NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Premeeting briefing

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

This premeeting briefing is a summary of:

- the evidence and views submitted by the manufacturer, the consultees and their nominated clinical specialists and patient experts and
- the Evidence Review Group (ERG) report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal. Please note that this document is a summary of the information available before the manufacturer has checked the ERG report for factual inaccuracies.

Key issues for consideration

Clinical effectiveness

- How robust is the relative effectiveness of eltrombopag compared with romiplostim as reported in the manufacturer's indirect analysis given:
  - RAISE and the 2 romiplostim randomised controlled trials (RCTs) had different baseline patient characteristics in terms of immune (idiopathic) thrombocytopenic purpura (ITP) duration, previous ITP medication use and the proportion of patients receiving concomitant medication. Is it appropriate to pool data from these studies to indirectly compare eltrombopag with romiplostim?
  - The manufacturer's indirect comparison assumes that sustained response in RAISE is equivalent to durable response in the romiplostim trials, and that sustained response plus transient response in RAISE is equivalent to overall response in the romiplostim trials. Is it clinically plausible to make these assumptions given how the responses were defined in the trials?

  - RAISE collected both WHO bleeding data and bleeding adverse events using the Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) scale. Kuter et al. (2008) only collected bleeding information through adverse event reporting using an unnamed scale, which was assumed to be equivalent to the CTCAE scale. Does using different scales for collating data on bleeding events in RAISE and Kuter et al. have a significant impact on the indirect comparison of eltrombopag and romiplostim?
  - The manufacturer had first combined the results of the 2 romiplostim studies and then performed an indirect comparison (using the Bucher method) of eltrombopag with romiplostim. The results of the analysis did not show statistically significant differences between eltrombopag and romiplostim. The ERG did a Bayesian meta-analysis for the indirect comparison of eltrombopag with romiplostim, in which the ERG treated the 2 romiplostim trials as separate studies. For the durable platelet response, the Bayesian approach gave similar results to those of the manufacturer using the Bucher method. However, for overall platelet response, when assuming moderate heterogeneity, the Bayesian approach gave results in favour of romiplostim. In addition, the manufacturer had presented the indirect comparison split by splenectomy status. The ERG indicated that these analyses do not preserve the randomisation within RAISE and are therefore essentially observational analyses.
- For the analysis comparing eltrombopag with non- thrombopoietin receptor agonists (non-TPO-RAs), the manufacturer had implemented additional exclusion criteria post hoc that had excluded most of the RCTs. The ERG had concerns over the methodological rigor of the indirect comparison. The ERG explained that using post-hoc exclusion criteria and pooling response estimates using a simple weighted average of treatment arms regardless of the definition of response may bias the results. How robust is the clinical effectiveness data for non-TPO-RAs?

Cost effectiveness

- The manufacturer presents cost-effectiveness results for a base case and an 'alternative' base case. The base case incorporates assumptions from the appraisal of romiplostim (technology appraisal 221) to relate short-term trial data to lifetime costs and outcomes, and the 'alternative' base case incorporates alternative data from the eltrombopag trials to inform assumptions relating to lifetime costs and outcomes. Which of the 2 data sets is most reasonable for the manufacturer to use?
- Given the uncertainty around the point estimates produced by the indirect comparison and the potential biases associated with the methodology, the manufacturer considered that assuming complete clinical equivalence between eltrombopag and romiplostim is appropriate. The treatment effectiveness of both interventions was modelled based on this assumption. Is this assumption reasonable in routine clinical practice?
- Within the modelling, the definition of response was based on the RAISE study (the odds of achieving a platelet count greater than or equal to $50x10^9$ per litre and less than or equal to $400x10^9$ per litre during the on-therapy period). However, other definitions of response have been used elsewhere (for example, outcomes relating to response duration). Which definition of response is most reasonable to apply within the modelling?
- The base-case modelling assumed that TPO-RAs come after rituximab but before other non-TPO-RAs in the treatment pathway. Although eltrombopag was placed after rituximab in sensitivity analyses, the optimal positioning of TPO-RAs within the treatment sequence has not been addressed. Should the modelling consider the optimal positioning of TPO-RAs in the treatment sequence? If TPO-RAs are not clinically equivalent, should the modelling consider the optimal positioning of eltrombopag and romiplostim?
- The manufacturer had assumed that response (reaching a platelet response at least once during RAISE) and being in continuous platelet response while on treatment are the same, and so applied event rates

derived from platelet response data to responders for the modelling. The ERG noted that, in RAISE, only 60–80% of eltrombopag responder's have a platelet count greater than $50x10^9$ per litre. Therefore, the manufacturer's assumption would underestimate the number of bleeds and lead to a lower ICER for TPO-RAs. What does the Committee think about the assumption used by the manufacturer?

- The ERG indicated that extrapolating TPO responders' time on treatment has a long tail, which flattens out considerably during the extrapolation period. Is the extrapolated duration of TPO response reasonable?
- Azathioprine responders' time on treatment in the base case is considerably shorter than that suggested by the manufacturer's own literature review (for people who have undergone splenectomy, the time on treatment was 618 and 2770 days in the base case and the manufacturer's literature review respectively). What is the most reasonable estimate for the duration of response with azathioprine?
- The doses for the TPO-RAs are drawn from the relevant trial averages across responders and non-responders. The ERG indicated that, in Kuter et al., the average TPO-RA dose among responders was up to 40–60% lower than that used across the trial as a whole. If a similar argument holds for eltrombopag, both the cost effectiveness of the TPO-RA compared with the non-TPO-RA and the cost effectiveness of eltrombopag compared with romiplostim could change considerably. Is there differential dosing between eltrombopag responders and non-responders? If so, what is the likely magnitude of this difference?
- The eltrombopag trials contained a high proportion of patients of Asian origin (17–18%). The summary of product characteristics notes a lower starting dose for those of Asian origin. Is the average dosing of RAISE and EXTEND representative of the probable UK average?
- The main source of utility data used in the base case and alternative evaluation was obtained from Szende et al. (2008) rather than from SF-36 data collected from RAISE and EXTEND. When the ERG carried out a

sensitivity analysis to explore the impact of applying the SF-6D utility values the ICER for eltrombopag compared with non-TPO-RAs increased to £85,026 per QALY gained for patients who have undergone splenectomy and £140,995 per QALY gained for patients who have not undergone splenectomy. Also, SF-6D analysis may itself overstate the benefit of the modelled additional survival from the TPO-RA. What is the Committee's view on using the utility data from the eltrombopag trials?

- Both the rates of rescue and the rates of severe bleeds applied within the modelling appear quite high to ERG expert opinion. Noting that these variables are key in the analysis, what rescue and severe bleed rates would the Committee deem appropriate?
- The modelling assumes that the severe bleed rate doubles for patients who are refractory to all prior treatments. Because of this, the fatal bleed rate is assumed to double. Dropping this assumption has a large impact on the net QALY gain compared with the non-TPO-RA sequence (ERG exploratory analysis). Is the doubling assumption justifiable to the Committee?

1 Background: clinical need and practice

1.1 ITP is an autoimmune disease of variable natural history characterised by reduced platelet production and, in some people, increased platelet destruction. Most adults with newly diagnosed ITP will eventually develop chronic ITP (cITP). In a blood test, a normal platelet count is between $150x10^9$ and $400x10^9$ per litre. Low platelet counts (below $30x10^9$ per litre) can result in bleeding, which varies from World Health Organization (WHO) grade 1 (petechiae), through grade 2 (mild blood loss) and grade 3 (gross blood loss), to grade 4 (debilitating blood loss). In the UK, approximately 3000 to 4000 people have ITP at any one time, and it mainly affects women of childbearing age. NICE has previously

estimated that people with severe cITP who are at high risk of bleeding, or whose disease is refractory to standard treatment, represent approximately 1–4% of the total ITP population.

1.2 cITP is not progressive, but it is associated with reduced quality of life and increased risk of mortality due to the higher bleed events. Morbidities associated with cITP are non-fatal bleeding, which may require hospitalisation (especially if the bleeds are gastrointestinal or intracranial); increased risk of infection; rash (purpura or petechiae caused by bleeding under the skin); severe mucosal haemorrhage; and bleeding after surgery or trauma. ITP may cause life-threatening bleeding if the platelet count falls below $30x10^9$ per litre.

1.3 The treatment of ITP aims to prevent major bleed events by raising platelet count to a safe level while minimising the risk of treatment-related adverse effects. Treatment is usually initiated with corticosteroids or intravenous immunoglobulin when the platelet count falls below $30x10^9$ per litre. For people with recurrent or persistent thrombocytopenia associated with bleeding after a first-line treatment course, there is limited evidence to guide a sequence of treatments and so clinical practice varies widely. Splenectomy (spleen removal) is considered as a second-line surgical option for people who are fit for surgery. ITP may not adequately respond to splenectomy, in which case third-line medical options may be offered. Eltrombopag and romiplostim are both TPO-RAs that are licensed for the third-line treatment of people with cITP (and second-line treatment for people in whom surgery is contraindicated). UK clinical guidelines, however, suggest that rituximab, a monoclonal antibody, is likely to be used before TPO-RAs. Other non-TPO-RA treatments that have been investigated in

refractory ITP include azathioprine, cyclophosphamide, vincristine, ciclosporin, and danazol.

1.4 In a previous NICE technology appraisal (TA 205) eltrombopag was not recommended for treating cITP. Technology appraisal 221 recommended romiplostim for treating adults with cITP whose condition is refractory to standard active treatment and rescue therapies, or who have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies.

2 The technology

2.1 Eltrombopag (Revolade, GlaxoSmithKline) increases platelet production by activating the thrombopoietin receptor so stimulating platelet production and reducing bleeding. Eltrombopag has a UK marketing authorisation for the treatment of adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) in splenectomised patients whose condition is refractory to other treatments (such as corticosteroids and intravenous immunoglobulin) and as a second-line treatment for adult non-splenectomised patients where surgery is contraindicated. Eltrombopag is taken orally. The summary of product characteristics states that the recommended initial dosage is 50 milligrams once daily. If, after 2–3 weeks of initial therapy, platelet counts are below the clinically targeted level ($50x10^9$ per litre), the dosage may be increased to a maximum of 75 milligrams once daily. Treatment should be stopped if the platelet count does not increase sufficiently to avoid clinically important bleeding after 4 weeks of therapy at a dosage of 75 milligrams once daily. For full details of dosage and administration, see the summary of product characteristics.

2.2 The summary of product characteristics lists the following adverse reactions for eltrombopag as common or very common: psychiatric disorders (insomnia), nervous system disorders (headache, paraesthesia), eye disorders (cataract, dry eye), gastrointestinal disorders (nausea, diarrhoea, constipation, upper abdominal pain), hepatobiliary disorders (increased alanine aminotransferase, increased aspartate aminotransferase, increased blood bilirubin, hyperbilirubinaemia, abnormal hepatic function), skin and subcutaneous tissue disorders (rash, pruritus, alopecia), and general disorders and administrative site conditions (fatigue, peripheral oedema). For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The British National Formulary (BNF, edition 63) states that the net price of a 28-tablet pack of 25 milligram eltrombopag is £770 (25 milligram dose costs £27.50). The net price of a 28-tablet pack of 50 milligram eltrombopag is £1540 (50 milligram dose costs £55). The cost per patient will vary with dose adjustment and treatment duration. The manufacturer indicated that the mean dose of eltrombopag is approximately 51.3 milligrams per day, corresponding to a daily cost of £56.43. The manufacturer of the technology has agreed a patient access scheme with the Department of Health, which offers a [redacted] discount on the list price of eltrombopag. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Remit and decision problem(s)

3.1 The remit from the Department of Health for this appraisal was to appraise the clinical and cost effectiveness of eltrombopag within

its licensed indication for the treatment of refractory chronic idiopathic (immune) thrombocytopenic purpura.

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	Adults with immune (idiopathic) thrombocytopenic purpura, who: • have had a splenectomy and are refractory to other treatments (e.g. corticosteroids, immunoglobulins) • have not had a splenectomy and for whom surgery is contraindicated, as second-line treatment.	
Intervention	Eltrombopag	
Comparators	• corticosteroids • intravenous normal immunoglobulin • immunosuppressive agents including rituximab • romiplostim	The cost-effectiveness model will compare a pathway of care incorporating eltrombopag to: • a pathway of care without the use of thrombopoietin receptor agonist (TPO-RAs) (non-TPO-RA pathway) • a pathway of care incorporating romiplostim. The non-TPO-RA pathway of care comprises a sequence of rituximab, azathioprine, mycophenolate mofetil, ciclosporin, dapsone, danazol, cyclophosphamide, vincristine and vinblastine. The positioning of TPO-RAs within this pathway in either a second- or third-line setting as per the guidelines and licence will be explored. Patients may also receive rescue treatment consisting of intravenous immunoglobulin, intravenous corticosteroids or platelet transfusion.

Outcomes	The outcome measures to be considered include: • platelet count • response rate • response duration • need for rescue treatments • use of concurrent treatments • symptom reduction (minor and/or severe) • mortality • adverse effects of treatment • health-related quality of life.	The outcome measures considered will be: • platelet count • response rate • response duration • time to response • need for rescue treatments • use of concurrent treatments • reduction in bleeding symptoms • mortality • adverse effects of treatment • health-related quality of life.
Economic evaluation	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The time horizon for the economic evaluation will be based on the appropriate time period over which costs and benefits can reasonably be expected to be experienced given the chronic nature of the condition. The analyses should consider the comparison of treatment sequences with and without eltrombopag, and the frequency of rescue therapies. The analyses must specify if eltrombopag is an addition to, or a replacement of an existing element in the treatment pathway. Costs will be considered from an NHS and Personal Social Services perspective.	The modelled health benefits will be expressed in terms of life years (LYs) gained and quality-adjusted life years (QALYs) gained and the cost effectiveness in terms of incremental cost per LY and cost per QALY gained. A lifetime time horizon will be used in the cost-effectiveness model. A treatment sequence including eltrombopag will be compared with treatment sequences without eltrombopag. The impact of different treatment sequences, the positioning of eltrombopag in the sequence and the frequency of rescue will be explored through sensitivity analysis. The model will take an NHS perspective and 2011 will be used as the costing year.
Subgroups to be considered	Consideration will be given to subgroups of patients who have: • had a splenectomy • not had a splenectomy when surgery is contraindicated. If the evidence allows, other subgroups may be identified for whom the technology may be particularly clinically and cost effective.	Results will be presented separately for patients who have or have not undergone splenectomy

3.2 Eltrombopag has a UK marketing authorisation as a second-line treatment of cITP in adults who have not had a splenectomy when surgery is contraindicated. The ERG noted that it is uncertain whether all people who had not had a splenectomy in eltrombopag's pivotal trial were contraindicated to surgery.

3.3 The ERG stated that it was unclear why the manufacturer considered treatment sequences excluding romiplostim, given that romiplostim has been approved by NICE and has the same licensed indication as eltrombopag. The ERG also indicated that there is evidence suggesting that a weekly flat dose of 100 milligram rituximab for 4 weeks is effective (compared with the standard weekly 375 milligrams per meter^2 for 4 weeks), but that this was not discussed by the manufacturer. Patients with cITP may experience a significant bleed for which short-term rescue therapy would be initiated. The manufacturer described the use of intravenous corticosteroids, immunoglobulins or platelet transfusions for this purpose, but the ERG indicated that the use of oral corticosteroids for rescue therapy or the consequences of increasing the dose of any current treatment as a rescue strategy were not considered by the manufacturer.

3.4 It is anticipated that eltrombopag would be used in the same way as romiplostim in the treatment pathway for cITP.

4 Clinical-effectiveness evidence

4.1 The manufacturer presented direct clinical-effectiveness evidence from 3 RCTs comparing eltrombopag plus standard care with placebo plus standard care (TRA 100773A, TRA 100773B and TRA 102537 RAISE), and did a meta-analysis of these trials. The manufacturer also presented 2 indirect comparisons; 1 between

eltrombopag and romiplostim, and the other between eltrombopag and non-TRO-RAs.

Direct Evidence

4.2 The manufacturer undertook a systematic review and identified 4 relevant RCTs (TRA 100773A, TRA 100773B, RAISE and Tomiyama et al. 2009). Tomiyama et al. reported results for a Japanese population, so was excluded by the manufacturer from the analysis. TRA 100773A, TRA 100773B and RAISE recruited patients who had had ITP for 6 months or more and who had received 1 or more prior ITP treatments. All participants had a platelet count less than $30x10^9$ per litre at baseline. In all 3 studies, randomisation was stratified by splenectomy status, use of ITP medication at randomisation and baseline platelet count (less than or equal to $15x10^9$ per litre, or greater than $15x10^9$ per litre).

4.3 TRA 100773A was a phase II multicentre RCT (including 13 UK centres) that established the optimal dose of eltrombopag for treating cITP. In TRA 100773A, patients were randomised to a 30 milligram, 50 milligram or 70 milligram dose of eltrombopag (n=82), or to placebo (n=27). The study duration was 6 weeks. TRA 100773B was a phase III multicentre RCT (including 13 UK centres) that investigated the safety and efficacy of the optimal dose of eltrombopag (50 milligrams) in adults with cITP. Participants were randomised to receive standard care and either eltrombopag (n=74) or placebo (n=38). The study duration was 6 weeks and participants were followed up at 1, 2, 4 and 6 weeks after stopping study medication.

4.4 RAISE was a phase III multicentre RCT (including 9 UK centres) that compared eltrombopag (n=135) with placebo (n=62) in adults with cITP. Patients in the treatment arm initially received a

50 milligram dose of eltrombopag once daily that was increased as appropriate to maintain a target platelet count of 50 to 400x10^9 per litre. The study duration was 6 months.

4.5 The long-term safety and efficacy of eltombopag was established through an open-label, single arm, extension study (EXTEND). The population in EXTEND was patients previously enrolled in TRA 100773A, TRA 100773B or RAISE who had completed treatment and follow-up periods. The study followed patients receiving eltrombopag for up to 4.5 years.

4.6 The primary outcome in both TRA 100773A and TRA 100773B was the proportion of patients with platelet counts greater than or equal to 50x10^9 per litre at the end of the study. In RAISE, the primary outcome was the odds of attaining a platelet count greater than or equal to 50x10^9 per litre and less than or equal to 400x10^9 per litre during the 6-month study period. Platelet counts between 50 and 400x10^9 per litre were not considered responses if the patient had been receiving rescue therapy, and until platelet counts had fallen below 50x10^9 per litre after stopping rescue therapy.

4.7 The secondary outcomes in RAISE were: the proportion of patients receiving a rescue treatment during the study period; the proportion of patients with at least 75% of their assessments greater than or equal to 50x10^9 per litre and less than or equal to 400x10^9 per litre; maximum continuous and cumulative duration of response (as per the primary outcome definition); the proportion of patients achieving a platelet count greater than or equal to 50x10^9 and less than or equal to 400x10^9 per litre during weeks 2–6 of the study period; the proportion of patients with a reduction in use of concomitant ITP medications from baseline; the incidence and severity of symptoms associated with ITP; health-related quality of life (HRQoL)

assessments; and safety and tolerability (including adverse events, serious adverse events, treatment-related adverse effects and adverse events leading to withdrawal).

4.8 A summary of the 3 eltrombopag trials is provided in table 1.

Table 1 Summary of the relevant eltrombopag RCTs

	TRA 100773A	TRA 100773B	RAISE
Intervention(s), comparator and doses	Eltrombopag 30 mg (n=29) Eltrombopag 50 mg (n=27) Eltrombopag 75 mg (n=26) Placebo (n=27) Patients who reached a platelet count >200x10^9/L stopped treatment but remained in the study.	Eltrombopag 50 mg as starting dose (n=74) Placebo (n=38) Dose increase to 75 mg allowed after 3 weeks if platelet count remained <50x10^9/L; Patients who reached a platelet count >200x10^9/L stopped treatment but remained in the study.	Eltrombopag 50 mg as starting dose (n=135) Placebo (n=62) Dose was adjusted based on individual platelet count: dose increase up to a maximum of 75 mg allowed after 22 days if platelet count remained <50x10^9/L; dose decrease to a minimum of 25 mg allowed if platelet count was >200x10^9/L; if platelet count was >400x10^9/L dose was interrupted and resumed at the next lowest dose once platelet count fell <150x10^9/L. Reduction in concomitant therapy allowed after 6 weeks if platelet count remained >100x10^9/L for 2 consecutive weeks.

Randomisation	Patients randomised in a 1:1:1:1 ratio to receive 30, 50 or 75 mg eltrombopag once daily, or placebo.	Patients randomised in a 2:1 ratio to receive standard care and either eltrombopag 50 mg or placebo.	Patients randomised in a 2:1 ratio to receive eltrombopag or placebo.
Primary outcomes	The proportion of 'responders', defined as people who had an increase in platelet count to ≥50x10^9/L on Day 43 of the study (patients withdrawn early due to platelet count exceeding 200x10^9/L were still considered responders).		The odds of attaining a platelet count ≥50x10^9/L and ≤400x10^9/L during the 6-month treatment period.
Study duration	6 weeks	6 weeks	6 months
Length of follow-up	Every 2 weeks for up to 6 weeks after stopping the study drug.	At 1, 2, 4 and 6 weeks after stopping the study drug.	At 1, 2 and 4 weeks after stopping the study drug then at 3 and 6 months.

4.9 In TRA 100773A, the proportion of responders (people whose platelet counts were greater than or equal to 50x10^9 per litre at the end of the study) in the eltrombopag arms was 28%, 70% and 81% for patients receiving 30, 50 and 75 milligrams eltrombopag respectively. People randomised to the control arm attained a response rate of 11%. The corresponding odds ratios relative to placebo were 3.1 (95% CI 0.7 to 13.8), 22.0 (95% CI 4.7 to 102.2) and 38.8 (95% CI 7.6 to 197.7) for the 30, 50 and 75 milligrams eltrombopag groups respectively. The manufacturer did not present response rates by splenectomy status.

4.10 The analysis of TRA 100773B on day 43 of dosing demonstrated a higher response rate among patients randomised to eltrombopag compared with those randomised to placebo: a total of 59% of the patients receiving eltrombopag had a platelet count greater than or equal to 50x10^9 per litre compared with 16% for patients receiving placebo. The odds ratio for active relative to placebo treatment was 9.61 (95% CI 3.31 to 27.86) and it was statistically significant at the

0.1% level. The manufacturer presented response rates separately by splenectomy status. Among patients who had had a splenectomy, 62% of the participants in the eltrombopag group had platelet counts greater than or equal to $50x10^9$ per litre compared with 15% in the placebo group. The results for patients who had not had a splenectomy were similar (57% and 17% for eltrombopag and placebo respectively).

4.11 In RAISE, the odds of responding during the 6-month study period were higher among patients receiving eltrombopag compared with those receiving placebo; the odds ratio was 8.2 (99% CI 3.59 to 18.73) and it was statistically significant at the 0.1% level. The proportion of patients whose disease responded to treatment was maintained throughout the study period in both arms. At the end of the study, 52% of patients receiving eltrombopag and 17% of patients receiving placebo had platelet counts between 50 and $400x10^9$ per litre. One week later, the proportion was 42% for eltrombopag and 15% for placebo but these proportions converged thereafter. The manufacturer indicated that the response to eltrombopag was irrespective of the splenectomy status (p-value for interaction was 0.89).

4.12 A post-hoc analysis of platelet response in RAISE was carried out to determine 'sustained', 'transient' and 'overall' platelet responses. Analyses were performed on the intention-to-treat population and in the subset of patients treated with study medication for 6 months or more. In both analyses, sustained response was defined as having a platelet count greater than or equal to $50x10^9$ per litre and less than or equal to $400x10^9$ per litre for at least 6 of the last 8 weeks of treatment. Transient response was defined as having a platelet response for 4 or more consecutive weeks during the treatment period and included all data up to the time of withdrawal. Overall

response refers to having either a sustained or a transient response, as defined above. The proportion of patients who attained a platelet response was higher for eltrombopag relative to placebo in both populations regardless of splenectomy status. The highest proportions of sustained and overall platelet responses were observed in the group of people who have not undergone splenectomy who received eltrombopag, with overall response reaching 72% in the intention-to-treat population (compared with 15% for placebo) and 88% in patients treated for 6 months or more (compared with 19% for placebo).

4.13 The manufacturer reported results for several secondary outcomes for RAISE. These are summarised in the table 2.

Table 2 Summary of the secondary outcome results from RAISE

	Eltrombopag		Placebo
Median platelet count throughout the study period	60–80x10^9 per litre		<30x10^9 per litre
Median duration of response in weeks (range)	Continuous: 8.1 (0–26) Cumulative: 10.9 (0–26)		Continuous and cumulative: 0 (0–25)
Proportion who required rescue medication* at any point during the study	18% (OR[a]=0.33[†]; 95% CI 0.16 to 0.64)		40%
Proportion who reduced or stopped ≥1 baseline concurrent ITP[b] medication	59% (OR=3.10[‡])		32%
Incidence and severity of bleeding		**WHO grades 1-4**	**WHO grades 2-4**
	Throughout the 6 months; OR (95% CI)	0.24 (0.16 to 0.38)	0.35[†] (0.19 to 0.64)
	At the end of the study; OR (95% CI)	0.25[†] (0.12 to 0.51)	0.63 (0.23 to 1.72)
	Any time during 6 months treatment; OR (95% CI)	0.21[‡] (0.06 to 0.71)	0.30[§] (0.14 to 0.66)

[a] OR, odds ratio; [b] ITP, immune (idiopathic) thrombocytopenic purpura

* defined as a composite outcome of new ITP medication, increased dose of a concomitant ITP medication, platelet transfusion, and/or splenectomy

[†] statistically significant at the 0.1% level

[‡] statistically significant at the 5% level

[§] statistically significant at the 1% level

4.14 Adverse effects of treatment reported in TRA 100773A, TRA 100773B and RAISE were graded according to CTCAE,

version 3 into ‘adverse events’, ‘serious adverse events’, ‘adverse events related to study medication’ and ‘adverse events leading to withdrawal’. The manufacturer listed adverse events reported in more than 5% of study participants. Adverse events reported during the studies were largely similar in the eltrombopag and placebo arms in all 3 trials; the largest difference was seen in TRA 100773B with 59% of patients receiving eltrombopag and 37% of patients receiving placebo experiencing an adverse event. Serious adverse events were also similar in treatment and control arms and did not exceed 10% except in RAISE (18% and 11% for eltrombopag and placebo respectively). The proportions of adverse events considered by the investigators to be treatment-related were higher for eltrombopag in the 75 milligram group of TRA 100773A (36%), TRA 100773B (26%) and RAISE (36%) compared with placebo (31%, 11% and 30% in the 75 milligram group of TRA 100773A, TRA 100773B and RAISE respectively). In all 3 trials, the most common adverse event was headache, with a similar proportion of reports in the placebo and eltrombopag groups. Other frequent adverse events were fatigue, diarrhoea, nausea, nasopharyngitis, upper respiratory tract infect and pain in the extremity. In RAISE bleeding adverse events were significantly lower in patients treated with eltrombopag.

4.15 The SF-36 instrument was used in all 3 eltrombopag RCTs to assess HRQoL. The manufacturer did not report HRQoL information in detail but the ERG did provide a summary of the information. In TRA 100773A, HRQoL was found to be similar at baseline and the end of study. The only statistically significant change from baseline was a decrease in the role-emotional score in the 75 milligram eltrombopag group (statistically significant at the 5% level). In TRA 100773B, the SF-36 sub-domain scores were

similar at baseline and the end of study. The RAISE trial assessed HRQoL at baseline, 6, 14 and 26 weeks. The manufacturer reported that participants in the eltrombopag group had greater improvements from baseline to week 26 across most health and well-being domains of the SF-36 instrument compared with those in the placebo group. There were statistically significant differences between groups in the change from baseline for role-physical functioning (5.4; 95% CI 0.5 to 10.3), vitality (3.9; 95% CI 0.1 to 7.7), role-emotional functioning (5.4; 95% CI 0.8 to 10.1) and the mental health component summary (2.1; 95% CI 0.2 to 4.0).

4.16 The manufacturer did a meta-analysis of TRA 100773A, TRA 100773B and RAISE. Results were reported as odds ratios for responding to treatment (attaining a platelet count greater than or equal to $50x10^9$ per litre) 6 weeks after beginning the study. Results were not reported separately by splenectomy status. Eltrombopag was found to be associated with higher odds of responding to treatment compared with placebo. The odds ratio from a fixed effects model was 8.23 (95% CI 4.68 to 14.48) and that from a random effects model was 8.16 (95% CI 4.63 to 14.37). Statistical heterogeneity was low according to the I^2 reported. This indicates that the proportion of variability in effect estimates due to heterogeneity rather than chance is low.

Indirect comparison: eltrombopag with romiplostim

4.17 No head-to-head trials comparing eltrombopag with romiplostim were available. The manufacturer undertook a systematic review and identified 2 RCTs of romiplostim (both reported in Kuter et al. 2008) for the indirect comparison. Both RCTs evaluated the safety and efficacy of romiplostim in people with cITP. One of the 2 RCTs recruited 63 patients who had had a splenectomy, and the other

recruited 62 patients who had not. In both studies people were enrolled if the mean of 3 platelet counts was less than or equal to $30x10^9$ per litre, with none above $35x10^9$ per litre. All participants were refractory to at least 1 previous treatment. Patients were randomised to either romiplostim plus standard care or standard care alone for 6 months. The primary outcome in both studies was the proportion of patients with durable platelet response, that is, a platelet count greater than or equal to $50x10^9$ per litre in 6 or more weekly assessments in the last 8 weeks of treatment without use of rescue medication. As the 2 romiplostim RCTs were presented within the same published article, the manufacturer combined the results of the 2 studies using standard meta-analysis techniques (Mantel-Haenszel techniques) and then treated them as a single trial. The indirect comparison was performed using the Bucher method.

4.18 The manufacturer performed the indirect comparison between eltrombopag and romiplostim using data from RAISE and the 2 romiplostim RCTs, with placebo as a common comparator. Data from TRA10077A and TRA10077B were not included in the comparison. The manufacturer considered 2 main outcome measures for the indirect comparison, platelet response and bleeding. The manufacturer stated that an analysis of durable platelet response would require at least 8 weeks of treatment data and that the small number of clinically significant bleeds observed in the studies would mean that an assessment of bleeding events would have been of little clinical value. Separate indirect comparisons were performed for people with and without a spleen. For these analyses, the manufacturer obtained data from RAISE split by splenectomy status and combined the relevant RAISE data with the respective romiplostim trial.

4.19 The platelet response endpoints, differed between RAISE and the Kuter et al. trials. The primary outcome in RAISE was the odds of attaining a platelet count greater than or equal to $50x10^9$ per litre and less than or equal to $400x10^9$ per litre during the 6-month study period. In Kuter et al., the primary outcome was the proportion of patients with platelet counts greater than or equal to $50x10^9$ per litre in 6 or more weekly assessments in the last 8 weeks of treatment without use of rescue medication (durable platelet response). So, to perform the indirect comparison, the manufacturer used the post-hoc analysis of RAISE carried out on the intention-to-treat population, with the term 'sustained response' in the post-hoc analysis referred to as 'durable response' for the purpose of the indirect comparison (section 4.12). In this indirect comparison, overall response therefore refers to having either a durable response or a transient response.

4.20 There were also differences in bleeding definitions between RAISE and the Kuter et al. trials. RAISE collected both WHO bleeding data and bleeding adverse events using the CTCAE scale. Kuter et al. collected bleeding information only through adverse event reporting using an unnamed scale. The CTCAE scale and that used in Kuter et al. were assumed to be the same but the manufacturer indicated that they may be different. For the indirect comparison, bleed events were restricted to events reported using the CTCAE scale into 2 categories: CTCAE grade greater than or equal to 2 (moderate or worse bleed events) and CTCAE grade greater than or equal to 3 (clinically significant bleed events).

4.21 The results of the indirect comparison are summarised in table 3.

Table 3 Results of the indirect comparison between eltrombopag and romiplostim – odds ratios for eltrombopag relative to romiplostim (95% CI)

	Durable response	**Overall response**
All people	0.32 (0.03 to 3.14)	0.22 (0.05 to 1.02)
Splenectomy	0.50 (0.01 to 17.32)	0.09 (0.00 to 2.52)
No splenectomy	0.41 (0.04 to 4.80)	0.34 (0.06 to 2.14)
	Grade 3-5 bleeds	**Grade 2-5 bleeds**
All people	0.60 (0.08, 4.29)	1.63 (0.46, 5.80)
Splenectomy	0.17 (0.01, 5.31)	0.83 (0.13, 5.49)
No splenectomy	0.75 (0.03, 16.1)	3.05 (0.48, 19.2)

4.22 The manufacturer highlighted that confidence intervals around the estimated treatment effects were wide and crossed 1.00 in all comparisons, suggesting that there is no statistically significant differences between the 2 interventions.

4.23 The manufacturer highlighted that the results of the indirect comparison should be interpreted in the light of the sources of heterogeneity between individual studies. The manufacturer indicated that there were differences in baseline patient characteristics between RAISE and the Kuter et al. trials particularly in terms of ITP duration, previous ITP medication use and the proportion of patients receiving concomitant medication. The manufacturer attributed these differences to the fact that the proportion of patients who had had a splenectomy was higher in the combined Kuter et al. study (50%) than in RAISE (36%). The manufacturer also indicated that there were differences in the design of RAISE and the Kuter et al. trials in terms of: timing of platelet count assessments, timeframes in which patients were allowed to reduce concomitant ITP medications, response

definitions (50-400x 10^9/litre in RAISE and 50 x 10^9/litre or more in Kuter et al.) and definitions of 'period of rescue medication' and 'transient response'.

4.24 The manufacturer concluded that the indirect comparison between eltrombopag and romiplostim does not provide evidence of clinical superiority for 1 treatment relative to the other because of the level of uncertainty and potential biases in the comparison. The manufacturer indicated that 2 published clinical guidelines, the International Consensus Guidelines and the American Society of Hematology guidelines do not favour 1 treatment over the other. The manufacturer therefore assumed that eltrombopag and romiplostim are clinically equivalent and applied this assumption for the cost-effectiveness analysis.

Indirect comparison: eltrombopag with non-TPO-RAs

4.25 The manufacturer presented an indirect comparison of eltrombopag with non-TPO-RA treatments. The non-TPO-RA treatments considered by the manufacturer were those that were included in the International Consensus Guidelines; these were: intravenous immunoglobulin G, Anti-D, rituximab, corticosteroids, vinca alkaloids, mycophenolate mofetil, cyclosporine, cyclophosphamide, danazol and dapsone. Although a total of 113 studies (including 20 RCTs) were initially identified by the manufacturer's systematic review, post-hoc criteria were applied, which resulted in most of the identified studies being excluded. The manufacturer combined results from 37 studies (including 6 RCTs) to calculate a weighted averages for response rate, time to response and duration of response for each non-TPO-RA, using study sizes as weights. Data were included in the pooled analysis regardless of the definition of response. The efficacy of each intervention was calculated using a

simple average. The weighted averages provided by the manufacturer are presented in table 4.

Table 4 Weighted average of efficacy measures for non-TPO-RAs

	Total N[a]	Response (%)	Time to response (days)	Duration of response (days)
Cyclophosphamide	20	85	NR[b]	NR
Danazol	14	36	NR	NR
Dapsone	42	45	3.5	NR
Mycophenolate mofetil	71	53	NR	50.5
Anti-D	257	42	NR	NR
IVIg[c]	285	82	24.4	17.2
Rituximab	463	59	6.6	748.4
Corticosteroids	154	54	NR	NR
Vinca alkaloids	12	58	NR	NR

[a] N, number of patients; [b] NR, not reported; [c] IVIg, intravenous immunoglobulin

4.26 The results above compare with a response rate of 79% for eltrombopag in RAISE. The responses for eltrombopag had been observed at between 15 and 28 days. Interim results from EXTEND had reported responses being maintained over 4 years in some patients on treatment. The manufacturer concluded that the response rate for eltrombopag appeared to be comparable with treatments typically used as rescue medications in people with ITP, such as intravenous immunoglobulin and Anti-D. The manufacturer highlighted that results of the weighted averages for each of the included non-TPO-RAs were obtained mainly from non-randomised, highly heterogeneous older trials. However, the results largely reflect response rates outlined in the International

Consensus Report and the economic model produced by the manufacturer of romiplostim for technology appraisal 221.

ERG critique and exploratory analyses

4.27 The ERG stated that the manufacturer identified all the relevant studies comparing eltrombopag with placebo and presented a suitable meta-analysis. The ERG also considered the literature review carried out by the manufacturer to arrive at efficacy estimates for the non-TPO-RAs to be reasonable.

4.28 The ERG expressed concern over the exclusion of the Tomiyama et al. (2009) RCT from the analysis. The manufacturer had used post-hoc criteria to select relevant studies, and the Tomiyama et al. study was deemed not representative of the UK population and was therefore excluded. The ERG considered that the exclusion of relevant studies based on post-hoc criteria indicated a lack of methodological rigour especially considering that the 3 main eltrombopag RCTs (TRA 100773A, TRA 100773B and RAISE) had included 17–18% people of Asian origin. Therefore, the ERG did an additional meta-analysis to investigate the inclusion of the Tomiyama et al. study for the platelet response outcome at 6 weeks after beginning the study but not for the bleeding outcome. The results of the exploratory meta-analysis did not change the interpretation of previous evidence: the fixed effects OR was 8.64 (95% CI 4.97 to 15.04) and the random effects OR was 8.47 (95% CI 4.86 to 14.78) compared with the manufacturer's OR (fixed effect) of 8.23 (95% CI 4.68 to 14.48) and OR (random effect) of 8.16 (95% CI 4.63 to 14.37).

4.29 For the indirect comparison between eltrombopag and romiplostim, the manufacturer had combined the results of the 2 Kuter et al. trials then treated them as a single trial. In addition to the

differences in baseline characteristics of people recruited to RAISE and the combined Kuter et al. studies and differences in trial designs highlighted by the manufacturer, the ERG had concerns over the methodology of the indirect comparison. The ERG indicated that heterogeneity exists between the 2 Kuter et al. trials and so pooling their results may introduce bias. Moreover, the manufacturer had presented the indirect comparison split by splenectomy status. The ERG indicated that these analyses do not preserve the randomisation within RAISE and are therefore essentially observational analyses. The ERG stated that there are other approaches to perform the indirect comparison and that these approaches would generally favour romiplostim for overall platelet response.The ERG agreed with the manufacturer that the results of the indirect comparison should be treated with caution.

4.30 The ERG performed an indirect comparison for durable and overall response, and for grade 3–5 and grade 2–5 bleeds between eltrombopag and romiplostim using a different method from the manufacturer (Bayesian network meta-analysis) to account for the heterogeneity between studies. For durable response and bleeding, the ERG found similar results to that of the manufacturer. However, for overall response the manufacturer found no evidence of difference between treatments with an OR of 0.22 (95% CI 0.05 to 1.02), while the ERG found favourable response for romiplostim (OR 0.15) because the 95% credible interval excluded 1.00 (0.02 to 0.84).

4.31 For the analysis comparing eltrombopag with non-TPO-RAs, the ERG had concerns over the methodological rigor of the indirect comparison. The ERG explained that using post-hoc exclusion criteria and pooling response estimates using a simple weighted average of treatment arms regardless of the definition of response

may bias the results. The ERG was of the opinion that the results of this comparison should be treated with extreme caution.

5 Comments from other consultees

5.1 Statements received at NICE from patients with ITP suggested that eltrombopag is a valuable treatment option for people with ITP. Patients indicated that some ITP treatments are received as injections in hospitals, and so the fact that eltrombopag is an oral treatment is viewed as a significant advantage that would save patients time and money. This is particularly beneficial for patients who have difficulty commuting to hospitals, such as disabled patients, those caring for children during the day and those in full time work or education. Patients also indicated that the effect of some available interventions is short-lived and patients may be worried about possible short- and long-term adverse events. Eltrombopag is a long-term treatment that requires relatively fewer check-up visits and so allows patients to be more in control of their treatment once an effective dose has been established.

6 Cost-effectiveness evidence

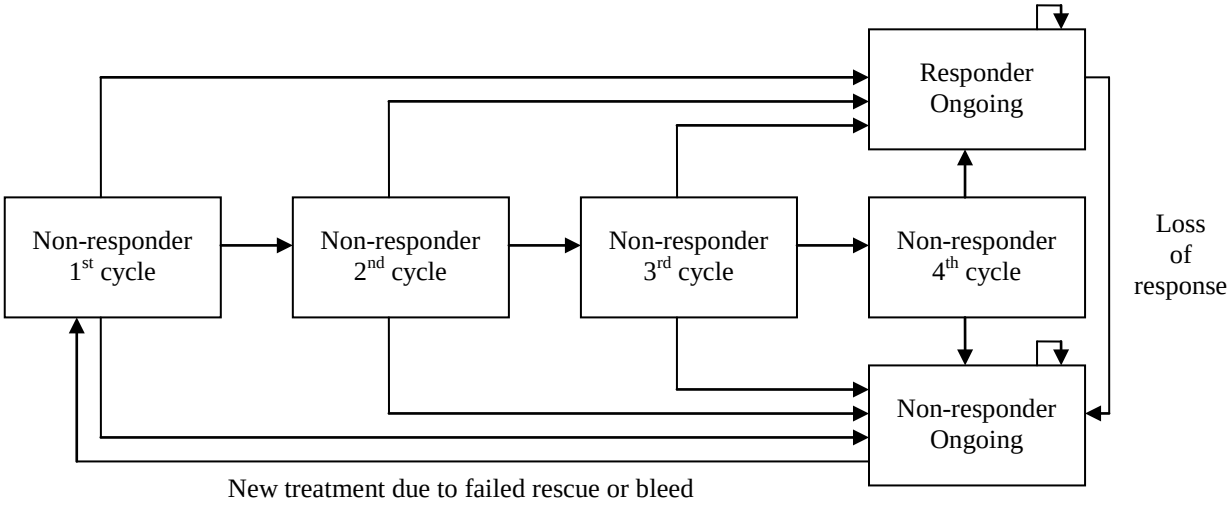
6.1 The manufacturer undertook a systematic review to identify relevant cost-effectiveness or cost-utility studies relating to the treatment of ITP but did not identify any.

6.2 The manufacturer developed a de novo economic model to assess the cost effectiveness of eltrombopag in 2 cITP populations: adults who have not undergone splenectomy and adults who have undergone splenectomy, who are refractory to prior treatments. The group of patients who have not undergone splenectomy was assumed to be representative of patients for whom splenectomy is

contraindicated. This is because reasons for not having had splenectomy were not recorded in RAISE, from which data on baseline patient characteristics were drawn.

6.3 The cost-effectiveness model presented by the manufacturer is a state-transition Markov cohort model that adopts a 4-week cycle length. The manufacturer assumed that the patients entering the model are refractory to first-line treatment with corticosteroids or immunoglobulins. A cohort of patients starting a treatment may respond (achieve a platelet count greater than or equal to 50×10^9 per litre) in the first, second, third or fourth cycle; the cycle of response being treatment specific. Those in response have a treatment-specific probability of loss of response each cycle. The model also contains the facility for a proportion of responders to receive rescue therapy. Those not responding become long-term non-responders off treatment. These patients may also receive rescue therapy, which may result in a temporary response of 1 cycle duration. During each cycle, a proportion of long-term non-responders exit this state and move on to other treatments further down the treatment sequence. Rate of rescue treatment, rates of non-severe bleeds treated in the outpatient setting and rates of severe bleeds treated in the inpatient setting are differentiated by response status, with responders experiencing lower rates than non-responders. These lead on to differential mortality risks. A diagrammatical representation of the model is presented in figure 1.

Figure 1 A diagrammatical representation of the manufacturer's model



6.4 The economic evaluation compared 3 treatment sequences: a non-TPO-RA pathway (sequence 'a': azathioprine, mycophenolate mofetil, ciclosporin, danazol, dapsone, cyclophosphamide, vinblastine and vincristine); eltrombopag in the non-TPO-RA pathway (eltrombopag followed by sequence 'a'); and romiplostim in the non-TPO-RA pathway (romiplostim followed by sequence 'a'). The non-TPO-RA sequence reflects that used by the manufacturer of romiplostim for technology appraisal 221, except that rituximab is removed from the sequence for the base-case analysis. The manufacturer explained that the modified non-TPO-RA treatment sequence represents UK clinical practice more accurately given local guidance suggesting that rituximab is likely to be offered before TPO-RAs. Costs and benefits are discounted at an annual 3.5% rate.

6.5 The manufacturer submitted 3 separate economic evaluations that modelled data inputs from different sources: the base case, an alternative evaluation and a scenario analysis. The base case applied a set of assumptions deemed by the manufacturer to be the most relevant to the decision problem, including assumptions from

the previous appraisal of romiplostim. The main source of data inputs for the base case was technology appraisal 221. The alternative evaluation incorporated data from RAISE and EXTEND along with clinical evidence retrieved by the manufacturer's updated systematic review to inform model parameters. In the scenario analysis, the manufacturer applied all available assumptions used in the economic evaluation for technology appraisal 221. The purpose of this analysis was to try and replicate the analysis for technology appraisal 221 as closely as possible. The sources of model inputs for the base case, alternative evaluation and scenario analysis are summarised in table 5.

Table 5 Sources of model inputs for the base case, alternative evaluation and scenario analysis

	Base case	Alternative evaluation	Scenario analysis
TPO-RA[a] treatment rates	Assumption	Assumption	Assumption
TPO-RA response rates	RAISE	RAISE	TA221[b]
TPO-RA time on treatment	RAISE+EXTEND	RAISE+EXTEND	TA221
TPO-RA AE[c]s	TA221	TA221	TA221
Non-TPO-RA treatment rates	TA221	TA221	TA221
Non-TPO-RA response rates	TA221	Man. lit review[d]	TA221
Non-TPO-RA time on treatment	TA221	Man. lit review	TA221
Non-TPO-RA AEs	TA221	TA221	TA221
Relationships and data inputs determined by platelet count			
Rescue rates	TA221	RAISE+EXTEND	Kuter et al.
Rescue treatment types	TA221	RAISE+EXTEND	TA221
Rescue response rates	TA221	Man. lit review	TA221
OP[e] bleeds	TA221	RAISE+EXTEND	TA221
IP[f] bleeds	TA221	RAISE+EXTEND	TA221
Mortality	TA221	TA221	TA221
HRQoL[g]	Szende et al.	Szende et al.	TA221
Eltrombopag dosing	RAISE+EXTEND	RAISE+EXTEND	RAISE+EXTEND
Romiplostim dosing	Kuter et al.	Kuter et al.	TA221

[a] TPO-RA, thrombopoietin receptor agonist; [b] TA221, technology appraisal 221; [c] AE, adverse event; [d] Man. lit review, manufacturer's literature review; [e] OP, outpatient; [f] IP, inpatient; [g] HRQoL, health-related quality of life

Base case and alternative evaluation

6.6 In the base case and alternative evaluation, the response rate for eltrombopag was drawn from RAISE. The primary endpoint in RAISE was the odds of attaining a platelet count greater than or equal to $50x10^9$ per litre and less than or equal to $400x10^9$ per litre during the 6-month study period. The response rate was derived from these data by assigning a response status for people who met the primary endpoint a least once during RAISE. It is important to note that this approach assumes that patients attaining a platelet response at least once during RAISE are in continuous platelet response while on treatment. This allowed the manufacturer to model event rates derived from platelet response data (continuous platelet response) on people whose condition responded at least once during RAISE. The base case and alternative evaluation assumed complete clinical equivalence between eltrombopag and romiplostim and so eltrombopag and romiplostim had the same response rate. The manufacturer considered it appropriate to make this assumption given the lack of comparative evidence between eltrombopag and romiplostim (section 4.24). Response rates derived from the estimates of the indirect comparison were used in a sensitivity analysis.

6.7 For non-TPO-RAs, response rates were taken from technology appraisal 221 for the base case. These were obtained from a systematic review undertaken by the manufacturer of romiplostim. In the alternative evaluation, the manufacturer used the weighted average response rate for each non-TPO-RA as determined for the indirect comparison between eltrombopag and non-TPO-RAs (section 4.25).

6.8 In the base case and alternative evaluation, the time to response for eltrombopag was drawn from RAISE. This was assumed to be 15 days, reflecting the duration at which the proportion of patients responding to eltrombopag levels out. For romiplostim, the maximum time to response was assumed to be 4 weeks as observed in Kuter et al.. For non-TPO-RAs, time to response was taken from technology appraisal 221 for the base case.In the alternative evaluation, the response rates for non TPO-RAs were as determined in the manufacturer's indirect comparison between eltrombopag and non-TPO-RAs (section 4.25).

6.9 Given the assumption of clinical equivalence between eltrombopag and romiplostim, the base case and alternative evaluation assumed that time on treatment for eltrombopag and romiplostim was equal. Time on treatment for TPO-RAs was extrapolated beyond the trial follow-up period over a lifetime horizon. It was modelled as a survival variable based on patient-level treatment discontinuation data from RAISE and EXTEND. An adjusted parametric analysis was carried out to establish time on treatment beyond the combined duration of RAISE and EXTEND, with splenectomy status included as a variable within a pooled analysis. The parametric curves fitted to the Kaplan-Meier curves showed that splenectomy status is a key determinant of time on treatment suggesting that people who have undergone splenectomy whose condition responds to treatment tend to spend less time on TPO-RAs than people who have not undergone splenectomy whose condition does not respond to treatment.

6.10 For non-TPO-RAs, the base case took time on treatment from technology appraisal 221. In the alternative evaluation, time on treatment was as determined in the manufacturer's indirect comparison between eltrombopag and non-TPO-RAs (section

4.25). In the absence of robust data and to avoid increasing the model complexity, time on treatment was assumed to follow an exponential distribution for all non-TPO-RAs.

6.11 The risk of bleeding in the model was differentiated by platelet response status (platelet counts greater than or equal to 50×10^9 per litre and platelet counts less than 50×10^9 per litre) and was so irrespective of treatment. Patients with platelet counts greater than or equal to 50×10^9 per litre were assumed to be at risk of non-severe bleeds while patients with platelet counts less than 50×10^9 per litre had a risk of severe and non-severe bleeds, severe bleeds being defined as bleeds requiring inpatient care. In the base case, the rates of both types of bleeds were derived from technology appraisal 221. For patients not attaining a platelet response, the rate of severe bleeds applied for the base-case modelling was 4.3%. In the alternative evaluation, the rate of severe bleeds from RAISE and EXTEND was 0.8%. The manufacturer assumed that patients who are refractory to all prior treatments (final non-responder state), have a rate of severe bleeds that is double the normal rate. The manufacturer indicated that this assumption was made to be in line with the modelling for technology appraisal 221.

6.12 Unlike bleed rates, cITP-related mortality was modelled as a function of severe bleeds in the base case and alternative evaluation. Treatment therefore impacts mortality by affecting the amount of time spent in the non-responder states and thus bleed rates. A mortality rate was applied to each bleed requiring hospitalisation, with mortality specific to the type of bleed. These rates were obtained from Danese et al. (2009). Three bleed categories were considered representative of the types of bleed requiring hospitalisation in RAISE and EXTEND: gastrointestinal

bleeds, intracranial haemorrhage and coagulation disorder (other). The mortality rates associated with these bleed types are applied to patients experiencing a bleed-related hospitalisation in the model, in proportion to the number of patients experiencing each bleed type in RAISE and EXTEND. Because cITP-related mortality was modelled as a function of severe bleeds, the rate of mortality would also double for patients who are refractory to all prior treatments. Mortality based on platelet response status (rather than severe bleeds) was modelled in sensitivity analyses.

6.13 In the base case, data inputs for rescue therapy parameters were obtained from technology appraisal 221. Rescue rate data were only available for patients with platelet counts less than 50×10^9 per litre in technology appraisal 221 and so the rescue rate for patients with platelet counts greater than or equal to 50×10^9 per litre was assumed to be 0. In the base case, 68% of patients who have undergone splenectomy and 33% of patients who have not undergone splenectomy received rescue therapy. The rescue medications considered were intravenous immunoglobulin, anti-D and corticosteroid. These rescue medications and the proportions in which they would be used were obtained from a survey by the manufacturer of romiplostim for technology appraisal 221. Rates of response to rescue medications were obtained from technology appraisal 221.

6.14 In the alternative evaluation, the number of rescue events per unit time was estimated for patients with platelet counts above and below 50×10^9 per litre in RAISE and EXTEND. In addition to intravenous immunoglobulin, anti-D and corticosteroids, platelet transfusions were also considered to be a rescue treatment. The proportions in which these rescue medications would be used were derived from RAISE and EXTEND. To reflect the rescue treatments

that are likely to be used in the UK, the manufacturer limited all analyses of rescue data from RAISE and EXTEND to countries with a per capita healthcare expenditure greater than $2000 per year.

6.15 In the economic model, adverse events were grouped as either severe adverse events or other adverse events. In the base case and alternative evaluation, the adverse event rates for the 2 TPO-RAs were assumed to be equivalent and were taken from technology appraisal 221. In the base case and alternative evaluation, adverse event rates for non TPO-RAs were taken from technology appraisal 221 because the systematic review undertaken by the manufacturer identified minimal data about toxicity.

6.16 HRQoL data from RAISE and EXTEND, which were collected using the SF-36 questionnaire, were mapped onto SF-6D scores to calculate utility values. HRQoL data were also available from technology appraisal 221 in which utility values were calculated based on EQ-5D data from the 2 romiplostim RCTs. However, for the base case (and alternative evaluation), the main source of utility data for the modelling was a study identified by the manufacturer's systematic review of utility studies (Szende et al. 2010). This study had developed 6 ITP-related health states that were evaluated by 359 members of the UK general public using time trade-off. The utility values from the different sources and those applied in the model are summarised in the table 6.

Table 6 Summary of the utility values from RAISE, TA221 and those applied in the model

	RAISE	TA[a]221	Applied value (source)
Platelet response: no bleed	0.737	0.835	0.863 (Szende et al.)
Platelet response: OP[b] bleed	0.693	0.734	0.734 (Szende et al.)
Platelet non-response: no bleed	0.712	0.800	0.841 (Szende et al.)
			0.732 (Szende et al.)
Platelet non-response: OP bleed	0.666	0.732	0.038 (Szende et al.)
IP[c] bleed: cranial	-	0.040	
IP bleed: GI[d]	-	0.540	0.450 (Leontiadis et al.)
IP bleed: other	-	0.540	0.450 (assumption)
Steroid rescue treatment	-	0.758	0.758 (Szende et al.)
AE[e] decrements			
TPO-RA[f] and rituximab SAE[g]	-	0.100	0.100 (TA221)
Non-TPO-RA SAE	-	0.400	0.400 (TA221)
Rescue SAE	-	0.100	0.100 (TA221)
Other AE[h]		0.100	0.100 (TA221)

[a]TA, technology appraisal; [b]OP, outpatient; [c]IP, inpatient; [d]GI, gastrointestinal; [e]AE, adverse event; [f]TPO-RA, thrombopoietin receptor agonist; [g]SAE, serious adverse event

6.17 The manufacturer undertook a systematic review of relevant resource data for the UK but did not identify any relevant studies. Therefore, unpublished data and assumptions were used to estimate the relevant costs in the model. The cost-effectiveness model incorporates a variety of costs including direct and administration costs of the intervention, comparators and rescue medications, as well as monitoring costs. The list prices of the different drugs were taken from BNF63 and the respective patient access schemes applied. The average doses of eltrombopag were calculated from RAISE by averaging doses for 4-week periods

across people whose disease had responded and people whose disease had not responded up to the end of the study. A stable dose estimated from EXTEND was applied thereafter. The average doses of romiplostim were calculated from Kuter et al. (2008) using the same approach. The last calculated dose was applied thereafter. Non-TPO-RA drug doses were taken from Provan et al. (2010), the International Consensus Report or technology appraisal 221. Eltrombopag and other oral treatments did not have administration costs. Romiplostim may be administered at home or at hospital; only hospital administrations were assumed to incur cost. The cost of bleed events covered direct drug costs as well as hospitalisation and subsequent follow-up costs. Monitoring was assumed to consist of 1 haematologist consultation and 2 laboratory tests every 4 weeks regardless of treatment.

6.18 A summary of the base-case results is presented in table 7.

Table 7 Deterministic cost-effectiveness results for the base case

	Total cost (£)	Incremental costs (£)	Total QALYs[b]	Incremental QALYs	ICER[a] (£/QALY)
Patients who have undergone splenectomy					
Eltrombopag	556,089	- 87,509	12.22	0.00	Dominates
vs. romiplostim	643,598		12.22		
Eltrombopag	556,089	- 24,984	12.22	1.27	Dominates
vs. non-TPO-RAs	581,073		10.95		
Patients who have not undergone splenectomy					
Eltrombopag	332,193	- 40,551	11.86	0.00	Dominates
vs. romiplostim	372,744		11.86		
Eltrombopag	332,193	34,901	11.86	2.31	15,105
vs. non-TPO-RAs[c]	297,292		9.55		

[a] ICER, incremental cost-effectiveness ratio; [b] QALY, quality-adjusted life year; [c] TPO-RA, thrombopoietin receptor agonist.

6.19 The manufacturer undertook a wide range of univariate sensitivity analyses for the base case. The impact of these sensitivity analyses' net costs and QALYs are presented in the manufacturer's submission using the eltrombopag treatment sequence or the non-TPO-RA treatment sequence as the referent, whichever was the least expensive. The results of the base-case analysis appeared sensitive to the assumption of TPO-RA equivalence, the bleed rates, the rescue rates, the proportion of rescue that is intravenous immunoglobulin, the mortality associated with platelet response status, whether severe bleeds double when the patient is refractory to all prior treatments and the time horizon. For patients who have undergone splenectomy, eltrombopag dominated (that is, was more effective and less expensive than) the non-TPO-RA pathway in all

analyses. For patients who have not undergone splenectomy, the ICER remained below £34,000 per QALY gained in all analyses except when a 6-month time horizon was used, in which case the ICER for eltrombopag compared with the non-TPO-RA pathway was £74,250 per QALY gained. For both patients who have and have not undergone splenectomy, eltrombopag consistently dominated romiplostim, the only exception being when the odds ratio from the indirect comparison was used to estimate the relative efficacy of the TPO-RAs with respect to response. In this case, the ICER for romiplostim compared with eltrombopag was £171,156 per QALY gained and £110,983 per QALY gained for patients who have or have not undergone splenectomy respectively. The manufacturer did not perform univariate sensitivity analyses on the results of the alternative evaluation.

6.20 Probabilistic sensitivity analyses were also carried out by simultaneously sampling from estimated probability distributions of model parameters to obtain 1000 sets of model input estimates. Results show that, for people who have undergone splenectomy, the probability of eltrombopag being cost effective is 65%, 67% and 70% at the £20,000, £25,000 and £30,000 per QALY thresholds respectively. For people who have not undergone splenectomy, the probabilities were 54%, 59% and 63% at the £20,000, £25,000 and £30,000 per QALY thresholds respectively.

6.21 A summary of the cost-effectiveness results for the alternative evaluation is presented in table 8.

Table 8 Deterministic cost-effectiveness results for the alternative evaluation

	Total cost (£)	Incremental costs (£)	Total QALYs[b]	Incremental QALYs	ICER[a] (£/QALY)
Patients who have undergone splenectomy					
Eltrombopag	315,148	- 87,111	14.48	0.00	Dominates
vs. romiplostim	402,259		14.48		
Eltrombopag	315,148	33,494	14.48	0.54	61,337
vs. non-TPO-RAs[c]	281,654		13.94		
Patients who have not undergone splenectomy					
Eltrombopag	232,335	- 40,345	14.96	0.00	Dominates
vs. romiplostim	272,680		14.96		
Eltrombopag	232,335	73,945	14.96	0.77	95,536
vs. non-TPO-RAs	158,390		14.19		

[a] ICER, incremental cost-effectiveness ratio; [b] QALY, quality-adjusted life year; [c] TPO-RA, thrombopoietin receptor agonist

Cost-effectiveness of eltrombopag compared with romiplostim

6.22 In both the base case and alternative evaluation eltrombopag and romiplostim were assumed to be equally effective. Therefore, the driver of the cost effectiveness of eltrombopag compared with romiplostim is the relative cost of the TPO-RAs. The total cost of romiplostim acquisition and administration is approximately [redacted] the cost of eltrombopag acquisition and administration for people who have undergone splenectomy. For people who have not undergone splenectomy, the total cost of romiplostim is approximately [redacted] than the cost of eltrombopag. This reflects the higher dose of romiplostim needed for people who have

undergone splenectomy. Changing the cost of romiplostim in sensitivity analyses did not affect the relative cost effectiveness of eltrombopag.

Cost-effectiveness of eltrombopag compared with non-TPO-RAs

6.23 The differential rescue rates used in the base case and alternative evaluation showed that rescue rates for patients with platelet counts less than 50×10^9 per litre is the key driver of the cost effectiveness of eltrombopag compared with the non-TPO-RA pathway. This is because rescue therapies are expensive, particularly intravenous immunoglobulin, which contribute to as much as 70% of the total management costs in some patients. The rescue rates applied in the base case are 68% and 33% for patients who have or have not undergone splenectomy respectively. Of the patients receiving rescue therapy, more than 50% receive intravenous immunoglobulin at a cost of £6863 per cycle. These were assumed to be reflective of the rates in the romiplostim trials. The average cost applied per rescue was £4772 for patients who have undergone splenectomy and £5195 for patients who have not undergone splenectomy. As a result, eltrombopag dominated the non-TPO-RA pathway and gave an ICER around £15,000 per QALY for the patients who have not undergone splenectomy. In moving from the base case to the alternative evaluation, the manufacturer applied lower rescue rates from RAISE and EXTEND (32% and 14% for patients without or with a spleen respectively). The corresponding average rescue event costs for patients who have undergone splenectomy became £3857, and for patients who have not undergone splenectomy, £4662. Given the lower response rate among patients receiving non-TPO-RAs than among those receiving eltrombopag or

romiplostim, a reduction in rescue rates provides a larger cost offset for non-TPO-RAs than for TPO-RAs. This in turn makes eltrombopag relatively less cost effective compared with non-TPO-RAs (the ICER for eltrombopag in the alternative evaluation increased to values above £60,000 and £95,000 per QALY for patients who have or have not undergone splenectomy respectively).

6.24 The results of the base case and alternative evaluation showed that the rate of severe bleeds (and thus mortality) had significant impact on the cost effectiveness of eltrombopag compared with non-TPO-RAs. The base case applies a rate of 4.3% to people with platelet counts less than 50×10^9 per litre, which suggests that half these people will experience a severe bleed that leads to inpatient treatment each year. The alternative evaluation applied a lower severe bleeds rate of 0.8%. The impact of this was mainly on QALYs, which partly explains the higher ICERs of eltrombopag compared with the non-TPO-RA pathway in the alternative evaluation. For patients who have undergone splenectomy, the incremental QALYs of eltrombopag were 1.27 in the base case and decreased to 0.54 in the alternative evaluation. Similarly, for patients who have not undergone splenectomy, incremental QALYs of eltrombopag were 2.31 in the base case and became 0.77 in the alternative evaluation. The impact of the lower rate from technology appraisal 221 should, however, be considered in the light of the fact that the manufacturer had derived romiplostim's bleed rates based on the reported probabilistic parameters in the manufacturer's submission for technology appraisal 221.

6.25 A comparison of the rates of rescue therapy from RAISE and EXTEND (used for alternative evaluation), and technology appraisal 221 (used for the base case) is available in appendix 1.

Scenario analysis

6.26 The purpose of the scenario analysis was to try and replicate the analysis for technology appraisal 221 as closely as possible. In the move from the base case to the scenario analysis, several modifications were made simultaneously to reflect more fully the assumptions made for technology appraisal 221:

- TPO-RAs were assumed to be administered before rituximab in the treatment pathway.
- Response rates for eltrombopag and romiplostim were remodelled to exclude patients whose condition responded to unlicensed doses.
- Time on treatment followed an exponential distribution (instead of a log-normal distribution for the base case).
- Rescue rates were calibrated to produce 24-week rescue rates when the treatment pathway is set to include no maintenance treatments.
- Utility values were based on pooled EQ-5D and vignette utility data as per the modelling for technology appraisal 221.
- The number of vials of romiplostim needed was obtained based on the manufacturer's submission for technology appraisal 221.
- Administration costs were set to £262 per cycle for all treatments and no additional administration cost was assumed for romiplostim.

6.27 In the scenario analysis, romiplostim and the non-TPO-RA pathway were dominated by eltrombopag for patients who have or have not undergone splenectomy. The deterministic cost-effectiveness results are presented in table 9. The manufacturer did not perform univariate sensitivity analyses on the results of the scenario analysis.

Table 9 Deterministic cost-effectiveness results for the scenario analysis

	Total cost (£)	Incremental costs (£)	Total QALYs[a]	Incremental QALYs	ICER[b] (£/QALY)
Patients who have undergone splenectomy					
Eltrombopag	575,374	- 58,340	12.28	0.00	Dominates
vs. romiplostim	633,714		12.28		
Eltrombopag	575,374	- 21,250	12.28	1.19	Dominates
vs. non-TPO-RAs[c]	596,624		11.09		
Patients who have not undergone splenectomy					
Eltrombopag	472,641	- 33,183	12.08	0.00	Dominates
vs. romiplostim	505,824		12.08		
Eltrombopag	472,641	- 3,015	12.08	1.63	Dominates
vs. non-TPO-RAs	475,656		10.45		

[a] QALY, quality-adjusted life year; [b] ICER, incremental cost-effectiveness ratio; [c] TPO-RA, thrombopoietin receptor agonist.

6.28 The deterministic ICERs generated by the manufacturer's 3 main analyses for people who have or have not undergone splenectomy are summarised in the table 10.

Table 10 Eltrombopag's deterministic ICERs for the base-case, alternative evaluation and scenario analyses (£/QALY)

Base case		Alternative		TA221 analysis	
vs. non-TPO-RA[a]	vs. romiplostim	vs. non-TPO-RA	vs. romiplostim	vs. non-TPO-RA	vs. romiplostim
Patients who have undergone splenectomy					
Dominates	Dominates	£61,337	Dominates	Dominates	Dominates
Patients who have not undergone splenectomy					
£15,105	Dominates	£95,536	Dominates	Dominates	Dominates

[a] TPO-RA, thrombopoietin receptor agonist

ERG critique and exploratory analyses

6.29 The ERG considered the manufacturer's model structure to be transparent, broadly reasonable and in line with that for technology appraisal 221. The ERG was satisfied with the breadth of the analyses carried out by the manufacturer and the literature review to establish the clinical effectiveness of non-TPO-RAs, and considered these to be suitable to inform the modelling.

6.30 The ERG stated that a major weakness in the manufacturer's submission relates to the fact that data from the eltrombopag RCTs and systematic review for this appraisal were not used to populate the base-case model. Instead, the manufacturer used data for technology appraisal 221 that are publicly available, and the ERG indicted that these data did not always have clear definitions. The ERG viewed the alternative base as the natural starting point for the analysis.

6.31 The base case and alternative evaluation assumed that TRO-RAs are positioned after rituximab in the treatment pathway but before other non-TPO-RAs. The ERG noted that the optimal positioning of the TPO-RAs within the treatment sequence was not addressed. In addition, the ERG indicated that there may be a question about the optimal place of eltrombopag and romiplostim in the treatment pathway if they are not clinically equivalent. The ERG was of the opinion that additional treatment sequences should have been explored by the manufacturer as part of the economic evaluation.

6.32 The ERG had concerns about the assumption made by the manufacturer that response and platelet response are the same. The ERG noted that, in RAISE, only 60–80% of patients whose condition responded to eltrombopag had a platelet count greater than 50×10^9 per litre. The manufacturer's assumption would

therefore underestimate the event rates, which would lead to improved ICERs for TPO-RAs. The ERG was of the opinion that model inputs derived for people with platelet counts greater than 50×10^9 per litre would need to be adjusted before they can be applied to people whose condition had responded in RAISE.

6.33 The ERG questioned whether eltrombopag and romiplostim are clinically equivalent given the uncertainty around the results of the indirect comparison (section 4.24).

6.34 The ERG questioned the extrapolated duration of TPO-RA response. The parametric curves fitted to the Kaplan-Meir curves gave long tails with a proportion of patients being extrapolated to remain on TPO-RAs for a considerable time. The ERG stated that it was not clear if these tails were reasonable.

6.35 The average TRO-RA doses were drawn from the relevant trials by averaging doses across responders and non-responders. The ERG noted that in Kuter et al., the average romiplostim dose among patients whose condition had responded was up to 40% to 60% lower than that across the trial as a whole. If a similar argument holds for eltrombopag, the ERG indicated that both the cost effectiveness of TPO-RAs compared with non-TPO-RAs and the cost effectiveness of eltrombopag compared with romiplostim may change considerably. The ERG was of the opinion that the TPO-RA doses should be response-specific and so applied reduced doses of romiplostim by 40% for patients who have undergone splenectomy and 60% for patients who have not undergone splenectomy to the base case. Romiplostim was found to dominate eltrombopag in the non-splenectomised group only.

6.36 The ERG considered that the SF-6D HRQoL data collected from RAISE and EXTEND should have been applied for the base-case

modelling because these are patient-level data reported using a validated generic instrument. The ERG therefore carried out a sensitivity analysis to explore the impact of applying the SF-6D utility values on the results of the base case and alternative evaluation. This was found to increase the ICER for eltrombopag to £85,026 per QALY gained and £140,995 per QALY gained for patients who have or have not undergone splenectomy respectively.

6.37 The ERG undertook sensitivity analyses to establish the impact of varying TPO-RA response rates on the results of the base case and alternative evaluation. The ERG first applied the overall response rates for eltrombopag and romiplostim as reported in their respective trials. In a second sensitivity analysis, the ERG applied the overall response rates from the manufacturer's indirect comparison (section 4.21). The ERG found an impact on the cost effectiveness of eltrombopag compared with romiplostim but the ICER for romiplostim remained above £30,000 per QALY gained.

6.38 The modelling assumed that the severe bleed rate doubles for patients who are refractory to all prior treatments. Because of this, the fatal bleed rate also doubles. The ERG explored the impact of dropping this assumption and found large impact on the net QALY gain over the non-TPO-RA pathway.

7 Equalities issues

7.1 Consultees at the scoping workshop held in February 2008 noted that blood products may not be acceptable to people with certain religious beliefs. However, the workshop considered that other treatment options (that are not blood products) are available and

that no revision to the scope would be necessary. No equality issues were raised by the manufacturer in its submission.

8 Innovation

8.1 It was recognised during the first draft scope consultation that eltrombopag is taken orally, and so avoids weekly subcutaneous injections, which may generate subsequent resource savings and may be considered as a major change in managing the condition. It was also suggested that there may be better compliance with an oral treatment and also a better quality of life.

9 Authors

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Appendix A: Supporting evidence

Rates of rescue therapy – patients who have undergone splenectomy

Platelet count	RAISE+EXTEND				TA221			
	<50x10^9/L		≥50x10^9/L		<50x10^9/L		≥50x10^9/L	
	n	%	n	%	n	%	n	%
Immunoglobulin	78	51	9	31	-	64	-	-
Anti-D	3	2	0	0	-	0	-	-
intravenous corticosteroids	17	11	4	14	-	36	-	-
Platelet transfusion	56	36	16	55	-	0	-	-
Total	154	100	29	100	-	100	-	-
Patient years	40.29		52.83		-		-	
Per year	382.2%		54.9%		-		-	
Per cycle	31.9%		4.6%		68.0%		0.0%	

Rates of rescue therapy – patients who have not undergone splenectomy

Platelet count	RAISE+EXTEND				TA221			
	<50x10^9/L		≥50x10^9/L		<50x10^9/L		≥50x10^9/L	
	n	%	n	%	n	%	n	%

Immunoglobulin	39	55	7	50	-	59	-	-
Anti-D	13	18	2	14	-	25	-	-
Intravenous corticosteroids	5	7	5	36	-	16	-	-
Platelet transfusion	14	20	0	0	-	0	-	-
Total	71	100	14	100	-	100	-	-
Patient years	41.28		85.12		-		-	
Per year	172.0%		16.4%		-		-	
Per cycle	14.3%		1.4%		33.0%		0.0%	

Related NICE guidance

Published

- Romiplostim for the treatment of chronic immune (idiopathic) thrombocytopenic purpura. NICE technology appraisal guidance 221 (2011). Available from www.nice.org.uk/guidance/TA221
- Eltrombopag for the treatment of chronic immune (idiopathic) thrombocytopenic purpura. NICE technology appraisal guidance 205 (2010). Available from www.nice.org.uk/guidance/TA205