NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Response to Appraisal Consultation Document

Eltrombopag for treating chronic immune (idiopathic) thrombocytopenic purpura

(Review of Technology Appraisal 205)

Amgen Limited

22 January 2013

Academic in confidence information is redacted [redacted]

Summary

Thank you for the opportunity to respond to the Appraisal Consultation Document (ACD) for eltrombopag. As an innovative biotechnology company with a mission to serve patients, Amgen welcomes the provision of access to new medicines for patients, and understands that this access should be based on good quality evidence, sound analysis and careful interpretation. We have reviewed the ACD and believe that recommendations have been made which accept arguments put forward by the manufacturer, particularly in comparison to our own product, which do not stand up to application of normal HTA methods and evidence standards. We set out our detailed arguments below and kindly request that they be given full consideration by the Appraisal Committee.

The provisional recommendations are not sound and are not a suitable basis for guidance to the NHS; since the wording of the recommendation is not consistent with that for romiplostim in TA221

There is no basis for the wording of the recommendation in Section 1 of the ACD to be any different to that for romiplostim in TA221. In the ACD, the Appraisal Committee clearly state that they consider **romiplostim to be the only relevant comparator** (Page 37); as such eltrombopag must be recommended in exactly the same group of patients in whom NICE recommended romiplostim, and in whom romiplostim is used in clinical practice. Any difference in wording between the ACD Section 1 and the romiplostim recommendation in TA221 implies that the two therapies are recommended in different patient groups; a conclusion which is clearly not supported by the evidence presented and is misleading to physicians, payers and patients. If, following the consultation period, the Appraisal Committee make a positive recommendation for eltrombopag, then the wording in Section 1 must surely be the same as for romiplostim in TA221, unless evidence and analysis is presented to support a positive recommendation for eltrombopag in patients in whom romiplostim is not used.

The assessment of clinical effectiveness is not a reasonable interpretation of the evidence, since the manufacturer's analysis of relative efficacy from indirect comparison is incorrect.

We are concerned by the methods used by the manufacturer in their indirect comparison to estimate the relative efficacy of eltrombopag and romiplostim. The analysis method used by the manufacturer estimated an odds ratio for overall response of 0.22, 95% CI (0.05, 1.02), from which they concluded that eltrombopag and romiplostim were equally clinically effective. However this analysis does not correctly adhere to the method outlined by Bucher, as the data from the two romiplostim studies have been pooled by simply, and incorrectly, summing the responses across the two studies. In Bucher's method, meta-analysis estimates of treatment effect are combined together to form indirect comparisons. Correctly combining the response data from the two romiplostim studies using a meta-analysis approach, as per Bucher's method, provides an odds ratio for overall response of 0.12, 95% CI (0.02, 0.84), indicating that romiplostim is significantly better than eltrombopag. **When correctly following Bucher's method, it is entirely incorrect to conclude that there is clinical equivalence between eltrombopag and romiplostim.** The only possible conclusion is that romiplostim is statistically significantly superior to eltrombopag.

We are reassured that the Appraisal Committee stated in the ACD that romiplostim is likely to be more effective than eltrombopag. However, we believe that the correct indirect

comparison results should be reported by the Appraisal Committee in any subsequent documentation and also used in the cost effectiveness analysis. In the ACD, the Appraisal Committee have been inappropriately generous to the manufacturer regarding this issue, and we would expect there to be more appropriate language; indicating that the correctly conducted indirect analysis is a credible assessment of relative efficacy, which unequivocally shows that romiplostim is statistically significantly superior to eltrombopag, also dismissing any reference to the entirely incorrect assumption of clinical equivalence for eltrombopag and romiplostim.

<u>The assessment of cost effectiveness of eltrombopag compared with romiplostim is not a reasonable interpretation of the evidence, since the assumptions for seven of the model inputs are incorrect and the sensitivity analysis is incomplete</u>

We have identified errors with seven of the inputs used to model the cost effectiveness of eltrombopag versus romiplostim. Our analysis highlights that the manufacturer has carefully selected input values that are not evidence-based, and which significantly favour eltrombopag over romiplostim. A key driver for the model is the assumption regarding romiplostim dosing, which, in the model, is significantly over estimated by the manufacturer. Furthermore, had the correct indirect comparison results been used in the model, then it would not be possible for eltrombopag to dominate romiplostim, as repeatedly stated incorrectly in the ACD. Finally, the sensitivity analysis employed is not robust; some model inputs are not included appropriately, some important model inputs are not included at all and there is no multivariate analysis which considers all of relevant factors together.

In conclusion, we think this analysis gives a misleading impression of the cost effectiveness of eltrombopag versus romiplostim. **As a consequence, we believe that the provisional recommendations are not sound and are not a suitable basis for guidance to the NHS.**

We would therefore request that:

1) If the recommendation for eltrombopag were to remain positive, then the wording should be identical to that used in the TA221 recommendation for romiplostim.

2) The ERG conduct an indirect comparison using the correct Bucher method, with the results clearly presented within the final recommendation, indicating that the analysis unequivocally shows romiplostim to be statistically significantly superior to eltrombopag and dismissing the incorrect assumption of clinical equivalence for eltrombopag and romiplostim.

3) The cost effectiveness analysis is repeated to a standard which would enable the Appraisal Committee to make a more adequately informed recommendation, i.e. correcting all seven input errors identified and conducting a complete set of deterministic and probabilistic sensitivity analyses.

1 The provisional recommendations are not sound and are not a suitable basis for guidance to the NHS: There is no evidence to justify a difference in wording between the eltrombopag recommendation and the romiplostim recommendation in TA221

Recommendation: If, following the consultation period the Appraisal Committee still decide eltrombopag deserves a positive recommendation, then the wording of the final recommendation should be identical to the romiplostim recommendation in TA221

NICE have no basis for using wording in the Appraisal Committee's preliminary recommendations (Section 1, page 3), which is different from that for romiplostim in TA221[1].

The Appraisal Committee concluded that romiplostim was the only relevant comparator, stating:

- In Section 4.6 (page 30), that *"The Committee therefore considered it appropriate for the manufacturer primarily to examine the clinical and cost effectiveness of eltrombopag compared with the pathway incorporating romiplostim"*

- In the Summary of Appraisal Committee's key conclusions (page 37), that *"The committee considered that the principle comparator for eltrombopag is romiplostim"*

As romiplostim is the only relevant comparator, then eltrombopag can only be recommended in the same group of patients in whom NICE recommended romiplostim, and in whom romiplostim is used in clinical practice. Any difference in the wording of Section 1, page 3, of this guidance and TA221 implies that they are recommended in different patient groups, which is not supported by the evidence considered by the Appraisal Committee.

Furthermore in the analysis presented to the Appraisal Committee, comparing eltrombopag to the other comparators (non-TPO arm) included in the scope of this appraisal, it was clear that eltrombopag is not a cost effective use of NHS resources, thus re-affirming that it is entirely inappropriate to make a recommendation for eltrombopag that is different in any way from the recommendation for romiplostim.

2 The assessment of clinical effectiveness is not a reasonable interpretation of the evidence, since the manufacturer's analysis of relative efficacy from indirect comparison is incorrect.

Recommendation: The final documentation should include the correctly conducted indirect analysis and recognise that it is a robust assessment of relative efficacy of eltrombopag versus romiplostim. It should also clearly state that the correctly conducted indirect analysis unequivocally shows that romiplostim is more effective than eltrombopag, with an odds ratio for overall response of 0.15 (95% CI 0.02, 0.84).

The final documentation should also highlight methodological differences between the romiplostim and eltrombopag trials, in both monitoring and overall response definitions, which mean that the overall response endpoint was more difficult to achieve in the romiplostim trials than in the eltrombopag trials.

The indirect analysis is a critical piece of analysis in this appraisal, as it determines the relative effectiveness of the two TPOs. It is essential that this analysis is correctly conducted, as it is a key source of information for treating physicians, payers and patients wishing to make an appropriate choice of treatment and is also a key driver in the cost effectiveness analysis.

Within the indirect comparison submitted by the manufacturer as part of this re-appraisal, we have identified issues with both the methods used for conducting the indirect comparison and also key methodological differences between the eltrombopag and romiplostim trials used.

Incorrectly conducted Bucher Analysis using revised eltrombopag overall response data

The first indirect comparison between eltrombopag and romiplostim was submitted by the manufacturer to NICE in 2010, as part of the first eltrombopag appraisal (TA 205[2]).This analysis clearly showed that romiplostim was more effective than eltrombopag, with an odds ratio for overall response of 0.17 (0.03, 0.82).

Since the first eltrombopag appraisal, the overall response and durable response data from the RAISE study was updated by the manufacturer. This data was included in both the revised eltrombopag estimate of response, and also in the updated indirect comparison to romiplostim, presented to NICE within this re-appraisal, and subsequently published[3]. The original data used in the 2010 analysis and the updated data used in the 2012 analysis are shown in Table 1; fourteen additional patients on eltrombopag have been assessed as having an overall response compared to one extra patient on placebo.

Table 1. Summary of changes to the eltrombopag overall response data in the RAISE study

	Overall response data presented by the manufacturer		
	2010 first eltrombopag appraisal (original data)	2012 recent re-appraisal of eltrombopag (updated data)	Difference in number of overall responders
Eltrombopag			
All Data	77/135	91/135	**14**
Splenectomised	26/50	30/50	**4**
Non-Splenectomised	51/85	61/85	**10**
Placebo			
All Data	7/62	8/62	**1**
Splenectomised	2/21	2/21	**0**
Non-Splenectomised	5/41	6/41	**1**

We thought it peculiar that the post-hoc, unblinded response rates for eltrombopag in the RAISE trial had improved between 2010 and 2012, despite there being no new data, and therefore contacted the manufacturer. Following a communication with them, it is our understanding that the revision to the response rates occurred due to a mistake in the subgroup population data that had been used in their 2010 analysis. The manufacturer has informed us that the Appraisal Committee have been made fully aware of this error and were happy with the revised data.

Table 2 shows the results of the manufacturer's indirect comparison (based on the Bucher et al. 1997 method[4]) using the original 2010 response rates and the updated response rates from the re-appraisal submission. The most notable effect of using the updated response rates in this analysis is that the 95% CIs for the odds ratio comparing the overall response between eltrombopag and romiplostim now includes 1; 0.22, 95% CIs (0.05, 1.02), consequently the submission made by the manufacturer for this re-appraisal assumes no difference in efficacy between eltrombopag and romiplostim.

Table 2. Manufacturer's indirect comparison based on the original and updated data

	2010 first eltrombopag appraisal (original data)	2012 recent re-appraisal of eltrombopag (updated data)
	Elt v Rom OR (95% CI)	Elt v Rom OR (95% CI)
Overall Response		
All Data	0.17 (0.03, 0.82)	0.22 (0.05, 1.02)
Splenectomised	0.05 (0.00, 1.43)	0.09 (0.00, 2.52)
Non-Splenectomised	0.29 (0.04, 1.95)	0.34 (0.06, 2.14)
Durable Response		
All Data	0.26 (0.03, 2.62)	0.32 (0.03, 3.14)
Splenectomised	0.46 (0.01, 15.91)	0.50 (0.01, 17.32)
Non-Splenectomised	0.33 (0.03, 3.79)	0.41 (0.04, 4.80)

However, on reviewing the recent indirect comparison submitted by the manufacturer as part of this re-appraisal, we have concluded that the method used is **not** that outlined by Bucher; since the data from the romiplostim studies have been pooled by simply, and incorrectly, adding the responses together. In Bucher's method, meta-analysis estimates of treatment effect across studies are combined together to form indirect comparisons. Combining the data from the two romiplostim studies using a meta-analysis approach (as recommended by Bucher) and then using Bucher's method provides the results shown in Table 3. **Using Bucher's method correctly provides an odds ratio for overall response of 0.12, 95% CIs (0.02, 0.84), supporting the conclusion that romiplostim is statistically significantly superior to eltrombopag.**

Table 3. Comparison of Incorrect and Correct Bucher's methods for indirect comparison

	Manufacturer's Incorrectly Conducted Bucher method – using the 2012 data (2012 submission for the recent re-appraisal of eltrombopag)	Correct Bucher Method - using the 2012 data (Amgen analysis)
	Elt v Rom OR (95% CI)	Elt v Rom OR (95% CI)
Overall Response		
All Data	0.22 (0.05, 1.02)	0.12 (0.02, 0.84)
Splenectomised	0.09 (0.00, 2.52)	0.09 (0.00, 2.56)
Non-Splenectomised	0.34 (0.06, 2.14)	0.34 (0.06, 2.14)
Durable Response		
All Data	0.32 (0.03, 3.14)	0.15 (0.01, 2.72)
Splenectomised	0.50 (0.01, 17.32)	0.53 (0.02, 18.42)
Non-Splenectomised	0.41 (0.04, 4.80)	0.41 (0.04, 4.80)

The ERG realised that the manufacturer's approach to the indirect analysis was misleading. They therefore analysed the data using a Bayesian random effects NMA approach (moderate heterogeneity) and calculated the odds ratio to be 0.15 (0.02, 0.84). Importantly, although the point estimate was slightly higher than that calculated by the correct Bucher method, the confidence intervals were identical and did not cross one. A summary of the analysis of the new data using each of the three methods is presented in Table 4.

In addition, probability calculations conducted by Amgen on the Bayesian analysis also show that the probability of the overall response for eltrombopag and romiplostim being equal is 1%, hence the probability of romiplostim being superior to eltrombopag is 99% (further details of methodology are available on request).

Table 4. Summary of results of indirect comparisons to estimate the odds ratio for overall response (using updated data); manufacturer's Incorrect Bucher Method, Correct Bucher Method and ERG Bayesian Network Meta Analysis

	Manufacturer 's Incorrect Bucher Method - using the 2012 data (from 2012 submission)	Correct Bucher Method - using the 2012 data (Amgen analysis)	ERG Bayesian NMA - using the 2012 data (from ACD)
	Elt v Rom OR (95% CI)	Elt v Rom OR (95% CI)	Elt v Rom OR (95% CI)
Overall Response - All Data	0.22 (0.05, 1.02)	0.12 (0.02, 0.84)	0.15 (0.02, 0.84)

We conclude that the odds ratio calculated from appropriately conducted indirect comparisons should be either 0.12 or 0.15 and although we believe 0.12 (using the correct Bucher Method) is the most appropriate estimate, we feel that the 0.15 estimate by the ERG (using a Bayesian NMA) would also be reasonable.

We were reassured by statements in the ACD indicating that romiplostim is likely to be more effective than eltrombopag (ACD Section 4.11, page 33). However it is crucial for treating physicians, payers and patients that the statistically significant superiority of romiplostim over eltrombopag is clearly recognised by the Appraisal Committee in any subsequent documentation; indicating that the correctly conducted indirect analysis is a credible assessment of relative efficacy, which unequivocally shows that romiplostim is statistically significantly superior to eltrombopag, also dismissing any reference to the entirely incorrect assumption of clinical equivalence for eltrombopag and romiplostim.

Methodological differences between trials

There were also methodological differences between the romiplostim and eltrombopag trials, which meant that the overall response endpoint was more difficult to achieve in the romiplostim trials than in the eltrombopag trial:

We welcome and agree with the Appraisal Committee's statement in Section 4.9, page 31, that the patients in the romiplostim trials were more severe as they "*had been on multiple previous therapies",* which in turn made it more difficult to achieve an overall response. In addition, the definition of overall response differs between the romiplostim and eltrombopag trials meaning that the overall response endpoint was more difficult to achieve in the romiplostim trials than in the eltrombopag trials:

- In the romiplostim trials, overall response was a **pre-defined** secondary endpoint defined as a durable response (weekly platelet count ≥50 x 10^9/L during ≥6 weeks of the last 8 weeks of treatment with no rescue medications at any time) plus a transient response (≥4 weekly platelet responses without a durable platelet response from week 2 to 25).

- In the eltrombopag RAISE trial, overall response was not a study endpoint, but a **post-hoc analysis** in which the definition of durable response (termed sustained response) was identical to romiplostim, but the definition of transient response was defined as ≥4 weekly consecutive responses during treatment.

Crucially, the 4 weekly monitoring schedule of the eltrombopag trial meant that it was impossible to assess transient response in the same way as in the romiplostim trials, because weekly monitoring would have been required. A weekly consecutive response for ≥ 4 weeks cannot be derived from a 4 weekly monitoring period, during which time, the platelet counts are likely to fluctuate. To address this issue the manufacturer has used the 'last observation forward' approach. As a consequence of the manufacturer using the last observation carried forward method to determine response after the first 6 weeks of the study, a patient needed only 1 platelet count above 50 (the last observation) to be classed as having a transient response.

In conclusion, the eltrombopag trials included less severe patients and used 'last observation carried forward' in the post hoc analysis to calculate the transient response ≥4 of consecutive weeks; consequently it was easier for a patient to achieve an overall response in the eltrombopag trial than in the romiplostim trials. Therefore we consider the odds ratio for overall response calculated from any indirect analysis using these trials to be a conservative figure (in favour of eltrombopag) when assessing the relative efficacy of

eltrombopag and romiplostim; further justifying the conclusions from the correct Bucher analysis and Bayesian NMA (moderate heterogeneity) that romiplostim is statistically significantly superior to eltrombopag.

3 The assessment of cost effectiveness is not a reasonable interpretation of the evidence, since the assumptions for seven of the model inputs are incorrect and the sensitivity analysis is incomplete.

The current ACD states in many places that eltrombopag dominates romiplostim. This is only possible because the Appraisal Committee has accepted the manufacturer's argument that the two treatments are of equal efficacy; an assessment we have addressed above and demonstrated to be simply wrong.

We have identified seven inputs to the model that are incorrect and which, if corrected, will change the relative cost effectiveness of eltrombopag and romiplostim in favour of romiplostim. Furthermore both the manufacturer's and the ERGs sensitivity analysis are incomplete and inadequate.

3.1 The appropriate odds ratio for overall response has not been included in the cost effectiveness analysis

Recommendation: The odds ratio of 0.15 for overall response, estimated by the ERG using the Bayesian NMA, should be included as the point estimate for overall response in the cost effectiveness analysis base case.

In the manufacturers cost effectiveness analysis, all three multivariate evaluations (base case, alternative evaluation, and TA221) assume the eltrombopag and romiplostim overall response odd ratio is 1. This is clearly an incorrect assumption which was questioned by the ERG (Section 6.33, page 52) and recognised by the Appraisal Committee (Section 4.15, page 34). The manufacturer also conducted a one way sensitivity analysis using the point estimate of 0.22; this analysis was then taken by the ERG to estimate the cost effectiveness of eltrombopag versus romiplostim within the alternative evaluation. This is inappropriate, as the analysis was conducted with a point estimate of 0.22 rather than 0.15 (derived from the Bayesian NMA conducted by the ERG).

We do not understand how the Appraisal Committee can make a final recommendation until an appropriate cost effectiveness analysis is conducted which applies the correct odds ratio of 0.15 as calculated by the ERG.

3.2 The treatment duration of eltrombopag and romiplostim are inappropriately considered to be equivalent

Recommendation: The final recommendation should acknowledge that there is no evidence for the assumption that treatment duration is the same for eltrombopag and romiplostim. The cost effectiveness analysis, including the sensitivity analysis, should be repeated using longer treatment durations for romiplostim than eltrombopag, in order to reflect available clinical evidence.

The manufacturer has incorrectly assumed that the treatment duration for eltrombopag and romiplostim are the same, based on the results of their indirect comparison, from which they incorrectly assumed equivalent efficacy (Section 3.24, page 17 of the ACD). The manufacturer has not attempted to validate this assumption by analysing the available evidence for romiplostim and eltrombopag.

The manufacturer modelled the treatment duration for both eltrombopag and romiplostim based on patient level data taken from the eltrombopag RAISE trial. The manufacturer's calculation of treatment duration is described in Appendix 15 of their submission. Upon request, we were provided with a copy of Appendix 15; however it was heavily redacted, preventing a detailed review of their analysis. It is important to note that neither the ERG nor the Appraisal Committee questioned the assumption that romiplostim and eltrombopag treatment duration is equal; even though they did not agree with the manufacturer's incorrect indirect comparison, concluding that eltrombopag and romiplostim are clinically equivalent. Clearly as the Appraisal Committee state that romiplostim has a superior response rate then they should also consider it possible that romiplostim has a longer treatment duration than eltrombopag.

Eltrombopag and romiplostim extension studies show a difference in the percentage of patients enrolled into these long term studies; with 59% of eltrombopag patients (52% splenectomised, 64% non-splenectomised) in the RAISE study enrolled onto the EXTEND study (page 72 of the ERG report), compared to 88% of romiplostim patients in the phase 3 studies enrolled into the open label extension.[5] These results clearly indicate that there is a difference in treatment duration between eltrombopag and romiplostim. Importantly, the assumption of equal treatment duration made by the manufacturer is based solely on their incorrectly calculated indirect analysis.

The manufacturer did include different types of curve fit in their sensitivity analysis (Section 6.26, page 46) however they did not explore scenarios in which romiplostim and eltrombopag had different treatment durations.

This parameter is a significant driver in the cost effectiveness model and needs to be fully investigated in order for the Appraisal Committee to make a more adequately informed recommendation.

3.3 The dosing of romiplostim is inappropriately high

Recommendation: The cost effectiveness analysis should be repeated to include romiplostim doses which have been calculated correctly. Furthermore we encourage the Appraisal Committee to acknowledge that the romiplostim dosing in clinical practice is lower than in phase 3 trials and to consider the impact of this on cost effectiveness in a sensitivity analysis.

In TA221, the dosing of romiplostim was robustly calculated from Amgen trial data (Kuter et al. 2008[6]): The average number of whole vials used per patient was calculated using actual doses administered each week from week 13 to the end of study at week 24, avoiding the initial titration period. This method was considered a conservative approach, as the exclusion of lower doses during the titration period from weeks 1 to 12 increased the average dose (number of whole vials required) of romiplostim per patient. It is worth noting that the number of whole vials stated takes into account wastage (assuming that all unused product is discarded) and does not assume vial-sharing. The detail of romiplostim dose calculation methodology is documented in the Amgen ACD response for TA221 (pages 13 to 18).

From this analysis the average dose of romiplostim (realistic versus conservative approach) was 1.37-1.42 whole vials per patient for the non-splenectomised patients and 1.70 – 1.83 whole vials per patient for splenectomised patients. It is important to note that romiplostim is dosed by weight and these doses were appropriately calculated using patients from the two romiplostim studies (Kuter et al 2008[6]) and it is noteworthy these patients were heavier than patients in the RAISE trial (74 kg for RAISE8 versus 79 kg for Kuter et al 20086)

As part of the development of TA221, the romiplostim dose was discussed by the Appraisal Committee (the same committee reviewing the current appraisal) together with clinical experts. They drew the following conclusion regarding romiplostim dosing, stating in Section 4.11 of the Guidance for TA221 that *"The Committee concluded that the most plausible scenario would be somewhere between the realistic and conservative scenarios modelled by the manufacturer".*

In this appraisal, the manufacturer did not reference TA221 for the base case and instead chose to calculate average doses from Kuter et al. 2008[6], assuming that the dose on which a patient is likely to remain (the stable dose) equals the last dose from the trials (Section 3.31 of the ACD). As a consequence, the manufacturer's cost effectiveness model assumes a romiplostim dose of 5.5 µg/kg in splenectomised patients after week 24, and 3.1 µg/kg in non-splenectomised patients. These doses are notably different from the average doses of 3 µg/kg for splenectomised patients and 2 µg/kg for non-splenectomised patients discussed by the Appraisal Committee in the development of TA221 (Section 4.11, TA221 Guidance).

This over inflation of the romiplostim dose was identified by the ERG and is highlighted by the Appraisal Committee: In Section 3.46, page 25, of the ACD, they state *"The manufacturer averaged eltrombopag and romiplostim doses from the relevant trials across patients whose condition had responded and patients whose condition had not. The ERG noted that, in the Kuter et al. (2008) trials, the average romiplostim dose in patients whose*

condition had responded was 40–60% lower than that across the trial as a whole. If a similar argument holds for eltrombopag, the ERG indicated that the cost effectiveness of eltrombopag compared with standard care may improve, but the cost effectiveness of eltrombopag compared with romiplostim may worsen given the low dose for patients attaining a durable response with romiplostim. The ERG stated that eltrombopag and romiplostim doses should be response-specific". On reviewing the model we agree that the manufacturer has derived the romiplostim dose incorrectly, which has resulted in a significant over estimate of the romiplostim dose and the resulting cost of romiplostim.

We have calculated the romiplostim dose using the ERG correction to the manufacturer's approach (i.e. excluding doses for non-responders), combined with the approach taken in TA221 (correcting for patients who were dosed above the maximum dose stated in the SPC i.e. 10 µg/kg). Using this approach we have calculated the romiplostim dose to be 1.54 whole vials for splenectomised patients and 1.10 whole vials for non-splenectomised patients. The small discrepancy between these calculated doses and those calculated for TA221 are explained by the lower weight of patients in the RAISE trial compared to those in the romiplostim trials (Kuter et al. 2008[6]), as romiplostim is dosed by weight.

In Section 4.14, page 34, of the ACD, the Appraisal Committee discussed ERG concerns regarding the inflated dose used in the modelling, and considered the one-way sensitivity analysis conducted by the ERG to evaluate reduced dosing. From this analysis the Appraisal Committee concluded that eltrombopag still dominates romiplostim even with a reduced dose. We would like to draw attention to two issues with these conclusions.

1) The romiplostim dose, a key driver to the cost effectiveness model, has been incorrectly calculated: The romiplostim dose included in the cost effectiveness calculations should be that calculated using the ERG corrected manufacturers method combined with the approach used in TA221 (1.54 whole vials for splenectomised and 1.10 whole vials for non splenectomised).

2) The romiplostim dose is one of seven incorrect inputs in the manufacturer's model. As a key driver, it should be investigated in a multivariate sensitivity analysis that evaluates the impact of all seven incorrect inputs together, so that appropriate conclusions on the relative cost effectiveness of eltrombopag and romiplostim can be made.

Additionally, it is important to highlight that whilst reviewing TA221, the Appraisal Committee recognised that the dosing of romiplostim in clinical practice may be lower than that observed in the phase 3 trials. 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."*

Since publication of TA221, the results of an observational study, conducted by Amgen, have confirmed the Appraisal Committee's earlier conclusions on the romiplostim dose used in clinical practice. Interim results, presented as an abstract at 54th ASH 2012 Annual Meeting (Selleslag et al 2012[7]), reported the mean romiplostim weekly dose in clinical

practice to be 2.8 (1.5,4.3) µg/kg /week. Further unpublished analysis shows that the mean dose is [redacted]. Given that the romiplostim dose is a key driver in the model, it is entirely possible that at the doses of romiplostim used in clinical practice, romiplostim would dominate eltrombopag.

We therefore request that the Appraisal Committee should have access to a cost effectiveness analysis including romiplostim doses derived from the ERG corrected manufacturers method combined with the approach used in TA221 (1.54 vials for splenectomised and 1.10 vials for non splenectomised). In addition we believe that a sensitivity analysis which includes the dosing observed in clinical practice would be important evidence in informing the Appraisal Committee's recommendation.

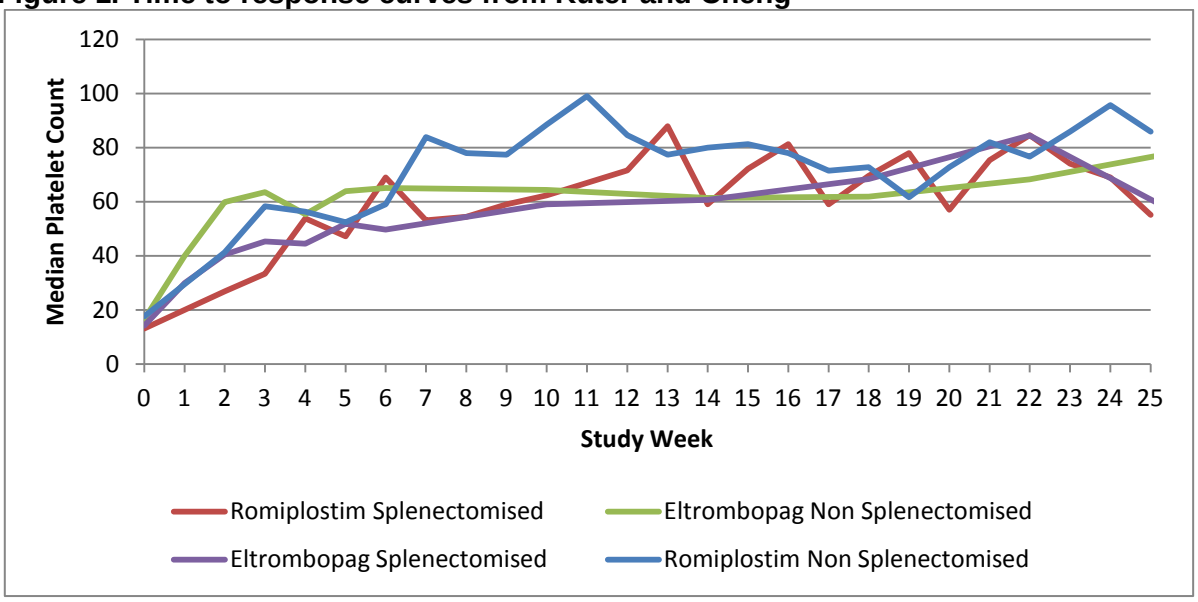
3.4 The time for response for eltrombopag is inappropriately assumed to be shorter than romiplostim

Recommendation: The Appraisal Committee acknowledges that eltrombopag has the same time to response as romiplostim. The cost effectiveness analysis should be updated to use the same time to response for eltrombopag and romiplostim (suggested to be 4 weeks).

In TA221 the time to response for romiplostim was conservatively assumed to be 4 weeks in the model. This was a conservative estimate given that in the Kuter et al 2008[6] trials 25% of patients responded after week 1 and 50% of patients responded within weeks 2 to 3. In the ACD, the time for response for eltrombopag was assumed to be 15 days, taken from the RAISE trial (Section 3.23, page 17).

We have digitised the data from the response curves presented in Kuter et al 2008[6] (Figure 3 parts A and B) and RAISE (Cheng et al. 2011[8]) (Figure 3 Part C) and plotted them on the same graph, Figure 1. This analysis of the available evidence clearly demonstrates that the profile, in terms of platelet count response time, is similar for romiplostim and eltrombopag for both splenectomised and non-splenectomised patients. Therefore the difference in response times (4 weeks for romiplostim and 15 days for eltrombopag) results from the romiplostim model assumption being more conservative than the eltrombopag model, rather than a true difference in response times. We kindly request this input be amended in the cost effectiveness modelling.

Figure 1. Time to response curves from Kuter and Cheng



3.5 The health state utility data for eltrombopag was not taken from the manufacturer's own trials

The cost effectiveness analyses and subsequent sensitivity analyses should be updated to include the health state utility scores collected from the RAISE and EXTEND trials.

As highlighted by the ACD (Section 3.30, page 19), although the RAISE and EXTEND trials collected health state utility data, the manufacturer chose to use utility data from an Amgen sponsored time-trade off study (Szende et al. 2010[9]), rather than their own trial data for both the base case and the alternative scenario.

Although the Appraisal Committee have already noted this issue, we would like to reinforce that the manufacturer should have used the health state utility data from their own trials in order to appropriately comply with the NICE methods. We would recommend that the manufacturer should use their own trial-based SF-36 data and evaluate it by mapping to the EQ-5D in line with NICE methods[10] (Section 5.46). It is noteworthy**,** that the health state utility scores for the different health states in the model are considerably higher in Szende than in the RAISE and EXTEND trials, see Table 5 below.

Table 5. Health state utilities

	RAISE	SZENDE et al	
Controlled plt (≥50Gi/L)	0.73	Plt response (≥ 50Gi/L)no bleed	0.863
Uncontrolled plt (≤50Gi/L)	0.70	Plt response (≥ 50Gi/L) outpatient bleed	0.734
Controlled plt (≥30Gi/L)	0.73	plt non response (≤50Gi/L) no bleed	0.841
Uncontrolled plt (≤30Gi/L)	0.69	plt non response (≤50Gi/L) outpatient bleed	0.732
Long term (chronic) complication from WHO grade 3 or 4 bleed	0.22	(≤50Gi/L) inpatient cranial bleed	0.038
Long term (acute) complication WHO grade 4 (ICH)	0.11	(≤50Gi/L) inpatient GI bleed	0.450
Short term impact from WHO grade 3 bleed (GI bleed)	0.45	(≤50Gi/L) inpatient other bleed	0.450

The ERG conducted an exploratory analysis with the RAISE and EXTEND health state utility data to try to calculate the impact of this assumption on the cost effectiveness of eltrombopag versus romiplostim; however this exploratory analysis was inadequate, for the following reasons:

- The ERG's exploratory analysis was undertaken on the manufacturer's alternative evaluation. This evaluation assumed that the efficacy of eltrombopag and romiplostim were the same and hence there was no difference in the health states between the two TPOs. As a consequence it is not surprising that there was limited change in the relative cost effectiveness by employing the different sources of health state utility.

- The health state utilities were only explored as a univariate analysis and to be meaningful, must be explored and considered at the same time as all the other variables in a multivariate analysis. Our recommendation is that the cost effectiveness analysis is repeated and that health state utility data be drawn from the manufacturer's own trials for the base case.

3.6 The cost of administering romiplostim was assumed to be inappropriately high

Recommendation: The cost effectiveness analysis should be conducted again including a more realistic approach to the cost of a simple subcutaneous injection of romiplostim.

The manufacturer's submission assumed that all patients had hospital administration of romiplostim for the first 4 weeks of treatment and 72.3% self-administered thereafter. The manufacturer also assumed that the administration cost of romiplostim was equivalent to that of simple chemotherapy (HRG code SB12Z (weighted average of £204.81 per infusion) (Section 6.5.6, page 268 of the manufacturer's submission). This is not an appropriate HRG code to assign to the cost of the simple subcutaneous administration of romiplostim in hospital, since it assumes 30 minutes of nurse time and 30-60 minutes of intravenous chemotherapy chair time for the delivery of a complete cycle. As romiplostim is a simple subcutaneous injection, it requires little preparation and would not require any intravenous chemotherapy chair time and less nurse time.

This misguided assumption leads to an inappropriately inflated administration cost of £819.14 for four simple subcutaneous injections. A more realistic cost per administration, for those unable to self-administer, would be £11.75 (assuming 15 minutes of a nurse's time[11]). We request that the Appraisal Committee and all subsequent documentation recognise that romiplostim is not an infusion but a simple to administer subcutaneous injection, which can be self-administered by the majority of patients. The manufacturer's assumptions on cost are clearly highly inflated and we request that they be corrected.

3.7 The use of anti D has been considered inappropriately within the model

Recommendation: An error relating to inclusion of anti D should be corrected within the cost effectiveness analysis.

We have identified an error relating to inclusion of anti D within the cost effectiveness analysis. The manufacturer's model includes use of Anti D (Section 6.5.6, Table B75, page 268 manufacturer's submission) for non-splenectomised patients, although this treatment was withdrawn from the market in 2009. In clinical practice this type of rescue therapy has been replaced by the more expensive treatment of IVIg.

We request that the cost effectiveness analysis be updated to include this point in any future documentation.

3.8 The sensitivity analysis presented in the ACD is incomplete and omits key inputs

Recommendation: In order to enable an adequately informed recommendation, the cost effectiveness analysis should be repeated by the ERG using more robust input assumptions. A more comprehensive set of sensitivity analyses (univariate, multivariate, and PSA) should also be conducted, which includes all input parameters associated with significant levels of uncertainty.

The manufacturer conducted a series of incomplete sensitivity analyses (univariate, multivariate and PSA), in which some cost effectiveness inputs were not considered

appropriately, whilst others were omitted entirely. We would like to draw the Appraisal Committee's attention to the following issues:

- The manufacturer considered the 0.22 odds ratio for overall response (taken from their incorrect, indirect comparison) in the deterministic and probabilistic sensitivity analysis, but not in their multivariate analysis. Furthermore there is no sensitivity analysis (in the ACD, ERG report or manufacturer's submission) which considers the 0.15 odds ratio for overall response from the ERG NMA.
- The manufacturer inadequately considered treatment duration in their deterministic and probabilistic sensitivity analyses: The manufacturer tested the dependence on the cost effectiveness on different types of curve fit (e.g. log normal, gamma, etc.) to the eltrombopag clinical data in order to derive the treatment duration. It is unacceptable that they omitted to include any analysis looking at the sensitivity of the cost effectiveness on differences in treatment duration between romiplostim and eltrombopag. If the difference in treatment duration between eltrombopag and romiplostim is significant, then this parameter may be a key driver to the cost effectiveness analysis.
- The manufacturer and the ERG have inadequately considered romiplostim dosing in their sensitivity analysis. Within the manufacturer's submission, the base case and the alternative evaluation analyses included incorrect and inflated romiplostim doses, resulting from a dose-calculation error which we have described in detail in Section 3.3 of this response. The ERG highlighted this error and conducted an exploratory one way sensitivity analysis of the alternative evaluation. However their analysis was incomplete, as they did not conduct a multivariate analysis with the correctly derived dose of romiplostim. As a consequence there is no multivariate analysis in the ACD which includes the correctly calculated dose of romiplostim.

  The manufacturer also conducted a single one way sensitivity analysis, but only considered higher romiplostim doses: The analysis used data from the Bussel trial[12] which allowed a maximum initial romiplostim dose of 30mcg/kg (significantly higher than the maximum dose of 10mcg/kg recommended in the romiplostim SPC) and which also had a target platelet count of 50-250 x 10^9 per litre (higher than the Kuter trial); as a consequence, the average romiplostim dose in the Bussel trial was significantly greater than that reported by Kuter. The manufacturer, in their one way sensitivity analysis, have therefore only considered romiplostim doses higher than those derived from Kuter and importantly, they have not considered the more realistic scenario in clinical practice, that the average romiplostim dose would be lower than that calculated from the Kuter trial (as observed in Selleslag et al[7]).

- The manufacturer did not include trial-based SF-36 data to drive health state utilities for use in their cost effectiveness analysis. As outlined in Section 3.49, page 26 of the ACD, the ERG did conduct this analysis but still assumed that the efficacy of eltrombopag and romiplostim were equivalent and therefore concluded, erroneously, that eltrombopag dominated romiplostim. The only way to test the impact of health state utility source data in the model is by first correcting the relative efficacy of eltrombopag to romiplostim, using the 0.15 odds ratio calculated by the ERG, i.e. romiplostim is superior. Health state utility data will only have an impact when the difference in efficacy is appropriately modelled.

- The manufacturer did include the percentage of patients who can self-administer in the sensitivity analysis, however neither they, nor the ERG, included an accurate cost of administering romiplostim in the hospital in either the deterministic (univariate or multivariate) or probabilistic sensitivity analysis.
- The manufacturer did not include time for response in the univariate, multivariate, or PSA.

Crucially, within the current set of sensitivity analysis, there is no multivariate analysis which combines the most realistic set of input parameters; the corrected odds ratio from the indirect comparison, a longer treatment duration for romiplostim compared with eltrombopag, correct dose calculations for romiplostim, correct health state utility data, the correct cost of administration, and finally the correct time for response.

This lack of appropriate sensitivity analysis was noted by the Appraisal Committee and was highlighted in Section 4.16, page 36, of the ACD, stating that *"The Committee was aware that no sensitivity analysis was available that included the point estimates from the indirect comparison, the SF-6D utility data collected from RAISE and EXTEND and the reduced dose of romiplostim but estimated that including all of these factors would not lower the ICERs to a degree where the Committee would change its decision."*

It is disappointing that the Appraisal Committee had to make a recommendation based on an estimated rather than a robustly modelled ICER. We kindly request that a revised and more robust cost effectiveness analysis be conducted, addressing all the issues described above, thereby negating the need for an estimated ICER. With a view to providing a set of recommendations that are a sound and suitable basis for guidance to the NHS.

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