NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Response to Appraisal Consultation Document (II)

Eltrombopag for treating chronic immune (idiopathic) thrombocytopenic purpura

(Review of Technology Appraisal 205)

Amgen Limited

15th April 2013

Academic in confidence information is redacted [redacted]

Summary

Thank you for the opportunity to comment on the second Appraisal Consultation Document (ACD) for eltrombopag. We have reviewed the ACD and acknowledge the change to the initial preliminary recommendation, so that the wording is now consistent with the Institutes recommendation for the comparator romiplostim. We also recognise that a number of changes that we requested have been made to the cost effectiveness analysis presented in the second ACD. However the revised cost effectiveness analysis remains incomplete, inconsistent with the NICE Guide to the Methods of Technology Appraisal and fails to acknowledge the high levels of uncertainty in the ICER of eltrombopag versus romiplostim. Consequently the cost effectiveness analysis is significantly biased in favour of eltrombopag. We have identified four reasons why the revised analysis conducted by the ERG is currently an insufficient basis for forming a recommendation:

1) The revised analysis uses the health related quality of life measure SF-6D which is collected using the standard gamble classification system. The SF-6D utility measure is not consistent with EQ-5D utility measure which is collected using a time trade off classification system. Section 5.4 of NICE's 'Guide to the Methods of Technology Appraisal' states that EQ-5D is the preferred measure of health related quality of life in adults and that other classification systems should only be considered in the absence of EQ-5D data. The guide highlights that this is important because different systems cannot always be compared and given the nature of the Institute's work and need for consistency across appraisals, a single classification system, is preferred. Furthermore, the guide states that non EQ-5D methods should only be included in technology appraisals in the absence of relevant EQ-5D utility data. Clearly in this technology appraisal there is relevant EQ-5D utility available and as such the use of SF-6D is not consistent with the NICE's 'Guide to the Methods of Technology Appraisal'.

We would kindly request that the cost effectiveness be analysed using utility scores which conform to those described in section 5.4 of the 'Guide to Methods of Technology Appraisal'

2) The revised analysis presented in the second ACD is based on the manufacturers 'alternative evaluation' using only inputs from the eltrombopag RAISE trial, which are applied to both eltrombopag and romiplostim. The resulting ICERs presented for eltrombopag versus romiplostim are large (in favour of eltrombopag in this reversed situation where the intervention is less effective than the comparator). This is a significant change from the original 'base case' analysis presented in the first ACD, in which inputs from the romiplostim Kuter trials were applied to both eltrombopag and romiplostim; this analysis yielded significantly lower ICERs closer to the reversed cost effectiveness threshold.

Adhering to NICE methods, it is essential to analyse all relevant data, taking inputs from both the eltrombopag RAISE, and the romiplostim Kuter trials, in order to assess the level of uncertainty in the cost effectiveness analysis. If the ERG had conducted their revised analysis to include all relevant data it would be clear that whilst the reversed ICERs for eltrombopag versus romiplostim using the eltrombopag RAISE trial data are large, the reversed ICERs using inputs from the romiplostim Kuter trial would be 70-80% less than those presented in the second ACD and considerably closer to the reversed cost effectiveness threshold.

The selection of inputs from either the RAISE or Kuter trials are particularly important for the probability of bleeds and rescue rates, as they are a significant driver in the cost effectiveness model. The inputs from the Kuter trial for these parameters should be used as they are the most generalisable to the patient group for which the Institute recommends the comparator (romiplostim) and in whom the preliminary recommendation is made for eltrombopag. It is entirely inappropriate that only the least relevant set of inputs (from RAISE) to the decision problem are used for the cost effectiveness analysis to inform the recommendation. At a minimum we would expect analyses using the probability of bleeds and rescue rate from the Kuter trials to be presented, so that the wide range of resultant reversed ICERs for eltrombopag versus romiplostim are clearly presented.

We would kindly request that the cost effectiveness be analysed using all the available data inputs (from both the RAISE and Kuter trials) and the results presented appropriately, highlighting the level of uncertainty in the ICER of eltrombopag versus romiplostim.

3) The source of the post 24 week eltrombopag dose input in the cost effectiveness model has been inappropriately taken from the EXTEND trial and not from the RAISE trial from which the clinical effectiveness (response rates) were sourced. This is inappropriate because it breaks the link between dose and response data, by taking data inputs from different trials, with no clear justification. In addition, by using this approach, the post 24 week eltrombopag dose is derived differently for the post 24 week romiplostim dose, which was assumed to be the average from weeks 12 to 23 from the Kuter trials. The post 24 week eltrombopag dose used in the model (sourced from EXTEND trial) is 11% lower than the average week 12 to 23 eltrombopag dose reported in the RAISE trial. This inconsistency in the approach to dosing across the two arms of the model clearly biases the cost effectiveness analysis in favour of eltrombopag.

We would kindly request that a consistent approach be taken in estimating the post 24 week eltrombopag and romiplostim doses be used in the cost effectiveness analysis that is linked to the response rates used in the model (i.e. the average from weeks 12 to 23 be applied post 24 weeks).

4) The reversed ICER of eltrombopag versus romiplostim is extremely sensitive to romiplostim dose, due to the potential for wastage. This issue was raised by the ERG in their comments included in the first ACD in which they highlight that reducing romiplostim dose by spacing out administrations rather than reducing the dose per administration would make romiplostim less costly than eltrombopag. The current ACD contains no sensitivity analysis on romiplostim dose and there is no mention that relatively small changes (reductions) in romiplostim dose, similar to those observed in clinical practice, render eltrombopag cost ineffective (reversed ICER below the threshold) compared with romiplostim. This sensitivity on romiplostim dose, and in particular clinical practice dosing, was acknowledged by the Appraisal Committee in section 4.12 of TA221 guidance.

We would like the Appraisal Committee to acknowledge that the ICER is highly dependent on romiplostim dose and that compared with romiplostim dose in clinical practice eltrombopag is not likely to be cost effective.

When these four issues are considered together, the cost effectiveness of eltrombopag versus romiplostim can range from £389,000, as presented in the ACD, to romiplostim

dominating eltrombopag. Currently the ACD does not discuss or acknowledge the very high level of uncertainty in the cost effectiveness; instead it quotes a definitive ICER which is at the highest end of the range and inappropriately biased in favour of eltrombopag. It is extremely important that the final guidance clearly highlights the range of ICERs as this document will be an important reference for NHS commissioners. The Innovation Health and Wealth report[1] highlights that NICE has a responsibility to make clear decisions to commissioners. The current cost effectiveness analysis and the stated ICERs presented in the ACD are biased in favour of eltrombopag and may inappropriately result in commissioners refusing to fund romiplostim in line with TA221. The ITP association highlighted in their comments to the first ACD that some patients were already being refused funding (which is in breach of the statutory funding obligation); it is highly possible that the ACD in its current form could exacerbate this situation.

We would kindly request that the cost effectiveness be analysed addressing the four issues identified above and the results presented appropriately so as not to mislead NHS commissioners.

Finally, we welcome the acknowledgement in the second ACD that the indirect comparison shows romiplostim to be more clinically effective than eltrombopag; however we do not think it appropriate that clinical opinion is being quoted as evidence to reduce the impact of the indirect analysis. According to the Institute's Methods on the hierarchy of evidence clinical opinion is a lower form of evidence than an indirect analysis of RCT data and as such it is inappropriate to use it to drive any conclusion on efficacy of one TPO over another. Particularly in the case of this appraisal where relatively small numbers of patients have been treated with eltrombopag in the UK outside a trial setting due to the absence of a positive NICE recommendation.

We would request that the inference in the ACD that clinical opinion is of equal strength to the indirect comparison of RCTs be revised in subsequent documents to align with NICE Methods

1 The recommendation in section 1.1 is now consistent with the comparator recommendation for romiplostim.

We have reviewed the ACD and acknowledge the change to the initial preliminary recommendation and agree that it is now consistent with the Institutes recommendation for the comparator romiplostim.

2 The cost effectiveness analysis has not been conducted correctly and the ICERs presented in the ACD are biased in favour of eltrombopag

Recommendation:

The ERG should calculate the cost effective analysis of eltrombopag versus romiplostim appropriately and correctly; as such we kindly request that:

i) The ICER of eltrombopag versus romiplostim be analysed using utilities which are consistent with the approach described in the 'Guide to the Methods of Technology Appraisal'

ii) The ICER of eltrombopag versus romiplostim be analysed using all the available model input data (from both the RAISE and Kuter trials) and the results presented appropriately, highlighting the level of uncertainty in the cost effectiveness of eltrombopag versus romiplostim.

iii) The ICER of eltrombopag versus romiplostim be calculated using the correct post 24 week eltrombopag dosing

iv) The Appraisal Committee acknowledge that the ICER for eltrombopag versus romiplostim is highly dependent on romiplostim dose and that compared with romiplostim dose in clinical practice eltrombopag is not likely to be cost effective.

We would kindly request that the cost effectiveness be analysed addressing the four issues identified above and the results presented appropriately so as not to mislead NHS commissioners.

In the second ACD the ERG have conducted a cost effectiveness analysis of eltrombopag versus romiplostim with a new base case using inputs from the RAISE trial. This version of analysis was mentioned by the ERG in the first ACD, where it was described as the 'alternative evaluation', but no figures were presented; as such the second ACD is the first time the new and very large (reversed) ICERs for eltrombopag versus romiplostim have been presented for stakeholder comment. The size of the ICERs appear counter-intuitive, since the [redacted] and romiplostim is more effective, therefore we have reviewed the ERGs most recent analysis and believe the quality of the analysis is not of a sufficient standard for the Appraisal Committee to form a recommendation.

We acknowledge that the ERG and Appraisal Committee have included some of our comments on the first ACD to update the second ACD cost effectiveness analysis; however the next four sections describe the new issues we have identified in the cost effectiveness analysis and our concerns about how this analysis has been presented in the second ACD.

2.1 The ERG have incorrectly used SF-6D utility scores in the cost effectiveness analysis

Whilst testing the reliability of the model sent to us by NICE we found it impossible to replicate the ERG analysis, and in particular the ICERs between eltrombopag and romiplostim presented in section 4.20 (page 42) of the second ACD even though we have changed the inputs to be exactly as described in the ERG comments and report. We highlighted this to NICE on 4th April and received the following e-mail response via NICE from the ERG on 12th April *"The costs are quite similar, the main discrepancies lie in the QALYs. I think the source of this is likely to be Amgen not having applied the SF-6D utilities, which is simply implemented within the drop down box of cell G29 of the Main worksheet. When I set this to "No" I get the same QALYs as per the Amgen analysis with the minor exception of -0.20 rather than -0.21 for the non-splenectomised."*

We think that it is important to highlight to the Appraisal Committee that Amgen did not incorporate SF-6D utilities when testing the reliability of the model as we do not believe SF-6D utilities are consistent with the Institutes 'Guide to the Methods of Technology Appraisal'.

SF-6D utilities are collected using the standard gamble classification system and as such are not consistent with the time trade off classification system for valuing utilities, as set out in section 5.4 of the 'Guide to the Methods of Technology Appraisal'. The guide clearly states that *"EQ-5D is the preferred measure of HRQL in adults".* The guide states "*Different classification systems produce different utility values; therefore, results from the use of different systems cannot always be compared. Given the comparative nature of the Institute's work and the need for consistency across appraisals, a single classification system, the EQ-5D, is preferred for the measurement and valuation of HRQL* (Section 5.4.4)*".* As such, SF-6D utility data should only be included in a NICE technology appraisal when there is no EQ-5D utility data available; this is clearly not the case in this technology appraisal as there are two alternative sources of EQ-5D data:

1. The SF-36 scores collected in the RAISE trial should have been mapped to EQ-5D utilities. This mapping approach is discussed in section 5.4.6 in the 'Guide to the Methods of Technology Appraisal' and is recommended if the EQ-5D instrument is not available. In Amgen's comments regarding the first ACD we requested that this analysis be conducted to provide the most appropriate source of utility data in line with the 'Guide to the Methods of Technology Appraisal'.
2. The EQ-5D utility scores published in Szende et al. 2010[2] should have been used, in line with the manufacturer's base case.

By inappropriately including the SF-6D utilities to model the cost effectiveness of eltrombopag versus romiplostim, the ERG have overestimated the reversed ICER in the second ACD (section 4.2 page 42). We kindly request that the cost effectiveness analysis be repeated using either utilities derived from the SF-36 scores collected during the RAISE trial mapped to EQ-5D or the EQ-5D data published in the Szende paper.

2.2 The ERG have incorrectly only considered inputs for the probability of bleeding and rescue rates from the RAISE trial

In the second ACD, the ERG have based the cost effectiveness analysis on the 'alternative evaluation' only (renamed the ERG base case) and have ignored the original manufacturer's base case presented in the first ACD. By taking this approach the ERG have applied inputs for the probability of bleeding and rescue rates to both eltrombopag and romiplostim from the RAISE trial; that is eltrombopag's main trial. This is in contrast to the first ACD where the base case presented applied the probability of bleeding and rescue rates from the Kuter trial; romiplostim's main trial. A schematic of this is presented in figure 1.

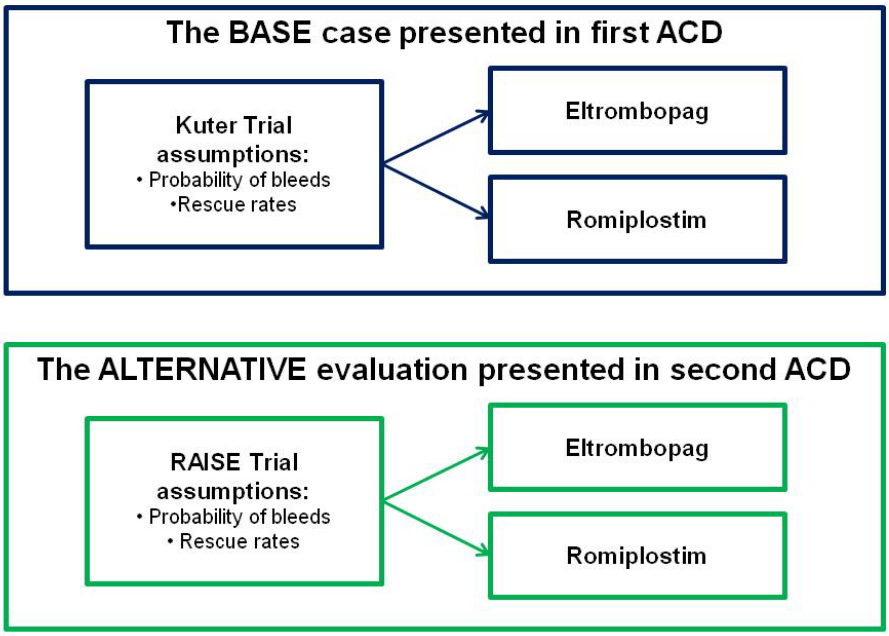

Figure 1: A schematic of the key differences between the cost effectiveness analysis presented in the first ACD and the second ACD

In the first ACD the ERG advised the Appraisal Committee to consider the base case as inappropriate because it did not use data directly from its own (eltrombopag) RAISE trial and advised the Appraisal Committee to consider the 'alternative evaluation' only. This would have been appropriate if the comparator in this appraisal had not been romiplostim. However as romiplostim is the main comparator then it is completely inappropriate to select one set of inputs over another without explicit justification.

In this appraisal the selection of the source of the inputs to the cost effectiveness analysis for the probability of bleeds and rescue rates is critical because the data reported in the trials are very different, Table 1.

	RAISE		Kuter		Difference	
Probability of bleeds	Splen	Non Splen.	Splen	Non Splen.	Splen	Non Splen.
Probability of bleed: platelets < 50,000 – inpatient	0.008	0.008	0.043	0.044	-0.035	-0.036
Probability of bleed: platelets < 50,000 – outpatient	0.341	0.214	0.455	0.442	-0.114	-0.228

	RAISE		Kuter		Difference	
Rescue rates per month	Splen	Non Splen.	Splen	Non Splen.	Splen	Non Splen.
Probability of bleed: platelets < 50,000	0.319	0.143	0.680	0.330	-0.361	-0.187

Table 1: A comparison of the probability of bleeding and rescue rates from the RAISE (eltrombopag) and Kuter (romiplostim) trials

The probability of bleeds and the rescue rates per month for patients with a low platelet as reported in the Kuter trials are significantly larger than those reported in the RAISE trial. The difference in these two parameters makes a very significant impact on the ICERs for eltrombopag versus romiplostim; we estimate this simple change could reduce the ICER by 70-80% taking the results close to the reversed threshold. Furthermore, it is clear that by only selecting the inputs from the RAISE trial the ERG have only conducted analysis which is going to result in the highest reversed ICERs for eltrombopag versus romiplostim.

In order to determine which trial inputs should be included in the analysis and presented in the guidance, the ERG and Appraisal Committee should consider the generalisibility and clinical relevance of the two data input sources. If it is unclear which inputs should be used, then NICE methods require that, at a minimum, the ERG should calculate the ICERs using both sets and then present a range of ICERs. It is clearly not aligned with NICE Methods to select only one of two relevant data sources, without evidence or justification.

For this appraisal we consider, as did the manufacturer in their original submission, that inputs sourced from the Kuter trials are the most generalisable to the decision problem and patient group for which the Institute recommends the comparator (romiplostim).

i. Probability of bleeding: The RAISE and Kuter trials used different scales to measure the severity of bleeding and it is therefore difficult to directly compare the trials. However, as already acknowledged by the Appraisal Committee, the Kuter trial included patients who were considered more severe than those in the RAISE trial (Section 4.11, page 36 of ACD II). This inclusion of more severe patients may explain why the Kuter trial reported higher bleeding rates than the RAISE trial. Given that the comparator (romiplostim) is recommended by the Institute in more severe patients, then the data for probability of bleeding from the Kuter trial seems the most appropriate to use as it is more generalisable to the patient group under consideration. At a minimum, the ERG should have considered both sets of bleeding inputs and presented the resultant ICERs between eltrombopag and romiplostim to the Appraisal Committee for consideration when forming a recommendation and for inclusion in the second ACD. We would welcome acknowledgement by the Appraisal Committee that the probability of bleeding data from the Kuter trial is more

representative of and generalisable to (than the RAISE trial) the more severe patient group in whom the Institute recommend romiplostim and have issued a draft recommendation for eltrombopag.

ii. Rescue rates: The romiplostim final guidance TA221[3] (section 4.16) states that clinical specialists agreed that the Kuter trial population had the most severe ITP (estimated as representing 1–4% of people with cITP), were at high risk of bleeding and therefore needed high levels of rescue therapies throughout the trial. We would therefore expect the ERG to have calculated ICERs based on rescue rates from both the RAISE and the Kuter trials. We would expect that, at a minimum, the ERG would present the Appraisal Committee with both sets of analysis and the Appraisal Committee acknowledge that the Kuter inputs are the most representative of the patient group in whom the comparator (romiplostim) is recommended.

In summary the Kuter trial should be used as the source of inputs for the probability of bleeding and rescue rates in the cost effectiveness analysis as it is the most generalisable data to the patient group in whom the comparator (romiplostim) is recommended. It is entirely inappropriate for the ERG to have only calculated ICERs based on the RAISE trial and this must be addressed in the forthcoming Appraisal Committee meeting and any resulting documentation. Given that these parameters have such an important impact in the relative size of the ICER for eltrombopag versus romiplostim we would expect the ERG to calculate both sets of analysis for the Appraisal Committee to consider in order to form a recommendation.

2.3 The post 24 week eltrombopag dose derives from a different study to the eltrombopag response rates used in the cost effectiveness model and is inconsistent with the approach used in the romiplostim arm of the model

The dosing of eltrombopag included in the model is time dependent, Table 2. The doses from week zero to 23 were sourced from the RAISE trial (from which the response rates were taken) and the long term post 24 week dose was sourced from the EXTEND trial. The selection of dose for eltrombopag post the 24 week period is the most impactful on the cost effectiveness because it is this dose that is applied over the lifetime of the patient cohort in the model.

	Eltrombopag dosing: RAISE trial								Eltrombopag dosing: EXTEND trial
	Week 0-3	Week 4-7	Week 8-11	Week 12-15	Week 16-19	Week 20-23	Average week 4 to 23	Average week 12 to 23	Post week 24
Non splenectomised	48.5	54.6	55.5	55.1	56.2	57.1	55.7	56.2	49.3
Splenectomised	49.0	56.8	57.8	56.9	54.7	57.4	56.7	56.3	52.6

Table 2: The time dependent dosing of eltrombopag

Table 2 clearly shows that the post 24 week eltrombopag dose used in the model is significantly lower than the dosing taken over the 24 week period of the RAISE trial:

- For splenectomised patients the post 24 week dose in the model is 11% lower than the average dose of week 4 to 23 from the RAISE trial and 12% lower than the average dose from week 12 to 24 from the RAISE trial.
- Similarly for non splenectomised patients the post 24 week dose is 7% lower than then the average dose of week 4 to 23 from the RAISE trial and 7% lower than the average dose from week 12 to 24 from the RAISE trial.

We believe that the input selected in the analysis for the post 24 week dose of eltrombopag is inappropriate for two reasons:

i. The dose does not derive from the same trial as the effectiveness data (response rates) used in the model.
ii. The post 24 week dose of romiplostim was derived using a different method (taking the average dose from weeks 12 to 23 from Kuter, from which the romiplostim effectiveness data was taken) and as such the model is not consistent between arms in its treatment of long-term dosing.

Changing the source of the eltrombopag post 24 week dose from EXTEND to RAISE (week 12 to 24) will make a significant difference to the ICER of eltrombopag versus romiplostim; this is particularly the case for the non splenectomised patients where we estimate that the reversed ICER could reduce by 30-50%. The impact of changing the source of the post 24 week dose will be lower for splenectomised patients as the dose in the EXTEND trial is similar to those in the RAISE trial; however we would estimate the ICER of eltrombopag versus romiplostim would decrease by approximately 10%. This important point was not considered in the ERG report and we think this should be corrected in the analysis presented in the forthcoming Appraisal Committee meeting and any resulting documentation.

2.4 The Appraisal Committee does not recognise that the cost effectiveness of eltrombopag versus romiplostim is extremely sensitive to the romiplostim dose.

A simple sensitivity analysis of the ICER of eltrombopag versus romiplostim dose shows that the results are extremely sensitive to the assumption regarding the dose of romiplostim. This 'hyper' sensitivity is driven by the potential waste from using multiple vials. This point has also been identified and recognised by the ERG in their comments on the first ACD (ERG ACD comments page 31) "*The ERG pointed out during first Appraisal Committee meeting that if romiplostim patients reduced their dose by spacing out administrations rather than reducing the dose per administration this could in itself reduce wastage to the point where romiplostim might be cheaper than eltrombopag, based upon the median doses among romiplostim responders.*" This point has not been recognised by the Appraisal Committee in the second ACD. We kindly request that the Appraisal Committee to acknowledge that the ICER is highly dependent on romiplostim dose and that compared with romiplostim dose in clinical practice eltrombopag is not likely to be cost effective. The Appraisal Committee recognised that the dosing of romiplostim in clinical practice may be lower than that observed in the phase 3 trials whilst they were reviewing TA221[3]. Section 4.12 of the TA221 Guidance states *"The Committee noted that in clinical practice it would be rare for clinicians to use doses of romiplostim that were aimed at obtaining a platelet count above 50 × 10^9 per litre (as was the case in the trials). Therefore, in practice, aiming for a*

lower target platelet count would mean less frequent use of romiplostim and lower doses of romiplostim when it is used. The Committee noted that, in the ERG's exploratory analyses, the ICERs were sensitive to a change in the number of vials used, and concluded that romiplostim would be more cost effective if less romiplostim was used in clinical practice than was assumed in the model."

By considering the four points described above it is clear that the second ACD only presents the upper boundary of the reversed ICER of eltrombopag versus romiplostim. This is very misleading, as the above analysis shows the ICERs of eltrombopag versus romiplostim can range over £300,000 to romiplostim being dominant. As such we kindly would request that the ERG run the analysis described above to allow the Appraisal Committee to consider the full range of ICERs relating to the cost effectiveness analysis and to understand, fully, the level of uncertainty around the cost effectiveness analysis.

We consider the presentation of the cost effectiveness of eltrombopag versus romiplostim in a balanced way is extremely important as the guidance will be used by local NHS commissioners to make funding decisions; as such it is essential they have the best quality evidence, analysis, and recommendations available to them. This point was highlighted in the Innovation, Health, and Wealth report[1], which aimed to ensure the rapid adoption of innovation in the NHS and which emphasised the need for local commissioners to implement NICE recommendations. It is clear, that to facilitate adoption of innovation in local practice, NICE have a duty to ensure that their guidance is clear and based on all the available evidence and is not open to misinterpretation. If the ACD were to remain unchanged, presenting only the very high and biased ICERs, then commissioners may incorrectly believe that eltrombopag is significantly more cost effective than romiplostim and as a result deny potential romiplostim patients funding in line with TA221; this would be based on incomplete analysis which has been inadequately communicated. Some commissioners are already denying funding for romiplostim, as was highlighted in the ITP associations comments on the first ACD *"We already have received feedback from clinicians that they are not being allowed access to (licensed) TPO drugs; this information was mentioned at the Appraisal Committee Meeting. To allow equitable access to these new treatments the guidance from NICE needs to be clear and robust otherwise the budget holders who have no understanding of the condition can choose to sidestep NICE guidance making the whole procedure a total waste of time and money".* We fear that the current wording in the cost effectiveness section of the second ACD could exacerbate this situation and inadvertently result in sub-optimal implementation of TA 221.

3 The indirect evidence is recognised, however clinical opinion is being inappropriately quoted as evidence to reduce the impact of this analysis

Recommendation: We request that the inference in the ACD that clinical opinion is of equal strength to the indirect comparison be revised in subsequent documents

The second ACD states in several places that *"the clinical specialists felt that eltrombopag and romiplostim were broadly interchangeable"* (Section 4.11, page 36, Section 4.15, page 39, Summary of Appraisal Committee's key conclusions, page 46 of the ACD). It also states that the Appraisal Committee *"concluded that if the odds ratio for overall response moved towards 1.0 (as implied by the clinical specialists' willingness to substitute one treatment for*

another), the ICERs would further increase leading to further savings per QALY lost" (page 39). The inclusion of these statements suggests that romiplostim and eltrombopag have equivalent clinical efficacy, even though the indirect analysis clearly shows that romiplostim is superior to eltrombopag. This point is even acknowledged by the Appraisal Committee themselves in a different section of the ACD where it is stated that *"The Committee had agreed that romiplostim is likely to be more clinically effective than eltrombopag"* (pages 41 & 49) and the *"Committee agreed with the clinical specialists that the available evidence suggests that romiplostim is likely to be more effective than eltrombopag rather than equally effective"* (page 36).

We would like to remind the Appraisal Committee, that although expert clinical opinion is an important and valuable source of evidence, the NICE Guideline Development Methods: Information for National Collaborating Centres and Guideline Developers[4] clearly shows that meta-analyses, systematic reviews of RCTs, or RCTs (level 1 evidence) is a higher quality of evidence than expert opinion (level 4 evidence). It is misleading to use clinical opinion to inform the relative efficacy of eltrombopag and romiplostim in the presence of more robust clinical data, particularly when the use and so clinical experience of eltrombopag has been restricted in the UK to date, in the absence of a positive NICE recommendation. We therefore request that all statements in the ACD which imply clinical opinion is of equal importance to a well conducted indirect analysis of RCT data be rephrased to align with the Institute's Methods on the hierarchy of evidence.

References

[1] https://www.gov.uk/government/news/accelerating-adoption-of-innovation-in-the-nhs

[2] Szende A, Brazier J, Schaefer C, Deuson R, Isitt JJ, Vyas P. Measurement of utility values in the UK for health states related to immune thrombocytopenic purpura. Curr Med Res Opin 2010;26:1893-903.

[3] NICE technology appraisal guidance 221: Romiplostim for the treatment of chronic immune or idiopathic thrombocytopenic purpura (2011).

[4] National Institute for Clinical Excellence (February 2004, updated 2005) Guideline Development Methods: Information for National Collaborating Centres and Guideline Developers. London: National Institute for Clinical Excellence. Available from: www.nice.org.