according to treatment pathways in UK clinical practice, would have more appropriately reflected treatment variability. The ERG did a scenario analysis simulating sequences of treatment options. It noted that, when compared with sequences without avatrombopag, sequences including avatrombopag appeared to provide similar value for money as avatrombopag compared with other TPO-RAs in the single-line model. But this assumed identical treatment durations among TPO-RAs. The clinical experts explained that treatment for ITP is highly individualised in practice because the condition is variable. Also, there is no fixed treatment sequence that is followed in clinical practice. People with ITP are also able to switch between TPO-RAs if their condition stops responding or they become intolerant to a specific one. The committee acknowledged that that it was difficult to determine fixed treatment sequences for ITP. It concluded that the company's approach to modelling subsequent treatments was acceptable.

## Defining response differently between TPO-RAs and non-TPO-RAs leads to uncertainties in the model

3.15 The company defined response for TPO-RAs as durable platelet response rate (see section 3.7). But it defined the response for non-TPO-RAs based on NICE's technology appraisal guidance on romiplostim for treating chronic ITP. This definition combined data on efficacy from different studies and took a weighted average. The subsequent lines of treatments that included a mix of TPO-RAs and non-TPO-RAs had mixed treatment response definitions. The ERG noted that the response rates used in subsequent lines of treatment for non-TPO-RAs were high relative to the response rates used in the model for TPO-RAs. The company explained that, because subsequent lines of treatment included treatments unlicensed for ITP, there was a lack of published evidence for durable platelet response rate for non-TPO-RAs. But avatrombopag, eltrombopag and romiplostim all had a similar definition of durable platelet response rate (platelet response over $50x10^9$ per litre for at least 6 of the last 8 weeks of treatment). The company also explained that its approach of using different definitions for TPO-RAs and non-TPO-RAs could have underestimated the response associated with avatrombopag. But it pointed out that a similar approach had been taken in previous NICE technology appraisals. The ERG highlighted that, in fact, the previous appraisals only included non-TPO-RAs at subsequent lines, which was different to the company's model. The ERG also noted that it was unclear whether this approach was conservative for avatrombopag. The committee considered that similar definitions for response for TPO-RAs and non-TPO-RAs would have been preferrable. But it was also aware that this was not possible given the lack of evidence for non-TPO-RAs. It concluded that having different definitions for responses for TPO-RAs and non-TPO-RAs led to uncertainties in the model. It took this into account in its decision making.

## Long-term treatment duration is likely the same between the TPO-RAs but should be based on stopping rates modelled from trial data

3.16 The company assumed long-term treatment duration to be 109 model cycles (436 weeks, or about 8.4 years) for all TPO-RAs. It assumed the constant stopping rate to be 0.9% per 4-week model cycle. The company took these estimates from Lee et al. (2013). This fitted a survival curve to:

- romiplostim data based on a phase 3, placebo-controlled, 24-week trial and a follow-on, open-label extension of up to 6.0 years
- eltrombopag data based on results from the open-label EXTEND trial of up to 5.5. years.

Lee et al. reported 393 cycles for romiplostim and 109 cycles for eltrombopag. The ERG highlighted that the difference in mean times on treatment between eltrombopag and romiplostim suggested that there was a difference in treatment durations and stopping rates between TPO-RAs. During technical engagement, the company provided the results from a survey that it did among 9 clinicians in the UK. It explained that the results supported similar long-term treatment duration between TPO-RAs. The clinical experts noted that 109 cycles is already a long time for people to be on treatments, so 393 cycles would be unrealistic. They noted that TPO-RAs may have similar treatment durations and stopping rates, but that some people might stay longer on oral treatment options with less dietary restrictions. The committee noted that about 31% (10 of 32) of people stopped avatrombopag in Study 302. This would equate to about 1.7% per month stopping avatrombopag during its 72-week extension period. The clinical experts explained that sometimes people stop treatments because their condition becomes stable. The committee was aware the company's approach of using stopping rates from Lee et al. represented a departure from the approach taken by NICE's technology appraisal guidance on romiplostim and eltrombopag. These appraisals modelled time on treatment using patient-level data from the pivotal trials. The company explained that the estimates from Lee et

al. were based on longer trial periods (up to 6.0 years for romiplostim and 5.5 years for eltrombopag) than Study 302 (26 weeks plus a 72-week extension). The committee considered that treatment duration might be similar between TPO-RAs. But it concluded that it would like the company to provide more scenario analyses to enable it to compare what the company assumed in the model, including:

- estimated treatment duration based on modelling stopping rates from Study 302
- a scenario using the empirical data from the extension of Study 302.

## Resource use and costing in the economic model

### It is appropriate to cost bleeding episodes based on NHS reference costs

3.17 In its original submission, the company stratified rescue therapy events into bleed related and non-bleed related. But it nested bleed-related rescue therapies within bleeding episodes. The company also commissioned independent market research to inform the resource use associated with non-minor bleeding episodes. Resources used included hospital stays, diagnostic imaging, blood test and therapeutic interventions. The ERG preferred to cost rescue therapies and bleed-specific unit costs independently. It noted that the company's bleed-specific unit costs informed by its market research data were much higher than those based on NHS reference costs, and those applied in NICE's technology appraisal guidance on romiplostim and eltrombopag. The ERG also noted that there was no clear reporting of which bleed-specific costs were excluded from NHS reference costs and how using the market research captured these alleged omissions. It explained that, because bleed-related rescue therapies were nested within bleeding episodes, the bleed-specific costs were also difficult to interpret. The company aligned its approach to costing to that of the ERG's by modelling bleeding episodes and rescue therapies independently after the technical

engagement, except for bleed-specific unit costs. The company took the midpoint between the NHS reference costs and its market research data to represent bleed-specific unit costs, which informed its revised model. The ERG remained concerned because the company's market research data for bleed-specific unit costs may still have included the costs of rescue therapies. It highlighted that taking this midpoint suggested that bleed-specific costs may not be independent from the costs of rescue therapy, and that this midpoint was still difficult to interpret. The committee noted that there was a lack of detail on the methods of the company's market research. The committee considered that the ERG's approach of using the NHS reference costs would have been appropriate. The committee recognised that there might be additional resources not covered by the NHS reference costs. But it concluded that it would have preferred to see the detailed methods of the company's market research, and how the company derived the bleed-specific unit costs from its qualitative survey questions.

## Cost-effectiveness estimate

### There are uncertainties in the evidence and in the company's modelling assumptions

3.18 The committee noted that there was a the high level of uncertainty in the company's evidence base and model assumptions, specifically:

- the recruitment and attrition issues with avatrombopag studies (see sections 3.6 and 3.7)
- the results from the NMA on durable platelet response rate (see sections 3.9, 3.10 and 3.11)
- that the modelled time-to-treatment response assessment did not reflect UK clinical practice (see section 3.13)
- the different definitions of response between TPO-RAs and non-TPO-RAs (see section 3.15)
- the long-term treatment duration and stopping rates (see section 3.16)

- the company's approach to costing bleeding episodes in the model (see section 3.17).

## The true incremental cost-effectiveness estimate (ICER) is unknown, and more analyses are needed

3.19 NICE's guide to the methods of technology appraisal notes that judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee considered that the true ICER was unknown because of the uncertainties in the clinical evidence that informed the model and the uncertainties in modelling. It also noted that probabilistic ICERs would have been more appropriate for decision making. The committee considered that further analyses were needed to understand the effect of uncertainty on the economic analysis. It requested:

- an NMA with the mean platelet count as a continuous outcome that, together with a distributional assumption, can be used to derive response probabilities
- scenario analyses that estimate treatment duration or stopping rates based on the:
  - patient-level data from Study 302
  - empirical data from the extension of Study 302
- details on the:
  - methods of the company's market research that informed the costs in the model
  - how the bleed-related unit costs were derived
- a probabilistic sensitivity analysis, including probabilistic incremental cost-effectiveness ratios, cost-effectiveness scatter plots and cost-effectiveness acceptability curves for £20,000 and £30,000 per quality-adjusted life year gained.

## Other factors

### There may be additional benefits of avatrombopag not captured but this is uncertain

3.20 There were no equality issues identified for avatrombopag. The company considers avatrombopag to be innovative because it will offer an additional effective treatment choice to those with chronic ITP. Increased treatment options are needed because people with ITP can experience loss of response or adverse events with current treatment options. The company also highlighted that there may be uncaptured benefits with avatrombopag because it is an oral treatment and can be taken without the need for dietary restrictions. This might may improve treatment adherence. The patient experts emphasised the importance of having the choice of a treatment such as avatrombopag because anxiety around injecting is common, and maintaining dietary restrictions is burdensome. The company also noted that, unlike eltrombopag, avatrombopag does not cause hepatoxicity. This means that less monitoring is needed, and that it can be used for people with ITP who also have liver disease. The committee concluded that there may be additional benefits with avatrombopag that are not captured in the cost-effectiveness analysis but there are uncertainties. The committee would like to consider this innovation alongside exploring other uncertainties in the model.

## Conclusion

### The committee is not able to make a recommendation for avatrombopag and requests further analysis

3.21 The committee was not able to make a recommendation for avatrombopag for treating chronic ITP. The base-case cost-effectiveness estimates are unknown because of the high degree of uncertainty in the clinical evidence and economic modelling. The committee requested further analyses to explore the uncertainties.

# 4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review 3 years after publication of the guidance. NICE welcomes comment on this proposed date. NICE will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Charles Crawley
Chair, appraisal committee B
June 2022

# 5 Appraisal committee members and NICE project team

## Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

## NICE project team

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

**Emily Leckenby, Rebecca Thomas**
Technical leads

**Yelan Guo**

Technical adviser

**Jeremy Powell**

Project manager

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