NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Eltrombopag for treating chronic immune (idiopathic) thrombocytopenic purpura (review of technology appraisal 205)

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

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

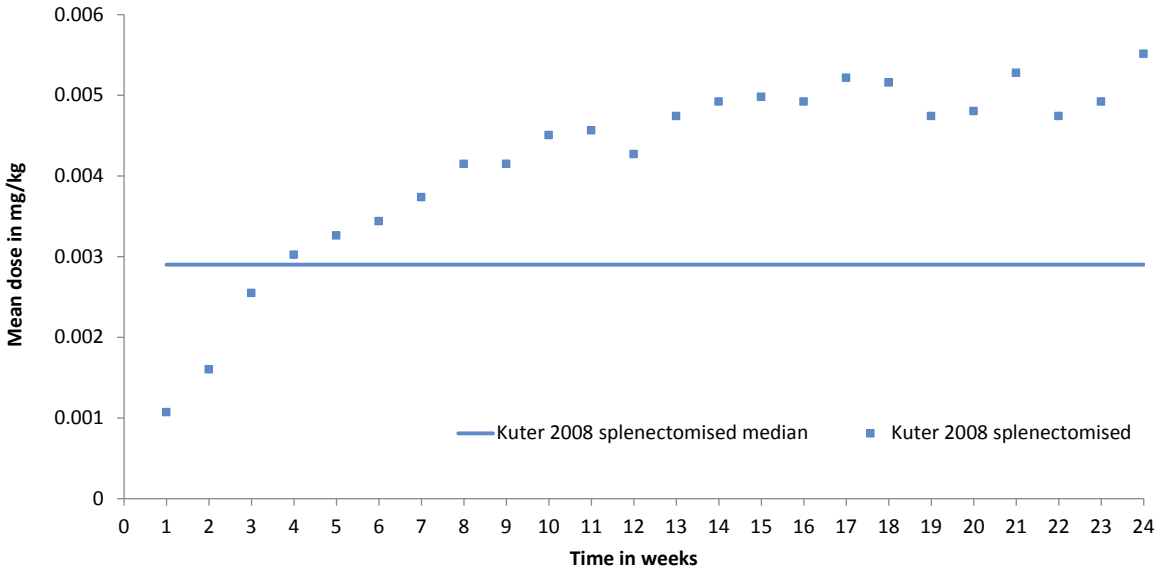
Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

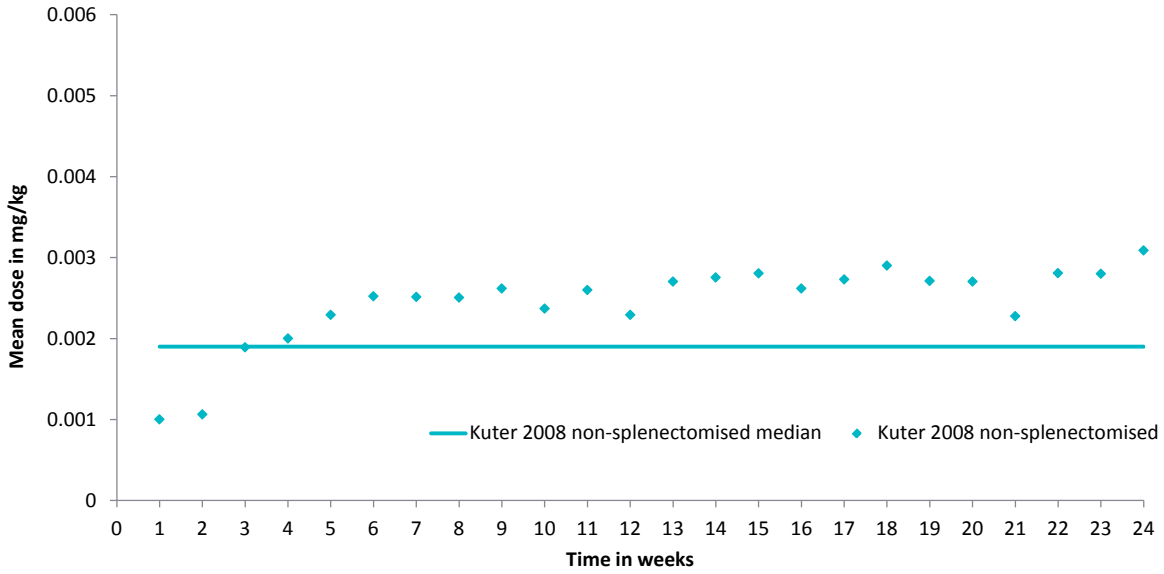
Comments received from consultees

Consultee	Comment	Response
GlaxoSmithKline	**Thrombocytopenic purpura - eltrombopag (rev TA205)** GlaxoSmithKline (GSK) appreciates the opportunity to respond to the Appraisal Consultation Document (ACD) for eltrombopag as a treatment for chronic thrombocytopenic purpura (cITP) (rev TA205). GSK has reviewed the ACD and welcomes the positive recommendation for eltrombopag as an alternative to romiplostim. Eltrombopag offers patients, clinicians and the NHS a less costly, oral alternative treatment in an orphan disease area where there are few evidence based therapies. We have structured our comments in line with the specific questions posed by NICE. **1. Has all of the relevant evidence been taken into account?** GSK considers that all the relevant evidence for eltrombopag has been taken into account and is reflected in the ACD. **2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** GSK has several concerns with respect to the Committee's interpretation of the available evidence. These are outlined below. **i) The Committee's assertion that romiplostim is likely to be more effective than eltrombopag.** GSK welcomes the Committee's acknowledgement of the uncertainty surrounding the indirect comparison, however we would like to reiterate our belief that there is no robust evidence (statistical or otherwise) of a clinically meaningful difference between the two TPO-RAs. The uncertainty associated with any indirect treatment comparison of these two treatments is to be expected given the small patient populations in this orphan disease area and the heterogeneity between the pivotal trials, specifically in terms of trial design and end point definitions. Furthermore, given that in clinical practice, supported by various published guidelines, the two TPO-RAs are deemed interchangeable, GSK believes that there is no robust basis for the Committee's assertion that romiplostim is likely to	Comment noted. Comment noted. The Committee agreed that the results of the manufacturer's and the ERG's indirect comparisons were associated with uncertainty. It was also aware that the use of eltrombopag and romiplostim in clinical practice is broadly interchangeable. However, given the results of the indirect comparisons, and the earlier romiplostim trials, which may have enrolled more patients with severe

Consultee	Comment	Response
	be superior to eltrombopag and that this statement is in fact misleading. cITP is an orphan disease area and the evidence base will always be limited. There is not sufficient evidence to be able to make robust conclusions regarding comparative efficacy of the two TPO-RAs and in light of the available evidence GSK do not believe that the Committee's conclusion can be reasonably justified.	chronic ITP than the eltrombopag trials, the Committee was satisfied that the available evidence suggested that romiplostim was likely to be more effective than eltrombopag. For further details, please see sections 4.10 and 4.11 of the FAD.
	ii) Misrepresentation of clinical expert opinion GSK believes that comments from the clinical experts at the first Committee meeting have been misrepresented on page 36 of the ACD. The ACD states "The committee agreed with the clinical specialists that the available evidence suggested that romiplostim was likely to be more effective than eltrombopag rather than equally effective…" This is not consistent with contemporaneous notes taken at the meeting, which suggest that the clinical experts stated that although there was not enough evidence to make any conclusions regarding comparative efficacy, they viewed the two TPO-RAs as interchangeable and would offer patients a choice of TPO-RA. It should also be noted that the current wording was not in the first ACD and so presumably was added as a result of discussions that took place at the second appraisal committee meeting, at which there were no clinical experts present.	Comment noted. The FAD has been amended to reflect more accurately the clinical specialists' view on the relative effectiveness of eltrombopag and romiplostim. For further details, please see section 4.11 of the FAD.
	iii) Assumption that patients in the romiplostim trials were likely to be more severe than those enrolled in the eltrombopag trial because the romiplostim trials preceded the eltrombopag trial Although the romiplostim trials were conducted before RAISE, this does not mean that they recruited more severe patients. RAISE was conducted at sites across 23 different countries whereas the romiplostim studies were conducted in the United States, the Netherlands, France and the UK. 73% of the subjects in RAISE were from countries where the romiplostim trials were not running and are therefore likely to reflect a similar severity of disease.	Comment noted. Because romiplostim preceded eltrombopag, the Committee considered that the clinical trials for romiplostim may have enrolled more patients with severe chronic ITP than the eltrombopag trials. The Committee further noted that more patients in the romiplostim trials had taken multiple previous therapies, which suggests that they better reflected patients whose condition had not responded. For further details, please see FAD section 4.11.

Consultee	Comment	Response
	iv) Inappropriate romiplostim dosing assumptions used in ERG's supplementary analysis GSK has concerns regarding the lower dosing assumptions used for romiplostim in the ERG's supplementary analysis. Although for the purpose of the economic model it may be appropriate to use the dose corresponding to patients classified as responders, the ERG's analysis only made this adjustment for romiplostim and not for eltrombopag. This introduces bias into the comparison as there may also be a lower dose of eltrombopag in patients classified as responders. Assuming there is a relationship between response and dosing, use of the durable responder dosing to represent all patients meeting the responder definition in RAISE or the overall response definition in Kuter 2008 is likely to be inappropriate (in the economic model the RAISE definition was used in the base case and the overall response definition used in a sensitivity analysis). Durable responders represent only 48% (splenectomised) and 69% (non-splenectomised) of overall responders in Kuter 2008. It is therefore expected that the romiplostim dose will be higher for patients classified as responders using the RAISE definition of response or the overall response definition. The use of the median rather than the mean may be driving a large majority of the dose reduction observed in this scenario. The FDA advisory committee reported median "stabilized" doses for the Kuter 2008 splenectomised (2.9µg/kg) and non-splenectomised (1.9µg/kg) trials[1]. Comparing these medians to the means reported in Kuter 2008[2] (Figure 1) suggests that the use of medians rather than means is likely to significantly underestimate the dose and therefore the cost. Amgen's response to the first ACD refers to an observational study which reports the mean dose of romiplostim as 2.8ug/kg[3]. This is incorrect and misleading, since the abstract states that this is actually a median dose, which as stated above is likely to be lower than the mean dose. The abstract also concludes that the real world dose of romiplostim is similar to that reported in Kuter 2008. GSK believes that using the mean doses reported in Kuter 2008 is therefore entirely justified. In fact, our approach may have been conservative as results from the romiplostim extension study and a French compassionate use program (both of which are likely to see non-responders withdrawn from therapy) suggest that higher average doses of romiplostim are used in clinical practice.[4,5] Figure 1. Comparison of mean and median romiplostim dose in Kuter 2008	Comment noted. The Committee understood from the ERG that, in the romiplostim trials, the median romiplostim dose in patients whose condition had responded was lower than that across the trial as a whole. The Committee therefore considered it more appropriate to apply doses for eltrombopag and romiplostim depending on whether or not the patient's condition had responded. The Committee was aware that the ERG's analysis did not incorporate a lower dose for eltrombopag. For further details, please see FAD sections 3.46, 3.49 and 4.17.

Consultee	Comment	Response
		

Consultee	Comment	Response
	 **3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** GSK welcomes the provisional recommendation for eltrombopag and considers this a sound and suitable basis for guidance to the NHS. The guidance will provide a well-tolerated and effective oral alternative to romiplostim for patients with cITP. *[References provided but not reproduced in this table.]*	Comment noted.
ITP Support Association	**Has all of the relevant evidence been taken into account?** No. NICE has not taken into account our comments to the first ACD regarding splenectomy and patient preference not to lose a healthy organ. Responses to splenectomy are highly variable in people with immune thrombocytopenia (ITP). Patients being asked to have a splenectomy can first	Comment noted. In its appraisals of health technologies, NICE is bound by the licensed indication of the intervention under consideration (see section 6.1.8 of the Guide to the Methods of Technology Appraisal). The Committee noted that the wording of the marketing authorisations for

Consultee	Comment	Response
	check that the spleen is involved in destroying their platelets by having an indium-labelled spleen scan. It is not sensible or acceptable to remove a healthy organ that defends the body against infection as a stepping stone to trying a new drug. This just increases the disease burden of the person involved and may lead to an early death.	eltrombopag and romiplostim stipulates that they should only be used if a person has had a splenectomy or has not had a splenectomy because such surgery is contraindicated. Therefore, the Committee could not change the wording of the recommendation in section 1. The Committee encouraged updating the wording in the romiplostim guidance to ensure clarity around the fact that the recommendations for eltrombopag and romiplostim are for exactly the same patient population. For further details, please see sections 2.1, 4.23 and 4.25 of the FAD.
	With regard to the ITP Registry (para 4.22) we are disappointed by your comment 'these data would be useful for future appraisals' instead of a much needed firm recommendation that all patients on these drugs should be monitored by a specialist haematologist and be enrolled on the ITP Registry for long term follow up.	Comment noted. Given the difficulties of conducting randomised controlled trials and in generalising their results, the Committee supported generating and analysing observational data including, but not limited to, the existing UK ITP Registry, which collects data on the long-term outcomes of patients treated with eltrombopag and romiplostim. For further details, please see section 4.24 of the FAD.
	Are the summaries of clinical and cost effectiveness reasonable interpretations of the data? Head-to-head clinical studies are desirable for all ITP treatments but large enough studies are difficult to achieve due to the small patient numbers available.	Comment noted. Please see response above.

Consultee	Comment	Response
	I participated in the appraisal meeting and am perplexed by your statement (para 4.11) 'The Committee agreed with the clinical specialists that the available evidence suggested that romiplostim was likely to be more effective than eltrombopag rather than equally effective'. I was not aware that the clinical experts stated or implied this at any time, and understood from them that the two drugs were equally effective.	Comment noted. The FAD has been amended to reflect more accurately the clinical specialists' view on the relative effectiveness of eltrombopag and romiplostim. For further details, please see section 4.11 of the FAD.
	Are the provisional recommendations sound and a suitable basis for guidance to the NHS The guidance for romiplostim and eltrombopag needs to be similar given that their marketing authorisations are identical (TA221 and TA205). The indication for romiplostim is as follows (romiplostim FAD TA221 February 2011): "Romiplostim has a marketing authorisation 'for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)'. The marketing authorisation also states that romiplostim 'may be considered as second line treatment for adult non-splenectomised patients where surgery is contra-indicated'." From this ACD (TA205 March 2013) for eltrombopag it is stated that: "Eltrombopag has a UK marketing authorisation for the treatment of adult chronic ITP in patients who have had a splenectomy and whose condition is refractory to other treatments (for example, corticosteroids or intravenous immunoglobulins), and as a second-line treatment for patients who have not had a splenectomy because surgery is contraindicated." It will be perverse and confusing if NICE guidance for eltrombopag insists on splenectomy where there is no evidence that the spleen is involved. The Association suggested before that the 'contraindications to splenectomy or surgery' were clarified and this has not been done in this draft guidance.	Comment noted. In its appraisals of health technologies, NICE is bound by the licensed indication of the intervention under consideration (see section 6.1.8 of the Guide to the Methods of Technology Appraisal). The Committee noted that the wording of the marketing authorisations for eltrombopag and romiplostim stipulates that they should only be used if a person has had a splenectomy or has not had a splenectomy because such surgery is contraindicated. Therefore, the Committee could not change the wording of the recommendation in section 1. The Committee encouraged updating the wording in the romiplostim guidance to ensure clarity around the fact that the recommendations for eltrombopag and romiplostim are for exactly the same patient population. For further details, please see sections 2.1, 4.23 and 4.25 of the FAD.

Consultee	Comment	Response
	As with romiplostim, eltrombopag should be prescribed and supervised by a haematologist to ensure its appropriate use. **Unlawful discrimination or groups who will be disadvantaged?** NICE, with this draft guidance, puts doctors in an indefensible position and lays the NHS wide open to a legal class action by patients that are forced into a surgical procedure that may not be relevant to, or in fact resolve, their ITP. Splenectomy failure may lead to early death in patients who already have a burden of disease from their ITP and other co-morbid conditions; this is indefensible medical management of people with ITP.	Comment noted. The Committee agreed that, because the summary of product characteristics stipulates that eltrombopag treatment should remain under the supervision of a physician who is experienced in the treatment of haematological diseases, it did not need to repeat this in its recommendations. For further details, please see sections 2.2 and 4.22 of the FAD. This comment does not highlight any unlawful discrimination or groups of patients with ITP that could be disadvantaged. The wording of the marketing authorisation for eltrombopag stipulates that eltrombopag should only be used if a person has had a splenectomy or has not had a splenectomy because such surgery is contraindicated. The regulatory agency has stated that the benefit-harm balance for eltrombopag could not be considered favourable for patients for whom a splenectomy remained a therapeutic option. NICE has to give recommendations in line with the marketing authorisation.
The Royal College of Pathologists and the British Committee for Standards in	Has all of the relevant evidence been taken into account? • Firstly, with respect to the removal of spleen as a treatment option for ITP, it needs to be stressed that this is not an effective treatment in older people, the cohort who are more likely	Comments noted. In its appraisals of health technologies, NICE is bound by the licensed indication of the intervention under consideration (see section 6.1.8 of

Consultee	Comment	Response
Haematology (endorsed by the Royal College of Physicians)	to be affected by ITP. • Secondly, coercion from physician should not be the reason for splenectomy but agreement after understanding in detail the several risks with this procedure including infection, thrombosis and pulmonary hypertension. It would be preferable to consider the clause that patients who may be offered indium labelled platelet survival scan to determine the need for splenectomy	the Guide to the Methods of Technology Appraisal). The Committee noted that the wording of the marketing authorisations for eltrombopag and romiplostim stipulates that they should only be used if a person has had a splenectomy or has not had a splenectomy because such surgery is contraindicated. Therefore, the Committee could not change the wording of the recommendation in section 1. For further details, please see sections 2.1 and 4.23 of the FAD.
	Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • Head to head comparisons of romiplostim and eltrombopag is unlikely.	Comment noted. Given the difficulties of conducting randomised controlled trials and in generalising their results, the Committee supported generating and analysing observational data including, but not limited to, the existing UK ITP Registry, which collects data on the long-term outcomes of patients treated with eltrombopag and romiplostim. For further details, please see section 4.24 of the FAD.
	• In clinical practice, especially in the patients who self-administer, wastage of romiplostim can	Comment noted.

Consultee	Comment	Response
	be a factor since the dosage is weight-based and vials come in 0.5 ml sizes. In this respect, eltrombopag is actually an advantage since there are only two dosages • Romiplostim has been suggested to be more effective – this is not true. Both these agents are equally effective	Comment noted. Given the results of the indirect comparisons, and the earlier romiplostim trials, which may have enrolled more patients with severe chronic ITP than the eltrombopag trials, the Committee was satisfied that the available evidence suggested that romiplostim was likely to be more effective than eltrombopag. For further details, please see sections 4.10 and 4.11 of the FAD.
	Are the provisional recommendations sound and a suitable basis for guidance to the NHS? • Eltrombopag should be prescribed and supervised by a haematologist to ensure its appropriate use.	Comment noted. The Committee agreed that, because the summary of product characteristics stipulates that eltrombopag treatment should remain under the supervision of a physician who is experienced in the treatment of haematological diseases, it did not need to repeat this in its recommendations. For further details, please see sections 2.2 and 4.22 of the FAD.
	• Some guidance on monitoring for visual problems from Eltrombopag should be included	Comment noted. Guidance on monitoring for visual problems is outside the remit of a NICE Technology Appraisal.
	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	Comment noted.

Consultee	Comment	Response
	• None	

Comments received from commentators

Commentator	Comment	Response
Amgen	**Summary (further details have been provided but not reproduced in this table)** 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	Comment noted. The Committee heard that mathematical algorithms exist to map from SF-36 (used in RAISE and EXTEND) on to EQ-5D, and that because no single algorithm is considered more valid than others, the EQ-5D data obtained from using a particular algorithm would be associated with further uncertainty. It also heard from the ERG that the Szende et al. study used by the manufacturer in its base-case analysis did not report EQ-5D utility values. The Committee was aware that the reference case outlined in 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. However, in the absence of EQ-5D data, the Committee

Commentator	Comment	Response
	Methods of Technology Appraisal'.	concluded that, of the utility data available, the SF-6D data provided by the manufacturer were the most appropriate to use within the alternative evaluation. For further details, please see section 4.16 of the FAD.
	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.	Comment noted. The Committee considered the manufacturer's cost-effectiveness analyses, and the ERG's critique of the analyses. The Committee agreed that, of the 3 economic evaluations, the alternative evaluation represented the most valid analysis because the modelling applied data derived directly from the pivotal trials of eltrombopag and the manufacturer's own systematic review. The Committee also noted comments received during consultation on the appraisal consultation documents regarding some of the parameters used in the model, and considered the analyses that mirrored its favoured assumptions and parameters. For further details, please see sections 4.13, 4.19 and 4.21 of the FAD.
	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	Comment noted. The Committee heard from the ERG that the SF-6D utility data for bleeding events were aligned with the definition of bleeds in RAISE, but not with the definition in the Kuter et al. trials. The Committee noted that there was no information available on bleeding and rescue rates in clinical practice, but it heard from the ERG that including the higher rates from Kuter et al. would not lower the cost effectiveness of eltrombopag compared with romiplostim below £30,000 saved per QALY lost. The Committee accepted that the ICER for

Commentator	Comment	Response
	Kuter trials to be presented, so that the wide range of resultant reversed ICERs for eltrombopag versus romiplostim are clearly presented.	eltrombopag compared with romiplostim would be lower in favour of romiplostim if the rates of bleeding and rescue therapy in clinical practice were higher than those applied in the cost-effectiveness analysis, but it would be extremely unlikely to affect the relative cost effectiveness of eltrombopag and romiplostim to a degree where the Committee would change its recommendations. For further details, please see FAD section 4.20 of the FAD.
	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.	Comment noted. The Committee heard from the ERG that the proposed dosing for eltrombopag would only minimally affect the relative cost effectiveness of the 2 treatments. The Committee was aware that patient experts indicated that some patients take a tablet of eltrombopag only once every 3 days rather than daily, which implies that the dose of eltrombopag in clinical practice might in fact be lower than that observed in the RAISE trial. The Committee concluded that that the dose of eltrombopag used in the model was appropriate. For further details see section 4.4 and 4.17 of the FAD.
	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	Comment noted. The Committee noted the ERG's concern about the dosing of romiplostim in the analyses, and it concluded that it was appropriate to use a median dose of romiplostim that is 40–60% lower than that used in the Kuter et al. trials. The Committee accepted that there was a degree of

Commentator	Comment	Response
	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.	uncertainty surrounding the ICER for eltrombopag compared with romiplostim, but it was satisfied that eltrombopag can be considered a cost-effective use of NHS resources. For further details see sections 3.46, 4.17 and 4.21 of the FAD.
	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[i] highlights that NICE has a responsibility to make clear decisions to commissioners.	Comment noted. The Committee considered the analysis that mirrored its favoured assumptions and parameters, and noted that the resulting ICERs for eltrombopag compared with romiplostim were £389,000 saved per QALY lost for patients who had had a splenectomy and £271,000 saved per QALY lost for patients who had not had a splenectomy. The Committee acknowledged that these ICERs are associated with considerable uncertainty. However, it was satisfied that, based on the evidence it had seen and the comments received during consultation on 2 appraisal consultation documents, eltrombopag can be considered a cost-effective use of NHS resources.
	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.	Comment noted. Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in NICE appraisals within 3 months of its date of publication.
	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.	

Commentator	Comment	Response
	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 a**n**y 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*	Comment noted. Views expressed by clinical specialists at the Committee meeting can inform the debate in a variety of ways. During the open part of the meeting, clinical specialists are encouraged to interact fully in the debate with the Committee, including responding to and posing questions. See sections 4.5.2 and 4.5.3 NICE's Guide to the Methods of Technology Appraisal (2008).

Summary of comments received from members of the public

Theme	Response
The limitation to patients who have undergone splenectomy, and the different recommendations for eltrombopag and romiplostim	In its appraisals of health technologies, NICE is bound by the licensed indication of the intervention under consideration (see section 6.1.8 of the Guide to the Methods of Technology Appraisal). The Committee noted that the wording of the marketing authorisations for eltrombopag and romiplostim stipulates that they should only be used if a person has had a splenectomy or has not had a splenectomy because such surgery is contraindicated. The Committee understood that this was because, as stated in the European public assessment report, the benefit-risk balance could not be considered favourable for patients for whom a splenectomy remained a therapeutic option. Therefore, the Committee could not change the wording of the recommendation in section 1. The Committee encouraged updating the wording in the romiplostim guidance to ensure clarity around the fact that the recommendations for eltrombopag and romiplostim are for exactly the same patient population. For further details, please see sections 2.1, 4.23 and 4.25 of the FAD.
The response to splenectomy being lower than quoted	The Committee heard from clinical specialists that approximately two-thirds of patients can expect remission after splenectomy. For further details, please see section 4.3 of the FAD.
Misinterpretation of clinical specialists' view on the relative effectiveness of eltrombopag and romiplostim	The FAD has been amended to reflect more accurately the clinical specialists' view. For further details, please see section 4.11 of the FAD.

Theme	Response
The equal effectiveness of eltrombopag and romiplostim	The Committee agreed that the results of the manufacturer's and the ERG's indirect comparisons were associated with uncertainty. It was also aware that the use of eltrombopag and romiplostim in clinical practice is broadly interchangeable. However, given the results of the indirect comparisons, and the earlier romiplostim trials, which may have enrolled more patients with severe chronic ITP than the eltrombopag trials, the Committee was satisfied that the available evidence suggested that romiplostim was likely to be more effective than eltrombopag. For further details, please see sections 4.10 and 4.11 of the FAD.
Haematologist supervision of treatment with eltrombopag	The Committee agreed that, because the summary of product characteristics stipulates that eltrombopag treatment should remain under the supervision of a physician who is experienced in the treatment of haematological diseases, it did not need to repeat this in its recommendations. For further details, please see sections 2.2 and 4.22 of the FAD.
The ITP registry	Given the difficulties of conducting randomised controlled trials and in generalising their results, the Committee supported generating and analysing observational data including, but not limited to, the existing UK ITP Registry, which collects data on the long-term outcomes of patients treated with eltrombopag and romiplostim. For further details, please see section 4.24 of the FAD.

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