NICE National Institute for Health and Care Excellence

# Single Technology Appraisal

# Avatrombopag in combination for treating chronic immune thrombocytopenia [ID3838]

# Committee Papers

NICE National Institute for Health and Care Excellence

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**SINGLE TECHNOLOGY APPRAISAL**

# Avatrombopag in combination for treating chronic immune thrombocytopenia [ID3838]

**Contents:**

The following documents are made available to consultees and commentators:



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

# Appraisal title

### Single Technology Appraisal

## Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

**Type of stakeholder:**

**Consultees –** Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

**Clinical and patient experts and NHS commissioning experts** – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

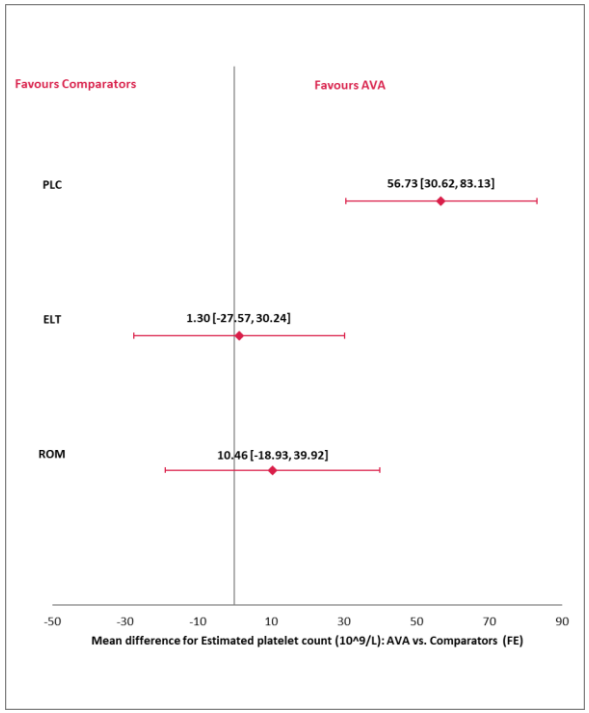
**Commentators –** Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

**Public –** Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

**Please note:** Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

| Comment number | Type of stakeholder | Organisation name | Stakeholder comment<br>Please insert each new comment in a new row | NICE Response<br>Please respond to each comment |
|---|---|---|---|---|
| 1 | Consultee - company | Sobi | Sobi has sought to provide additional analyses as well as points of clarification with the aim of removing uncertainty for the committee in terms of the clinical evidence and the economic model. This supports our belief that avatrombopag is efficacious, safe, and a cost-effective use of resources to the NHS.<br><br>Sobi believe that avatrombopag fulfils a clear unmet need that was supported by both patient and clinical experts in the first committee meeting.<br><br>Avatrombopag is a vital addition to current treatments since patients who are intolerant or unresponsive to one of the existing reimbursed TPO-RA options can successfully switch and respond to avatrombopag.<br><br>Furthermore, as patient testimony highlighted during the committee, there are potentially significant improvements in patient quality of life attributable to avatrombopag vs other TPO-RA options. Importantly, avatrombopag does not cause deranged liver function and is more convenient for patients as there are no dietary restrictions, unlike eltrombopag. | Thank you for your comment. The committee considered the additional analyses during their decision making. Avatrombopag is now recommended in adults with chronic immune thrombocytopenia. |
| 2 | Consultee - company | Sobi | Sobi acknowledge that the committee perceived that there is a limited evidence base for the clinical efficacy of avatrombopag because of recruitment and attrition issues in the clinical trials. We would like to provide additional commentary on this point to demonstrate that there is a growing evidence base and clinical experience of using avatrombopag.<br><br>The pivotal trial for avatrombopag demonstrated statistical and clinical significance leading to marketing authorisation in Europe and the UK. [1]<br><br>There is also growing clinical experience of using avatrombopag in Ireland and Scotland following reimbursement in both countries. Both the provided NMA and our responses elsewhere draw on multiple published observational studies reflecting positive real-world experience even in heavily pre-treated ITP populations or those who have been previously treated with TPO-RAs. [2-5]<br><br>In summary the efficacy of avatrombopag has been demonstrated in both an RCT and real-world setting. | Thank you for your comment. Discussion around the clinical effective evidence can be seen in sections 3.6 and 3.7 of the FAD. |
| 3 | Consultee - company | Sobi | The company notes that the committee concluded that the 24-week timeframe to assess response did not reflect clinical practice. We would like to clarify that we previously accepted the ERG's views on this issue during the technical engagement stage and altered our base case analysis by correcting it to a 3-cycle duration for assessing response (corresponding to a 12-week timeframe).<br><br>A 12-week duration aligns with the evidence provided by the clinical experts during the first committee meeting. | Thank you for your comment. Discussion around the timeframe to assess response can be seen in section 3.15 of the FAD. |

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment<br>Please insert each new comment in a new row</th><th>NICE Response<br>Please respond to each comment</th></tr>
<tr><td>4</td><td>Consultee - company</td><td>Sobi</td><td>
The company has submitted as a separate appendix to these comments an additional network meta-analysis (NMA) that compares avatrombopag (AVA) versus eltrombopag (ELT) and romiplostim (ROM) with mean change in platelet count in patients with immune thrombocytopaenia (ITP).<br><br>
The analysis was conducted in response to the request from the appraisal committee to conduct an additional NMA with the mean platelet count as a continuous outcome that, together with a distributional assumption, can be used to derive response probabilities. The key findings are presented below.<br><br>
A Bayesian NMA showed that all treatments (AVA, ELT, ROM) were associated with significantly greater improvement of platelet count compared with placebo (PLC), although the differences between active regimens were not statistically significant. The highest probability for being the best treatment was achieved by AVA (51%) followed by ELT (42%).<br><br>
Table 1: Estimated mean difference in platelet count – fixed effect model
<table>
<tr><th colspan="2">MD for all comparisons (×10$^9$/L) (FE model)</th><th>vs. PLC</th><th>vs. AVA</th><th>vs. ELT</th><th>vs. ROM</th><th>Probability of being best</th><th>SUCRA</th></tr>
<tr><td>PLC</td><td>PLC</td><td>-56.73<br>[-83.13, -30.62]</td><td>-55.50<br>[-67.64, -43.27]</td><td>-46.34<br>[ -59.58, -33.08]</td><td>0%</td><td>0%</td></tr>
<tr><td>AVA</td><td>56.73 [30.62, 83.13]</td><td>AVA</td><td>1.30 [-27.57, 30.24]</td><td>10.46 [-18.93, 39.92]</td><td>51%</td><td>75%</td></tr>
<tr><td>ELT</td><td>55.50<br>[43.27, 67.64]</td><td>-1.30<br>[-30.24, 27.57]</td><td>ELT</td><td>9.18<br>[-8.81, 27.07]</td><td>42%</td><td>77%</td></tr>
<tr><td>ROM</td><td>46.34<br>[33.08, 59.58]</td><td>-10.46<br>[-39.92, 18.93]</td><td>-9.18<br>[-27.07, 8.81]</td><td>ROM</td><td>7%</td><td>48%</td></tr>
</table>
</td><td>Thank you for your comment. The committee considered the additional analyses during their decision making. Discussion around the NMAs provided in the appraisal can be seen in sections 3.9 to 3.13 of the FAD.</td></tr>
</table>

| Comment number | Type of stakeholder | Organisation name | Stakeholder comment<br>Please insert each new comment in a new row | NICE Response<br>Please respond to each comment |
|---|---|---|---|---|
| | | | **Figure 1: Forest plot for comparison AVA vs comparators regarding estimated absolute mean difference – fixed effect model**<br>  <br><br>The estimates for the probabilities of reaching ≥30×$10^9$/L and ≥50×$10^9$/L are detailed in an appendix document and shows that all active treatments were associated with very high likelihood of reaching target PLT count.<br><br>It should be noted that the marginal differences in results between AVA and ELT may be due to differences in study design around titration of treatments. Titration of AVA during the core study was with a platelet target range of 50-150 x $10^9$/L, and the primary end point required a platelet count ≥50 x $10^9$/L, therefore it is likely that a clinically meaningful response was achieved in more patients than is suggested by the primary end point. In comparison, the core study for ELT also allowed titration but patients were assessed for response to treatment over a wider platelet range (response defined as a platelet count of 50–400 × 10^$^9$/L)<br><br>Nevertheless, the results show that the clinical effectiveness of each TPO-RA is similar, according to the mean difference in platelet count outcome. | |

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| 5 | Consultee - company | Sobi | Sobi welcomes the appraisal committee's recognition in the ACD that there might be additional resources not covered by the NHS reference costs for bleed events, but we also acknowledge the committee's concerns with not using NHS reference costs as a basis for calculating costs associated with bleeding events.<br><br>Sobi has therefore updated its costs associated with bleeding events to include NHS reference costs. However, the NHS reference cost codes used differ from those used by the Evidence Review Group (ERG) based on our findings from independent market research as well as clinical advice received following the publication of the ACD. As requested within the ACD, we have provided below information to clarify how the company's market research informed the original bleed-related unit costs used - despite these costings no longer being used in this ACD response - and the subsequent clinical advice received to inform our ACD response.<br><br>**Background to how bleeding costs were derived in the original core submission**<br><br>Costs associated with bleeding events in the company's original submission were informed by market research, which was conducted by an independent agency, that aimed to explore the utilisation of different healthcare resource use elements for outpatient and inpatient bleeds. This research was commissioned following feedback from an Advisory Board that bleed related care costs may differ between patients with ITP and patients in the general population due to differing resource needs, and therefore NHS reference costs could undervalue the cost of treating ITP patients [6].<br><br>113 ITP physicians completed a survey across the EU5 [UK, Germany, France, Spain, Italy] + Netherlands, including 20 from the UK, to quantify frequency of bleeding events, segmentation of severity of bleeds, and length of hospitalisation for ITP patients [7]. Alongside the survey, interviews were conducted with 23 ITP physicians and 12 payors, including 4 haematologists and 2 payors in the UK, to further understand and verify the frequency of bleeding events and healthcare resource utilisation within ITP [7].<br><br>UK payors provided answers with referenceable sources to questions surrounding hospitalisation costs in the NHS, including the average cost per night in hospital, average cost per night in ICU, ER visit cost, cost of diagnostic imaging and blood tests, and rescue therapy costs [7] [please see Table 64, pages 101-102 of Document B, company submission, for a breakdown on the value of these costs].<br><br>Physicians provided clinical information on the estimated treatment and resources required for outpatient and inpatient bleeds in ITP patients [7]. This includes answers to questions on the number of bleeds, use of various treatments (e.g. rescue therapies), number of patient days in hospital, number of patient days in ICU, and number of days patients are followed up [7] [please see Table 63 (labelled 64), page 101 of Document B, company submission, for a breakdown on the utilisation of resources].<br><br>With the insights from both the payors and physicians, the therapy cost for ITP was determined on a per patient basis [i.e. combining frequency of each bleeding event type, utilisation of therapies per each bleeding event, and utilisation of healthcare and human resources per each bleeding event] [7]. A breakdown on the costs per outpatient and inpatient bleed used in the original model were presented in Table 65, pages 102-103 of Document B, company submission. | Thank you for your comment explaining how bleeding costs were derived. Discussion around bleeding costs can be seen in section 3.19 of the FAD. |

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment<br>Please insert each new comment in a new row</th><th>NICE Response<br>Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
<u>Clinical advice received post-core submission</u><br><br>
Following the publication of the ACD, Sobi still maintains that the cost estimates from the performed market research better reflect the actual costs of treatment of bleeds in the UK compared to the ERG's estimates, however, the company understands the concerns of the committee and sought clinical advice from several UK clinicians to find a more appropriate way of costing bleeds [8].<br><br>
Clinicians stated that the duration of different bleeds in ITP patients tends to be longer in comparison to the general population, as it takes a relatively long time to bring an ITP patient's platelet count up and stabilise bleeding [8]. Moreover, they stated that the severity of bleeds in patients with low platelet count tends to be increased [8].<br><br>
Consequently, clinicians suggested that the resource needs could be higher for an ITP patient, for example, "they take significantly more bed days" as they are "in hospital for longer", and "patients with ITP will need longer duration of treatment as they will require ITP specific therapy to bring up their count, and may have endoscopy or other investigations delayed whilst this takes place" [8].<br><br>
Therefore, the company suggest using NHS reference costs in line with the ERG approach but based on the highest considered unit costs. This is to account for the greater bleed related care costs for ITP patients relative to the general population.<br><br>
Table 2: NHS reference bleed costs – ERG and company suggestion<br><br>
<table>
<tr><th rowspan="2">Type of bleed</th><th colspan="2">ERG</th><th colspan="2">Company suggestion</th></tr>
<tr><th>Cost (£)</th><th>Source (NHS reference cost 19/20)</th><th>Cost (£)</th><th>Source (NHS reference cost 19/20)</th></tr>
<tr><td>Outpatient bleed</td><td>459.65</td><td>Weighted average FD03F-FD03H</td><td>493.74</td><td>FD03F</td></tr>
<tr><td>Gastrointestinal bleed</td><td>3,091.79</td><td>Weighted average FD03A to FD03E</td><td>5,502.62</td><td>FD03A</td></tr>
<tr><td>Intercranial haemorrhage</td><td>4,690.02</td><td>Weighted average AA23C to AA23G</td><td>7,044.18</td><td>AA23C</td></tr>
<tr><td>Other inpatient bleed</td><td>2,890.37</td><td>Weighted average, FD03B and FD03E</td><td>3,625.70</td><td>FD03B</td></tr>
</table>
<br>
These new care costs have been added to the company's updated base case cost-effectiveness analysis, which is detailed in subsequent sections.
</td><td></td></tr>
<tr><td>6</td><td>Consultee - company</td><td>Sobi</td><td>In line with the committee's request for new evidence, we have analysed the patient-level data on the duration of treatment with avatrombopag from Study 302 and its extension. The first graph below presents data from the extension of the Study 302 and the second one from the core trial.</td><td>Thank you for your comment. The committee considered the additional analyses during their decision</td></tr>
</table>

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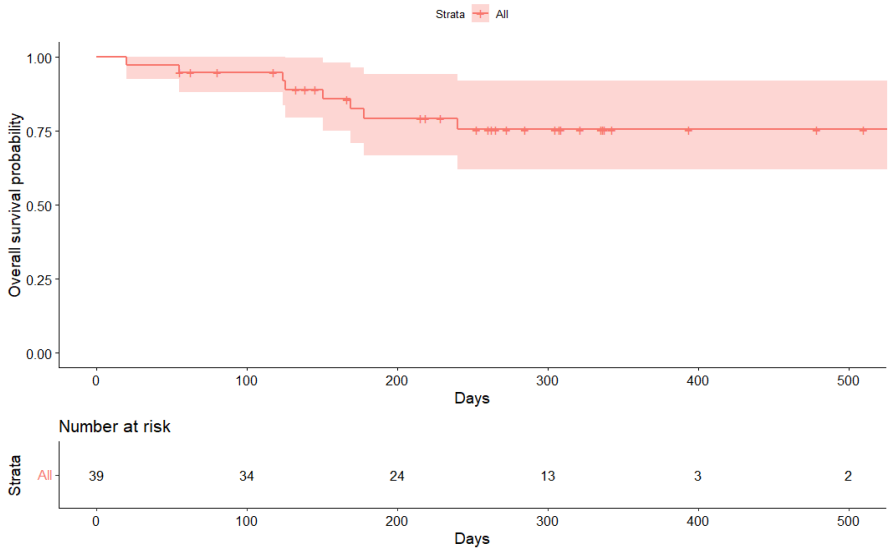
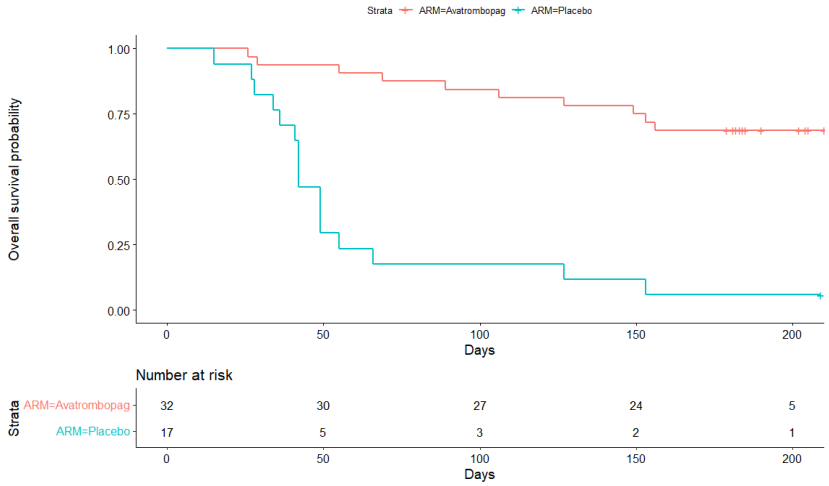
|---|---|---|---|---|
| | | | **Figure 2: Scenario analysis for duration of treatment based on extension of Study 302**<br>  <br><br>**Figure 3: Scenario analysis for patient-level data from Study 302**<br>  <br> | making. Discussion around long-term duration of treatment can be seen in section 3.18 of the FAD. |

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| | | | After fitting the log-normal distribution to the trial data (in an analogous way for the company submissions of ELT and ROM) the average duration of treatment with AVA was estimated for 57.31 cycles based on the core study and 632.70 cycles after inclusion of the trial extension.<br><br>It should be noted that the treatment duration considered in the company submission was based on the long-term trials for comparators and hence should be compared with estimates that consider the extension of the 302 study. Such a comparison confirms the expectation that treatment with AVA can persist at least as long as the use of other TPO-RAs.<br><br>Estimated duration of treatment based on the data for AVA was included in the cost-effectiveness model. Three scenarios were considered:<br>• the same duration of treatment for all TPO-RAs based on core 302 study<br>• the same duration of treatment for all TPO-RAs based on core 302 study + extension<br>• different duration of treatment for ELT, ROM and AVA based on the long-term trials i.e. (109 cycles ELT, 393 cycles ROM, 633 cycles AVA)<br><br>The other assumptions of the model were the same as in the company response to the ERG report with one difference concerning the costs of bleeds, which is detailed earlier within this response in Table 2.<br><br>The cost-effectiveness results of listed scenarios have been presented in Table 5 below. They are consistent with the base case scenario if only the same treatment duration is assumed for all TPO-RAs. The extreme scenario assuming different duration between comparators indicates that AVA is more effective than ROM and also less costly (i.e. dominant). In this scenario, treatment with AVA was shown to be more expensive than ELT but more effective. This result is driven, however, by an assumed 6-fold longer treatment duration, which is highly unlikely according to clinical advice provided by experts during the first committee meeting, as well as shown in the company's survey results of 9 UK clinicians [n.b. shared during technical engagement].<br><br>In a retrospective study in the United States of America (USA) of adults with ITP (both primary and secondary) who switched to AVA following prior treatment with ELT or ROM, the median duration on AVA was recorded as 9.2 months, whilst time on a prior TPO-RA before switching to AVA was a median duration of 9.7 months [2]. Although there are limitations for comparison purposes in terms of study design and population, the results of the study suggest there may be similar treatment durations between TPO-RAs in the real world [2].<br><br>No further published evidence allowing for reliable comparison of treatment duration between TPO-RAs has been identified. At the same time, the company understands from clinicians that they do not expect any important differences between considered comparators in terms of treatment duration [8].<br><br>**Table 5 – ICER scenario analyses for duration of treatment** | |

<table>
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<tr><td></td><td></td><td></td><td>
<table>
<tr><th colspan="4">Base case</th></tr>
<tr><th>AVA vs</th><th>Incremental cost</th><th>Incremental QALYs</th><th colspan="2">ICER / Cost-effectiveness plane</th></tr>
<tr><td>ROM</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>ELT</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><th colspan="4">Treatment duration from the core study (the same for all TPO-RAs)</th></tr>
<tr><th>AVA vs</th><th>Incremental cost</th><th>Incremental QALYs</th><th colspan="2">ICER / Cost-effectiveness plane</th></tr>
<tr><td>ROM</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>ELT</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><th colspan="4">Treatment duration from the core study + extension (the same for all TPO-RAs)</th></tr>
<tr><th>AVA vs</th><th>Incremental cost</th><th>Incremental QALYs</th><th colspan="2">ICER / Cost-effectiveness plane</th></tr>
<tr><td>ROM</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>ELT</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><th colspan="4">Duration from different long-term trials (109 cycles ELT, 393 cycles ROM, 633 cycles AVA)</th></tr>
<tr><th>AVA vs</th><th>Incremental cost</th><th>Incremental QALYs</th><th colspan="2">ICER / Cost-effectiveness plane</th></tr>
<tr><td>ROM</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>ELT</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td><td></td></tr>
<tr><td>7</td><td>Consultee - company</td><td>Sobi</td><td>
In the response to another committee request, Sobi performed a probabilistic sensitivity analysis for the new base case scenario 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. The results of this PSA are presented below.<br><br>
Table 6 – PSA results vs ELT<br><br>
AVA vs ELT
<table>
<tr><th></th><th>Incremental Costs</th><th>Incremental QALYs</th><th colspan="2">ICER / Cost-effectiveness plane</th></tr>
<tr><td>Base Case</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>PSA (mean)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td><td>Thank you for your comment. The committee considered the additional analyses during their decision making. Avatrombopag is now recommended in adults with chronic immune thrombocytopenia.</td></tr>
</table>

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<tr><td></td><td></td><td></td><td>[figures redacted]<br><br>Table 7 – PSA results vs ROM<br><br>AVA vs ROM
<table>
<tr><th></th><th>Incremental Costs</th><th>Incremental QALYs</th><th>ICER / Cost-effectiveness plane</th></tr>
<tr><td>Base Case</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>PSA (mean)</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
[figures redacted]</td><td></td></tr>
<tr><td>8</td><td>Consultee - company</td><td>Sobi</td><td>To make sure that all committee recommendations are fulfilled in this response, Sobi performed additional scenario analyses with inclusion of the results of a network meta-analysis with the mean platelet count as a continuous outcome. These results, together with a distributional assumption, have been used to derive response probabilities of achieving two types of response:<br>• reaching PLT ≥30×10$^9$/L<br>• reaching PLT ≥50×10$^9$/L<br><br>The results of performed NMA and obtained probabilities have been described earlier. In general, the point estimate of the absolute difference in the platelet count is the highest for AVA, however, due to higher uncertainty the probabilities of achieving specified threshold of platelet count are the lowest for AVA. This discrepancy together with the fact that the highest response probabilities have been obtained for ELT indicates the limited usability of this response definition in the economic model. ELT has been shown to have lower efficacy than both AVA and ROM when other types of outcomes were considered. Platelet count often fluctuates over time in ITP patients and the most meaningful response can be considered the sustaining of platelet count at or above a certain level. Therefore, durable platelet response, as considered in the base case scenario, is the most important outcome when comparing treatment efficacy. This is especially pertinent considering durable response allows for differentiation of comparators whereas all TPO-RAs have been shown fully effective in reaching platelet count ≥30/50×10$^9$/L. Nevertheless, the response probabilities for two additional types of response have been implemented in the model with the following results.<br><br>Table 8 – cost-effectiveness results with new response probabilities
<table>
<tr><th colspan="4">New response rates based on PLT > 30</th></tr>
<tr><th>AVA vs</th><th>Incremental cost</th><th>Incremental QALYs</th><th>ICER / Cost-effectiveness plane</th></tr>
<tr><td>ROM</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table></td><td>Thank you for your comment. The committee considered the additional analyses during their decision making. Discussion around the NMAs provided in the appraisal can be seen in sections 3.9 to 3.13 of the FAD.</td></tr>
</table>

| Comment number | Type of stakeholder | Organisation name | Stakeholder comment<br>Please insert each new comment in a new row | NICE Response<br>Please respond to each comment |
|---|---|---|---|---|
| | | | <table><tr><td>ELT</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td colspan="5">New response rates based on PLT > 50</td></tr><tr><td>AVA vs</td><td>Incremental cost</td><td>Incremental QALYs</td><td>ICER / Cost-effectiveness plane</td><td></td></tr><tr><td>ROM</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr><tr><td>ELT</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr></table><br>Difference in efficacy translates to small gains in QALYs in favour of ROM and ELT at significant additional cost. These results confirm that considering any type of response neither ROM nor ELT are cost-effective vs AVA. | |
| 9 | Clinical expert | - | I have read the Appraisal consultation document “Avatrombopag for treating primary chronic immune thrombocytopenia”. The provisional recommendations appear sound and I look forward to the further analysis requested and subsequent review. | Thank you for your comment. Avatrombopag is now recommended in adults with chronic immune thrombocytopenia. |
| 10 | Consultee – patient group | ITP Support Association | Ms White has experienced, over many years, the roller coaster of physical and emotional challenges in monitoring platelet counts, balancing side effects of treatment and managing the reality of platelets dropping, frequent hospital visits for both routine and rescue treatment, dealing with debilitating levels of fatigue as a result of low platelet counts and the impact living with chronic ITP has on mental health and quality of life. | Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Avatrombopag is now recommended in adults with chronic immune thrombocytopenia. |
| 11 | Consultee – patient group | ITP Support Association | **Do we believe all the relevant evidence has been taken into account?**<br>We believe the initial hearing was afforded due time, however given that the drug has already been used and proven its worth for chronic ITP since June 2019 in both the United States and Europe, The SMC in Scotland approved this drug some time ago in December 2020 (August 2021 for ITP) and it has also been used for Thrombocytopenia in liver disease patients in NHS England, we believe there was an over focus on particular scientific elements of this specific SOBI trial in respect of this application. Avatrombopag has a proven safety record and efficacy across all the regions and countries for which it has received approval. Furthermore, our Medical Advisors on the ITP UK Forum (across several centres of excellence) have advised us that Avatrombopag has been requested via the IFR route a number of times in the past year and has been approved for chronic ITP patients in NHS England. | Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Avatrombopag is now recommended in adults |

| Comment number | Type of stakeholder | Organisation name | Stakeholder comment<br>Please insert each new comment in a new row | NICE Response<br>Please respond to each comment |
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| | | | | with chronic immune thrombocytopenia. |
| 12 | Consultee – patient group | ITP Support Association | **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**<br>We do not believe emphasis was necessarily given enough weight in terms of the wastage specifically with Romiplostim. This comes in vials of fixed dose (300 mcg vials). Residual drug is thereby wasted after a dose is made up.<br><br>There are significant financial benefits of Avatrombopag being made available. The cost saving against wastage with other treatments seemed to be lost or ignored during the submission hearing.<br>Cost effectiveness – by way of personal demonstration, Dianne White explained her own case with the injectable dose of Romiplostim. The highest dose for her body weight of 57kg keeps her platelet count around 40-50 x 109/L, subject to no infections, physical traumas, or extreme stress. This costs c. £960 per week, so a total of £56K per year. Arguably for Dianne and other patients with a similar requirement, having been on this drug and injecting for 6 years, Avatrombopag would be a worthy and cost effective alternative if available.<br><br>As was highlighted in Dianne White's initial statement – switching 149 patients from Romiplostim to Avatrombopag would conservatively save the NHS in the region of 850K per annum.<br><br>Avatrombopag clinical effectiveness is well illustrated already with ITP patients, giving more robust results, enhancing QOL and reducing rescue situations and hospital visits. | Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Avatrombopag is now recommended in adults with chronic immune thrombocytopenia. |
| 13 | Consultee – patient group | ITP Support Association | **Are the provisional recommendations sound and a suitable basis for guidance for the NHS?**<br><br>We are surprised at the provisional recommendations and don't believe they are good guidance for the NHS.<br><br>This drug has proven its efficacy and application in the United States across 20 ITP referral centres (as evidenced in Dianne's initial statement), Europe and Scotland.<br><br>It has undergone scrutiny across all those geographical areas over a period of nearly 4 years and prior to that will have undergone significant clinical trials to prove itself.<br><br>It is economically advantaged in an NHS setting.<br><br>Its worst listed side effects are more comparable to some of the milder side effects of the other 2 comparable drugs, used at this level of chronic ITP.<br><br>There are a number of patients for whom neither of these drugs produce good results, side effects are intolerable, or they simply do not fit into lifestyle scenarios – one of the drugs having significant food restrictions – some of which are not always obvious to the user (hidden fortified calcium in foodstuffs potentially eradicating the drug in the body).<br><br>One of the main advantages of taking avatrombopag is that it is an oral medication and can be taken without food restrictions, when compared with other treatments. Our ITPSA recent survey on patients' attitudes to treatment (TRAPeze study) highlighted their preference for oral treatment and there was a significant dislike of the food restrictions, which they find quite irksome and downright difficult. | Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Avatrombopag is now recommended in adults with chronic immune thrombocytopenia. |

| Comment number | Type of stakeholder | Organisation name | Stakeholder comment<br>Please insert each new comment in a new row | NICE Response<br>Please respond to each comment |
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| | | | Up to two thirds of patients suffer from fatigue which is severe in half of these. It is believed it is attributed to a low platelet count and can often pin-point relapses by their change in energy levels and necessity for rescue visits and additional treatment, such as scans, IVig transfusions.<br><br>The thrombopoietin receptor agonists increase the platelet count in a significant proportion of patients and may be associated with improvement of their fatigue and general quality of life. This has been shown in specific health related QOL studies. This contrasts to other medications (e.g., steroids), where fatigue is a reported side-effect of treatment. Avatrombopag is generally well tolerated, and we would expect it to show the same or an enhanced impact as the two currently available agents (Romiplostim and Eltrombopag).<br><br>In addition, as has been said about other medicines, this provides the health care professional with another item in their toolbox of treatments if another TPO-RA does not work or the patient has suffered intolerable side effects from the use of other treatments. | |
| 14 | Consultee – patient group | ITP Support Association | **Key Messages about Avatrombopag:**<br><br>The TPO RA class of drugs are important for ITP patients because they offer a good response rate, and importantly, do not suppress the immune system. This is a particularly relevant factor, given that we all now live in a period of Covid and potentially more aggressive similar type infections in the future may well come along.<br><br>Avatrombopag is an important treatment advance because it is given by a preferred treatment route (oral), without the dietary restrictions of the alternative oral medication, and provides a non-immunosuppressive option, with a good response rate, for those patients who do not tolerate or respond to the alternative TPO RA drugs.<br><br>Following on from all the content in this statement it is important and indeed part of medical progress and innovation that this drug should be available to haematologists to use in suitable chronic ITP patients across the UK and we believe that this will also represent a cost saving to the NHS. | Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Avatrombopag is now recommended in adults with chronic immune thrombocytopenia. |

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**Avatrombopag in combination for treating chronic immune thrombocytopenia [ID3838]**

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| | Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.<br><br>The Appraisal Committee is interested in receiving comments on the following:<br>• has all of the relevant evidence been taken into account?<br>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?<br>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?<br><br>NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:<br>• could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;<br>• could have any adverse impact on people with a particular disability or disabilities.<br><br>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.** |
| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | Swedish Orphan Biovitrum Ltd (Sobi) |
| **Disclosure**<br>Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | None |
| **Name of commentator person completing form:** | |

| **Comment number** | **Comments** |
|---|---|
| **Comment 1:** Company position | Sobi has sought to provide additional analyses as well as points of clarification with the aim of removing uncertainty for the committee in terms of the clinical evidence and the economic model. This supports our belief that avatrombopag is efficacious, safe, and a cost-effective use of resources to the NHS. |

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| | Sobi believe that avatrombopag fulfils a clear unmet need that was supported by both patient and clinical experts in the first committee meeting.<br><br>Avatrombopag is a vital addition to current treatments since patients who are intolerant or unresponsive to one of the existing reimbursed TPO-RA options can successfully switch and respond to avatrombopag.<br><br>Furthermore, as patient testimony highlighted during the committee, there are potentially significant improvements in patient quality of life attributable to avatrombopag vs other TPO-RA options. Importantly, avatrombopag does not cause deranged liver function and is more convenient for patients as there are no dietary restrictions, unlike eltrombopag. |
| **Comment 2:** Efficacy | Sobi acknowledge that the committee perceived that there is a limited evidence base for the clinical efficacy of avatrombopag because of recruitment and attrition issues in the clinical trials. We would like to provide additional commentary on this point to demonstrate that there is a growing evidence base and clinical experience of using avatrombopag.<br><br>The pivotal trial for avatrombopag demonstrated statistical and clinical significance leading to marketing authorisation in Europe and the UK. [1]<br><br>There is also growing clinical experience of using avatrombopag in Ireland and Scotland following reimbursement in both countries.<br><br>Both the provided NMA and our responses elsewhere draw on multiple published observational studies reflecting positive real-world experience even in heavily pre-treated ITP populations or those who have been previously treated with TPO-RAs. [2-5]<br><br>In summary the efficacy of avatrombopag has been demonstrated in both an RCT and real-world setting. |
| **Comment 3:** Time to treatment response in the model | The company notes that the committee concluded that the 24-week timeframe to assess response did not reflect clinical practice. We would like to clarify that we previously accepted the ERG's views on this issue during the technical engagement stage and altered our base case analysis by correcting it to a 3-cycle duration for assessing response (corresponding to a 12-week timeframe).<br><br>A 12-week duration aligns with the evidence provided by the clinical experts during the first committee meeting. |
| **Comment 4:** Network meta-analysis | The company has submitted as a separate appendix to these comments an additional network meta-analysis (NMA) that compares avatrombopag (AVA) versus eltrombopag (ELT) and romiplostim (ROM) with mean change in platelet count in patients with immune thrombocytopaenia (ITP).<br><br>The analysis was conducted in response to the request from the appraisal committee to conduct an additional NMA with the mean platelet count as a continuous outcome that, together with a distributional assumption, can be used to derive response probabilities. The key findings are presented below.<br><br>A Bayesian NMA showed that all treatments (AVA, ELT, ROM) were associated with significantly greater improvement of platelet count compared with placebo (PLC), although the differences between active regimens were not statistically significant. The highest probability for being the best treatment was achieved by AVA (51%) followed by ELT (42%). |

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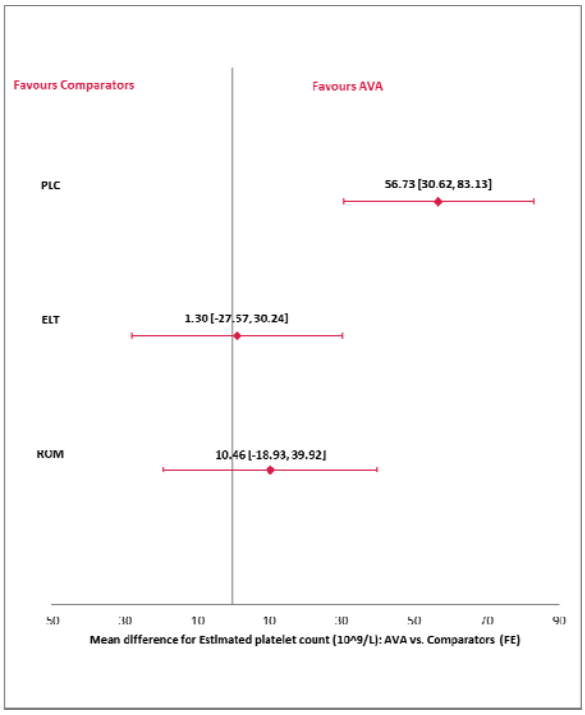
**Table 1: Estimated mean difference in platelet count – fixed effect model**

| MD for all comparisons (×$10^9$/L) (FE model) | | | | | | |
|---|---|---|---|---|---|---|
| | vs. **PLC** | vs. **AVA** | vs. **ELT** | vs. **ROM** | **Probability of being best** | **SUCRA** |
| **PLC** | **PLC** | **-56.73 [-83.13, -30.62]** | **-55.50 [-67.64, -43.27]** | **-46.34 [ -59.58, -33.08]** | 0% | 0% |
| **AVA** | **56.73 [30.62, 83.13]** | **AVA** | 1.30 [-27.57, 30.24] | 10.46 [-18.93, 39.92] | 51% | 75% |
| **ELT** | **55.50 [43.27, 67.64]** | -1.30 [-30.24, 27.57] | **ELT** | 9.18 [-8.81, 27.07] | 42% | 77% |
| **ROM** | **46.34 [33.08, 59.58]** | -10.46 [-39.92, 18.93] | -9.18 [-27.07, 8.81] | **ROM** | 7% | 48% |

**Figure 1: Forest plot for comparison AVA vs comparators regarding estimated absolute mean difference – fixed effect model**




The estimates for the probabilities of reaching ≥30×$10^9$/L and ≥50×$10^9$/L are detailed in an appendix document and shows that all active treatments were associated with very high likelihood of reaching target PLT count.

It should be noted that the marginal differences in results between AVA and ELT may be due to differences in study design around titration of treatments. Titration of AVA during the core study was with a platelet target range of 50-150 x $10^9$/L, and the primary end point required a platelet count ≥50 x $10^9$/L, therefore it is likely that a clinically meaningful response was achieved in more patients than is suggested by the primary end point. In comparison, the core study for ELT also allowed titration but patients were

| | |
|---|---|
| | assessed for response to treatment over a wider platelet range (response defined as a platelet count of 50–400 × 10^9/L)<br><br>Nevertheless, the results show that the clinical effectiveness of each TPO-RA is similar, according to the mean difference in platelet count outcome. |
| **Comment 5:** Bleed-related unit costs | Sobi welcomes the appraisal committee's recognition in the ACD that there might be additional resources not covered by the NHS reference costs for bleed events, but we also acknowledge the committee's concerns with not using NHS reference costs as a basis for calculating costs associated with bleeding events.<br><br>Sobi has therefore updated its costs associated with bleeding events to include NHS reference costs. However, the NHS reference cost codes used differ from those used by the Evidence Review Group (ERG) based on our findings from independent market research as well as clinical advice received following the publication of the ACD. As requested within the ACD, we have provided below information to clarify how the company's market research informed the original bleed-related unit costs used - despite these costings no longer being used in this ACD response - and the subsequent clinical advice received to inform our ACD response.<br><br>**<u>Background to how bleeding costs were derived in the original core submission</u>**<br><br>Costs associated with bleeding events in the company's original submission were informed by market research, which was conducted by an independent agency, that aimed to explore the utilisation of different healthcare resource use elements for outpatient and inpatient bleeds. This research was commissioned following feedback from an Advisory Board that bleed related care costs may differ between patients with ITP and patients in the general population due to differing resource needs, and therefore NHS reference costs could undervalue the cost of treating ITP patients [6].<br><br>113 ITP physicians completed a survey across the EU5 [UK, Germany, France, Spain, Italy] + Netherlands, including 20 from the UK, to quantify frequency of bleeding events, segmentation of severity of bleeds, and length of hospitalisation for ITP patients [7]. Alongside the survey, interviews were conducted with 23 ITP physicians and 12 payors, including 4 haematologists and 2 payors in the UK, to further understand and verify the frequency of bleeding events and healthcare resource utilisation within ITP [7].<br><br>UK payors provided answers with referenceable sources to questions surrounding hospitalisation costs in the NHS, including the average cost per night in hospital, average cost per night in ICU, ER visit cost, cost of diagnostic imaging and blood tests, and rescue therapy costs [7] [please see Table 64, pages 101-102 of Document B, company submission, for a breakdown on the value of these costs].<br><br>Physicians provided clinical information on the estimated treatment and resources required for outpatient and inpatient bleeds in ITP patients [7]. This includes answers to questions on the number of bleeds, use of various treatments (e.g. rescue therapies), number of patient days in hospital, number of patient days in ICU, and number of days patients are followed up [7] [please see Table 63 (labelled 64), page 101 of Document B, company submission, for a breakdown on the utilisation of resources].<br><br>With the insights from both the payors and physicians, the therapy cost for ITP was determined on a per patient basis [i.e. combining frequency of each bleeding event type, utilisation of therapies per each bleeding event, and utilisation of healthcare and human resources per each bleeding event] [7]. A breakdown on the costs per outpatient and inpatient bleed used in the original model were presented in Table 65, pages 102-103 of Document B, company submission.<br><br>**<u>Clinical advice received post-core submission</u>**<br><br>Following the publication of the ACD, Sobi still maintains that the cost estimates from the performed market research better reflect the actual costs of treatment of bleeds in the UK compared to the ERG's |

estimates, however, the company understands the concerns of the committee and sought clinical advice from several UK clinicians to find a more appropriate way of costing bleeds [8].

Clinicians stated that the duration of different bleeds in ITP patients tends to be longer in comparison to the general population, as it takes a relatively long time to bring an ITP patient's platelet count up and stabilise bleeding [8]. Moreover, they stated that the severity of bleeds in patients with low platelet count tends to be increased [8].

Consequently, clinicians suggested that the resource needs could be higher for an ITP patient, for example, "*they take significantly more bed days*" as they are "*in hospital for longer*", and "*patients with ITP will need longer duration of treatment as they will require ITP specific therapy to bring up their count, and may have endoscopy or other investigations delayed whilst this takes place*" [8].

Therefore, the company suggest using NHS reference costs in line with the ERG approach but based on the highest considered unit costs. This is to account for the greater bleed related care costs for ITP patients relative to the general population.

**Table 2: NHS reference bleed costs – ERG and company suggestion**

| Type of bleed | ERG | | Company suggestion | |
|---|---|---|---|---|
| | Cost (£) | Source (NHS reference cost 19/20) | Cost (£) | Source (NHS reference cost 19/20) |
| Outpatient bleed | 459.65 | Weighted average FD03F-FD03H | 493.74 | FD03F |
| Gastrointestinal bleed | 3,091.79 | Weighted average FD03A to FD03E | 5,502.62 | FD03A |
| Intercranial haemorrhage | 4,690.02 | Weighted average AA23C to AA23G | 7,044.18 | AA23C |
| Other inpatient bleed | 2,890.37 | Weighted average, FD03B and FD03E | 3,625.70 | FD03B |

These new care costs have been added to the company's updated base case cost-effectiveness analysis, which is detailed in subsequent sections.

**Comment 6:** Scenario analyses for treatment duration

In line with the committee's request for new evidence, we have analysed the patient-level data on the duration of treatment with avatrombopag from Study 302 and its extension. The first graph below presents data from the extension of the Study 302 and the second one from the core trial.

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**Figure 2: Scenario analysis for duration of treatment based on extension of Study 302**

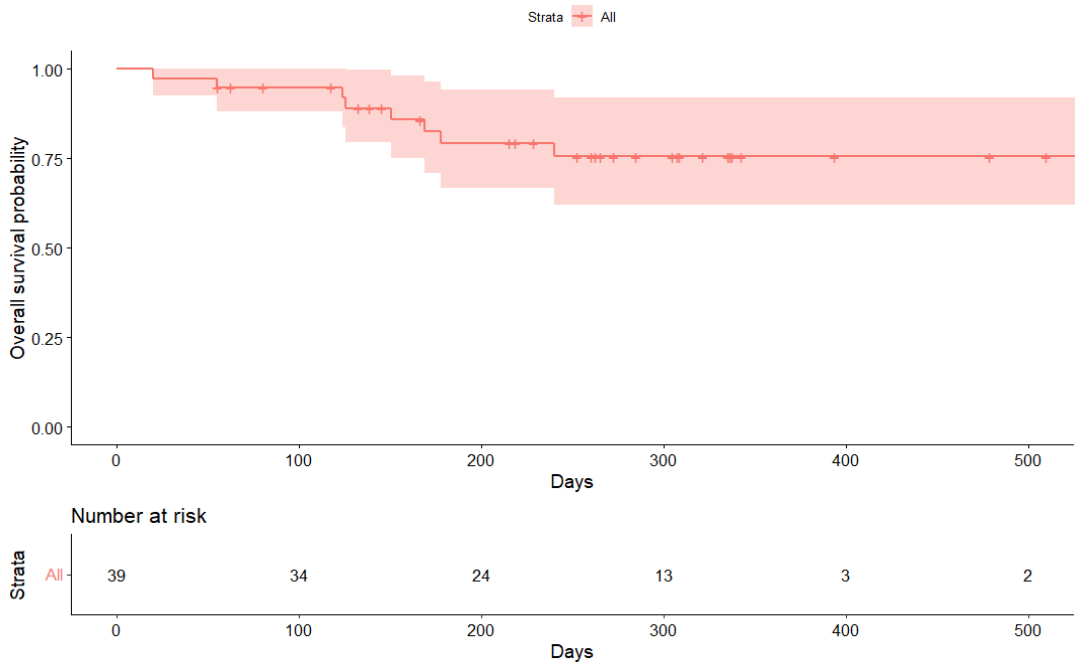
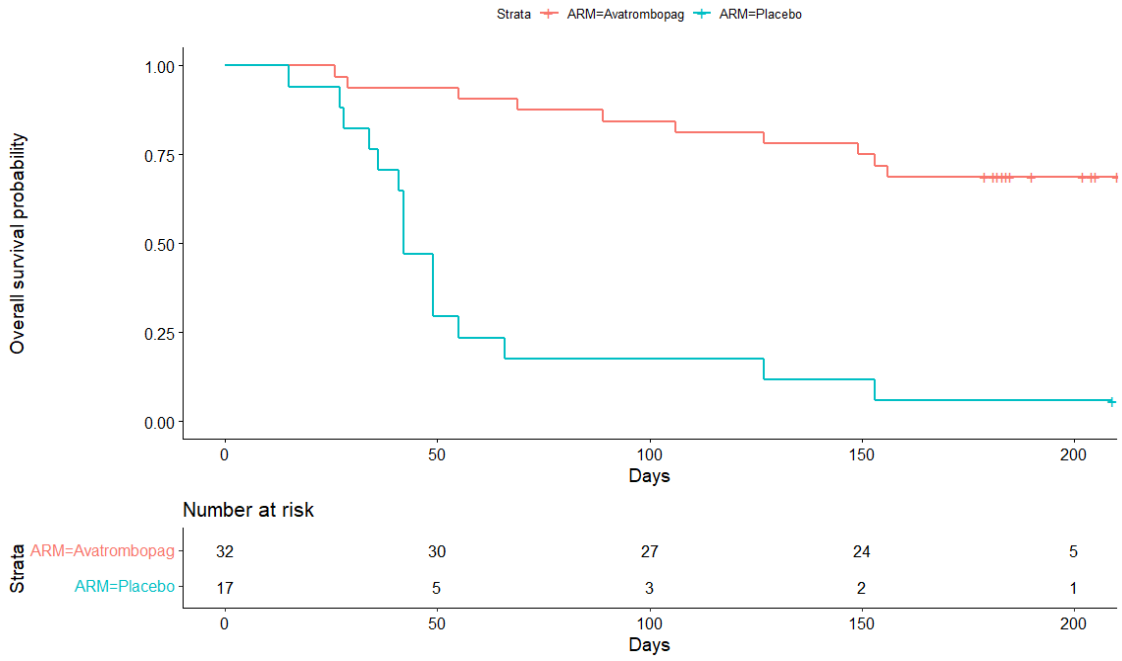



**Figure 3: Scenario analysis for patient-level data from Study 302**




After fitting the log-normal distribution to the trial data (in an analogous way for the company submissions of ELT and ROM) the average duration of treatment with AVA was estimated for 57.31 cycles based on the core study and 632.70 cycles after inclusion of the trial extension.

It should be noted that the treatment duration considered in the company submission was based on the long-term trials for comparators and hence should be compared with estimates that consider the extension of the 302 study. Such a comparison confirms the expectation that treatment with AVA can persist at least as long as the use of other TPO-RAs.

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Estimated duration of treatment based on the data for AVA was included in the cost-effectiveness model. Three scenarios were considered:

- the same duration of treatment for all TPO-RAs based on core 302 study
- the same duration of treatment for all TPO-RAs based on core 302 study + extension
- different duration of treatment for ELT, ROM and AVA based on the long-term trials i.e. (109 cycles ELT, 393 cycles ROM, 633 cycles AVA)

The other assumptions of the model were the same as in the company response to the ERG report with one difference concerning the costs of bleeds, which is detailed earlier within this response in Table 2.

The cost-effectiveness results of listed scenarios have been presented in Table 5 below. They are consistent with the base case scenario if only the same treatment duration is assumed for all TPO-RAs. The extreme scenario assuming different duration between comparators indicates that AVA is more effective than ROM and also less costly (i.e. dominant). In this scenario, treatment with AVA was shown to be more expensive than ELT but more effective. This result is driven, however, by an assumed 6-fold longer treatment duration, which is highly unlikely according to clinical advice provided by experts during the first committee meeting, as well as shown in the company's survey results of 9 UK clinicians [n.b. shared during technical engagement].

In a retrospective study in the United States of America (USA) of adults with ITP (both primary and secondary) who switched to AVA following prior treatment with ELT or ROM, the median duration on AVA was recorded as 9.2 months, whilst time on a prior TPO-RA before switching to AVA was a median duration of 9.7 months [2]. Although there are limitations for comparison purposes in terms of study design and population, the results of the study suggest there may be similar treatment durations between TPO-RAs in the real world [2].

No further published evidence allowing for reliable comparison of treatment duration between TPO-RAs has been identified. At the same time, the company understands from clinicians that they do not expect any important differences between considered comparators in terms of treatment duration [8].

**Table 5 – ICER scenario analyses for duration of treatment**

| **Base case** | | | | |
|---|---|---|---|---|
| **AVA vs** | **Incremental cost** | **Incremental QALYs** | **ICER / Cost-effectiveness plane** | |
| **ROM** | [redacted] | [redacted] | [redacted] | [redacted] |
| **ELT** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Treatment duration from the core study (the same for all TPO-RAs)** | | | | |
| **AVA vs** | **Incremental cost** | **Incremental QALYs** | **ICER / Cost-effectiveness plane** | |
| **ROM** | [redacted] | [redacted] | [redacted] | [redacted] |
| **ELT** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Treatment duration from the core study + extension (the same for all TPO-RAs)** | | | | |
| **AVA vs** | **Incremental cost** | **Incremental QALYs** | **ICER / Cost-effectiveness plane** | |
| **ROM** | [redacted] | [redacted] | [redacted] | [redacted] |
| **ELT** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Duration from different long-term trials (109 cycles ELT, 393 cycles ROM, 633 cycles AVA)** | | | | |
| **AVA vs** | **Incremental cost** | **Incremental QALYs** | **ICER / Cost-effectiveness plane** | |
| **ROM** | [redacted] | [redacted] | [redacted] | [redacted] |

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| | | | | | |
|---|---|---|---|---|---|
| | | | | | [redacted] |
| **ELT** | [redacted] | [redacted] | [redacted] | | [redacted] |

**Comment 7**: PSA results

In the response to another committee request, Sobi performed a probabilistic sensitivity analysis for the new base case scenario 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. The results of this PSA are presented below.

**Table 6 – PSA results vs ELT**

**AVA vs ELT**

| | Incremental Costs | Incremental QALYs | ICER / Cost-effectiveness plane | |
|---|---|---|---|---|
| **Base Case** | [redacted] | [redacted] | [redacted] | [redacted] |
| **PSA (mean)** | [redacted] | [redacted] | [redacted] | [redacted] |

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**Table 7 – PSA results vs ROM**

**AVA vs ROM**

| | Incremental Costs | Incremental QALYs | ICER / Cost-effectiveness plane | |
|---|---|---|---|---|
| **Base Case** | [redacted] | [redacted] | [redacted] | [redacted] |
| **PSA (mean)** | [redacted] | [redacted] | [redacted] | [redacted] |

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**Comment 8:** Results with new response probabilities

To make sure that all committee recommendations are fulfilled in this response, Sobi performed additional scenario analyses with inclusion of the results of a network meta-analysis with the mean platelet count as a continuous outcome. These results, together with a distributional assumption, have been used to derive response probabilities of achieving two types of response:

- reaching PLT ≥30×$10^9$/L
- reaching PLT ≥50×$10^9$/L

The results of performed NMA and obtained probabilities have been described earlier. In general, the point estimate of the absolute difference in the platelet count is the highest for AVA, however, due to higher uncertainty the probabilities of achieving specified threshold of platelet count are the lowest for AVA. This discrepancy together with the fact that the highest response probabilities have been obtained for ELT indicates the limited usability of this response definition in the economic model. ELT has been shown to have lower efficacy than both AVA and ROM when other types of outcomes were considered. Platelet count often fluctuates over time in ITP patients and the most meaningful response can be considered the sustaining of platelet count at or above a certain level. Therefore, durable platelet response, as considered in the base case scenario, is the most important outcome when comparing treatment efficacy. This is especially pertinent considering durable response allows for differentiation of comparators whereas all TPO-RAs have been shown fully effective in reaching platelet count ≥30/50×$10^9$/L. Nevertheless, the response probabilities for two additional types of response have been implemented in the model with the following results.

**Table 8 – cost-effectiveness results with new response probabilities**

| New response rates based on PLT > 30 | | | |
|---|---|---|---|
| **AVA vs** | **Incremental cost** | **Incremental QALYs** | **ICER / Cost-effectiveness plane** |
| **ROM** | | | |
| **ELT** | | | |
| **New response rates based on PLT > 50** | | | |
| **AVA vs** | **Incremental cost** | **Incremental QALYs** | **ICER / Cost-effectiveness plane** |
| **ROM** | | | |
| **ELT** | | | |

Difference in efficacy translates to small gains in QALYs in favour of ROM and ELT at significant additional cost. These results confirm that considering any type of response neither ROM nor ELT are cost-effective vs AVA.

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6. Sobi. Sobi ITP UK advisory board meeting. Data on file. 2020.

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| | 7. L.E.K. consulting. ITP epidemiology and treatment paradigm review. Data on file; 2020<br>8. Sobi, Independent clinical advice. Data on file. July 2022 |

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Creativ Ceutical

The enlightened decision

# Network meta-analysis of avatrombopag versus eltrombopag and romiplostim in the treatment of immune thrombocytopenia.

## Analysis of platelet count

Date: 27-07-2022

Prepared for:
SOBI

Sebastian Guterres
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# 1. Table of contents

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# 4. Abbreviations

| | |
|---|---|
| AVA | Avatrombopag |
| CrI | Credible interval |
| DIC | Deviance information criterion |
| ELT | Eltrombopag |
| IQR | Interquartlie range |
| ITP | Immune thrombocytopaenia |
| LOCF | Last observation carried forward |
| NMA | Network meta-analysis |
| PLC | Placebo |
| PLT | Platelet |
| RCP | Randomised controlled trial |
| ROM | Romiplostim |
| SUCRA | Surface under the cumulative ranking line |

# 5. Objectives and methods

## 5.1.Objectives

The objective of this analysis is to conduct a network meta-analysis (NMA) to compare avatrombopag (AVA) versus eltrombopag (ELT) and romiplostim (ROM) regarding mean change in platelet count in patients with immune thrombocytopaenia (ITP).

This analysis was conducted in response to the recommendation of the Appraisal committee to conduct an additional 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.

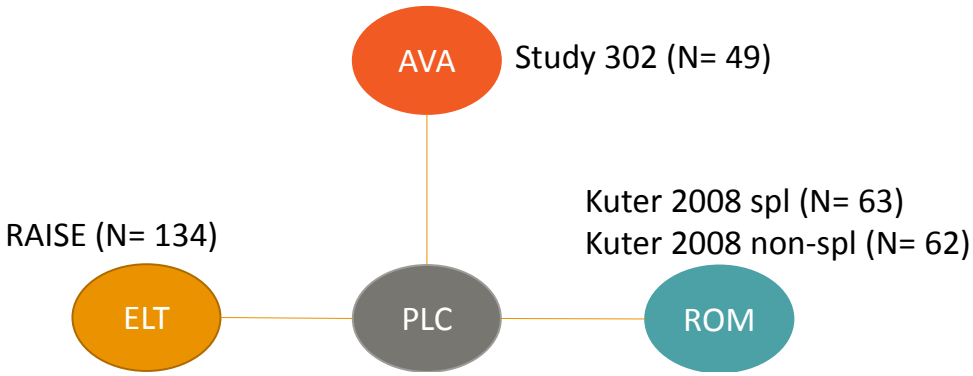
## 5.2.Available clinical evidence

This analysis was conducted as the supplementary analysis to previous NMA, which was carried out to support the submission of AVA in the treatment of patients with ITP.

Overall, 4 randomised controlled trials (RCT) were included in this supplementary analysis, which reported estimates for platelet count for either AVA or relevant comparators, including ELT and ROM.

The network of evidence is presented in the Figure 1 below.

**Figure 1 Network of evidence for the comparison regarding platelet count**




## 5.3. Statistical methods

A network meta-analysis (NMA) in a Bayesian framework was conducted in order to compare data regarding platelet count between AVA and comparators. The analysis was conducted in accordance with the methodological guidelines and tutorials developed by NICE Decision Support Unit.[1]

## 5.4.Input data

The analysis was conducted with the modified normal likelihood, identity link model, which required following input data:

- Mean change from baseline in PLT count in each treatment group
- Standard error (SE) for the corresponding mean change from baseline

Individual patient data were available for Study 302, which allowed to calculate the required input data.

Mean change from baseline in PLT count were not reported in the comparator trial. Instead, the available publications presented figures showing median PLT count together with interquartile ranges (IQRs) at different timepoints of the trials. Due to the inadequate reporting following activities were undertaken to derive the required input data:

1. Medians together with the corresponding IQRs were read from the figures presented in respective publications at baseline and end-of-study.
2. Mean values and standard deviations were estimated based on extracted medians and IQRs and/or ranges using the algorithms proposed by Luo 2018[1] and Shi 2020[2]
3. Mean difference from baseline together with the corresponding standard deviations were estimated based on means and standard deviations estimated in point 2 using the method provided in the Cochrane Handbook for Systematic Reviews[3]

## 5.5.Last observation carried forward (LOCF)

The pivotal trial assessing AVA versus PLC was conducted, when therapeutic alternatives were available for patients with ITP, therefore all participants were allowed to discontinue treatment early in particular in case of inadequate efficacy. Finally, there was only one patient left in the PLC group at the end of 26 weeks randomised period. These data were insufficient to properly estimate standard errors for the estimates either versus baseline or between treatments. Therefore, a single imputation method using last observation carried forward (LOCF) method was adopted to input missing data. This means that the difference from baseline in PLT count were estimated based on the last observations before early drop-out. For consistency, the LOCF method was adopted in both: AVA and PLC arms.

[1] D. Luo, X. Wan, J. Liu and T. Tong* (2018), "Optimally estimating the sample mean from the sample size, median, mid-range and/or mid-quartile range", *Statistical Methods in Medical Research*, **27**: 1785-1805

[2] J. Shi, D. Luo, H. Weng, X. Zeng, L. Lin, H. Chu and T. Tong* (2020), "Optimally estimating the sample standard deviation from the five-number summary", *Research Synthesis Methods*, **11**: 641-654.

[3] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.

## 5.6.Outputs of the NMA

A network diagram representing all direct comparisons between treatments included in the analysis was produced.

Results are presented with summary statistics:

- Median and mean odds ratios with 95% credible intervals (95% CrI) are reported for AVA versus other treatments
- The probability of being the best treatment
- The surface under the cumulative ranking line (SUCRA) for each treatment are calculated according to the method proposed by Salanti 2011[2]. For each treatment *j* out of the *a* competing treatments, a vector of cumulative probabilities $cum_{j,b}$ calculated to be among the *b* best treatments, *b*= 1,…,*a*. Then, the surface below the cumulative step function for treatment is given using the equation:

$$\mathrm{SUCRA}_j = \frac{\sum_{b=1}^{a-1} \mathrm{cum}_{j,b}}{a-1}$$

- Deviance information criterion (DIC)
- Model parameters

# 6. NMA Results

## 6.1.Input data

Input data for the analysis are presented in Table 1. Median values together with IQRs or ranges were extracted from the digitalised graphs presented in the publications of the comparator trials (RAISE, Kuter 2008 spl. and Kuter 2008 non-spl). Mean values at baseline and end of study were then estimated together with the corresponding standard deviations as described in the Section 5.4.

Relevant information for AVA and the corresponding PLC group were derived directly for the database of the Study 302 containing patient-level data.



**Table 1 Table presenting extracted data and inputs for the NMA**

| Study | Arm | Baseline | | | | | | | | Last observation | | | | | | | | Estimated change from baseline | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | SD | Median | [IQR] | [min, max] | Estimated mean** | Estimated SD*** | Time point (weeks) | N | Mean | SD | Median | [IQR] | Estimated mean** | Estimated SD*** | Mean | SD | SE |
| Study 302 | AVA | 32 | 14.06 | 8.64 | | | | | | 26 | 32 | 71.68* | 79.02* | | | | | 57.61* | 76.24* | 13.48* |
| | PLC | 17 | 12.71 | 7.84 | | | | | | | 17 | 12.46* | 10.06* | | | | | -0.24* | 4.91* | 1.19* |
| Kuter 2008 (spl.) | ROM | 42 | n/d | n/d | 14[¥] | n/d | [3, 29][¥] | 14.39 | 5.98 | 25 | 40 | n/d | n/d | 55.37[£] | [16.95, 89.27][£] | 53.77 | 55.61 | 39.38[€] | 52.08[€] | 8.24[€] |
| | PLC | 21 | n/d | n/d | 15[¥] | n/d | [2, 28][¥] | 15 | 6.88 | | 19 | n/d | n/d | 19.21[£] | [11.3, 31.07][£] | 20.63 | 15.84 | 5.63[€] | 12.73[€] | 2.92[€] |
| Kuter 2008 (non-spl) | ROM | 41 | n/d | n/d | 19[¥] | n/d | [2, 29][¥] | 18.307 | 6.23 | | 39 | n/d | n/d | 86.08[£] | [50.85, 138.01][£] | 92.01 | 67.08 | 73.70[€] | 63.38[€] | 10.15[€] |
| | PLC | 21 | n/d | n/d | 19[¥] | n/d | [5, 31][¥] | 18.71 | 6.88 | | 17 | n/d | n/d | 25.79[£] | [15.98, 37.77][£] | 26.57 | 17.61 | 7.86[€] | 14.36[€] | 3.48[€] |
| RAISE | ELT | 135 | n/d | n/d | 18.08[£] | [8.08, 25.00][£] | n/a | 17 | 12.68 | 26 | 110 | n/d | n/d | 73.46[£] | [41.15, 131.54][£] | 82.53 | 67.90 | 65.53[€] | 60.79[€] | 5.80[€] |
| | PLC | 61 | n/d | n/d | 16.15[£] | [8.08, 22.69][£] | n/a | 15.61 | 11.09 | | 53 | n/d | n/d | 22.69[£] | [12.69, 40.38][£] | 25.41 | 21.10 | 9.80[€] | 16.61[€] | 2.28[€] |

AVA – avatrombopag, ELT – eltrombopag, PLC – placebo, ROM, N – number of patients, SD – standard deviation, [IQR] – interquartile range

* values calculated based on available individual patient data with single imputation for missing values using LOCF approach

** Mean values were estimated with the methods described by Luo 2018[4]

*** Standard deviations were estimated using the algorithm described by Shi 2020[5]

[¥] Estimates reported in the corresponding publications

[£] Estimates read from the figures

[€] Values estimates using the method proposed by the Cochrane Handbook for Systematic reviews based on estimates from Study 302 (Corr.[6]

[4] D. Luo, X. Wan, J. Liu and T. Tong* (2018), "Optimally estimating the sample mean from the sample size, median, mid-range and/or mid-quartile range", *Statistical Methods in Medical Research*, **27**: 1785-1805

[5] J. Shi, D. Luo, H. Weng, X. Zeng, L. Lin, H. Chu and T. Tong* (2020), "Optimally estimating the sample standard deviation from the five-number summary", *Research Synthesis Methods*, **11**: 641-654.

[6] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.

## 6.2.Overall information and input data

A summary of the data for the NMA, for the platelet count, is presented in Table 2. A fixed-effect model was selected based on the value of deviance information criterion (DIC), as described in Section 10.3.

**Table 2. Summary of the data for the NMA for the proportion of patients with stabilisation of haemoglobin**

| Characteristic | | Value |
|---|---|---|
| **Number of studies** | | 4 |
| **Number of treatment regimens** | | 4 |
| **Number of patients** | | 317 |
| **DIC** | **Fixed-effects model (y + y_baseline + y_change = total)** | **58.24 + 39.01 + 34.95 = 132.20** |
| | **Random-effects model** | 57.70+ 39.01 + 34.96 = 131.67 |

## 6.3.NMA results

### 6.3.1.Absolute mean difference in platelet count

Results of the NMA regarding the mean difference in the estimated mean change from baseline in PLT count are depicted in Figure 2 and summarised in Table 3.

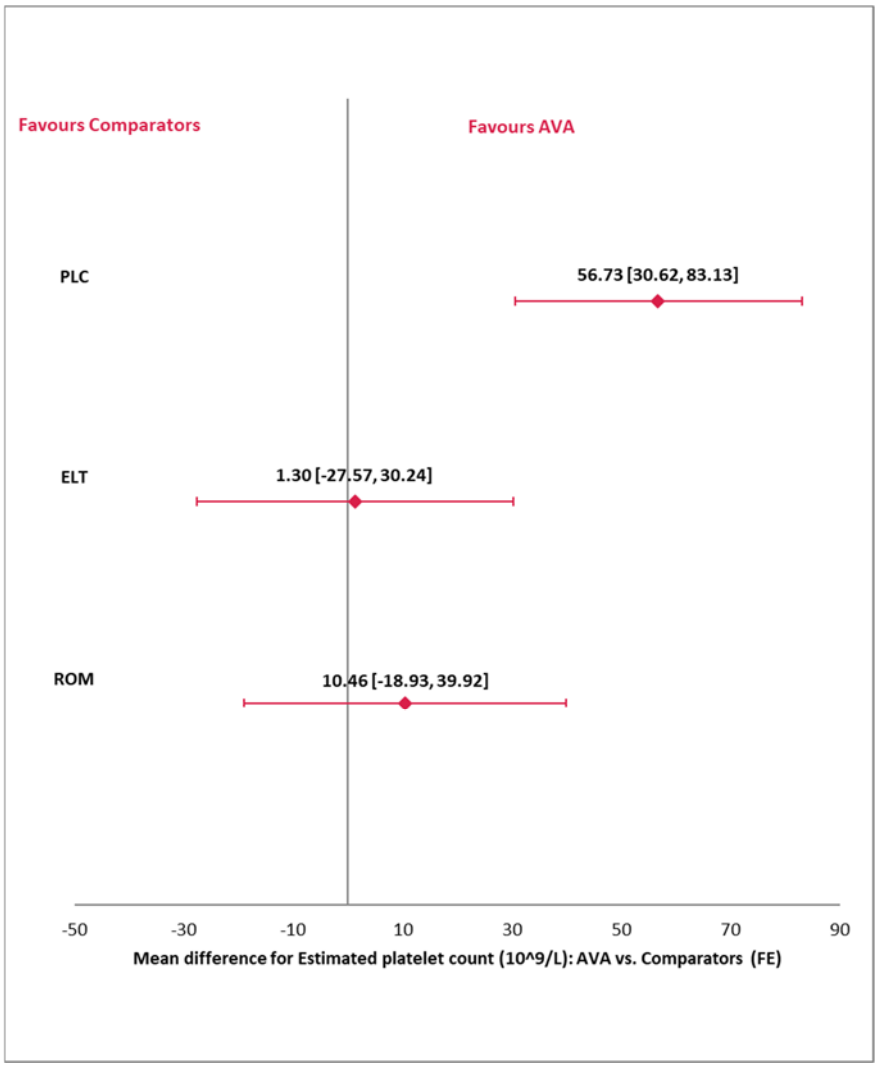
Bayesian NMA showed that all treatments were associated with significantly greater improvement of platelet count compared with PLC, although the differences between active regimens were not statistically significant. The highest probability for being the best treatment was achieved by AVA (51%) followed by ELT (42%) (Table 3).

**Table 3. Estimated mean difference in platelet count – fixed effect model**

| | MD for all comparisons ($\times 10^9$/L) (FE model) | | | | | |
|---|---|---|---|---|---|---|
| | vs. **PLC** | vs. **AVA** | vs. **ELT** | vs. **ROM** | **Probability of being best** | **SUCRA** |
| **PLC** | **PLC** | **-56.73 [-83.13, -30.62]** | **-55.50 [-67.64, -43.27]** | **-46.34 [ -59.58, -33.08]** | 0% | 0% |
| **AVA** | **56.73 [30.62, 83.13]** | **AVA** | 1.30 [-27.57, 30.24] | 10.46 [-18.93, 39.92] | 51% | 75% |
| **ELT** | **55.50 [43.27, 67.64]** | -1.30 [-30.24, 27.57] | **ELT** | 9.18 [-8.81, 27.07] | 42% | 77% |
| **ROM** | **46.34 [33.08, 59.58]** | -10.46 [-39.92, 18.93] | -9.18 [-27.07, 8.81] | **ROM** | 7% | 48% |

Statistically significant values were presented in bold; OR – Odds Ratio, FE – fixed effect, SUCRA - surface under the cumulative ranking curve.

**Figure 2 Forest plot for comparison AVA vs comparators regarding estimated absolute mean difference – fixed effect model**



## 6.3.2. Probability of reaching PLT ≥30×10$^9$/L

The distributions of the platelet count at the end of study for each treatment were estimated by summing up of:

- the mean distribution of platelet count at baseline averaged across all arms,
- the mean effect of placebo from baseline to end of study averaged across all placebo arms,
- the respective effects of each treatment versus placebo (*d*[treatment])

**Table 4 Posterior distributions of baseline platelet count and treatment effects**

| No. | Variable | mean | sd | 2.50% | median | 97.50% |
|---|---|---|---|---|---|---|
| 1 | Baseline | 16.0423 | 0.440692 | 15.1794 | 16.0432 | 16.9026 |
| 2 | Effect of placebo | 2.75717 | 0.955756 | 0.889354 | 2.75675 | 4.62436 |
| 3 | #1 + #2 | 18.7994 | 1.05195 | 16.7441 | 18.7983 | 20.8591 |
| 4 | *d*[AVA] | 56.7882 | 13.3804 | 30.6212 | 56.7329 | 83.1332 |
| 5 | *d*[ELT] | 55.4976 | 6.2067 | 43.2655 | 55.4952 | 67.6446 |
| 6 | *d*[ROM] | 46.3461 | 6.75883 | 33.0801 | 46.3428 | 59.5753 |

Probability of reaching PLT ≥30×10$^9$/L was estimated for each treatment using two approaches:

1. By counting simulations with the outcomes ≥ 30 (using 'step' WinBUGS function)
2. Through standard normal cumulative density function (using 'phi' WinBUGS function)

The estimates for the probabilities are presented in the Table 5. Both methods produced consistent estimates, which showed that all active treatments were associated with very high likelihood of reaching target PLT count.

**Table 5 Estimates for the probabilities of reaching ≥30×10$^9$/L**

| | Probability of reaching ≥30×10$^9$/L estimates using 'step' function | | Probability of reaching ≥30×10$^9$/L estimates using 'phi' function | |
|---|---|---|---|---|
| | Proportion | SD | Median | 95% Credible interval |
| PLC | 0.00 | 0.00 | 0.00 | [0.00, 0.00] |
| AVA | 0.9997 | 0.0181 | 0.9997 | [0.9243, 1.000] |
| ELT | 1.00 | 0.00 | 1.00 | [1.00, 1.00] |
| ROM | 1.00 | 0.00 | 1.000 | [0.9993, 1.00] |

### 6.3.3.Probability of reaching PLT ≥50×10$^9$/L

The distributions of the platelet count at the end of study for each treatment were estimated by summing up of:

- the mean distribution of platelet count at baseline averaged across all arms,
- the mean effect of placebo from baseline to end of study averaged across all placebo arms,
- the respective effects of each treatment versus placebo (*d*[treatment])

**Table 6 Posterior distributions of baseline platelet count and treatment effects**

| No. | Variable | mean | sd | 2.50% | median | 97.50% |
|---|---|---|---|---|---|---|
| 1 | Baseline | 16.0423 | 0.440692 | 15.1794 | 16.0432 | 16.9026 |
| 2 | Effect of placebo | 2.75717 | 0.955756 | 0.889354 | 2.75675 | 4.62436 |
| 3 | #1 + #2 | 18.7994 | 1.05195 | 16.7441 | 18.7983 | 20.8591 |
| 4 | *d*[AVA] | 56.7882 | 13.3804 | 30.6212 | 56.7329 | 83.1332 |
| 5 | *d*[ELT] | 55.4976 | 6.2067 | 43.2655 | 55.4952 | 67.6446 |
| 6 | *d*[ROM] | 46.3461 | 6.75883 | 33.0801 | 46.3428 | 59.5753 |

Probability of reaching PLT 50×10$^9$/L was estimated for each treatment using two approaches:

3. By counting simulations with the outcomes ≥ 50 (using 'step' WinBUGS function)
4. Through standard normal cumulative density function (using 'phi' WinBUGS function)

The estimates for the probabilities are presented in the Table 5. Both methods produced consistent estimates, which showed that ELT was associated with highest chance for reaching the level of PLT≥50×10$^9$/L- followed by AVA and ROM (Table 7).

**Table 7 Estimates for the probabilities of reaching ≥50×10$^9$/L**

| | Probability of reaching ≥50×10$^9$/L estimates using 'step' function | | Probability of reaching ≥50×10$^9$/L estimates using 'phi' function | |
|---|---|---|---|---|
| | Proportion | SD | Median | Credible interval |
| PLC | 0.00 | 0.00 | 0.00 | [0.00, 0.00] |
| AVA | 0.9718 | 0.1656 | 0.9714 | [0.4778, 0.9999] |
| ELT | 0.9999 | 0.0089 | 0.9999 | [0.9706, 1.0000] |
| ROM | 0.9866 | 0.1148 | 0.9865 | [0.6004, 1.0000] |

# 7. Limitations

This analysis has following limitations, therefore presented outcomes should be interpreted with caution:

- Neither of comparator studies reported mean change from baseline in PLT count, therefore the input data had to be estimated from medians and corresponding IQRs
- Distribution of PLT count in the comparator trials were reported on figures, therefore the extraction required digitalisation of the presented graphs.
- Only one patient remined until the end of randomised period in the PLC group of the AVA 302 trial. Therefore, missing data were imputed using LOCF approach. For consistency the imputation was applied in both PLC and AVA arms.
- The proportion of patients reaching PLT count ≥30x$10^9$/L was not calculated based on observed data but estimated assuming normal distribution of the posterior distributions of mean PLT counts.

# 8. References


1. Dias S, Sutton AJ, Ades AE, et al. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Medical decision making : an international journal of the Society for Medical Decision Making* 2013;33(5):607-17. doi: 10.1177/0272989x12458724 [published Online First: 2012/10/30]
2. Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011;64(2):163-71. doi: 10.1016/j.jclinepi.2010.03.016 [published Online First: 08/05]
3. Goodman SN. Toward evidence-based medical statistics. 1: The P value fallacy. *Ann Intern Med* 1999;130(12):995-1004.
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6. Spiegelhalter. Bayesian Approaches to Clinical Trials and Health-Care Evaluation2003.

# 9. Appendix 1: Results for random effect model

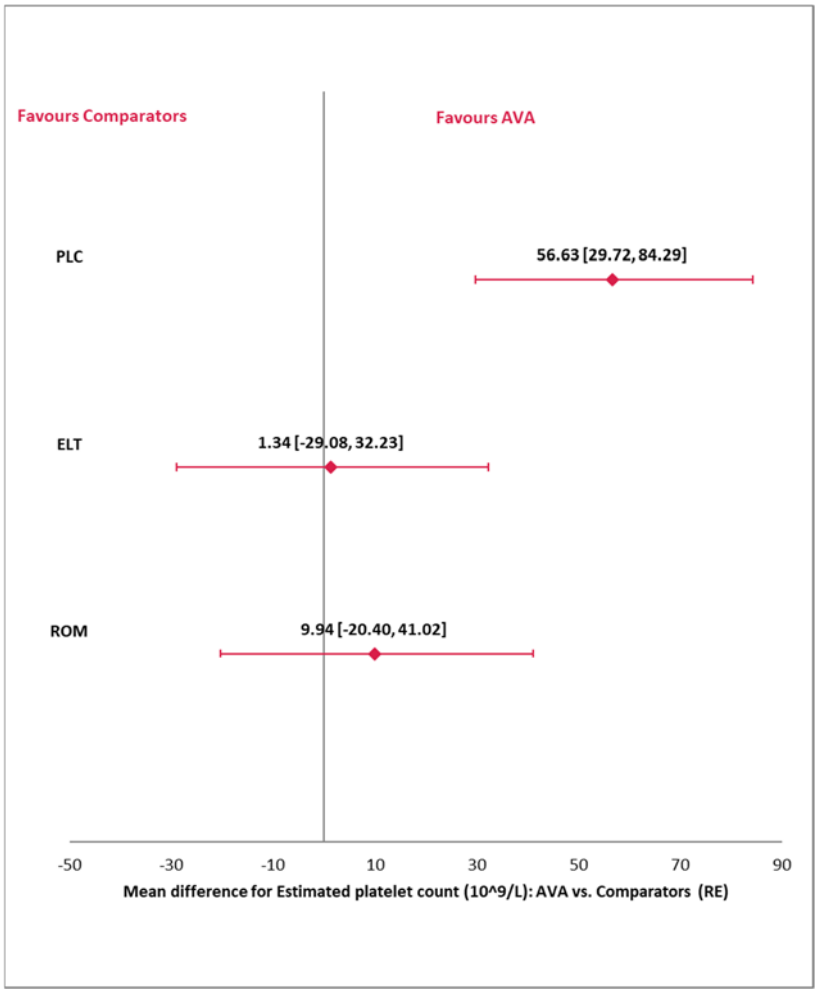
## 9.1.1. Absolute mean difference in platelet count

Table 8. Estimated mean difference in platelet count – random effect model

| | MD for all comparisons ($\times 10^9$/L) (RE model) | | | | | |
|---|---|---|---|---|---|---|
| | vs. PLC | vs. AVA | vs. ELT | vs. ROM | Probability of being best | SUCRA |
| PLC | PLC | **-56.63 [-84.29, -29.72]** | **-55.30 [-68.93, -41.55]** | **-46.60 [ -60.86, -32.68]** | 0% | 0% |
| AVA | **56.63 [29.72, 84.29]** | AVA | 1.34 [-29.08, 32.23] | 9.94 [-20.40, 41.02] | 51% | 76% |
| ELT | **55.30 [41.55, 68.93]** | -1.34 [-32.23, 29.08] | ELT | 8.70 [-10.98, 28.07] | 41% | 76% |
| ROM | **46.60 [32.68, 60.86]** | -9.94 [-41.02, 20.40] | -8.70 [-28.07, 10.98] | ROM | 8% | 49% |

Statistically significant values were presented in bold; OR – Odds Ratio, RE – random effect, SUCRA - surface under the cumulative ranking curve.

Figure 3 Forest plot for comparison AVA vs comparators regarding estimated absolute mean difference – random effect model



## 9.1.2.Probability of reaching PLT ≥30×10$^9$/L

The distributions of the platelet count at the end of study for each treatment were estimated by summing up of:

- the mean distribution of platelet count at baseline averaged across all arms,
- the mean effect of placebo from baseline to end of study averaged across all placebo arms,
- the respective effects of each treatment versus placebo (*d*[treatment])

**Table 9 Posterior distributions of baseline platelet count and treatment effects**

| No. | Variable | mean | sd | 2.50% | median | 97.50% |
|---|---|---|---|---|---|---|
| 1 | Baseline | 16.0383 | 0.4415 | 15.1728 | 16.0389 | 16.9019 |
| 2 | Effect of placebo | 2.7573 | 0.9576 | 0.8873 | 2.7524 | 4.6333 |
| 3 | #1 + #2 | 18.7956 | 1.0551 | 16.7290 | 18.7946 | 20.8640 |
| 4 | *d*[AVA] | 56.6735 | 13.8866 | 29.7238 | 56.6277 | 84.2871 |
| 5 | *d*[ELT] | 55.2843 | 6.9298 | 41.5481 | 55.2950 | 68.9262 |
| 6 | *d*[ROM] | 46.6509 | 7.2013 | 32.6762 | 46.6038 | 60.8567 |

Probability of reaching PLT ≥30×10$^9$/L was estimated for each treatment using two approaches:

5. By counting simulations with the outcomes ≥ 30 (using 'step' WinBUGS function)
6. Through standard normal cumulative density function (using 'phi' WinBUGS function)

The estimates for the probabilities are presented in the Table 5. Both methods produced consistent estimates, which showed that all active treatments were associated with very high likelihood of reaching target PLT count.

**Table 10 Estimates for the probabilities of reaching ≥30×10$^9$/L**

| | Probability of reaching ≥30×10$^9$/L estimates using 'step' function | | Probability of reaching ≥30×10$^9$/L estimates using 'phi' function | |
|---|---|---|---|---|
| | Proportion | SD | Median | 95% Credible interval |
| PLC | 0.00 | 0.00 | 0.00 | [0.00, 0.00] |
| AVA | 0.9996 | 0.0200 | 0.9994 | [0.9064, 1.000] |
| ELT | 1.00 | 0.00 | 1.00 | [1.00, 1.00] |
| ROM | 1.00 | 0.00 | 1.000 | [0.9983, 1.00] |

### 9.1.3.Probability of reaching PLT ≥50×10$^9$/L

The distributions of the platelet count at the end of study for each treatment were estimated by summing up of:

- the mean distribution of platelet count at baseline averaged across all arms,
- the mean effect of placebo from baseline to end of study averaged across all placebo arms,
- the respective effects of each treatment versus placebo (*d*[treatment])

**Table 11 Posterior distributions of baseline platelet count and treatment effects**

| No. | Variable | mean | sd | 2.50% | median | 97.50% |
|---|---|---|---|---|---|---|
| 1 | Baseline | 16.0383 | 0.4415 | 15.1728 | 16.0389 | 16.9019 |
| 2 | Effect of placebo | 2.7573 | 0.9576 | 0.8873 | 2.7524 | 4.6333 |
| 3 | #1 + #2 | 18.7956 | 1.0551 | 16.7290 | 18.7946 | 20.8640 |
| 4 | *d*[AVA] | 56.6735 | 13.8866 | 29.7238 | 56.6277 | 84.2871 |
| 5 | *d*[ELT] | 55.2843 | 6.9298 | 41.5481 | 55.2950 | 68.9262 |
| 6 | *d*[ROM] | 46.6509 | 7.2013 | 32.6762 | 46.6038 | 60.8567 |

Probability of reaching PLT 50×10$^9$/L was estimated for each treatment using two approaches:

7. By counting simulations with the outcomes ≥ 50 (using 'step' WinBUGS function)
8. Through standard normal cumulative density function (using 'phi' WinBUGS function)

The estimates for the probabilities are presented in the Table 5. Both methods produced consistent estimates, which showed that ELT was associated with highest chance for reaching the level of PLT≥50×10$^9$/L- followed by AVA and ROM (Table 7).

**Table 12 Estimates for the probabilities of reaching ≥50×10$^9$/L**

| | Probability of reaching ≥50×10$^9$/L estimates using 'step' function | | Probability of reaching ≥50×10$^9$/L estimates using 'phi' function | |
|---|---|---|---|---|
| | Proportion | SD | Median | Credible interval |
| PLC | 0.00 | 0.00 | 0.00 | [0.00, 0.00] |
| AVA | 0.9670 | 0.1787 | 0.9660 | [0.4535, 0.9999] |
| ELT | 0.9996 | 0.0198 | 0.9997 | [0.9273, 1.0000] |
| ROM | 0.9842 | 0.1244 | 0.9829 | [0.5714, 1.0000] |

# 10.Appendix 2: Bayesian model

## 10.1.Likelihood and link-functions

To perform the NMA within a Bayesian framework, likelihood distributions needed to be defined to relate the data to the parameters of the models. This analysis was conducted on continuous data with the assumption of normal distribution, therefore the identity link with normal likelihood was used as presented in Table 13.

Dichotomous data for the probability of reaching platelet thresholds, either ≥30×$10^9$/L or ≥50×$10^9$/L were derived using standard normal cumulative density function.

**Table 13. Likelihood and link functions for different types of outcome data**

| | Likelihood | Link function |
|---|---|---|
| Normally distributed continuous data | $y_{jk} \sim normal\left(\theta_{jk}, \sigma^2_{jk}\right)$ | Identity |

## 10.2.Prior distributions

In order not to influence the observed results by the prior distribution, non-informative prior distributions were used for the model parameter(s). With such a 'flat' prior, it is assumed that before seeing the data any parameter value is 'equally' likely. As a consequence, posterior results are not influenced by the prior distribution but driven by the data as with a conventional frequentist meta-analysis. This approach is consistent with NICE requirements as stated in the NICE DSU technical support document[1] and Table 14 presents the prior distributions to be used in the planned Bayesian analysis.

**Table 14. Prior distributions for model parameters used for analysis in a Bayesian framework**

| Model parameters | Prior distribution |
|---|---|
| Nuisance parameters | $\mu_{jb} \sim normal(0, 10\,000)$ |
| Treatment effect parameters | $d_{Ak} \sim normal(0, 10\,000)$ |
| Heterogeneity parameters | $\sigma \sim uniform(0, 5)$ |

## 10.3.Selection of FE versus RE model

In order to identify the most appropriate model given the evidence base, the goodness-of-fit of model predictions to the observed data can be measured by calculating the posterior mean residual deviance, $\overline{D}$ . The deviance information criterion (DIC) provided a measure of model fit that penalises model complexity according to $DIC = \overline{D} + pD$ , $pD = \overline{D} - \hat{D}$ [3]. $pD$ is the 'effective number of parameters' and $\hat{D}$ is the deviance evaluated at the posterior mean of the model parameters.

The model with the lower DIC has been selected as it is the best compromise between adequacy and complexity[4]. However, a small difference in DIC between the fixed and random effects models (3-5 points) implies that the better fit obtained by adding random effects does not justify the additional complexity. If the difference in DIC between the fixed and random effect models was lower than 5 points, then the fixed effect model was selected, as it contains a lower number of parameters and is easier for clinical interpretation compared with the random effects model.[5]

## 10.4.Analysis of consistency

The available evidence form a star-like network of evidence without closed loops, therefore there was no source of inconsistency.

## 10.5.Software

The parameters of the different models were estimated within a Bayesian framework using a Markov Chain Monte Carlo (MCMC) method as implemented in the WinBUGS software package [6].

## 10.6.Planned number of iterations

Three independent Monte-Carlo chains were run for each analysis.

For fixed- and random-effect models, an initial burn-in of 50,000 iterations were discarded and all the results are based on a further sample of 50,000 iterations.

## 10.7.Assessment of convergence

The convergence of models has been assessed based on two diagnostics tools:

- Trace plot:
  - If the model has converged, the trace plot moves around the mode of the distribution.
  - A clear sign of non-convergence with a trace plot occurring when we observe some trending in the sample space.

- The scale of the trace plot can be used to identify instability in the chains with very high values

- Brooks-Gelman-Rubin diagnostic tool:
  - The green is the width of an 80% credible interval from the simulations pooled from all chains (a measure of the between-chain variability); the blue line is the average width of the 80% credible intervals for each chain separately (a measure of the within-chain variability), the red line is the ratio of the between- and within-chain measures.
  - Convergence is reached when the red line settles down too close to 1 and the blue and green lines converge together to stability.

In case of convergence issues, several technics were considered such as increasing the number of iterations, reducing the variance of the prior distributions or removing some studies from the analyses.

This report would inform further if the convergence occurred for all parameters in each analysis.

## 10.8. WinBUGS code

### 10.8.1.Fixed-effect model

```
model {

    for (i in 1: ns) {

        mu[i] ~dnorm(0, .0001)
        for all trial baselines
        for (k in 1: na[i]) {
            var [i, k] <- pow(se[i, k], 2)
            prec[i, k] <- 1 /var [i, k]
            y[i, k] ~dnorm(theta[i, k], prec[i, k])
            theta[i, k] <- mu[i] + d[t[i, k]] - d[t[i, 1]]

            dev[i, k] <- (y[i, k] - theta[i, k]) * (y[i, k] - theta[i, k]) * prec[i, k]
        }
        resdev[i] <- sum(dev[i, 1: na[i]])
    }
    totresdev <- sum(resdev[]) #Total Residual Deviance
    d[1] <- 0

    for (k in 2: nt) {
        d[k] ~dnorm(0, .0001)
    }

#Meta-analusis of change from baseline in platelet count in PLC groups
    for (i in 1: ns) {
        precision[i] <-  pow(se[i, 1], -2)
```

```
        y_change[i] ~dnorm(mu_change, precision[i])
    }

    mu_change ~ dnorm(m_change, tau_change)
    m_change ~ dnorm(0, .0001)
    var_change <- 1 / tau_change
    tau_change <- pow(sd_change, -2)
    sd_change ~ dunif(0, 5)


#Meta-analysis of baseline platelet count
    for (i in 1: ns) {
        for (k in 1: na[i]) {
            precision2[i,k] <-  pow(se_baseline[i, k], -2)
            y_baseline[i,k] ~dnorm(mu_baseline, precision2[I,k])
        }
    }

    mu_baseline ~ dnorm(m_baseline, tau_baseline)
    m_baseline ~ dnorm(0, .0001)
    var_baseline <- 1 / tau_baseline
    tau_baseline <- pow(sd_baseline, -2)
    sd_baseline ~ dunif(0, 5)


#Calculation of absolute mean difference in PLT count as well as RRs for dichotomised outcomes
    for (c in 1: (nt - 1)) {
        for (k in (c + 1): nt) {
            mean_diff[c, k] <- d[c] - d[k]
        }
    }

#Calculation of probability of reaching PLT >=30x10^9/L & >=30x10^9/L with 2 methods)
    for (k in 1: nt) {
        P_30[k] <- step((mu_baseline + mu_change + d[k]) - 30)
        P_50[k] <- step((mu_baseline + mu_change + d[k]) - 50)
        T_50[k] <- phi((mu_baseline + mu_change + d[k] - 50) / sd1[k])
        T_30[k] <- phi((mu_baseline + mu_change + d[k] - 30) / sd1[k])
    }
}
```

### 10.8.2.Random-effect model

```
model {

    for (i in 1: ns) {

        mu[i] ~dnorm(0, .0001)
        for all trial baselines
        for (k in 1: na[i]) {
            var [i, k] <- pow(se[i, k], 2)
            prec[i, k] <- 1 /var [i, k]
            y[i, k] ~dnorm(theta[i, k], prec[i, k])
            theta[i, k] <- mu[i] + d[t[i, k]] - d[t[i, 1]]

            dev[i, k] <- (y[i, k] - theta[i, k]) * (y[i, k] - theta[i, k]) * prec[i, k]
        }
        resdev[i] <- sum(dev[i, 1: na[i]])
    }
    totresdev <- sum(resdev[]) #Total Residual Deviance
    d[1] <- 0

    for (k in 2: nt) {
        d[k] ~dnorm(0, .0001)
    }

#Meta-analusis of change from baseline in platelet count in PLC groups
    for (i in 1: ns) {
        precision[i] <-  pow(se[i, 1], -2)
        y_change[i] ~dnorm(mu_change, precision[i])
    }

    mu_change ~ dnorm(m_change, tau_change)
    m_change ~ dnorm(0, .0001)
    var_change <- 1 / tau_change
    tau_change <- pow(sd_change, -2)
    sd_change ~ dunif(0, 5)


#Meta-analysis of baseline platelet count
    for (i in 1: ns) {
        for (k in 1: na[i]) {
            precision2[i,k] <-  pow(se_baseline[i, k], -2)
            y_baseline[i,k] ~dnorm(mu_baseline, precision2[I,k])
        }
    }
```

```
    mu_baseline ~ dnorm(m_baseline, tau_baseline)
    m_baseline ~ dnorm(0, .0001)
    var_baseline <- 1 / tau_baseline
    tau_baseline <- pow(sd_baseline, -2)
    sd_baseline ~ dunif(0, 5)


#Calculation of absolute mean difference in PLT count as well as RRs for dichotomised outcomes
    for (c in 1: (nt - 1)) {
        for (k in (c + 1): nt) {
            mean_diff[c, k] <- d[c] - d[k]
        }
    }

#Calculation of probability of reaching PLT >=30x10^9/L & >=30x10^9/L with 2 methods)
    for (k in 1: nt) {
        P_30[k] <- step((mu_baseline + mu_change + d[k]) - 30)
        P_50[k] <- step((mu_baseline + mu_change + d[k]) - 50)
        T_50[k] <- phi((mu_baseline + mu_change + d[k] - 50) / sd1[k])
        T_30[k] <- phi((mu_baseline + mu_change + d[k] - 30) / sd1[k])
    }
}
```

## Appendix B - Company additional evidence for ACD (not including NMA)

The committee requested further analyses and evidence from the company, which we have provided below and includes:

- Details on bleed-related unit costs
- 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
- 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.

*Please note that the NMA is provided separately in Appendix A.*

New NHS reference costs from the company are presented below and discussed within the company's ACD response.

**Table 1: NHS reference bleed costs – ERG and company suggestion**

| Type of bleed | ERG | | Company suggestion | |
|---|---|---|---|---|
| | Cost (£) | Source (NHS reference cost 19/20) | Cost (£) | Source (NHS reference cost 19/20) |
| Outpatient bleed | 459.65 | Weighted average FD03F-FD03H | 493.74 | FD03F |
| Gastrointestinal bleed | 3,091.79 | Weighted average FD03A to FD03E | 5,502.62 | FD03A |
| Intercranial haemorrhage | 4,690.02 | Weighted average AA23C to AA23G | 7,044.18 | AA23C |
| Other inpatient bleed | 2,890.37 | Weighted average, FD03B and FD03E | 3,625.70 | FD03B |

We have analysed the patient-level data on the duration of treatment with avatrombopag from Study 302 and its extension. The first graph below presents data from the extension of the Study 302 and the second one from the core trial.

**Figure 1: Scenario analysis for duration of treatment based on extension of Study 302**

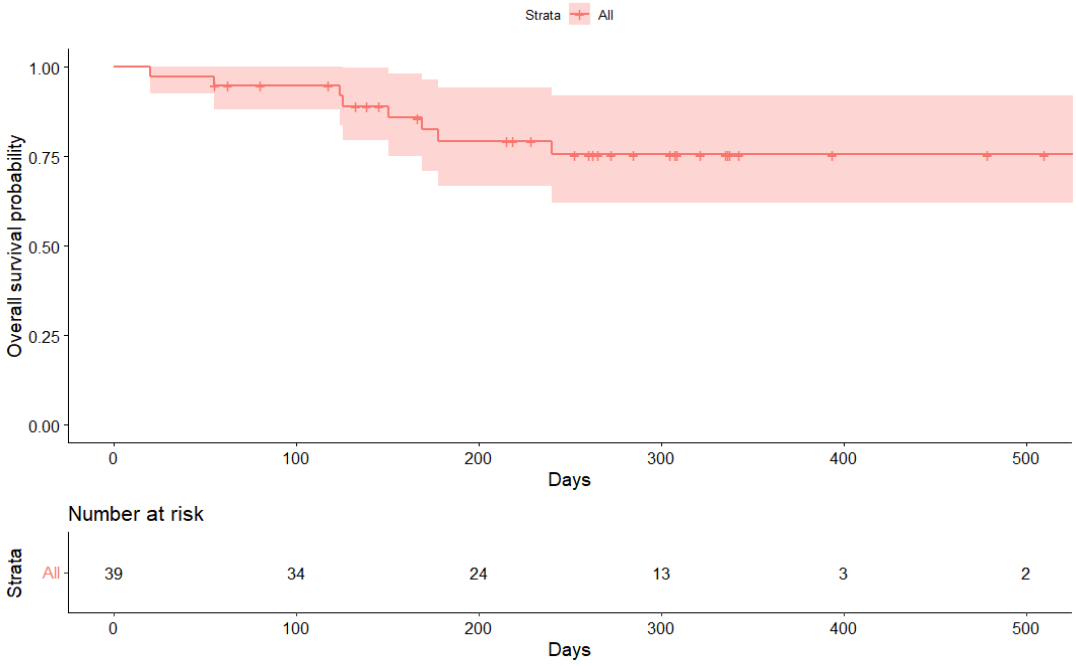
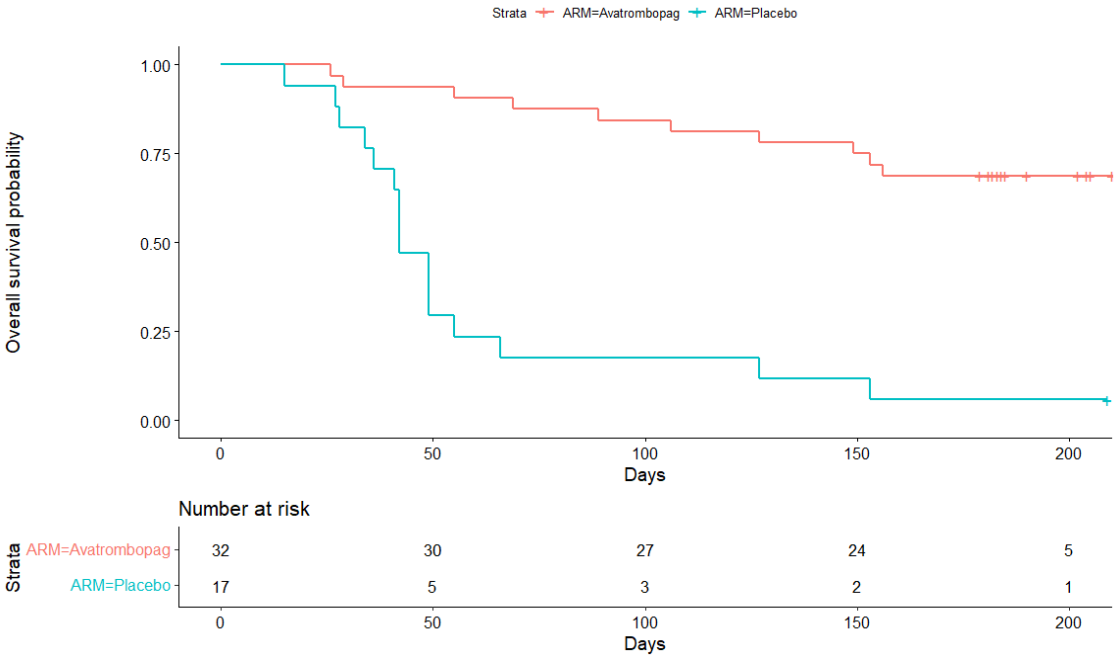



**Figure 2: Scenario analysis for patient-level data from Study 302**




After fitting the log-normal distribution to the trial data (in an analogous way for the company submissions of ELT and ROM) the average duration of treatment with AVA was estimated for 57.31 cycles based on the core study and 632.70 cycles after inclusion of the trial extension.

It should be noted that the treatment duration considered in the company submission was based on the long-term trials for comparators and hence should be compared with estimates that consider the extension of the 302 study. Such a comparison confirms the expectation that treatment with AVA can persist at least as long as the use of other TPO-RAs.

Estimated duration of treatment based on the data for AVA was included in the cost-effectiveness model. Three scenarios were considered:

- the same duration of treatment for all TPO-RAs based on core 302 study
- the same duration of treatment for all TPO-RAs based on core 302 study + extension
- different duration of treatment for ELT, ROM and AVA based on the long-term trials i.e. (109 cycles ELT, 393 cycles ROM, 633 cycles AVA)

The other assumptions of the model were the same as in the company response to the ERG report with one difference concerning the costs of bleeds, which is detailed earlier within this document in Table 1.

The cost-effectiveness results of listed scenarios have been presented in Table 2 below, and are discussed within the company's ACD response.

**Table 2 – ICER scenario analyses for duration of treatment**

| **Base case** | | | | |
|---|---|---|---|---|
| **AVA vs** | **Incremental cost** | **Incremental QALYs** | **ICER / Cost-effectiveness plane** | |
| **ROM** | [redacted] | [redacted] | [redacted] | [redacted] |
| **ELT** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Treatment duration from the core study (the same for all TPO-RAs)** | | | | |
| **AVA vs** | **Incremental cost** | **Incremental QALYs** | **ICER / Cost-effectiveness plane** | |
| **ROM** | [redacted] | [redacted] | [redacted] | [redacted] |
| **ELT** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Treatment duration from the core study + extension (the same for all TPO-RAs)** | | | | |
| **AVA vs** | **Incremental cost** | **Incremental QALYs** | **ICER / Cost-effectiveness plane** | |
| **ROM** | [redacted] | [redacted] | [redacted] | [redacted] |
| **ELT** | [redacted] | [redacted] | [redacted] | [redacted] |
| **Duration from different long-term trials (109 cycles ELT, 393 cycles ROM, 633 cycles AVA)** | | | | |
| **AVA vs** | **Incremental cost** | **Incremental QALYs** | **ICER / Cost-effectiveness plane** | |
| **ROM** | [redacted] | [redacted] | [redacted] | [redacted] |
| **ELT** | [redacted] | [redacted] | [redacted] | [redacted] |

In the response to another committee request, Sobi performed a probabilistic sensitivity analysis for the new base case scenario 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. The results of this PSA are presented below.

**Table 3 – PSA results vs ELT**

**AVA vs ELT**

| | **Incremental Costs** | **Incremental QALYs** | **ICER / Cost-effectiveness plane** | |
|---|---|---|---|---|
| **Base Case** | [redacted] | [redacted] | [redacted] | [redacted] |
| **PSA (mean)** | [redacted] | [redacted] | [redacted] | [redacted] |

Commercial in confidence information removed

**Table 4 – PSA results vs ROM**

**AVA vs ROM**

| | Incremental Costs | Incremental QALYs | ICER / Cost-effectiveness plane |
|---|---|---|---|
| **Base Case** | [redacted] | [redacted] | [redacted] |
| **PSA (mean)** | [redacted] | [redacted] | [redacted] |

Commercial in confidence information removed

To make sure that all committee recommendations are fulfilled in this response, Sobi performed additional scenario analyses with inclusion of the results of a network meta-analysis with the mean platelet count as a continuous outcome. These results, together with a distributional assumption, have been used to derive response probabilities of achieving two types of response:

- reaching PLT ≥30×$10^9$/L
- reaching PLT ≥50×$10^9$/L

**Table 5 – cost-effectiveness results with new response probabilities**

| **New response rates based on PLT > 30** | | | |
|---|---|---|---|
| **AVA vs** | **Incremental cost** | **Incremental QALYs** | **ICER / Cost-effectiveness plane** |
| **ROM** | [redacted] | [redacted] | [redacted] |
| **ELT** | [redacted] | [redacted] | [redacted] |
| **New response rates based on PLT > 50** | | | |
| **AVA vs** | **Incremental cost** | **Incremental QALYs** | **ICER / Cost-effectiveness plane** |
| **ROM** | [redacted] | [redacted] | [redacted] |
| **ELT** | [redacted] | [redacted] | [redacted] |

*ENDS*

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**Avatrombopag in combination for treating chronic immune thrombocytopenia [ID3838]**

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| | |
|---|---|
| | Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.<br><br>The Appraisal Committee is interested in receiving comments on the following:<br>• has all of the relevant evidence been taken into account?<br>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?<br>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?<br><br>NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:<br>• could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;<br>• could have any adverse impact on people with a particular disability or disabilities.<br><br>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.** |
| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | **ITP Support Association** |
| **Disclosure** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | None |
| **Name of commentator person completing form:** | [redacted] |

| **Comment number** | **Comments**<br><br>Insert each comment in a new row. |
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| | Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| Example 1 | We are concerned that this recommendation may imply that …….. |
| 1 | Ms White has experienced, over many years, the roller coaster of physical and emotional challenges in monitoring platelet counts, balancing side effects of treatment and managing the reality of platelets dropping, frequent hospital visits for both routine and rescue treatment, dealing with debilitating levels of fatigue as a result of low platelet counts and the impact living with chronic ITP has on mental health and quality of life. |
| 2 | **Do we believe all the relevant evidence has been taken into account?**<br>We believe the initial hearing was afforded due time, however given that the drug has already been used and proven its worth for chronic ITP since June 2019 in both the United States and Europe, The SMC in Scotland approved this drug some time ago in December 2020 (August 2021 for ITP) and it has also been used for Thrombocytopenia in liver disease patients in NHS England, we believe there was an over focus on particular scientific elements of this specific SOBI trial in respect of this application. Avatrombopag has a proven safety record and efficacy across all the regions and countries for which it has received approval. Furthermore, our Medical Advisors on the ITP UK Forum (across several centres of excellence) have advised us that Avatrombopag has been requested via the IFR route a number of times in the past year and has been approved for chronic ITP patients in NHS England. |
| 3 | **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**<br>We do not believe emphasis was necessarily given enough weight in terms of the wastage specifically with Romiplostim. This comes in vials of fixed dose (300 mcg vials). Residual drug is thereby wasted after a dose is made up.<br><br>There are significant financial benefits of Avatrombopag being made available. The cost saving against wastage with other treatments seemed to be lost or ignored during the submission hearing. Cost effectiveness – by way of personal demonstration, Dianne White explained her own case with the injectable dose of Romiplostim. The highest dose for her body weight of 57kg keeps her platelet count around 40-50 x 109/L, subject to no infections, physical traumas, or extreme stress. This costs c. £960 per week, so a total of £56K per year. Arguably for Dianne and other patients with a similar requirement, having been on this drug and injecting for 6 years, Avatrombopag would be a worthy and cost effective alternative if available.<br><br>As was highlighted in Dianne White's initial statement – switching 149 patients from Romiplostim to Avatrombopag would conservatively save the NHS in the region of 850K per annum.<br><br>Avatrombopag clinical effectiveness is well illustrated already with ITP patients, giving more robust results, enhancing QOL and reducing rescue situations and hospital visits. |
| 4 | **Are the provisional recommendations sound and a suitable basis for guidance for the NHS?**<br><br>We are surprised at the provisional recommendations and don't believe they are good guidance for the NHS.<br><br>This drug has proven its efficacy and application in the United States across 20 ITP referral centres (as evidenced in Dianne's initial statement), Europe and Scotland.<br><br>It has undergone scrutiny across all those geographical areas over a period of nearly 4 years and prior to that will have undergone significant clinical trials to prove itself.<br><br>It is economically advantaged in an NHS setting.<br><br>Its worst listed side effects are more comparable to some of the milder side effects of the other 2 |

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| | |
|---|---|
| | comparable drugs, used at this level of chronic ITP.<br><br>There are a number of patients for whom neither of these drugs produce good results, side effects are intolerable, or they simply do not fit into lifestyle scenarios – one of the drugs having significant food restrictions – some of which are not always obvious to the user (hidden fortified calcium in foodstuffs potentially eradicating the drug in the body).<br><br>One of the main advantages of taking avatrombopag is that it is an oral medication and can be taken without food restrictions, when compared with other treatments. Our ITPSA recent survey on patients' attitudes to treatment (TRAPeze study) highlighted their preference for oral treatment and there was a significant dislike of the food restrictions, which they find quite irksome and downright difficult.<br>Up to two thirds of patients suffer from fatigue which is severe in half of these. It is believed it is attributed to a low platelet count and can often pin-point relapses by their change in energy levels and necessity for rescue visits and additional treatment, such as scans, IVig transfusions.<br><br>The thrombopoietin receptor agonists increase the platelet count in a significant proportion of patients and may be associated with improvement of their fatigue and general quality of life. This has been shown in specific health related QOL studies. This contrasts to other medications (e.g., steroids), where fatigue is a reported side-effect of treatment. Avatrombopag is generally well tolerated, and we would expect it to show the same or an enhanced impact as the two currently available agents (Romiplostim and Eltrombopag).<br><br>In addition, as has been said about other medicines, this provides the health care professional with another item in their toolbox of treatments if another TPO-RA does not work or the patient has suffered intolerable side effects from the use of other treatments. |
| 5 | **Key Messages about Avatrombopag:**<br><br>The TPO RA class of drugs are important for ITP patients because they offer a good response rate, and importantly, do not suppress the immune system. This is a particularly relevant factor, given that we all now live in a period of Covid and potentially more aggressive similar type infections in the future may well come along.<br><br>Avatrombopag is an important treatment advance because it is given by a preferred treatment route (oral), without the dietary restrictions of the alternative oral medication, and provides a non-immunosuppressive option, with a good response rate, for those patients who do not tolerate or respond to the alternative TPO RA drugs.<br><br>Following on from all the content in this statement it is important and indeed part of medical progress and innovation that this drug should be available to haematologists to use in suitable chronic ITP patients across the UK and we believe that this will also represent a cost saving to the NHS. |
| 6 | |

Insert extra rows as needed

**Checklist for submitting comments**

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See

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the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.

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

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

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

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| | |
|---|---|
| | Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.<br><br>The Appraisal Committee is interested in receiving comments on the following:<br>• has all of the relevant evidence been taken into account?<br>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?<br>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?<br><br>NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:<br>• could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;<br>• could have any adverse impact on people with a particular disability or disabilities.<br><br>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.** |
| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | [**Insert organisation name**] |
| **Disclosure** Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | [**None**] |
| **Name of commentator person completing form:** | [**Dr Quentin A Hill**] |

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| | Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| Example 1 | We are concerned that this recommendation may imply that …….. |
| 1 | I have read the Appraisal consultation document "Avatrombopag for treating primary chronic immune thrombocytopenia". The provisional recommendations appear sound and I look forward to the further analysis requested and subsequent review. |
| 2 | |
| 3 | |
| 4 | |
| 5 | |
| 6 | |

Insert extra rows as needed

**Checklist for submitting comments**

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# Evidence Review Group's Critique of the Company's Response to the Appraisal Consultation Document (ACD)

# Avatrombopag in combination for treating chronic immune thrombocytopenia [ID3838]


| | |
|---|---|
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| **Date completed** | 03/08/2022 |


**Note on the text**

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data are highlighted in yellow and underlined, all depersonalised data (DPD) are highlighted in pink and underlined.

# Table of Contents

# 1 OVERVIEW OF THE COMPANY'S RESPONSE TO THE ACD

The company have provided eight comments in response to the Appraisal Consultation Document (ACD). These relate to:

Comment 1: Company position on avatrombopag;

Comment 2: Efficacy of avatrombopag;

Comment 3: Time to treatment response used in the economic model;

Comment 4: Additional network meta-analysis (NMA) comparing avatrombopag with eltrombopag and romiplostim for mean change in platelet count in patients with immune thrombocytopaenia;

Comment 5: Bleed-related unit costs;

Comment 6: Additional scenario analyses for treatment duration and cost-effectiveness results for a new base case analysis following ACD;

Comment 7: Results of probabilistic sensitivity analysis (PSA) for the company's new base case cost-effectiveness analysis following ACD;

Comment 8: Results of additional scenario analyses with inclusion of treatment response probabilities from the NMA conducted in response to comment 4.

The ERG provides a critical evaluation of the company's comments to the ACD where the company have provided additional evidence (comments 4, 5 and 6), comments where additional clarification is required (comment 3), and the company's new base case and scenario analyses following ACD (comments 6, 7 and 8). The ERG critique should be read in conjunction with the company's ACD response document, the ERG report, and the ERG critique of the company's response to technical engagement.

# 2 CRITIQUE OF THE COMPANY'S COMMENTS IN RESPONSE TO THE ACD

## *2.1 Comment 3: Time to treatment response used in the economic model*

The ERG would like to provide additional clarification on the comments made by the company on time to treatment response used in the economic model. The company states that they had previously accepted, in response to technical engagement, the ERG's view that patients would not wait a full 24 weeks to assess non-response to TPO-RA treatment (avatrombopag, eltrombopag and romiplostim) as used in the company's model. The company implies that this issue was resolved during the technical engagement stage by altering their base case analysis to a 12-week timeframe for time to treatment response (corresponding to a 3-cycle duration in the model), in line with the ERG's base case. However, although the ERG highlighted the issue that it is unlikely that patients would remain on treatment for a full 24 weeks before response to treatment is assessed (and noted the stopping rules in the product SmPCs), the ERG's base case did not use a 12-week timeframe. Instead, the ERG conducted an exploratory scenario analysis (ERG Scenario 1 in the ERG report) that used an 8-week timeframe to assess response to first-line TPO-RA treatment. This scenario was exploratory (to assess the impact of removing 16 weeks of treatment costs for patients that are considered non-responders in the model) and did not form part of the ERG's preferred assumptions because an 8-week (or 12-week) timeframe does not align with the definition of durable platelet response (at least 6 weekly platelet counts ≥50×109/L in the final 8 weeks of a 24-26-week study) used for the response probabilities in the model. Consequently, the company's updated base case results in response to technical engagement did not include a 12-week timeframe for time to treatment response.

## *2.2 Comment 4: Additional network meta-analysis (NMA) for mean change in platelet count*

The company submitted additional NMA comparing avatrombopag with eltrombopag and romiplostim for mean change in platelet count in patients with immune thrombocytopaenia (ITP). This analysis was submitted in response to a request from the appraisal committee to conduct *"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"* (ACD). The appraisal committee suggested this alternative approach in order to avoid two critical issues identified in the NMA for durable platelet response rates: high attrition rate in the placebo group of Study 302 (see Section 3.2 of the ERG report) and uncertainties associated with the correction of zero events in Studies 302 and Kuter 2008 SPL (see Section 3.4 of the ERG report).

The company's additional NMA in response to the ACD was performed within a Bayesian framework on the outcome *mean change from baseline in platelet count* over the 25 or 26-week study period, under both a fixed and random effects model. Individual participant data were available from Study 302 to calculate the required mean change from baseline in platelet count (and corresponding standard error) in each treatment group (avatrombopag and placebo). However, because participants were permitted to discontinue treatment early (e.g., in the case of inadequate efficacy), there was only one participant left in the placebo group at the end of the 26-week randomised period. The company used a single imputation method of last observation carried forward (LOCF) to input missing data. This means that the change from baseline in platelet count was estimated based on the last observations before early drop-out. This method was used in both the avatrombopag and placebo groups. In addition, because the mean change from baseline was not reported in the comparator trials (RAISE for eltrombopag versus placebo; Kuter 2008 SPL and Kuter 2008 non-SPL for romiplostim versus placebo), mean values and standard deviations were estimated for the comparators based on reported median platelet count and interquartile ranges at different time points.

The ERG would like to highlight the following points in relation to the company's additional NMA:

- Firstly, the company does not provide justification for their choice of continuous outcome of mean change from baseline in platelet count. The ERG notes that other alternative outcomes could have been explored by the company, such as the Bayesian repeated measures NMA model that would allow the synthesis of multiple time points and flexible temporal patterns (Tallarita et al., 2019), or the ANCOVA NMA model that synthesises the outcome at follow-up, whilst adjusting for baseline imbalances (Riley et al., 2013; Saramago et al., 2016; Hong et al., 2015).
- Secondly, the ERG agrees with the limitations of the analysis carried out by the company as listed on page 16 of Appendix A NMA ACD response. The ERG considers that these limitations are of concern, in particular the imputation using LOCF in Study 302, and highlights that these are likely to have been enhanced by the company's choice of outcome measure. In the company's new NMA, the LOCF approach was the only method used to address the issue of missing data, i.e., the impact of using alternative methods was not explored. This is problematic since LOCF is a less conservative approach to imputing missing outcome data than the non-responder imputation approach, which was used for NMA for the durable platelet response outcome (in the original company submission). The LOCF method is generally considered not to be statistically valid, since it can lead to serious bias and usually causes standard errors to be very small because it fails to account for uncertainty associated with the missing values. For the Study 302 dataset, bias may arise from imputing data from participants whose data were missing due to adverse events or loss of efficacy (i.e. loss of an

initial treatment response). This is because the last recorded trial observation might have been made when the participant was still receiving treatment (i.e., before the adverse event or loss of efficacy) and so may overestimate efficacy when compared to (the expected) data at later follow up timepoints. The ERG's view is that other, more conservative, imputation approaches could also have been explored by the company (e.g. baseline observation carried forward).

- Thirdly, the mean platelet count fluctuates over time for avatrombopag in Study 302 (see Figure 6 of the company's original submission for the median platelet count over the 26-week study period). The ERG believes that the outcome chosen by the company in the additional NMA provides a restricted view of treatment response over time compared to the previously modelled outcome of durable platelet response (platelet response above $50\times10^9$/L for ≥6 of the last 8 weeks of treatment), where response rates appeared to fluctuate less in the maintenance period of Study 302. Also, the ERG's clinical advisor considered durable platelet response as the best metric of treatment response (ERG report, section 4.2.2.2, page 74).
- Fourthly, given the company's response to Comment 3 above (i.e., the company agreed that a 12-week treatment duration aligns with the evidence provided by the clinical experts at the appraisal committee meeting), the ERG is unclear why the company has not presented a NMA for the outcome of mean platelet count at 12 weeks (or mean change from baseline in platelet count at 12 weeks). An analysis at 12 weeks would align with the company's response to Comment 3 and would be expected to have the added advantage that fewer missing data points are needed to be imputed (because there were fewer drop-outs at 12 weeks than at 26 weeks in Study 302).

The results of the company's additional NMA for mean change from baseline in platelet count are markedly different from the results of the company's original NMA (and the ERG's NMA) for the outcome of durable platelet response, in terms of the ranking of efficacy of TPO-RAs. In the additional NMA, avatrombopag has the highest probability of being the best treatment (51%), followed by eltrombopag (42%) and romiplostim (7%). The estimates of the probabilities of reaching a platelet count of $\geq50\text{x}10^9$/L (the response threshold that is used in the economic model) are very close to 100% for all TPO-RAs (see Table 7 of Appendix A NMA ACD response). In contrast, in the company's original NMA for durable platelet response outcome, avatrombopag has the highest probability of being the best treatment (58%), followed by romiplostim (32%) and eltrombopag (3%), with probabilities of response (vs. placebo) used in the economic model of 81% for avatrombopag, 66% for romiplostim and 37% for eltrombopag. In the ERG's base case for the outcome of durable platelet response, romiplostim has the highest probability of being the best treatment, followed by

avatrombopag and eltrombopag, with probabilities of response (vs. placebo) used in the model of 55% for romiplostim, 44% for avatrombopag, and 31% for eltrombopag.

In summary, the ERG does not consider that the additional NMA presented by the company in response to the ACD resolves the uncertainties of avatrombopag's clinical effectiveness relative to other TPO-RAs.

### *2.3 Comment 5: Bleed-related unit costs*

In response to a request from the appraisal committee, the company have provided additional details on the market research that was used to inform bleeding costs in their original submission. The company have also acknowledged the committee's concern with not using NHS reference costs for costing bleeding events, and welcomes the committee's recognition that there might be additional resources not covered by the NHS reference costs. The company sought further clinical advice from UK clinicians, which stated that the duration of different bleeds in ITP patients tend to be longer than those in the general population because it takes additional time to bring the platelet count up and stabilise bleeding, and that the severity of bleeds in patients with low platelet count tends to be increased [Company response to ACD]. Consequently, the company proposes using NHS reference costs for costing bleeding events, in line with the ERG's approach, but based on the highest unit cost for the different types of bleed in order to account for additional resources associated with bleeding in ITP patients.

The ERG considers the proposed approach of uplifting NHS reference costs for bleeding events to be reasonable in light of the information from clinicians that resources may be higher for bleeds in ITP patients; however, the company have selected the highest unit cost for each type of bleed corresponding to those with the highest complication and comorbidity (CC) score. Table 2 of the company's response to the ACD compares the NHS reference costs used in the ERG's base case with the company's proposed unit costs (noting that a minor error is reported for the NHS reference costs under code FD03B, which is reported as £3,626 rather than £3,485 in Table 2); the unit costs are increased by £34 for outpatient bleed, £2,411 for gastrointestinal bleed, £2,354 for intercranial haemorrhage and £595 for other inpatient bleed, which correspond to the highest unit cost associated with the higher CC score rather that a weighted average of unit costs associated with different CC scores from NHS reference costs.

### *2.4 Comment 6: Treatment duration*

In response to a request from the appraisal committee, the company have provided additional evidence on the duration of treatment with avatrombopag from Study 302 and its extension (see Figures 2 and 3 of the company's response to the ACD). The company fitted a log-normal distribution

to the Kaplan-Meier data from the trial, which resulted in an average duration of treatment with avatrombopag of 57.31 cycles (229 weeks or 4.4 years) based on the core study and 632.70 cycles (2,531 weeks or 48 years) with the trial extension. The company states that since the treatment duration used in the model is based on the long-term trials for the comparators, it is appropriate to consider the extension of Study 302.

The ERG considers the approach used by the company to analyse the data from Study 302 to be reasonable as it is analogous to that used in Lee et al., (2013) for estimating the mean treatment duration for eltrombopag and romiplostim. In Lee et al., (2013) log-normal curves were fitted to Kaplan-Meier data for the eltrombopag and romiplostim arms of the respective long-term, open label, extension studies (EXTEND for eltrombopag and Kuter et al, 2008 for romiplostim, respectively). This resulted in estimates of the mean times on treatment of 109 cycles (436 weeks or 8.4 years) for eltrombopag and 393 cycles (1,572 weeks or 30 years) for romiplostim. In the company's original submission, the longer-term durability of treatment response on TPO-RA treatment (avatrombopag, eltrombopag or romiplostim) was assumed to be the same for the TPO-RAs and the lowest of the mean times on treatment of 109 cycles over a patients' lifetime.

Although the ERG considers the approach used to analyse Study 302 data to be reasonable it is important to recognise that the extension data into the longer term (approximately 1.4 years) have much fewer patients at risk, e.g. there are less than 10 patients at risk at one year (Figure 2 of the company response to ACD). These data based on small numbers at risk are being extrapolated into the long-term to give an average duration of treatment of approximately 48 years for avatrombopag.

Furthermore, it is important to recognise that even if the treatment duration is assumed to be identical between the TPO-RA treatments, the actual mean estimate used in the model (whether this is 109 cycles, 393 cycles or 633 cycles) will have an important impact on the cost-effectiveness of avatrombopag relative to eltrombopag and romiplostim. This is because the higher the treatment response rate between the alternative TPO-RAs, the longer (greater mean time on treatment) or shorter (lower mean time on treatment) this response is maintained over time, which impacts the time to the 'no treatment no response' health state in the model that incurs an elevated risk of bleeding (and associated high costs of hospitalisation and mortality) and need for rescue therapy. Lower discontinuation rates for a more effective treatment will only result in improved cost-effectiveness when the movement to the 'no treatment no response' health state occurs late enough in time so that the elevated risk of severe bleeding events and need for rescue therapy are significantly discounted, and the next subsequent line of therapy is less cost-effective than the TPO-RA.

In summary, the ERG does not consider that the additional evidence presented by the company in response to the ACD resolves the uncertainties about the average duration of treatment.

# 3 CRITIQUE OF THE COMPANY'S NEW BASE-CASE AND SCENARIO ANALYSES FOLLOWING ACD

The company presented new base-case results (included in their response to comments 6 and 7) and scenario analyses (in response to comments 6 and 8) following ACD. The company states that the new base case has the same assumptions as in the company response to the ERG report (i.e., following technical engagement), but with the one exception that new costs of bleeding events are included in response to Comment 5 (i.e., NHS reference costs for bleeding events based on the highest CC scores). The ERG interprets this to mean that all the ERG-preferred assumptions are incorporated within the company's model, with the exception of the following assumptions:

- Comparative effectiveness estimates are based on the NMA for durable platelet response from the company's analysis in response to technical engagement. The company presented revised estimates for the odds ratio of avatrombopag vs. placebo and romiplostim vs. placebo, based on a continuity correction adjustment for zero-event cells according to the proportion of individuals in each treatment group.
- Costs of bleeding events are based on NHS reference costs but using the highest unit costs for each type of event (see Table 2 of the company response to ACD).
- The time to treatment response is 12 weeks rather than 24 weeks as used in the company's original submission and ERG's preferred assumptions due to a misinterpretation of the ERG's base case (see response to Comment 3 above).

The company have presented deterministic results of their new base-case in Table 5 of the company response to the ACD and corresponding probabilistic results in Tables 6 and 7 in response to Comment 7.

The company have presented additional scenario analyses in Table 5 of the company response to the ACD for three alternative treatment durations:

- The same duration of treatment for all TPO-RAs based on core Study 302 (i.e., 57.31 cycles);
- The same duration of treatment for all TPO-RAs based on core Study 302 and extension (i.e., 632.70 cycles);
- Different durations of treatment for avatrombopag (633 cycles), eltrombopag (109 cycles) and romiplostim (393 cycles) based on the long-term trial data.

The company have also presented additional scenario analyses in Table 8 of the company response to the ACD with inclusion of the results of the additional NMA for mean platelet count to derive the

estimate of probabilities of reaching a platelet count of ≥30x$10^9$/L and ≥50x$10^9$/L (see response to Comments 4 and 8).

### *3.1 Critique of the company's base case results*

The ERG has a number of concerns about the new base case results presented by the company. The first is that the company has not used the updated version of the model following technical engagement, instead the original version of the model has been used to make the changes above. This means that the set of ERG-preferred assumptions that the company accepted at technical engagement stage have not been incorporated within the company's revised model (despite the fact that the company states that they have used the same assumptions as in the company response to the ERG report). The following accepted ERG-preferred assumptions do not appear to be included in the company's new base case:

- Fully incremental comparison of alternative treatment strategies (ERG Scenario 2 in ERG report).
- Using updated guidance to inform dosages for non-TPO-RAs in the model (ERG Scenario 4 in ERG report).
- Health-related quality of life utility values adjusted by age over time (ERG Scenario 8 in ERG report).
- Administration costs for romiplostim (ERG Scenario 9d in ERG report).
- Romiplostim dosing costs (ERG Scenario 10a in ERG report).
- Rescue therapy and bleed events costed independently (ERG Scenario 11 in ERG report).

In addition, the company have not corrected their comparative effectiveness estimates for durable platelet response, which was highlighted in the ERG critique of the company's response to technical engagement document, i.e., the company's approach of adjusting 'events' only in the zero-event cells, without making any adjustment to 'no events' is inappropriate (note that this is a correction required in the methods used by the company rather than a judgement about the approach used to estimate comparative effectiveness estimates).

Moreover, the company have presented their new base case results in a pairwise comparison approach (avatrombopag vs. eltrombopag and avatrombopag vs. romiplostim) despite the fact that the ERG highlighted this concern in the ERG report and updated their model to allow a fully incremental comparison of the TPO-RAs, which the company used in their response to technical engagement. This also means that it is not possible to conduct a probabilistic fully incremental analysis; therefore, the probabilistic results for the company's new base-case analysis are presented as pair-wise comparisons in response to Comment 7.

It is also worth noting that the company have not provided a version of the model with the changes clearly marked in response to the ACD (i.e. a list of changes made to worksheets and cells in the model workbook) so that the ERG can validate the changes accordingly.

### *3.2 ERG correction of the company's base case results*

The ERG has corrected the company's new base case by using the updated version of the model following technical engagement, but with the company's preferred assumptions, i.e.,

- Comparative effectiveness estimates are based on the NMA for durable platelet response from the company's analysis in response to technical engagement, but with the ERG correction to zero-event cells (events and no events) according to the proportion of individuals in each treatment group (i.e., the odds ratios for avatrombopag, eltrombopag and romiplostim vs. placebo are 26.91, 10.60 and 33.39, respectively, compared to the corresponding company estimates of 27.49, 10.60 and 33.56).
- Costs of bleeding events are based on NHS reference costs but using the highest unit costs for each type of event (see Table 2 of the company response to ACD), but with rescue therapy and bleed events costed independently in line with company response following technical engagement. The ERG also corrected a minor error in Table 2 for NHS reference costs under code FD03B, which was reported as £3,626 rather than £3,485.
- The time to treatment response is 12 weeks rather than 24 weeks as used in the company's original submission and ERG's preferred assumptions because this is now the company's preferred assumption.
- All other assumptions match the ERG's preferred base case in line with company response following technical engagement.

Table 1 shows the results of the ERG-corrected company base case results following ACD.

**Table 1 Results of ERG-corrected company base case following ACD**

| | Treatment | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|
| **Company's new base-case** | ELT | [redacted] | [redacted] | | | |
| | AVA | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | ROM | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Abbreviations:** AVA, avatrombopag; ELT, eltrombopag; ROM, romiplostim

The ERG refers the committee to the addendum with the ERG-corrected company base case results following ACD with confidential prices included for the comparators.

### *3.3 Critique of the company's scenario analyses*

As per the company's new base case analysis, the company scenario analyses are not based on the updated version of the model following technical engagement. The ERG has corrected the company scenario analyses for the three alternative treatment durations; however, the ERG has not presented corrected scenario analyses for response probabilities reaching a platelet count of $\geq 30x10^9$/L and $\geq 50x10^9$/L because these probabilities were all close to 100% for all TPO-RAs.

Table 2 shows the results of the ERG-corrected company scenario results for treatment duration following ACD.

**Table 2 Results of ERG-corrected company scenario analyses for treatment duration following ACD**

| | Treatment | Total costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|
| **Company scenario 1** | **The same duration of treatment for all TPO-RAs based on core Study 302 (i.e., 57.31 cycles).** | | | | | |
| | ELT | [redacted] | [redacted] | | | |
| | AVA | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | ROM | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Company scenario 2** | **The same duration of treatment for all TPO-RAs based on core Study 302 and extension (i.e., 632.70 cycles).** | | | | | |
| | ELT | [redacted] | [redacted] | | | |
| | AVA | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | ROM | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Company scenario 3** | **Different durations of treatment for avatrombopag (633 cycles), eltrombopag (109 cycles) and romiplostim (393 cycles) based on the long-term trial data.** | | | | | |
| | ELT | [redacted] | [redacted] | | | |
| | AVA | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| | ROM | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Abbreviations:** AVA, avatrombopag; ELT, eltrombopag; ROM, romiplostim

The ERG refers the committee to the addendum with the ERG-corrected company scenario analyses results following ACD with confidential prices included for the comparators.

# 4 REFERENCES


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# Avatrombopag for chronic immune thrombocytopenia ID3838

# Additional company budget impact analysis

## September 2022



 

# Contents



# Tables and figures



# Abbreviations

| Abbreviation | Definition |
|---|---|
| AVA | Avatrombopag |
| ELT | Eltrombopag |
| ITP | Immune thrombocytopenia |
| ONS | Office for National Statistics |
| PAS | Patient access scheme |
| ROM | Romiplostim |
| SmPC | Summary of medical product characteristics |
| TPO-RA | Thrombopoietin receptor agonist |



 

# 1 Objectives

1.1 The objective of this analysis is to compare the budget impact to the NHS in England and Wales of the introduction of avatrombopag (AVA) relative to existing standard of care [eltrombopag (ELT) and romiplostim (ROM)] for the treatment of immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments.

1.2 The analysis was conducted in response to a request from the NICE appraisal committee to provide additional analysis that compares the cost and resource impact of AVA relative to ELT and ROM over a five and ten-year horizon, and provide scenario analyses using 109 cycles for all thrombopoietin receptor agonist (TPO-RAs) and the weighted average NHS costs for bleeds.

1.3 Budget impact analysis may form a key component of appraisal decision-making since evidence provided in the core submission, including indirect treatment comparisons, demonstrate that AVA has similar efficacy and outcomes to ELT and ROM.

1.4 It should be noted when reviewing this analysis that Sobi has agreed a patient access scheme with NHS England, consisting of a [redacted] off the list price of all presentations of AVA. The net prices to the NHS of ELT and ROM are commercially confidential, and therefore list prices of these treatment are only used within this document. We recommend that NICE separately runs the same analysis with patient access scheme (PAS) prices of each (TPO-RA).

# 2 Eligible population

2.1 Eligible population estimates have been described in core submission documents and therefore to prevent duplication, only an abbreviated explanation is provided.



 

2.2 ITP is a chronic disorder in the majority of diagnosed cases; therefore, it is considered an appropriate simplification to exclude incidence for the budget impact analysis.

2.3 Estimates for the population eligible for treatment with AVA have been calculated using a combination of Office for National Statistics (ONS) 2018-based population projections, the assumed prevalence of ITP and patient flow assumptions which were used in both the ELT NICE appraisal and the NICE costing template for ROM (TA221, TA293 (1, 2)).

The general population projections for the next 10 years through 2022-2031 from the ONS (2018) for England and Wales is estimated at 48,970,118 in 2022, rising to 51,039,274 in 2032 (Table 1). Based on an ITP prevalence rate of 10/100,000 people amongst the general population, the number of patients across England and Wales with ITP is estimated at 4,897 in 2022, rising to 5,103 in 2031 (Table 1).

Applying the patient flow assumptions, it is estimated that 551 patients will be eligible for treatment with AVA in 2022, rising to 565 in 2026 and 574 in 2031 (Table 1).



 

## Table 1: Estimated eligible patient population

| Eligible patient population | Reference | Assumption applied | Year | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 2022 | 2023 | 2024 | 2025 | 2026 | 2027 | 2028 | 2029 | 2030 | 2031 |
| **Population >18 (England and Wales)** | ONS 2018 based population projections | | 48,970,178 | 49,272,297 | 49,584,924 | 49,879,125 | 50,180,389 | 50,361,038 | 50,537,302 | 50,709,129 | 50,876,469 | 51,039,274 |
| **Patients with ITP (UK prevalence)** | Pooled rate of ITP prevalence (10 per 100,000) | 0.01% | 4,897 | 4,927 | 4,958 | 4,988 | 5,018 | 5,036 | 5,053 | 5,070 | 5,087 | 5,103 |
| **ITP patients requiring treatment** | ELT NICE submission & ROM costing template | 60% | 2,938 | 2,956 | 2,975 | 2,993 | 3,011 | 3,022 | 3,032 | 3,042 | 3,052 | 3,062 |
| **ITP patients with unsuccessful first-line treatment** | ELT NICE submission & ROM costing template | 67% | 1,969 | 1,981 | 1,993 | 2,005 | 2,017 | 2,024 | 2,031 | 2,038 | 2,045 | 2,051 |
| **Refractory ITP patients requiring long-term treatment** | ELT NICE submission & ROM costing template | 40% | 787 | 792 | 797 | 802 | 807 | 810 | 813 | 815 | 818 | 821 |
| **ITP patients receiving treatment with a TPO-RA** | Assumption (clinical opinion (10)) | 70% | 551 | 555 | 558 | 561 | 565 | 567 | 569 | 571 | 573 | 574 |



 

# 3 Resources

3.1 The following budget impact analysis incorporates costs directly related to active treatment with the TPO-RAs, including drug acquisition costs, and the costs associated with drug administration and patient monitoring.

In relation to current standard of care for patients with ITP, the technology is not expected to have any impact on patient monitoring. This is a conservative assumption considering hepatoxicity monitoring is required with ELT treatment which may be reduced with the uptake of AVA which does not require monitoring in the same way.

For the purposes of the budget impact analysis, equivalent efficacy has been assumed, apart from when calculating the costs associated with bleeding events.

3.2 Drug acquisition costs were sourced from the BNF and are summarised in Table 2. For AVA, a simple discount patient access scheme (PAS) has been agreed with NHS England, therefore drug costs for AVA were applied at the discount of [redacted] in the budget impact calculations. Both ELT and ROM have been approved by NICE with a PAS. However, as the PAS in both cases is confidential, list prices have been assumed.

**Table 2: Drug acquisition costs applied in the budget impact analysis**

| Drug | Formulation (pack size) | Cost per pack (list price) | Discount | Cost per pack (net price) | Source |
|---|---|---|---|---|---|
| AVA | 30x20mg tablets | £1,920.00 | [redacted] | [redacted] | BNF (3) |
| ELT | 28x50mg tablets | £1,540.00 | - | £1,540.00 | BNF (3) |
| ROM | 125 µg vial | £241.00 | - | £241.00 | BNF (3) |

Abbreviations: AVA, avatrombopag; ELT, eltrombopag; ROM, romiplostim, British National Formulary

The dosing of TPO-RAs in ITP is individualised and based on a patient's platelet count. The product SmPCs for AVA, ELT and ROM recommend the



 

lowest dose to achieve and maintain a platelet count ≥50x$10^9$/L. For AVA and ELT, the recommended starting doses are 20mg and 50mg once daily, respectively. The dose titration and dose reduction regimens for both treatments are summarised in the core submission. ROM is available as a subcutaneous injection and patients receive a dose according to both their body weight and platelet count. The recommended initial dose of ROM is 1 µg/kg once weekly but can be increased up to a maximum dose of 10 µg/kg per week.

In Study 302 and the ELT Phase III trial, RAISE, the mean doses received by patients throughout the studies were 22.34 mg and 51.3 mg, respectively (4, 5). Furthermore, the most common dosing regimens patients received were the daily doses of 20mg and 50mg, respectively. Therefore, doses for AVA and ELT adopted in the budget impact analysis were 20mg and 50mg, respectively. For ROM, the dose applied in the model base case was set at 4µg/kg, which was the mean dose from the pivotal long-term trial (6). As dosing of ROM is also weight based, the median patient weight from Study 302 was applied (82.97kg). Dosages for each modelled therapy are shown in Table 3.

**Table 3: Dosing assumptions applied in the budget impact analysis**

| Drug | Dose | Source |
|---|---|---|
| AVA | 20mg once daily | SmPC (7) |
| ELT | 50mg once daily | SmPC (8) |
| ROM | 332µg weekly<br>(4µg x 82.97kg) | SmPC (9) |

Abbreviations: AVA, avatrombopag; ELT, eltrombopag; ROM, romiplostim

3.3 Based on UK clinical opinion (10), there are assumed to be no additional monitoring costs between the TPO-RA treatments.

Administration costs were considered relevant for ROM as treatment can be administered either at home or via a specialist nurse at an outpatient or community clinic. The proportion of patients who were eligible to receive home administration was derived using figures from a congress abstract of Phase III trial data presented at the ASH annual meeting 2010 (11). In that



 

study, 82% of patients had initiated home administration and, of these, 88.3% continued until the end of the study. This equates to 211 of 292 patients (72.3%) who received home administration. For the 27.7% of ROM treated patients whose treatment was administered at the clinic, a per visit unit cost of £166.51 was applied using NHS reference costs (2018/19) (Clinical haematology, code 303) (NHS Reference costs (12)). For AVA and ELT, no administration costs were applied as patients administer treatment independently at home.

The annual drug costs per patient on each TPO-RA are presented in Table 4, and the annual per patient healthcare costs by resource category are presented in Tables 5, 6 and 7 for AVA, ELT, and ROM, respectively.

**Table 4: Annual drug costs per patient for AVA, ELT and ROM**

| Drug | Cost per pack | Pack | Size (mg) | Cost per mg | Mean dose (mg) | Cost per administration | Nb of administrations per year per patient | Drug cost per year per patient |
|---|---|---|---|---|---|---|---|---|
| **ELT** | £1,540 | 28x50mg | 1400 | £1 | 50 | £55 | 365 | £20,075 |
| **ROM** | £241 | 0.125mg | 0.125 | £1,928 | 0.38 | £723 | 52 | £37,596 |
| **AVA** | [redacted] | 30x20mg | 600 | £2 | 20 | £40 | 365 | [redacted] |

Abbreviations: AVA, avatrombopag; ELT, eltrombopag; ROM, romiplostim

**Table 5: Annual costs per patient for avatrombopag, by resource category**

| Cost item | Annual cost (£) |
|---|---|
| Drug costs [PAS price] | [redacted] |
| Monitoring costs | 2,127 |
| Administration costs | 0 |
| Total costs | [redacted] |



 

**Table 6: Annual costs per patient for eltrombopag, by resource category**

| Cost item | Annual cost (£) |
|---|---|
| Drug costs [List price] | 20,075 |
| Monitoring costs | 2,127 |
| Administration costs | 0 |
| Total costs | 22,202 |

**Table 7: Annual costs per patient for romiplostim, by resource category**

| Cost item | Annual cost (£) |
|---|---|
| Drug costs [List price] | 37,596 |
| Monitoring costs | 2,127 |
| Administration costs | 2,401 |
| Total costs | 42,124 |

3.4 The committee requested scenario analysis '*using 109 cycles for all TPO-RAs and using the weighted average NHS costs for bleed-related'*.

Given the limitations noted by the committee of using the company's NMAs and acknowledgement that it is not unreasonable to consider the efficacy may be broadly similar for TPO-RAs, and the complexity of showing results informed by different NMAs, Sobi has shown results using NMAs for only bleed related costs with 109 cycles.

The annual costs of bleeds per patient have been obtained based on the results of the cost-effectiveness model depending on the treatment used. The model submitted by the company in the response to ACD was run with the following assumptions:

- Unit costs of bleeds according to ERG approach i.e. weighted average NHS reference costs
- Efficacy scenarios
    - ERG sensitivity analysis NMA results
    - ERG base case NMA results
    - The same efficacy



 

- Time horizon
    - 5 years
    - 10 years
- Average duration of treatment of 109 cycles, the same for all TPO-RAs
- No discounting was included

The annual costs of bleeds per patient have been obtained by dividing the total costs estimated in the economic model in a given option (i.e. efficacy scenario) by the duration of the time horizon (Table 8).

Table 8 demonstrates that AVA is expected to result in fewer bleed related costs than ELT under both of the ERG scenarios and the same cost if the same efficacy for each TPO-RA is assumed. ROM is associated with marginal savings in terms of bleed related costs relative to AVA, except if the same efficacy is assumed.

**Table 8: Annual costs of bleeds per patient per treatment (5- & 10-year horizon)**

| | 5-year time horizon | | | 10-year time horizon | | |
|---|---|---|---|---|---|---|
| | **AVA** | **ELT** | **ROM** | **AVA** | **ELT** | **ROM** |
| **ERG sensitivity analysis NMA results (from technical engagement)** | | | | | | |
| **Bleeding costs (£)** | 2,992 | 3,677 | 2,828 | 3,414 | 3,981 | 3,278 |
| **Difference from AVA (£)** | n/a | +685 | -164 | n/a | -567 | -136 |
| **ERG base case NMA results (from technical engagement)** | | | | | | |
| **Bleeding costs (£)** | 3,271 | 3,677 | 2,919 | 3,645 | 3,981 | 3,354 |
| **Difference from AVA (£)** | n/a | +406 | -352 | n/a | +336 | -291 |
| **The same efficacy** | | | | | | |
| **Bleeding costs (£)** | 2,828 | 2,828 | 2,828 | 3,278 | 3,278 | 3,278 |
| **Difference from AVA (£)** | n/a | 0 | 0 | n/a | 0 | 0 |

Abbreviations: AVA, avatrombopag; ELT, eltrombopag; ROM, romiplostim



 

# 4 Uptake and market share

4.1 Currently, patients on a TPO-RA will be receiving either ELT or ROM. [redacted] If approved by NICE, it is assumed that AVA will only displace ELT – the other orally administered TPO-RA.

4.2 In year 1 (i.e. 2022), it is estimated that AVA will accrue a 30% share of the ELT treated population, which is equivalent to a 27% share of the total TPO-RA market. The AVA market share is forecast to rise to 72% in year 5 and 80% in year 10. A summary of the market share estimates are provided in Table 9 and the patient uptake estimates are provided in Table 10.



 

**Table 9: Market share assumptions included in the budget impact analysis**

| Technology | Current practice | 2022 | 2023 | 2024 | 2025 | 2026 | 2027 | 2028 | 2029 | 2030 | 2031 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| AVA | 0% | 27% | 40% | 54% | 63% | 72% | 76% | 80% | 80% | 80% | 80% |
| ELT | 90% | 63% | 50% | 36% | 27% | 18% | 14% | 10% | 10% | 10% | 10% |
| ROM | 10% | 10% | 10% | 10% | 10% | 10% | 10% | 10% | 10% | 10% | 10% |

Abbreviations: AVA, avatrombopag; ELT, eltrombopag; ROM, romiplostim

**Table 10: Patient uptake with and without avatrombopag**

| Technology | 2022 | 2023 | 2024 | 2025 | 2026 | 2027 | 2028 | 2029 | 2030 | 2031 |
|---|---|---|---|---|---|---|---|---|---|---|
| **Without AVA** | | | | | | | | | | |
| AVA | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| ELT | 496 | 500 | 502 | 505 | 509 | 510 | 512 | 514 | 516 | 517 |
| ROM | 55 | 55 | 56 | 56 | 56 | 57 | 57 | 57 | 57 | 57 |
| **With AVA** | | | | | | | | | | |
| AVA | 149 | 225 | 301 | 354 | 407 | 431 | 455 | 457 | 459 | 460 |
| ELT | 347 | 275 | 201 | 152 | 102 | 79 | 57 | 57 | 57 | 57 |
| ROM | 55 | 55 | 56 | 56 | 56 | 57 | 57 | 57 | 57 | 57 |

Abbreviations: AVA, avatrombopag; ELT, eltrombopag; ROM, romiplostim



 

# 5 Benefits and savings

5.1 AVA may provide savings through improved adherence to treatment due to a lack of dietary restrictions and no need for fasting, which in turn may lead to better disease management and the associated budgetary benefits (i.e. reduced bleeds/inpatient visits). Furthermore, cost savings may also be gained through the avoidance of hepatoxicity monitoring, which is required for patients receiving ELT. For ROM, patients often require injection training and/or drug administration by a specialist nurse at an outpatient centre or community clinic, and vial wastage was highlighted by patient experts in the first appraisal committee meeting.

However, for simplicity these considerations have been conservatively excluded from this budget impact analysis.

# 6 Estimated annual budget impact

6.1 The estimated annual budget impact under the list price and PAS discount scenarios for AVA are presented in Table 11 and Table 12.

6.2 The rows named '*Net budget impact (without bleeds*)' represent the core budget impact analysis requested by the committee. The rows named '*Net budget impact (with bleeds)*' represent scenario analyses with the additional costings for bleeds (modelling using the weighted average NHS costs for bleed-related and 109 cycles for all TPO-RAs).



 

**Table 11: Estimated budget impact, AVA PAS price and other TPO-RAs at list price**

| | 2022 | 2023 | 2024 | 2025 | 2026 | 2027 | 2028 | 2029 | 2030 | 2031 |
|---|---|---|---|---|---|---|---|---|---|---|
| Eligible population for treatment with AVA | 551 | 555 | 558 | 561 | 565 | 567 | 569 | 571 | 573 | 574 |
| Population expected to receive AVA | 149 | 225 | 301 | 354 | 407 | 431 | 455 | 457 | 459 | 460 |
| **World without technology (current treatment pathway)** | | | | | | | | | | |
| Drug costs | 12,026,734 | 12,114,043 | 12,179,525 | 12,217,237 | 12,235,535 | 12,375,969 | 12,419,622 | 12,462,277 | 12,506,930 | 12,528,758 |
| Monitoring costs | 1,172,126 | 1,180,635 | 1,187,017 | 1,193,398 | 1,201,908 | 1,206,162 | 1,210,417 | 1,215,671 | 1,218,926 | 1,221,053 |
| Administrations costs | 132,344 | 133,304 | 134,024 | 134,745 | 135,706 | 136,186 | 136,667 | 137,147 | 137,628 | 137,868 |
| **Total cost of current treatment pathway** | **13,331,204** | **13,427,982** | **13,500,566** | **13,545,380** | **13,573,149** | **13,718,317** | **13,766,706** | **13,815,095** | **13,863,484** | **13,887,679** |
| **World with technology (future treatment pathway)** | | | | | | | | | | |
| Drug costs | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Monitoring costs | 1,172,126 | 1,180,635 | 1,187,017 | 1,193,398 | 1,201,908 | 1,206,162 | 1,210,417 | 1,215,671 | 1,218,926 | 1,221,053 |
| Administrations costs | 132,344 | 133,304 | 134,024 | 134,745 | 135,706 | 136,186 | 136,667 | 137,147 | 137,628 | 137,868 |
| **Total cost of future treatment pathway** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Net budget impact (without bleeds)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Difference in bleeding costs – 5 year scenario*** | | | | | | | | | | |



 

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **ERG sensitivity analysis NMA results** | -101,955 | -152,141 | -206,501 | -242,213 | -278,788 | -295,318 | -311,958 | -313,054 | -314,151 | -314,699 |
| **Net budget impact (with bleeds)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **ERG base case NMA results** | -60,490 | -90,265 | -122,517 | -143,705 | -165,405 | -175,212 | -185,084 | -185,735 | -186,385 | -186,711 |
| **Net budget impact (with bleeds)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **The same efficacy** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Net budget impact (with bleeds)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Difference in bleeding costs – 10 year scenario*** | | | | | | | | | | |
| **ERG sensitivity analysis NMA results** | -84,341 | -125,857 | -170,825 | -200,367 | -230,624 | -244,298 | -258,063 | -258,970 | -259,877 | -260,331 |
| **Net budget impact (with bleeds)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **ERG base case NMA results** | -50,039 | -74,671 | -101,350 | -118,878 | -136,829 | -144,942 | -153,109 | -153,647 | -154,185 | -154,454 |
| **Net budget impact (with bleeds)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **The same efficacy** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Net budget impact (with bleeds)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

* see appendix for calculations



 

**Table 12: Estimated budget impact, All TPO-RAs at list price**

| | 2022 | 2023 | 2024 | 2025 | 2026 | 2027 | 2028 | 2029 | 2030 | 2031 |
|---|---|---|---|---|---|---|---|---|---|---|
| Eligible population for treatment with AVA | 551 | 555 | 558 | 561 | 565 | 567 | 569 | 571 | 573 | 574 |
| Population expected to receive AVA | 149 | 225 | 301 | 354 | 407 | 431 | 455 | 457 | 459 | 460 |
| **World without technology (current treatment pathway)** | | | | | | | | | | |
| Drug costs | 12,026,734 | 12,114,043 | 12,179,525 | 12,217,237 | 12,235,535 | 12,375,969 | 12,419,622 | 12,462,277 | 12,506,930 | 12,528,758 |
| Monitoring costs | 1,172,126 | 1,180,635 | 1,187,017 | 1,193,398 | 1,201,908 | 1,206,162 | 1,210,417 | 1,215,671 | 1,218,926 | 1,221,053 |
| Administrations costs | 132,344 | 133,304 | 134,024 | 134,745 | 135,706 | 136,186 | 136,667 | 137,147 | 137,628 | 137,868 |
| **Total cost of current treatment pathway** | **13,331,204** | **13,427,982** | **13,500,566** | **13,545,380** | **13,573,149** | **13,718,317** | **13,766,706** | **13,815,095** | **13,863,484** | **13,887,679** |
| **World with technology (future treatment pathway)** | | | | | | | | | | |
| Drug costs | 12,515,443 | 12,843,313 | 13,169,361 | 13,375,074 | 13,396,553 | 13,791,541 | 13,914,954 | 13,962,865 | 14,012,774 | 14,037,230 |
| Monitoring costs | 1,172,126 | 1,180,635 | 1,187,017 | 1,193,398 | 1,201,908 | 1,206,162 | 1,210,417 | 1,215,671 | 1,218,926 | 1,221,053 |
| Administrations costs | 132,344 | 133,304 | 134,024 | 134,745 | 135,706 | 136,186 | 136,667 | 137,147 | 137,628 | 137,868 |
| **Total cost of future treatment pathway** | **13,819,913** | **14,157,252** | **14,490,402** | **14,703,217** | **14,734,167** | **15,133,889** | **15,262,038** | **15,315,683** | **15,369,328** | **15,396,151** |
| **Net budget impact** | **488,709** | **729,270** | **989,836** | **1,157,837** | **1,161,018** | **1,415,572** | **1,495,332** | **1,500,588** | **1,505,844** | **1,508,472** |
| **Difference in bleeding costs – 5 year scenario*** | | | | | | | | | | |
| **ERG sensitivity analysis NMA results** | -101,955 | -152,141 | -206,501 | -242,213 | -278,788 | -295,318 | -311,958 | -313,054 | -314,151 | -314,699 |



 

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Net budget impact (with bleeds)** | **386,754** | **577,129** | **783,335** | **915,624** | **882,230** | **1,120,254** | **1183374** | **1,187,534** | **1,191,693** | **1,193,773** |
| **ERG base case NMA results** | -60,490 | -90,265 | -122,517 | -143,705 | -165,405 | -175,212 | -185,084 | -185,735 | -186,385 | -186,711 |
| **Net budget impact (with bleeds)** | **428,219** | **639,005** | **867,319** | **1,014,132** | **995,613** | **1,240,360** | **1310248** | **1,314,853** | **1,319,459** | **1,321,761** |
| **The same efficacy** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Net budget impact (with bleeds)** | **916,928** | **1,368,275** | **1,857,155** | **2,171,969** | **2,156,631** | **2,655,932** | **2,805,580** | **2,815,441** | **2,825,303** | **2,830,233** |
| **Difference in bleeding costs – 10 year scenario*** | | | | | | | | | | |
| **ERG sensitivity analysis NMA results** | -84,341 | -125,857 | -170,825 | -200,367 | -230,624 | -244,298 | -258,063 | -258,970 | -259,877 | -260,331 |
| **Net budget impact (with bleeds)** | **404,368** | **603,413** | **819,011** | **957,470** | **930,394** | **1,171,274** | **1,237,269** | **1,241,618** | **1,245,967** | **1,248,141** |
| **ERG base case NMA results** | -50,039 | -74,671 | -101,350 | -118,878 | -136,829 | -144,942 | -153,109 | -153,647 | -154,185 | -154,454 |
| **Net budget impact (with bleeds)** | **438,670** | **654,599** | **888,486** | **1,038,959** | **1,024,189** | **1,270,630** | **1,342,223** | **1,346,941** | **1,351,659** | **1,354,018** |
| **The same efficacy** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Net budget impact (with bleeds)** | **488,709** | **729,270** | **989,836** | **1,157,837** | **1,161,018** | **1,415,572** | **1,495,332** | **1,500,588** | **1,505,844** | **1,508,472** |

* see appendix for calculations



 

6.3 Introducing AVA into the treatment pathway has no impact on monitoring costs since these costs remain fixed for each TPO-RA. Administrations costs also do not vary since this analysis assumes the percentage of patients treated with ROM will not alter with the introduction of AVA.

6.4 Given the committee acknowledges that it is reasonable to assume equal efficacy between the TPO-RA class, Sobi believe that the most useful comparison be on drug acquisition cost alone. In this scenario AVA at PAS price is represents a lower acquisition cost than both ELT and ROM.

6.5 Overall, the budget impact analysis shows that the introduction of AVA will require no additional service or infrastructure changes to the NHS and will be cost saving when taking into consideration the [redacted] PAS discount.

Although not presented, it should be noted that AVA also remains cost saving in budget impact scenarios if the cost of ELT and ROM is reduced to account for confidential discounts.

6.6 Further savings are accrued from introducing AVA into the treatment pathway if one accounts for the budget impact of including bleeds. This is because AVA is assumed to displace ELT and is associated with lower bleeding costs than ELT in the scenarios.

6.7 If approved, AVA will provide an additional effective, tolerable, and easily administrable treatment option for patients with chronic ITP who are currently considered eligible to receive an available TPO-RA, at no additional cost vs. current expenditure.



 

# 7 References


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# 8. Appendix

### Table 12: Bleeding costs (£) calculations

| | 2022 | 2023 | 2024 | 2025 | 2026 | 2027 | 2028 | 2029 | 2030 | 2031 |
|---|---|---|---|---|---|---|---|---|---|---|
| **World without technology (current treatment pathway)** | | | | | | | | | | |
| **Bleeding costs – 5 year scenario** | | | | | | | | | | |
| **ERG sensitivity analysis NMA results** | 1,979,494 | 1,993,864 | 2,004,642 | 2,015,419 | 2,029,789 | 2,036,975 | 2,044,160 | 2,051,345 | 2,058,530 | 2,062,122 |
| **ERG base case NMA results** | 1,984,504 | 1,998,911 | 2,009,716 | 2,020,521 | 2,034,927 | 2,042,130 | 2,049,334 | 2,056,537 | 2,063,740 | 2,067,342 |
| **The same efficacy** | 1,558,239 | 1,569,551 | 1,578,035 | 1,586,519 | 1,597,832 | 1,603,488 | 1,609,144 | 1,614,800 | 1,620,456 | 1,623,284 |
| **Bleeding costs – 10 year scenario** | | | | | | | | | | |
| **ERG sensitivity analysis NMA results** | 2,154,856 | 2,170,500 | 2,182,232 | 2,193,964 | 2,209,608 | 2,217,429 | 2,225,251 | 2,233,072 | 2,240,894 | 2,244,805 |
| **ERG base case NMA results** | 2,159,001 | 2,174,674 | 2,186,429 | 2,198,184 | 2,213,858 | 2,221,694 | 2,229,531 | 2,237,368 | 2,245,204 | 2,249,123 |



 

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **The same efficacy** | 1,806,379 | 1,819,492 | 1,829,327 | 1,839,162 | 1,852,276 | 1,858,832 | 1,865,389 | 1,871,946 | 1,878,503 | 1,881,781 |
| **World with technology (future treatment pathway)** | | | | | | | | | | |
| **Bleeding costs – 5 year scenario** | | | | | | | | | | |
| **ERG sensitivity analysis NMA results** | 1,877,539 | 1,841,723 | 1,798,141 | 1,773,207 | 1,751,001 | 1,741,657 | 1,732,202 | 1,738,291 | 1,744,379 | 1,747,424 |
| **ERG base case NMA results** | 1,924,014 | 1,908,646 | 1,887,199 | 1,876,816 | 1,869,522 | 1,866,919 | 1,864,250 | 1,870,802 | 1,877,355 | 1,880,631 |
| **The same efficacy** | 1,558,239 | 1,569,551 | 1,578,035 | 1,586,519 | 1,597,832 | 1,603,488 | 1,609,144 | 1,614,800 | 1,620,456 | 1,623,284 |
| **Bleeding costs – 10 year scenario** | | | | | | | | | | |
| **ERG sensitivity analysis NMA results** | 2,070,515 | 2,044,643 | 2,011,407 | 1,993,597 | 1,978,984 | 1,973,131 | 1,967,188 | 1,974,102 | 1,981,017 | 1,984,474 |
| **ERG base case NMA results** | 2,108,962 | 2,100,004 | 2,085,079 | 2,079,307 | 2,077,029 | 2,076,752 | 2,076,422 | 2,083,721 | 2,091,019 | 2,094,669 |
| **The same efficacy** | 1,806,379 | 1,819,492 | 1,829,327 | 1,839,162 | 1,852,276 | 1,858,832 | 1,865,389 | 1,871,946 | 1,878,503 | 1,881,781 |



 

**CONFIDENTIAL UNTIL PUBLISHED**

**Evidence Review Group's critique of the additional information from the company following the 2nd Appraisal Committee Meeting (ACM2)**

# Avatrombopag in combination for treating chronic immune thrombocytopenia [ID3838]


| | |
|---|---|
| **Produced by** | CRD and CHE Technology Assessment Group, University of York, Heslington, York, YO10 5DD |
| **Date completed** | 29/09/2022 |


**Note on the text**

All commercial-in-confidence (CIC) data have been [redacted], all academic-in-confidence (AIC) data are [redacted], all depersonalised data (DPD) are [redacted].

# Table of Contents

# 1 OVERVIEW OF THE COMPANY'S RESPONSE TO ACM2

The company have responded to a request from the NICE Appraisal Committee following its second meeting (ACM2) to provide a cost comparison analysis with annual costs, a 5-year and 10-year time horizon. The committee also requested the company to provide a scenario analysis using a treatment duration of 109 cycles for all TPO-RAs and using the weighted average NHS costs for bleed-related events. The company have provided a response to both requests and a budget impact analysis to the NHS in England and Wales of the introduction of avatrombopag relative to existing standard of care (eltrombopag and romiplostim) for the treatment of immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments.

The ERG provides a critique of the company information for the cost-comparison analysis and the scenarios for the cost of bleed-related events using weighted average NHS bleed event costs and treatment duration of 109 cycles for all TPO-RAs. The company have presented the results using the [redacted] the list price of avatrombopag and the list prices for eltrombopag and romiplostim. The ERG have presented the same results in a separate confidential appendix with inclusion of the patient access scheme (PAS) prices for all TPO-RAs. The ERG have not commented on the separate budget impact analysis.

# 2 CRITIQUE OF THE COMPANY'S COST-COMPARISON ANALYSIS

## *2.1 Drug acquisition and administration costs*

For the cost-comparison analysis, the company assumes equivalent efficacy and safety across the TPO-RAs and only incorporates a difference in drug acquisition and administration costs.

### *Annual drug acquisition costs*

The ERG is satisfied that the annual drug acquisition costs presented in Table 4 of the company's response are reasonable, with the possible exception of romiplostim which may be overestimated. The weight-based dose of 332mcg weekly for romiplostim requires three 125mcg vials, with approximately one-third vial wastage (note that this vial wastage is the reason for the difference in mean dose reported in Table 3 (332mcg) and Table 4 (0.38mg) of the company's response). The ERG considers vial wastage of romiplostim to be a reasonable assumption given that the majority of vials are prescribed for home administration. However, the ERG previously expressed two concerns about the company's assumptions for the dosage of romiplostim (see Section 4.2.9.2 of the ERG report). Firstly, dosing is dependent on efficacy with upward titrations initiated if response is not achieved.

The SmPC states that "*the initial dose is 1 mcg/kg*" and that "*the once weekly dose of romiplostim should be increased by increments of 1 mcg/kg until the patient achieves a platelet count ≥ 50 x $10^9$/L*". The company's approach assumes patients initiate treatment at 4μg/kg, which means that patients expend three vials immediately from treatment initiation. The ERG believes that, at least in the short term, this overestimates treatment acquisition costs for romiplostim. This is exemplified by the median dose administered in the pivotal romiplostim phase 3 trials (non-splenectomised: 2mcg/kg and splenectomised: 3mcg/kg), which is below the extension-phase median dose of 4mcg/kg. Second, the romiplostim dose is based on the weight of an average patient in Study 302, which means that the dosing does not take into account the distribution of weights seen in the patient population. Therefore, the ERG considers that the romiplostim acquisition cost in Table 4 is an upper estimate of the likely cost incurred by the NHS.

***Administration costs***

The ERG is satisfied that there are no administration costs associated with avatrombopag and eltrombopag as both are oral treatments self-administered at home. For romiplostim, the company assumed that treatment would be administered at home in 72.3% of patients, based on figures from a congress abstract of phase III trial data at the ASH annual meeting 2010, while 27.7% of patients would receive treatment administered by a specialist nurse at clinic, with a per visit unit cost of £166.51 based on NHS reference costs (Clinical haematology, code 303). The ERG previously sought expert clinical feedback on the proportion of patients likely to self-administer at home in the UK and was informed that "*almost all patients self-administer at home*". This conclusion also aligns with more recent research that indicates self-administration is effective, well tolerated and achieves high levels of adherence in eligible patients with ITP.[1,2] Schipperus et al's (2018) analysis of romiplostim self-administration reported 87.5% of patients correctly administer romiplostim when provided with administration training materials.[1] Therefore, in the ERG report a scenario was considered whereby 12.5% of romiplostim administrations are conducted in clinic at a unit cost equivalent to a clinical haematology outpatient visit (£167). The ERG considers that the romiplostim administration cost in Table 7 of the company's response is an upper estimate of the likely cost incurred by the NHS. Under the ERG scenario of 12.5% (rather than 27.7%) for clinic visits, the annual administration cost per patient for romiplostim falls from £2,401 to £1,085.

## *2.2 Cost of bleeds*

The company conducted separate scenario analyses for the annual cost of bleeds per patient, where three alternative efficacy assumptions were considered (same efficacy for all TPO-RAs, efficacy estimates based on ERG base case network meta-analysis (NMA) and ERG sensitivity analysis NMA), a treatment duration of 109 cycles for all TPO-RAs, and the use of weighted average NHS bleed event costs according to the ERG approach and preference of the NICE Appraisal Committee.

The company presented the annual cost of bleeds per patient per treatment in Table 8 of its response using a time horizon of 5 years and 10 years, with no discounting.

The ERG have validated the costs presented in Table 8 using the company's model submitted in response to the ACD (with the ERG corrections that were noted in the ERG critique of the company's response following the ACD) and reproduced the costs to within £1-£5 using the approach outlined by the company; the ERG believes that this small discrepancy is likely to be the result of rounding error. The ERG notes that the company have not stated what the probability of treatment response is for the scenario where all TPO-RAs are assumed to have the same efficacy; importantly, the ERG notes that the magnitude of the bleeding costs reported in Table 8 for the scenario of equal efficacy will depend on the probability of treatment response. This is important because the difference in total costs between the alternative TPO-RAs (or magnitude of total cost savings from lower drug acquisition and administration costs) will depend on the probability of treatment response, even if the response rate is the same across all the TPO-RAs.

**The ERG is not clear why the company have presented the annual cost of bleeds per patient using a 5- and 10-year time horizon and without discounting. To obtain these annual costs the company estimated the total cost of bleeds over a 5-year (and 10-year) time horizon and then divided the total cost by the duration of the time horizon, i.e., 5 (and 10), without discounting. The ERG believes that the more appropriate approach to estimate the annual cost of bleeds per patient is to divide the total discounted cost over the modelled lifetime horizon by the number of discounted life years lived. When a shorter time horizon is to be considered, the ERG believes that the equivalent annual bleeding costs should be estimated by dividing the total discounted bleeding costs over the time horizon by the total discounted life years over that same time horizon.**

Table 1 and Table 2 below present the ERG results for the cost of bleeds per patient per treatment over different time horizons for efficacy results based on the ERG base-case NMA and the ERG sensitivity analysis NMA, respectively. The results demonstrate that avatrombopag is expected to result in lower bleed-related costs than eltrombopag under both ERG efficacy scenarios because the probability of treatment response is higher for avatrombopag compared to eltrombopag in these efficacy scenarios. The bleed costs are lowest for romiplostim across all the TPO-RAs because the treatment response rate is highest for romiplostim in both ERG efficacy scenarios.

When equivalent efficacy is assumed across the TPO-RAs there is no difference in bleeding costs between the treatments because the response to treatment is directly linked to the likelihood of inpatient and outpatient bleeds. However, the magnitude of total cost savings from a treatment with lower drug acquisition and administration costs will depend on the probability of treatment response (even if the response rate is the same across the TPO-RAs). The ERG illustrates this in Table 3 for a scenario of equal efficacy under two alternative response rates: (i) probability of treatment response

set to 30% (i.e., close to the response rate of eltrombopag vs. placebo from the NMA); and (ii) probability of treatment response set to 60% (i.e., close to the response rate of romiplostim vs. placebo from the NMA), and where the only difference in total costs between the TPO-RAs is the difference in drug acquisition and administration costs.

**Table 1: Discounted cost of bleeds per patient per treatment over different time horizons for efficacy results based on the ERG base-case network meta-analysis**

| **ERG base case NMA** | | | | |
|---|---|---|---|---|
| | **Total bleeding costs (£)** | **Total life years lived (years)** | **Equivalent annual bleeding costs (£)** | **Difference from AVA (£)** |
| | **Lifetime time horizon** | | | |
| **AVA** | 77,162 | 16.010 | 4820 | |
| **ELT** | 80,154 | 15.751 | 5089 | + 269 |
| **ROM** | 74,575 | 16.234 | 4594 | - 226 |
| | **10-year time horizon** | | | |
| **AVA** | 30,523 | 7.877 | 3875 | |
| **ELT** | 33,433 | 7.813 | 4279 | + 404 |
| **ROM** | 28,007 | 7.933 | 3530 | - 344 |
| | **5-year time horizon** | | | |
| **AVA** | 14,990 | 4.443 | 3374 | |
| **ELT** | 16,860 | 4.424 | 3811 | + 438 |
| **ROM** | 13,374 | 4.460 | 2998 | - 375 |

**Abbreviations:** AVA, avatrombopag; ELT, eltrombopag; ROM, romiplostim

**Table 2: Discounted cost of bleeds per patient per treatment over different time horizons for efficacy results based on the ERG sensitivity analysis network meta-analysis**

| **ERG sensitivity analysis NMA** | | | | |
|---|---|---|---|---|
| | **Total bleeding costs (£)** | **Total life years lived (years)** | **Equivalent annual bleeding costs (£)** | **Difference from AVA (£)** |
| | **Lifetime time horizon** | | | |
| **AVA** | 75,113 | 16.187 | 4640 | |
| **ELT** | 80,154 | 15.751 | 5089 | + 449 |
| **ROM** | 73,906 | 16.292 | 4536 | - 104 |
| | **10-year time horizon** | | | |
| **AVA** | 28,530 | 7.921 | 3602 | |
| **ELT** | 33,433 | 7.813 | 4279 | + 677 |
| **ROM** | 27,356 | 7.947 | 3442 | - 159 |
| | **5-year time horizon** | | | |
| **AVA** | 13,710 | 4.457 | 3076 | |

| | | | | |
|---|---|---|---|---|
| **ELT** | 16,860 | 4.424 | 3811 | + 735 |
| **ROM** | 12,956 | 4.465 | 2902 | - 174 |

**Abbreviations:** AVA, avatrombopag; ELT, eltrombopag; ROM, romiplostim

**Table 3: Discounted total costs per patient per treatment over a lifetime horizon for an equal efficacy scenario under two alternative response rates**

| **Lifetime horizon** | | | | |
|---|---|---|---|---|
| | **Total costs (£)** | **Total life years lived (years)** | **Equivalent annual costs (£)** | **Difference from AVA (£)** |
| | **Probability of treatment response set to 30% for all TPO-RAs** | | | |
| **AVA** | [redacted] | 15.739 | [redacted] | |
| **ELT** | 165,515 | 15.739 | 10516 | [redacted] |
| **ROM** | 203,312 | 15.739 | 12918 | [redacted] |
| | **Probability of treatment response set to 60% for all TPO-RAs** | | | |
| **AVA** | [redacted] | 16.328 | [redacted] | |
| **ELT** | 196,630 | 16.328 | 12043 | [redacted] |
| **ROM** | 270,718 | 16.328 | 16580 | [redacted] |

# 3 REFERENCES


1. Schipperus M, Kaiafa G, Taylor L, Wetten S, Kreuzbauer G, Boshier A, et al. Assessment of self-administration of romiplostim in patients with immune thrombocytopenic purpura after receipt of home administration training materials: a cross-sectional study. *Drug Saf* 2019;42:77-83.
2. Kuter DJ, Arnold DM, Rodeghiero F, Janssens A, Selleslag D, Bird R, et al. Safety and efficacy of self-administered romiplostim in patients with immune thrombocytopenia: results of an integrated database of five clinical trials. *Am J Hematol* 2020;95:643-51. ISBN: 978-1-4731-4885-7