Eltrombopag for the treatment of chronic immune thrombocytopenic purpura (ITP): A Single Technology Appraisal

Produced by: Aberdeen HTA Group

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Ewen Cummins reviewed the cost-effectiveness evidence, carried out further sensitivity analyses, and drafted Section 5. Kieran Rothnie and Miriam Brazzelli reviewed the methods of the clinical effectiveness evidence synthesis. Mark Crowther provided clinical advice and drafted the background and the critique of the manufacturer's decision problem. Shona Fielding and Neil Scott critiqued the statistical methods used, checked all the numerical results, tables and figures, and conducted additional statistical analyses. Cynthia Fraser critiqued the methods used for identifying relevant studies in the literature and conducted additional literature searches. Miriam Brazzelli supervised the work throughout the project. All authors assisted in preparing the final manuscript and commenting on early drafts.

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LIST OF ABBREVIATIONS

AE	Adverse Event
AIC	Academic in confidence
CEAC	Cost effectiveness acceptability curve
CEAF	Cost effectiveness acceptability frontier
CIC	Commercial in confidence
CITP	Chronic idiopathic thrombocytopenic purpura
CRD	Centre for Reviews and Dissemination
CTCAE	Common Terminology Criteria for Adverse Events
ELTR	Eltrombopag
ERG	Evidence Review Group
FACIT	Functional Assessment of Chronic Illness Therapy
FACT	Functional Assessment of Cancer Therapy
FAD	Final appraisal determination
GSK	Glaxo SmithKline
HRQoL	Health related quality of life
ICER	Incremental cost effectiveness ratio
ITP	Idiopathic thrombocytopenic purpura
IVIg	Intravenous immunoglobulins
MeSH	Medical subject headings
NICE	National Institute for Health and Clinical Excellence
Non-Splen	Non-splenectomised patients
Non-TPO-RA	Non thrombopoietin receptor agonist
PAS	Patient access scheme
QALY	Quality adjusted life year
RCT	Randomised controlled trial
ROMI	Romiplostim
SA	Sensitivity analysis
SAE	Serious Adverse Event
SF-36	Short Form 36
SF-6D	Short Form 6 dimensions
Splenect	Splenectomised patients
STA	Single technology appraisal
TPO-RA	Thrombopoietin receptor agonist
TTO	Time trade off
WHO	World Health Organisation

1 SUMMARY

1.1 Scope of the submission

The manufacturer submission from GSK addressed the use of eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura (ITP) in:

- Adult splenctomised patients refractory to other treatments; and
- Adult non-splenectomised patients for whom surgery is contraindicated (second line treatment)

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The evidence on clinical effectiveness of eltrombopag came mainly from one phase II randomised trial and two phase III randomised trials (TRA100773A, TRA100773B and RAISE). All three trials were sponsored by GSK. The primary outcome in all three trials was platelet response as surrogate for risk of bleeding.

Efficacy

Platelet response defined as $\geq 50 \times 10^9$/L at day 43 (end of treatment for TRA100773A and B, but an interim assessment for RAISE) was the only outcome considered for meta-analysis.

Within these three trials, response after eltrombopag ranged from 54% to 59% but was between 11% and 16% following placebo. A fixed effect meta-analysis found in favour of eltrombopag over placebo (OR = 8.23 [95% CI (4.68 to 14.18)]).

The primary outcome for the RAISE trial was platelet response ($\geq 50 \times 10^9$/L and $< 400 \times 10^9$/L) at any point during the six month treatment period. In the eltrombopag group 106/134 (79%) participants responded to treatment compared with 17/60 (28%) participants in the placebo group (OR 8.2 [99% CI (3.59 to 18.73)]. RAISE reported information on duration of response in two ways. For continuous duration of response there was a median of 8.1 weeks duration in the eltrombopag group and zero weeks after placebo. For cumulative duration of response, the median in the eltrombopag group was 10.9 weeks compared with zero in the placebo group.

RAISE provided information on the need for rescue treatment (a composite of new ITP medication, increased dose of a concomitant ITP medication, platelet transfusion, and/or splenectomy). In the placebo group 25/62 (40%) required rescue medication compared with 25/135 (18%) in the eltrombopag group (p=0.001). RAISE also reported that 63/135 (47%) participants in the eltrombopag arm and 31/62 (50%) in the placebo arm used ITP medications at baseline. Within the eltrombopag arm 37 (59%) reduced or discontinued at least one concomitant ITP medication, compared with 10 (32%) in the placebo group.

Safety

In RAISE at least one occurrence of clinically significant bleeding (defined as grades 2-4 on the WHO bleeding scale) occurred in 79% (106/135) of participants treated with eltrombopag and 93% (56/60) of those treated with placebo. Of those splenectomised, 25/85 (29%) receiving eltrombopag suffered clinically significant bleeding compared with 18/40 (45%) receiving placebo (OR 0.31, 95% CI [0.11 to 0.83]). Within the non-splenectomised group, 19/50 (38%) participants treated with eltrombopag compared with 14/20 (70%) participants on placebo suffered clinically significant bleeding during treatment (OR 0.27, 95% CI [0.08 to 0.95]).

Within the three trials, the rates of adverse events ranged from 47% to 87% in the eltrombopag arm and from 37% to 92% in the placebo arm. Adverse events related to study medication ranged from 26% to 36% for eltrombopag participants and from 11% to 31% for placebo participants. Types of adverse events were similar between the trials with headache being the most common adverse event.

Eltrombopag versus romiplostim

The RAISE study (eltrombopag versus placebo) was combined with data from the two Kuter 2008 trials (romiplostim versus placebo) in an indirect comparison. The manufacturer used the Bucher approach to indirect comparison whilst the ERG tried also a Bayesian approach to account for the heterogeneity between studies. For durable response, the point estimate favoured romiplostim but this was not statistically significant (manufacturer reported OR 0.32 [95% CI 0.03 to 3.14], ERG OR 0.20 [95% CrI (0.01 to 2.13)]. For overall platelet response however, the manufacturer found no difference in effectiveness of eltrombopag and romiplostin, but the ERG analysis did (manufacturer reported OR 0.22 [95% CI 0.05 to 1.02], ERG OR 0.15 [95% CrI 0.02 to 0.84]. The manufacturer also reported the indirect comparison split by splenectomy status, finding no difference in effectiveness between eltrombopag and romiplostin for both overall and durable response in each of the splenetcomised and non-splenetcomised participant groups. The ERG did not undertake this analysis split by splenectomy status since it fails to preserve the randomisation.

With regard to bleeding, no statistically significant differences were found in the odds of bleeding (both grade 2-5 and 3-5) between eltrombopag and romiplostim treatments. For grade 3-5 bleeds the manufacturer reported OR 0.60 [95% CI (0.08 to 4.29)] and the ERG OR 0.55 [95% CrI (0.06 to 5.04)]. For grade 2-5 bleeds, the manufacturer reported OR 1.63 [95% CI (0.46 to 5.80)] and the ERG OR 1.72 [95% CrI (0.39 to 7.72)]. The manufacturer reported also the indirect comparisons for risk of bleeding according to splenectomy status. No differences in odds of bleeding between the two treatments, in both the splenectomised group and the non-splenectomised group, were observed.

Eltrombopag versus non-TPO-RA

The manufacturer considered a number of non-TPO-RA treatments within the treatment pathway for the economic model. These included IVIg, Anti-D, rituximab, corticosteroids, vina alkaloids, mycophenolate mofetil, cyclosporine, cyclophosphamide, danazol and dapsone. No RCT data were included but weighted averages of the response rates (using any definition of response) were calculated for each non-TPO-RA treatment using observational data.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

In the indirect comparison of eltrombopag versus romiplostim the manufacturer combined the two Kuter 2008 trials data using a standard meta-analysis approach and then treated them as single trial data in the indirect comparison with RAISE.[1] The ERG was concerned with this assumption as well as with the considerable clinical differences between the eltrombopag trial and the two Kuter 2008 trials. Therefore an alternative method for the meta-analysis (Baysian network meta-analysis) was undertaken by the ERG to account for the heterogeneity between studies.

1.4 Summary of cost effectiveness submitted evidence by the manufacturer

The optimal positioning of the TPO-RA within the current treatment sequence is not considered.

The manufacturer compares three treatment sequences:

a. Azathioprine → mycophenolate mofetil → ciclosporin → danazol → dapsone → cyclophosphamide → vinblastine → vincristine

b. Eltrombopag followed by sequence 'a'

c. Romiplostim followed by the sequence 'a'

Rituximab is not considered in the base case, with the apparent implicit assumption of patients being refractory or contraindicated to rituximab. The licensed, and proposed, indications would allow physicians to use eltrombopag before rituximab.

The manufacturer constructs a Markov model with a 4 week cycle length. A cohort of patients starting a treatment may respond in the 1st, 2nd, 3rd or 4th cycle, the cycle of response being treatment specific.

Those in response have a treatment specific probability of loss of response each cycle. The manufacturer fits parametric curves to the eltrombopag responder time on treatment Kaplan Meier curves to estimate the duration of therapy among TPO-RA responders. Duration of therapy for the non-TPO-RA participants is drawn from the literature.

Those not responding cease their current treatment and become long-term non-responders off treatment. These patients may receive rescue therapy, which may result in a temporary response of

one cycle duration. During each cycle a proportion of these long-term non-responders exit this state and move on to treatments further down the treatment sequence.
Rate of rescue treatment, rates of non-severe bleeds treated as outpatients and rates of severe bleeds treated as inpatients are differentiated by those in response and on treatment and those not in response and off treatment. Those in response have lower event rates. Mortality is associated with severe bleeds, and as a consequence responders also experience a survival gain.

Due to intravenous immunoglobulin being a major portion of rescue therapies, rescue therapy is expensive. Avoiding the need for rescue therapy is estimated to provide a large cost offset to the costs of the TPO therapies. As a consequence, the costs of rescue and the rates of rescue for responders and non-responders drive much of the analysis.

When the manufacturer uses its own trial data and its own literature review, eltrombopag is cost effective relative to romiplostim due to the lower drug and administration costs. The cost effectiveness of eltrombopag compared to the non-TPO-RA containing sequence is poor: £61,337 per QALY for the splenectomised and £95,356 per QALY for the non-splenectomised.

But for what the manufacturer describes as the base case, the data drawn from the publicly available TA221 documents is the main source of evidence. The only elements drawn from the RAISE+EXTEND data are the TPO response rates and the TPO time on treatment. This results in cost effectiveness estimates for eltrombopag dominating the non-TPO-RA containing sequence for the splenectomised, and showing reasonable cost effectiveness of £15,105 per QALY for the non-splenectomised.
Results are also sensitive to the source of the HRQoL data, rescue rates, rescue costs, severe bleed rates, severe bleeds' mortality rates and an assumption that severe bleed rates double for those at the end of the line and off treatment.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG opinion is that the natural starting point for populating the model is the manufacturer's own data and own literature review. Some combination of this data with the data reported in TA221 where the data definitions for the TA221 data are clear could be performed. But it does not seem tenable for the manufacturer to largely discard its own data for the base case, and rely upon that which it gleans from the TA221 reports.

The model structure is transparent, broadly reasonable and in line with that of TA221 on romiplostim. The main uncertainty relates to which data source is the most reasonable to use for the derivation of event rates.

An additional problem is that the manufacturer model assumes that those having had a response at any point and remaining on treatment have a platelet count of more than $50x10^9$/L. This enables the manufacturer to apply event rates related to having a platelet count of more than $50x10^9$/L to responders. But the RAISE trial data suggest that only between 60% and 80% of eltrombopag responders' assessments showed a platelet count of more than $50x10^9$/L. It seems likely that the event rates estimated from the eltrombopag trial data are too low for responders, and should be adjusted.

There may be additional uncertainties about the relative effectiveness of the TPO-RA in terms of whether they have the same response rate, but this may not particularly affect conclusions unless other aspects are also differentiated between the TPO-RA. The extent that the average responder dose is below the average all patients dose may differ between the TPO-RA. The average duration of response may also differ. The manufacturer electronic model may suggest a longer within trial duration for romiplostim for splenectomised patients, though not for the non-splenectomised patients.

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

1.6.1 Strengths

The manufacturer identified all the relevant studies comparing eltrombopag versus placebo and presented a suitable meta-analysis.

The manufacturer presents a number of analyses of the RAISE+EXTEND data in order to populate the model. These occur alongside with what appears to be a reasonable literature review conducted by the manufacturer to arrive at effectiveness estimates for the non-TPO-RA therapies.

1.6.2 Weaknesses and areas of uncertainty

The manufacturer conducted an indirect comparison despite the clinical heterogeneity in the patient populations and outcome definitions between the RAISE trial and the two Kuter 2008 trials.[1] The methodology used by the manufacturer to undertake the indirect comparison was not necessarily optimal. There were concerns over the lack of methodological rigour in the manufacturer's review of non-TPO-RA evidence.

The manufacturer discarding its own data and literature for the base case in favour of what can be taken from the TA221appraisal is a major weakness and is somewhat peculiar. No real justification for this approach is given.

A very basic uncertainty is what definition of responder should be used for the modelling, and how well this definition is aligned with the event rate equations.

Another area of uncertainty is whether the extrapolation of the duration of TPO response is reasonable. The parametric fitted curves flatten noticeably for the extrapolation period beyond the Kaplan Meier curves, and there may be concerns about the length of the tails.

It can be argued that the manufacturer SF-6D HRQoL data should also be applied for the base case, because this is patient level data reported using a generic instrument for which a peer reviewed and respected UK population mapping function to utilities exists.

The analysis does not consider the optimal sequencing of treatments. It may be possible for some patients to achieve response more cheaply with other treatments. Those who do not could then progress to the more expensive TPO-RA, if these are found to be cost effective.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG included the Tomiyama study[2] into the meta-analysis for eltrombopag versus placebo. The inclusion of this study did not affect the interpretation of the results (excluding Tomiyama gave OR (fixed): 8.23 [95% CI (4.68 to 14.48)], while including Tomiyama gave OR(fixed): 8.64 [95% CI (4.97 to 15.04)].

The ERG undertook the indirect comparison for durable and overall response and for grade 3-5 and grade 2-5 bleeds between eltrombopag and romiplostin using a different method from the manufacturer. With regard to 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 OR 0.22 [95% CrI (0.05 to 1.02)] while the ERG found in favour of romiplostim (OR 0.15 [95% CI (0.02 to 0.84)].

The ERG has made minor revisions to the manufacturer cost effectiveness model, but these have little real impact upon results. The alternative base case modelling results in cost effectiveness estimates of £75,297 per QALY for the splenectomised and £106,800 per QALY for the non-splenectomised.

Applying the SF-6D RAISE+EXTEND utilities worsens the cost effectiveness of eltrombopag to £90,753 per QALY for the splenectomised and £133,508 per QALY for the non-splenectomised.

The impact of applying the overall response rates for eltrombopag, and of applying the results of the manufacturer indirect comparison, is felt mainly in the comparison between eltrombopag and romiplostim. But of itself it is not sufficient to make romiplostim cost effective compared with eltrombopag.

Applying an approximation of the median romiplostim responder dose does not change the overall conclusions, but does lessen the degree of dominance of eltrombopag over romiplostim. But note that this sensitivity analysis is partial as the ERG does not have access to the parallel dosing information for eltrombopag.

Dropping the assumption of a doubling in the fatal bleed rate for those last in line has a large impact upon the net QALY gain over the non-TPO-RA sequence.

Removing adverse events has little impact upon the model results. Altering the cost of non-severe bleeds from day-case to outpatient has some impact upon costs, but it is also relatively minor.

The above must be qualified by the existence of TA221 data and the possibility of it being incorporated into the RAISE+EXTEND data.

Key points:

- Eltrombopag (compared with placebo) appears to be effective and safe for the short-term treatment of ITP
- Platelet count response rate and risk of bleeding appear to be similar between eltrombopag and romiplostim interventions (indirect comparison)
- There is no robust evidence on which to judge the effectiveness of eltrombopag compared with existing non-TPO-RA therapies
- Eltrombopag appears to be a more cost-effective option than romiplostim

The above summary conclusions should be weighed against the ERG concerns with regard to the effectiveness and cost effectiveness evidence.

2 BACKGROUND

Platelets are bloods cells whose role is to arrest bleeding by plugging any breeches in the vascular system and to initiate and propagate blood coagulation. Immune thrombocytopenic purpura (ITP) is an autoimmune condition where antibodies are formed against the body's own platelets. Antibody binding leads to increased clearance of platelets by the reticuloendothelial system, predominately in the spleen, and possibly reduced platelet production. If the rate of clearance exceeds the rate of production the platelet count will fall. The normal platelet count is 150-400 x 10^9/L but spontaneous bleeding does not usually occur until the platelet count falls below 30 x 10^9/L. Higher platelet counts, however, are required for certain operative procedures (e.g. major surgery or invasive diagnostic procedures) to be performed.

ITP can occur in any age group, although this submission is limited to adult patients. It is also associated with certain medical conditions e.g. other autoimmune diseases, HIV and hepatitis C. ITP may present as bleeding and/or bruising or be asymptomatic and picked up on blood counts taken for other reasons.

Spontaneous remission of adult ITP is rare. Both British Committee for Standards in Haematology (BCSH)[3]) and the American Society for Hematology (ASH)[4] recommend treatment in their guidelines if the platelet count is below 30 x 10^9/L, if there is bleeding, or if an operative procedure requires a higher platelet count. The International Consensus Report,[5] an industry funded expert led guideline, gives similar recommendations but does not make the distinction of a platelet count of 30 x 10^9/L as a trigger for treatment. In the UK there are only three licensed medical therapies for first-line treatment of ITP (corticosteroids, intravenous immunoglobulin (IVIg) and anti-D) and evidence for these and other therapies for ITP is very limited and often confined to case series. Recently anti-D has been withdrawn as a treatment for ITP from the European market by the manufacturer due to safety concerns (although it is still marketed as a treatment for ITP in the USA and in the UK other unlicensed preparations of anti-D are available).

Splenectomy, a surgical treatment, is possibly curative in 66% of patients[6] but carries mortality risk from the operation itself and has the long term complications of asplenia**.** It is recommended as second line treatment for those patients who are fit enough when first line treatment fails.

Eleven to 35% of patients fail to respond to first and second line treatments or require unacceptably high doses of steroids.[3] Data for other treatments, which are all immune-suppressants and carry considerable side-effects, are limited. Other treatments that have been investigated include cyclophosphamide, vinca alkaloids, high dose steroids, danazol, azathioprine, ciclosporin, rituximab, mycophenolate mofetil, dapsone, campath, autologous stem cell transplantation, interferon and

combination chemotherapy. Recently however thrombopoietin analogues and receptor agonists (romiplostim and eltrombopag respectively) have been demonstrated to increase platelet production and count in randomised controlled trials in ITP patients failing first line therapies. Romiplostim and eltrombopag have been licensed in Europe for the treatment of ITP and were approved for use by the Scottish Medicines Consortium for adult chronic ITP splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) and for restricted use as second line treatment for adult non-splenectomised patients where surgery is contra-indicated.[7] Romiplostim has been approved by NICE based on a single technology assessment with indications similar to the above license.[8]

2.1 Critique of manufacturer's description of underlying health problem

The manufacturer's description of the underlying health problem appears accurate. They firstly discuss the incidence and prevalence of the disease. The data come from population registries and the incidence varies from 1.6 to 3.9 per 100,000[9] while the prevalence ranged from 23 to 50 per 100,000.[10,11] The variation in rates could be expected using population registries of different populations. The ERG group couldn't find better data.

The pathology of the disease, being autoimmune in nature, is consistent with several peer -reviewed reviews on the subject [12,13]

The manufacturer is correct in stating that bleeding is the major, and potentially life-threatening, side-effect of ITP. Several studies have demonstrated that patients with ITP have a higher rate of bleeding and death compared to age matched controls. For example the most recently published study[14] showed an increased risk ratio of 4.4 (C.I. 1.8-3.2) for hospital admission with bleeding and 2.3 (C.I. 1.8-3.2) for death. They are also correct in stating that the risk of bleeding appears to increase as the platelet count falls, for example one study[15] followed up 104 patients with chronic ITP and none of those with a platelet count over $30x10^9$/L died from bleeding but 37% of the patients with a count less than $30x10^9$/L died due to bleeding.

The exact mortality from ITP is hard to truly quantify, given that many studies use historical patients when supportive care may have been inferior, for example Cohen's[16] figure of a 5 year mortality for those over 60 years is derived from two small studies, including 40 and 31 patients respectively.[17,18] It is doubtful how accurate this figure is given the papers were published more than 20 years ago. A more recent paper suggests that the mortality rate in ITP patients older than 60 years of age is 2.2 (95% confidence intervals 1.7-2.9) times greater than that of matched controls.[14]

2.2 Critique of manufacturer's overview of current service provision

The manufacturer discusses the two most up-to-date English language guidelines on ITP.[4,5] These are likely to be the most referred to guidance for physicians treating ITP. These guidelines suggest the therapeutic use of eltrombopag in situations similar to those described in the manufacturer's submission and the license indication. The submission is also in line with the recommendations of the referenced Scottish Medicines Committee's report.[19]

The manufacturer in figure A1 and table A4 summarises what they consider to be the most likely treatment options for ITP patients together with dose indications and cost information for eltrombopag therapy. Given the lack of definitive published data on this specific clinical subject, and the recommendations contained in the existing clinical guidelines (referenced above), the manufacturer's summary can be seen as a reasonable description of the current service provision.

3 DEFINITION OF THE DECISION PROBLEM

3.1 Population

The manufacturer's submission states that the eltrombopag is indicated for:

- adult splenectomised ITP patients who are refractory to other treatments; or
- adult non-splenectomised ITP patients where splenectomy is contraindicated (second line treatment).

The definition of the population is in line with the final scope of the appraisal, the license indications and the clinical guidelines discussed in section 2.2.

3.2 Intervention

The technology submitted is a thrombopoietin agonist (eltrombopag) that is given as a daily oral tablet with the aim of increasing the platelet production and hence count in ITP. The drug is titrated dependent on the platelet count, starting at a dose of 50mg daily (25mg for those of East Asian ancestry), aiming for a platelet count of between 50 and 200 x 10^9/L (normal range 150-400 x 10^9/L). The method of administration, monitoring and side-effects are those described in the summary of product characteristics.

3.3 Comparators

Eltrombopag is to be used as a third line treatment for ITP (second line for patients for whom splenectomy is contraindicated). First line therapy includes steroids, and/or occasionally intravenous immunoglobulin. Second line therapy is splenectomy if a patient is fit enough to undergo surgery. Third line therapies encompass a wide range of different treatments - e.g. azathioprine, cyclosporine A, cyclophosphamide, danazol, dapsone, mycophenolate mofetil, rituximab and vinca alkaloids.

A change in therapy is initiated when a patient becomes refractory to the prescribed drug or develops significant side-effects. The existing clinical guidelines take different views regarding the best sequencing of drugs. The International Consensus[5] lists all the third line treatments alphabetically whilst the American Society Guidelines[9] highlight rituximab and the thrombopoietin receptor agonists, romiplostim and eltrombopag, as those with the most evidence about safety and efficacy, which should be considered before other options. Patients may not be taking any drugs despite having a low platelet count.

Given that there is no defined care pathway it is reasonable that various sequences are explored. It is unclear why the manufacturer examines treatment sequences that exclude romiplostim, considering that the drug has been approved by NICE and can in theory be used in this group of patients. There is some indication that a flat dose of 100 mg of rituximab weekly for four weeks is effective (compared

to the standard 375 mg/m^2 weekly for four weeks)[20] but this is not discussed by the manufacturer. There is also no discussion on the long-term use of first line therapies (steroids and intravenous immunoglobulin). The doses and treatment schedules of the other third line drugs are similar to those in the guidelines, the British National Formulary and the referenced papers.

Patients with chronic ITP may relapse, require a higher platelet count for an operative procedure, or suffer a significant bleed for which a short-term 'rescue' therapy may be initiated. The manufacturer describes the use of intravenous steroids, intravenous immunoglobulin or platelet transfusions for this purpose. The manufacturer does not discuss, however, the use of oral steroids for rescue therapy or the consequences of increasing the dose of any current treatment as a rescue strategy.

3.4 Outcomes

The outcomes considered by the manufacturer are acceptable. They include mortality, response rate (platelet count), symptoms reduction, adverse events, need for rescue therapy, and quality of life. The main focus is on platelet count as a surrogate outcome for risk of bleeding. This is justified by the fact that bleeding symptoms (including serious or fatal bleeding) are infrequent in patients with platelet count over $50x10^9$/L. Section 2.1 of the report discusses the problems of determining the true mortality rates in patients with ITP. There are data that confirm that there is an increased risk of bleeding with a lower platelet count.[15]

3.5 Other relevant factors

No other relevant factors noted.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

In the current submission the manufacturer updated the systematic review which they conducted for the previous TA205 submission. Two reports detailing the methods used for conducting the original TA205 review and the current update review were made available by the manufacturer in response to the ERG clarification letter. The critique of the review methods is based on both the information in the main submission and on the two supplementary systematic review reports.

4.1.1 Description of manufacturer's search strategies and critique

Details of the literature searches undertaken on 6th and 27th February 2012 are reported in Appendix 2 of the submission report. MEDLINE, MEDLINE In-Process, EMBASE and CENTRAL were searched and were supplemented by searching the conference proceedings of the European Haematology Association and American Society of Hematology for the years 2004 to present. The searches were identical to those undertaken in 2009 for the original submission so were therefore run from January 2009 and any records previously retrieved in the original searches were excluded at the abstract review stage. Other databases such as Science Citation Index, CINAHL and Biosis would have been appropriate to search but the included sources were the main ones and as such should have provided adequate coverage of the literature.

The full search strategies that were used are provided and were therefore reproducible. The approach adopted was to carry out one search to find all relevant clinical and quality of life information on the intervention and comparators included in the systematic review. The searches were constructed using three sets of terms; (a) ITP terms, (b) intervention/comparator terms, (c) methodology terms. These were correctly combined using the Boolean operator OR for each set of terms. Then the summary of each set were combined using AND. Both controlled vocabulary terms and free text terms were used but some key terms were omitted which may have compromised the sensitivity of the search. Free text searching did not always include common variations. Most notable omissions were variation for "thrombocytopenic" (thrombocytopaenic and thrombocytopenia) and "romiplostim" (nplate, AMG 532 AMG531 and remiplistim).

The methodology part of the MEDLINE and EMBASE search strategies were the weakest sections and were difficult to follow. This was largely due to the duplicate use of some controlled vocabulary terms both as single terms and as part of higher order exploded terms. For example in MEDLINE, "Controlled Clinical Trial/" is captured by "exp Clinical Trial/" and "Prospective Studies/" by "exp Cohort Studies/". Some appropriate terms were excluded: for example the MeSH term "Comparative Study/" and EMTREE terms "Controlled Study/" and "Retrospective Study/". The strategy would also

have benefited from additional methodology – related text terms. In particular, the term "retrospective" was omitted even though retrospective studies were listed in the inclusion criteria.

The search strategy used in CENTRAL also included a methodology section. This seemed unnecessary since this database consists mostly of trials and inclusion risked compromising the sensitivity of the search.

Due to concerns over the sensitivity of the manufacturer's clinical effectiveness search strategies, the ERG undertook independent searches for eltrombopag and the comparators. MEDLINE, MEDLINE In-Process and EMBASE databases were searched. The eltrombopag search comprised ITP related and eltrombopag terms only to maximise the sensitivity of the search. The multifile search in MEDLINE and EMBASE for comparators was similar to the structure of the manufacturers search but included additional controlled vocabulary and text terms. The terms used relating to methodology included those used in the Cochrane Highly Sensitive RCT filter and a published filter selective for comparative and case series studies.[21] Details are provided in Appendix 1.

4.1.2 Inclusion criteria

The inclusion criteria used in the systematic review of clinical effectiveness are tabulated in Table 1.

Table 1 Inclusion criteria for the systematic review of clinical effectiveness

Population	Adults (≥ 18 years) with ITP (platelet counts ≤ 30 x 10^9/L) as a primary diagnosis. Patients with ITP due to other causes were excluded.
Interventions and comparators	Evaluated ≥ 1 of: • Eltrombopag • Romiplostim • Corticosteroids (dexamethasone, methylprednisolone) • Danazol • Dapsone • Intravenous immunoglobulin (IVIg) • Anti-D immunoglobulin • Rituximab • Immunosuppressive agents (azathioprine, ciclosporin, mycophenolate mofetil) • Cytotoxic agents (vincristine, vinblastine,

	cyclophosphamide) • Autologous stem cell transplantation or • Any combination of the above treatments. Studies reporting the outcome of splenectomy were excluded.
Outcomes	Studies reporting ≥ 1 of the following outcomes were included: ***Efficacy and safety outcomes****:* • Platelet count (median, response rate, durability of response) • Need for rescue treatment or concurrent ITP treatment • Symptoms reduction • Adverse events • Bleeding events (incidence, severity and outcome) • Mortality ***Health related quality of life*** ***Economic outcomes:*** • Total costs • Total effectiveness • Life years gained • Quality adjusted life years gained (QALYs) gained • Cost per life year gained • Cost per QALY
Study design	Prospective clinical studies (RCTs and non-RCTs) and retrospective studies including ≥ 10 patients
Language restriction	English language studies only

The final scope issued by NICE stated that the population of interest is adults with ITP who have had a splenectomy and are refractory to other treatments; or who have not had a splenectomy and for whom surgery is contraindicated as a second line treatment. The inclusion criteria for the manufacturer's systematic review are not as restrictive as the NICE scope, and allow inclusion of any adults with primary ITP who had received more than one prior ITP therapy.

Although the exclusion criteria for the manufacturer's review make no mention of specific ethnic groups, a number of studies were excluded on the basis that they were confined to a Japanese population. [2,22,23] If Japanese ethnicity is indeed a valid reason for excluding studies, this should have been pre-specified in the inclusion/exclusion criteria of the assessment.

The manufacturer's approach to conducting the systematic review presented in the current submission was to update the systematic review carried out in May-June 2009 for TA205 with new searches from January 2009 onwards.[24] They state that any studies which were retrieved by the original search were excluded at abstract stage in the updated 2012 review. Although this approach can be considered acceptable, it may have resulted in the exclusion of potentially relevant studies since the inclusion criteria of the 2009 review were not exactly the same as those adopted for the present review. The inclusion of studies in the TA205 original review was restricted to prospective studies. However, in the updated review, the criteria were stretched to allow inclusion of retrospective studies. Potentially relevant retrospective studies published before May-June 2009 may have, therefore, been missed in the current systematic review.

Furthermore, the manufacturer applied a set of *post hoc* criteria for non-TPO-RA studies. Non-TPO-RA studies which met the inclusion criteria for the systematic review, but failed to meet the *post hoc* criteria, were excluded from further discussion and analyses. The justification given for this choice was that studies which met the additional criteria would be more comparable with the RAISE study, and consequently they would be more suitable for inclusion in the indirect comparisons. The ERG considers that it was inappropriate to modify the inclusion criteria for the non-TPO-RA studies post hoc, as this may potentially introduce bias. The additional inclusion criteria applied by the manufacturer for non-TPO-RA studies are shown in Table 2. Reporting of bleeding events is not mentioned in the additional inclusion criteria for non-TPO-RA studies. Since bleeding rates are, arguably, a relevant outcome measure for this review, reporting of bleeds should also have been considered for non-TPO-RA studies. In the response to the ERG clarification letter (clarification response: A9), the manufacturer stated that only five of the non-TPO-RA included studies reported bleeding endpoints but they were heterogeneous and not detailed enough to allow a meaningful comparison or quantitative synthesis. Nonetheless, all relevant outcomes should have pre-specified within the inclusion criteria in order to minimise bias.

Table 2 Inclusion criteria for non-TPO-RA studies applied *post hoc* by the manufacturer

Population	Studies were included if they: • Included patients only with platelet count $\leq 20 \times 10^9$/L; or if this was not specified had an average baseline platelet count of $\leq 20 \times 10^9$/L • Included any patients who had received prior ITP therapies Studies which included no patients who had received previous ITP therapy, or did not report that patients had prior treatment were excluded.
Outcomes	Studies which reported any of the following outcomes were included: • Response as a platelet count of $>50 \times 10^9$/L • Time to response • Duration of response

4.1.3 Identified studies

The manufacturer's search identified: i) 11 eltrombopag studies of which 4 were RCTs, ii) 4 romiplostim studies of which 2 were RCTs, and iii) 113 non-TPO-RA studies. However, 76 of the non-TPO-RA studies were subsequently excluded as they did the *post hoc* criteria, leaving 37 non-TPO-RA included studies (of which 6 RCTs).

All relevant eltrombopag and romiplostim RCTs retrieved using the manufacturer's search are summarised in Table 3, and all relevant eltrombopag and romiplostim non-RCTs are summarised in Table 4.

Table 3 Identified eltrombopag and romiplostim RCTs

Eltrombopag			
Study	***Population***	***Intervention***	***Treatment duration***
TRA100773A	Patients with ≥ 6 month history of ITP and had received ≥ treatment for ITP	Eltrombopag 30, 50 or 75mg	6 weeks
TRA100773B	Patients with ≥ 6 month history of ITP and had received ≥ treatment for ITP	Eltrombopag 50mg	6 weeks
TRA102537 RAISE	Patients with chronic ITP which had responded to a previous treatment	Eltrombopag 50mg	6 months
Tomiyama 2009[2]	Japanese patients with previously treated chronic ITP	Eltrombopag 12.5mg	6 weeks
Romiplostim			
Study	***Population***	***Intervention***	
Kuter 2008[1] Splenectomised	Splenectomised patients with ITP who had received at least 1 previous treatment for ITP	Romiplostim 1µg/kg adjusted according to response	24 weeks
Kuter 2008[1] Non-splenectomised	Non-splenectomised patients with ITP who had received at least one previous treatment for ITP	Romiplostim 1µg/kg adjusted according to response	24 weeks

Table 4 Identified eltrombopag and romiplostim non-RCTs

Eltrombopag		
Study	***Population***	***Intervention***
TRA 108057 REPEAT	Patients who had received ≥1 prior treatments for ITP and had a platelet count between 20 000/ μL – 50 000/ μL	Eltrombopag (in 3 cycles of repeated intermittent dosing)
TRA 105325 EXTEND	Patients previously enrolled in TRA 100773A, TRA 100773B, TRA 102537 RAISE or TRA 108057 REPEAT	Eltrombopag
Meyer 2011[25]	Patients who had received ≥1 prior treatments for chronic ITP and had a platelet count < 10 000/μL	Eltrombopag or romiplostim
Kuter 2011[26]	Adults with chronic ITP who have been treated with a TPO-RA for at least 4 weeks	Eltrombopag or romiplostim
Haselboeck 2011[27,28]	Not reported	Eltrombopag and steroids
Cooper 2011[29]	Adults with ITP recruited onto TRA100773A, TRA100773B, TRA102537 RAISE, TRA 108057 REPEAT and TRA 105325 EXTEND	Eltrombopag
Olney 2011[28]	Adults with ITP recruited onto TRA100773A, TRA100773B, TRA102537 RAISE, TRA 108057 REPEAT and TRA 105325 EXTEND	Eltrombopag

Romiplostim		
Study	***Population***	***Intervention***
Bussel 2009,[30] Bussel (ASH) 2009,[31] Kuter (ASH) 2010[32]	Patients who have had ≥1 prior treatment for ITP and had participated in one of the romiplostim trials. Patients were enrolled after their platelet count dropped to ≤50 000/μL	Romiplostim
Janssens (ASH) 2011,[33] EHA 2011[34]	Patients with ≥1 prior treatment for ITP and a platelet count ≤30 000/μL	Romiplostim

Because of concerns about the sensitivity of the manufacturer's search, the ERG conducted additional searches. Citations from the search results were screened for potential relevance. The ERG identified 19 full-text studies (Table 5) and 10 conference proceedings (Table 6) which may potentially meet the inclusion criteria of the manufacturer's review. Although these studies were all identified by the ERG's search, it should be noted that some of the studies published in 2012 may not have been available at the time of the manufacturer's review. All studies published before 2012, however, should have been available to the manufacturer.

Table 5 Potentially missed studies

Study	Intervention	Design
Tomiyama 2012[35]	Eltrombopag	RCT
Zeng 2011[36]	Eltrombopag, romiplostim	Systematic review
George 2009[37]	Romiplostim	RCT (HRQoL data)
Gernsheimer 2010[38]	Romiplostim	RCT plus open label extension
Kellaf 2011[39]	Romiplostim	Case series
Kuter 2012[40]	Romiplostim	RCT (HRQoL data)
Michel 2011[41]	Romiplostim	Controlled trial (unclear from abstract if randomised)
Sanz 2011[42]	Romiplostim	RCT (HRQoL data)
Shirasugi 2012[43]	Romiplostim	Open label extension
Stasi 2012[44]	Romiplostim	RCT
Zaja 2012[45]	Dapsone	Case series
Naithani 2010[46]	Dexamethasone	Case series
Nakazaki 2012[47]	Dexamethasone, corticosteroids	Non-randomised comparative study
Qin 2010[48]	Intravenous immunoglobulin	Meta-analysis
Aleem 2010[49]	Rituximab	Case series
Arnold 2012[50]	Rituximab	RCT
Auger 2012[51]	Rituximab	Systematic review and meta-analysis
Brah 2012[52]	Rituximab	Case series
Dabak 2009[53]	Rituximab	Case series
Dierick 2009[54]	Rituximab	Case series
Mahevas 2012 [55]	Rituximab	Case series
Zaja 2010[56]	Rituximab	Case series

Table 6 Potentially missed studies – conference abstracts

Study	Intervention	Design
Gaman 2012[57]	Eltrombopag	Case series
Grotzinger 2012[58]	Eltrombopag	Open label extension study (HRQoL data)
Miyazaki 2010[59]	Romiplostim	Open label extension study
Rodeghiero 2012[60]	Romiplostim	Pooled analysis of two case series
Thornton 2012[61]	Romiplostim	Cost-effectiveness study
von Depka 2012[62]	Romiplostim	Cost-effectiveness study
Wadenvik 2012[63]	Romiplostim	Case series
Appelby 2012[64]	Rituximab	Case series
Tran 2012[65]	Rituximab	Case series
Untama 2012[66]	Rituximab	Case series

4.1.4 Critique of data extraction

Details on data extraction were provided in the supplementary information sent by the manufacturer in response to the ERG clarification letter.

Few details were provided on how data were extracted for the original review. The report mentions the use of a pre-determined data extraction table. However, no information was provided on who actually extracted data from included studies. Ideally data extraction would have been performed independently by two reviewers, and any disagreements would have been resolved by discussion.

More details were provided on how data extraction was performed for the updated review. We consider that all of the listed study and patient characteristics and outcomes are relevant. However, it was also unclear from this report who carried out data extraction.

4.1.5 Quality assessment

Details on the assessment of the methodological quality of included studies were provided in both the manufacturer's submission and the supplementary information sent by the manufacturer in response to the ERG clarification letter.

The manufacturer appraised the methodological quality of RCTs, (except those non-TPO-RA trials which were excluded *post hoc*). Quality assessment was not performed on studies reported as conference proceedings or on non-randomised studies. Whilst we consider it appropriate not to attempt quality assessment on conference abstracts, to avoid appraising non randomised evidence is less justifiable.

Details on who performed quality assessment were provided in the two supplementary systematic review reports. Two reviewers independently assessed the risk of bias of each included study and final agreement was reached by consensus. We consider this strategy appropriate. The tool used for quality assessment was akin to the Cochrane Collaboration risk of bias tool[67] and was judged appropriate by the ERG.

Eltrombopag RCTs

Overall, the quality of the eltrombopag RCTs was good. Randomisation was achieved using an in-house randomisation system using a computerised schedule. Investigators and assessors were blind to treatment status and blinding was maintained in patients using matching placebo tablets. The manufacturer stated that participants could be unblinded when knowledge of treatment status was necessary for the care of the subject. However, it is not clear if any patients were unblinded, and if so if these patients continued in the trial. It is also unclear how blinding was maintained in patients who had large platelet responses to eltrombopag, particularly if eltrombopag treatment was interrupted or discontinued because of a high platelet level.

We have a few minor concerns related to the quality assessment of the three eltrombopag RCTs. Although it was reported that intention to treat analysis was carried out in trials TRA100773A [68] and TRA100773B,[69] some patients were excluded from the analysis after randomisation. The analysis of these trials was therefore not strictly on an intention to treat basis. Furthermore, even though 'randomisation' did not achieve a balance of patient characteristics in terms of age and ethnicity in TRA100773A, the manufacturer considered this item as 'low risk'. It would have been more appropriate to mark this item as 'unclear', as this imbalance may have introduced potential biases.

Romiplostim RCTs

The manufacturer's submission reported quality assessment of the two romiplostim RCTs.[1]

The quality of the two romiplostim RCTs was good. Patients were randomly assigned to either romiplostim or placebo using an interactive voice response system and a random allocation sequence generated by Amgen. Patient and physicians were blind to treatment status. Blinding was maintained using identical vials for romiplostim and placebo.

The manufacturer rated all of the items on the quality assessment tool as 'low risk'. The ERG agrees with this assessment.

Non-TPO-RA RCTs

Information related to the quality assessment of the non-TPO-RA RCTs was provided in the supplementary material (updated systematic review details) sent by the manufacturer in response to

the ERG clarification letter. This material was not included, or referred to, in the main submission document. Only the methodological quality of the included RCTs[70-75] was critically appraised (6 trials) but not the quality of the non-randomised studies (31 non-TPO-RA studies).

Overall, the manufacturer considered the quality of the six RCTs to be of 'low risk'. The ERG did not validate the quality assessment of these studies.

4.1.6 Evidence synthesis

The manufacturer submitted a substantial amount of evidence (more than 200 pages for the main submission; more than 100 pages for the Appendices; and more than 300 pages for two systematic review reports).

Quantitative synthesis of eltrombopag evidence as regards to its clinical effectiveness consisted of: i) a direct comparison between eltrombopag and placebo, ii) an indirect comparison between eltrombopag and romiplostim, and iii) a systematic review of non-TPO-RA interventions.

The comparison between eltrombopag and placebo used data from the three included eltrombopag RCTs. A fourth eltrombopag RCT (Tomiyama)[2] was initially identified as potentially relevant but subsequently excluded because based on a Japanese patient population. Reasons for excluding the Tomiyama trial were not entirely justifiable and the manufacturer could have attempted to include it in further analyses, where appropriate. Data on platelet count $\geq 50 \times 10^9$/L at day 43 from TRA100773A, TRA100773B and RAISE were combined in a meta-analysis. Although data for bleeding rates and quality of life were also available, these data were not meta-analysed.

An indirect comparison between eltrombopag and romiplostim was carried out using data from the RAISE trial and the two romiplostim RCTs,[1] with placebo as a common comparator. Data from TRA100773A and TRA100773B were not included in the indirect comparison. In a response to an ERG query (Response: A6), the manufacturer explained that TRA100773A and TRA100773B could not be included in the analysis of durable platelet response, as this would require at least 8 weeks of treatment data. They further argued that since a small number of clinically significant bleeds were observed in TRA100773A and TRA100773B, assessment of bleeding events in the indirect comparison would have been of little clinical value. The ERG agrees with this interpretation.

The efficacy of non-TPO-RA interventions versus eltrombopag was assessed by means of a systematic review of non-TPO-RA studies (mainly observational studies), which met both the original inclusion criteria and the more stringent *post hoc* criteria. Three main outcomes were assessed: platelet response, time to response and duration of response. Simple weighted averages were used for

all outcomes to derive pooled results for each included non-TPO-RA comparator, regardless of the outcome definitions used. Analysis of bleeding rates was not conducted. Since the included non-TPO-RA studies were non-randomised and highly heterogeneous and no direct comparisons with eltrombopag were possible, the observed results are likely to be prone to bias and should therefore be interpreted with extreme caution.

The ERG assessed the methodological quality of the manufacturer's updated systematic review of clinical effectiveness using the CRD criteria (Table 7). The methodological quality of the review was mixed. In particular, weaknesses were noticed in the development of the literature searches and in the quality assessment of included studies.

Table 7 Quality assessment of the manufacturer's review.

CRD quality item	Score
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	**Yes**
2. Is there evidence of a substantial effort to search for all of the relevant research?	**Partial** - further searches were required by ERG
3. Is the validity of included studies adequately assessed?	**No** - quality assessment was only conducted for some of the studies
4. Are sufficient details of the individual studies presented?	**Yes**
5. Are the primary studies summarised appropriately?	**Yes**

4.2 Summary of submitted evidence

4.2.1 Comparison of eltrombopag versus placebo

The evidence provided by the manufacturer on the clinical effectiveness of eltrombopag came from three RCTs (TRA100773A, TRA100773B and TRA102537 (RAISE)). The ERG has summarised this evidence by outcome measure.

The three included studies had similar inclusion and exclusion criteria (Table B9 in the manufacturer's submission). Tables B10 (TRA100773A and TRA100773B) and Table B11 (RAISE) in the submission describe the characteristics of participants at trial entry. This includes: age, gender, race, splenectomy status, concomitant ITP medication, platelet count and number of prior treatments. TRA100773A was a four-arm study and randomised participants to placebo or to 30mg, 50mg or

75mg eltrombopag, while the other two RCTs (TRA100773B and RAISE) randomised to 50mg eltrombopag or placebo (with dose adjustment as required). TRA100773A and TRA100773B both had a six week treatment phase compared with a six month treatment phase in RAISE.

A summary of these three eltrombopag trials is provided in Table 8.

Table 8 Comparison of characteristics of RAISE, TRA100773A and TRA100773B

	RAISE	TRA100773A	TRA100773B
Main inclusion criteria	• Aged 18 years or older • Diagnosis of primary ITP of at least 6 months duration • Baseline platelet count < 30 000/μL • Had responded to one or more previous treatments for ITP	• Aged 18 years or older • Diagnosis of primary ITP of at least 6 months duration • Baseline platelet count < 30 000/μL • Had received one or more prior therapies for ITP • Values within normal range for neutrophils, reticulocyte count, creatinine and liver enzymes	• Aged 18 years or older • Diagnosis of primary ITP of at least 6 months duration • Baseline platelet count < 30 000/μL • Had received one or more prior therapies for ITP • Values within normal range for creatinine and liver enzymes
Main exclusion criteria	• Participation in previous eltrombopag study • Evidence of HIV infection • Hepatitis B or C infection • Cardiovascular disease or arrhythmia • History of malignant disease, chemotherapy or radiotherapy • History of arterial or venous thrombosis and two or more thrombosis risk factors	• Secondary immune thrombocytopenia • Haemoglobin levels <10g/dL • Congestive heart failure, arrhythmia or thrombosis within one year of enrolment • Myocardial infarction within three months of enrolment • Pregnant or breastfeeding women	• Evidence of HIV infection • Evidence of hepatitis B or C infection • Congestive heart failure, arrhythmia or thrombosis within one year of enrolment • Myocardial infarction within three months of enrolment • Pregnant or breastfeeding women • Patients who required drugs containing calcium or magnesium

	RAISE	TRA100773A	TRA100773B
Minimum time since other ITP therapy	• IVIg – 1 week • Splenectomy, rituximab and cyclophosphamide – 4 weeks • Romiplostim – 30 days	All other therapies (apart from maintenance immunotherapy) must have been completed at least two weeks before treatment	• Immunoglobulins, immunomodulators, Rituximab and cyclophosphamide – 2 weeks
Concurrent therapy criteria	Allowed as long as dose was stable for at least 4 weeks before randomisation (3 months for ciclosporin, mycophenolate and danazol) and remained unchanged during the last 6 weeks of the trial	Maintenance immunotherapy regimens were allowed as long as the dose had been stable for one month and did not change during the study	Allowed as long as dose had been stable for at least 1 month and was intended to remain stable during the treatment period
Duration of treatment	Six months	Six weeks	Six weeks
Intervention and dosing schedule	Eltrombopag 50mg • Eltrombopag dose could be increased to a maximum of 75mg after 22 days if platelet count was <50 000/µL • Dose could be decreased to a minimum of 25mg if platelet count >200 000/µL • If platelet count >400 000/µL eltrombopag was interrupted and reintroduced at the next lowest dose once platelet count fell <150 000/µL	Eltrombopag 30, 50 or 75mg	Eltrombopag 50mg

	RAISE	TRA100773A	TRA100773B
	• After 6 weeks of treatment, patients with a platelet count >100 000/μL could have their concomitant therapy reduced		
Primary outcome	Odds of achieving a platelet count 50 000 – 400 000/μL during the treatment period	Proportion of patients with platelet count ≥ 50 000/μL	Proportion of patients with platelet count ≥ 50 000/μL
Definition of durable (or sustained) response	Weekly platelet responses (platelet count 50 000-400 000/μL) during at least 6 of the last 8 weeks of treatment. Patients who received rescue treatment at any time during the study, or who withdrew early were not considered to have had a durable response.	N/A	N/A
Proportion who had ≥3 previous ITP treatments	54%	51%	51%
Proportion receiving concomitant ITP therapy	48%	32%	43%
Number randomised	197; eltrombopag – 135, placebo - 62	118; eltrombopag – 88, placebo – 29, post-randomisation withdrawal - 1	114; eltrombopag – 76, placebo - 38

	RAISE	TRA100773A	TRA100773B
Number analysed (efficacy analysis)	197; eltrombopag – 135, placebo -62	109; eltrombopag- 82, placebo - 27	112; eltrombopag – 74, placebo - 38

Platelet response at 43 days

Platelet response, defined as $\geq 50x10^9$/L at the end of treatment (day 43), was reported for studies TRA100773A and B. The response after these six weeks of eltrombopag treatment ranged from 28% (8/29, 30mg/day) to 81% (21/26, 75mg/day). A greater proportion of participants in the eltrombopag groups responded to treatment compared to placebo (Table 9).

Table 9 Platelet response ($\geq 50x10^9$/L) at end of treatment (43 days)

	Placebo	**Eltrombopag 30mg**	**Eltrombopag 50mg**	**Eltrombopag 75mg**
TRA100773A (6 week intervention)				
Responders, n/N (%)	3/27 (11%)	8/29 (28%)	19/27 (70%)	21/26 (81%)
Odds Ratio (relative to placebo) 95% CI	N/A	3.1 (0.7,13.8)	22.0 (4.7, 102.2)	38.8 (7.6, 197.7)
TRA100773B (6 week intervention)				
Responders, n/N (%)	6/37 (16%)	-	43/73 (59%)	-
Odds Ratio (relative to placebo) 95% CI	N/A	-	9.6 (3.3, 27.9)	-

Source: Tables B15/B16 in manufacturer's submission

Platelet response rates were only presented separately by splenectomy status for TRA100773B in graphical format by the manufacturer. Among non-splenectomised participants, 57% (20/35) of participants in the eltrombopag group had a platelet response $\geq 50x10^9$/L at the end of the intervention compared with 17% (4/24) in the placebo group. The results for splenectomised participants were similar (62% [19/31] vs. 15% [2/14]).

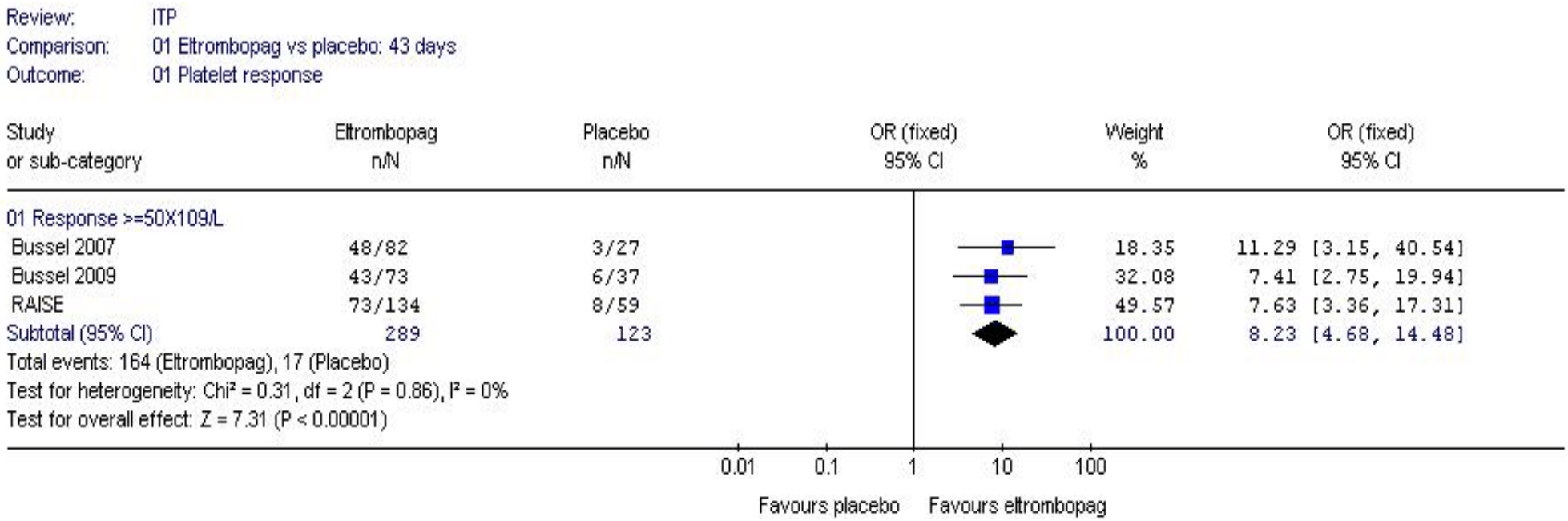
Platelet response at 43 days was not a defined outcome in RAISE but the manufacturer was able to acquire these data in order to include it in a meta-analysis with the TRA10073A and B studies (Table B20 in manufacturer's submission). Responders in RAISE were defined as having platelet counts $>50x10^9$/L and $<400x10^9$/L. Table 10 shows the data used in the manufacturer's meta-analysis of the three studies. The three eltrombopag arms of TRA10073A have been combined by summing the numerators and denominators in the three treatment groups.

Table 10 Platelet response at 43 days

	Placebo	Eltrombopag
TRA100773A	3/27 (11%)	48/82 (59%)
TRA100773B	6/37 (16%)	43/73 (59%)
RAISE	8/59 (14%)	73/134 (54%)

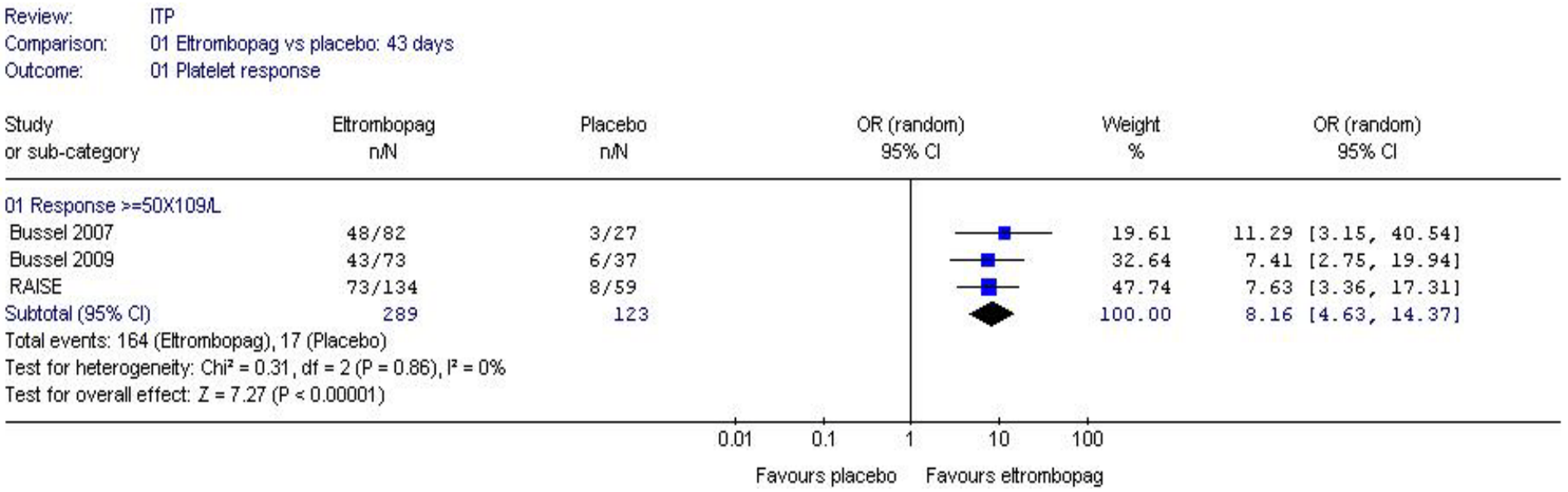
The Mantel-Haenszel method of meta-analysis (using both fixed and random effects models) was employed. Figure 1 and 2 present the meta-analysis forest plots provided by the manufacturer. The results provide evidence that the odds of responding were greater after eltrombopag than following placebo groups [OR (fixed): 8.23 (95% CI: 4.68 to 14.48), OR (random): 8.16 (95% CI: 4.63 to 14.37)].

Figure 1 Eltrombopag versus placebo: forest plot of platelet response at day 43 (fixed effect model)



Source: Figure B11 in manufacturer submission

Figure 2 Eltrobopag versus placebo: forest plot of platelet response at day 43 (random effects model)



Source: Figure B12 in manufacturer submission

Platelet response at any point during the intervention

Platelet response ($\geq 50x10^9$/L) at any time during treatment was available for TRA100773B (six week intervention) and for RAISE (six month intervention). This was in fact the primary endpoint of the RAISE trial. In TRA100773B the actual numbers were not reported but the odds ratio for response in the eltrombopag group compared with the placebo group was 8.8 (3.5, 21.9) (Table B17 of the manufacturer's submission). Results were similar in RAISE, with 106/134 (79%) in the eltrombopag group responding at least once in the six month treatment period compared to 17/60 (28%) in the placebo group (OR 8.2 [99% CI (3.59, 18.73)]) (Table B19 of the manufacturer's submission).

Duration of platelet response

Duration of platelet response was reported for the RAISE trial. Duration was defined in two ways: continuous duration of response (weeks) and cumulative duration of response (weeks). For continuous duration of response, the eltrombopag group had a median of 8.1 weeks compared with zero weeks in the placebo group (Table B21 of the manufacturer's submission). For cumulative duration of response, the median in the eltrombopag group was 10.9 weeks compared with zero in the placebo group. For both definitions the range of values was similar in each group, but no interquartile range was provided.

Health related quality of life (HRQoL)

The SF-36 instrument, which consists of eight sub-domains and two component summary scores (representing physical and mental health), was used in all three eltrombopag RCTs. RAISE also included subscales of the FACT and FACIT instruments. The manufacturer did not report this quality of life information in detail but the ERG have summarised the SF-36 information here. In TRA100773A, 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 75mg/day eltrombopag group ($p = 0.02$). No details were provided for these scores and there was no indication of whether they differed between treatment groups. In TRA100773B the SF36 sub-domain scores were similar at baseline and the end of study, but no numerical details were given. 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 the majority of health and well-being domains of the SF-36 instrument compared to 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]).

Use of rescue medication during treatment

No information was provided for this outcome for TRA100773A and B. In RAISE rescue treatment was defined as a composite of: new ITP medication, increased dose of a concomitant ITP medication, platelet transfusion, and/or splenectomy. Forty per cent (25/62) of the placebo group required rescue medication at some time during the study compared with 18% (25/135) in the eltrombopag group (OR 0.33 [95% CI 0.16 to 0.64], p=0.001).

Reduction in dose/frequency of concomitant ITP medications taken at baseline

RAISE reported that 63/135 (47%) participants in the eltrombopag arm and 31/62 (50%) in the placebo arm used ITP medications at baseline. Of the eltrombopag-treated participants, 37 (59%) reduced or discontinued at least one concomitant ITP medication, compared with 10 (32%) in the placebo group. The odds of reducing or discontinuing at least one baseline ITP medication were three times higher in the eltrombopag-treated group (OR 3.10 [95% CI 1.24 to 7.75], p=0.016). Of those who permanently discontinued or had a sustained reduction of at least one ITP medication (31 eltrombopag participants and 6 placebo participants), 77% and 67% respectively discontinued ≥1 baseline ITP medication, while 68% and 50% respectively, discontinued all baseline ITP therapies.

Haemostatic challenge during or after the intervention

In TRA100773A four participants faced situations of haemostatic challenge. One in the placebo group required IVIg prior to surgery. The other three, all from the 50mg/day eltrombopag group, did not require rescue treatment, with two undergoing surgery and one involved in a car accident. In TRA100773B three participants underwent haemostatic challenge. One participant in the eltrombopag group had a tooth extraction one week after treatment discontinuation with no additional medication was required. Two placebo group participants underwent surgery and received IVIg, platelet transfusion and tranexamic acid in preparation. During RAISE, 14 (10%) eltrombopag participants and 4 (7%) placebo participants experienced haemostatic challenge. Four of the 14 eltrombopag participants required rescue treatment and 2/4 placebo participants required rescue treatment after dental procedures. No further details on these haemostatic challenges were provided.

Safety

No deaths were reported in the three eltrombopag studies in the current submission. The ERG checked the published trial reports and found that one participant treated with 50mg eltrombopag in TRA100773A died. This participant had chronic obstructive pulmonary disease, asthma, and peripheral oedema when entering the study. After 21 days of eltrombopag therapy he developed grade 3 pneumonia, hepatitis, renal insufficiency, and grade 4 obstructive pulmonary disease. Twenty five days after entering the study the participant died due to cardiopulmonary failure.

Another patient in the placebo group in the RAISE trial had fatal brain-stem haemorrhage.

Adverse events

Adverse events in all three trials were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3. Table 11 provides a summary of the overall adverse event rates for the three trials. During the treatment phase, in TRA 100773A rates of adverse events were similar between the placebo group and each of the eltrombopag dose groups (59% on placebo and 47%-61% on eltrombopag) (Table 11). In TRA 100773B a greater proportion of participants receiving eltrombopag experienced an adverse event (59% versus 37%) compared with those receiving placebo. Adverse event rates were higher in RAISE, which had a longer period of follow-up. Eighty-seven per cent (118/135) of participants in the eltrombopag group experienced any adverse event compared with 92% (56/61) of those in the placebo group. In TRA100773A in both the placebo and 50mg eltrombopag group two serious adverse events (SAEs) were reported with no SAEs in the 30mg and the 75mg groups. In TRA100773B, SAEs were reported in two participants in each of the eltrombopag and placebo groups and in RAISE this was 18% (11/61) and 11% (15/135) respectively.

In TRA100773A adverse events considered by the investigators as related to study medication were similar in each group; in TRA100773B a higher proportion was reported in the eltrombopag group compared with placebo (26% (20/76) versus 11% (4/38)). Similarly in RAISE, 36% (18/61) in the eltrombopag group reported this compared with 30% (48/135) in the placebo group. In RAISE adverse events considered to lead to withdrawal occurred in a slightly higher proportion of eltrombopag participants (9/135, 12%) compared with placebo participants (4/61, 7%). Rates were similar in each group for TRA10073A and TRA10073B.

Table 11 Summary of adverse events (AEs) during intervention, number of participants (%)

		Any AE	Any SAE	Any AE related to study med	AEs leading to withdrawal
TRA100773A[a]	Placebo	59% (17/29)	7% (2/29)	31% (9/29)	7 % (2/29)
	Eltrombopag 30mg	47% (14/30)	0% (0/30)	30 % (9/30)	0% (0/30)
	Eltrombopag 50mg	47% (14/30)	7% (2/30)	27% (8/30)	7 % (2/30)
	Eltrombopag 75mg	61% (17/28)	0% (0/28)	36% (10/28)	4% (1/28)
TRA100773B[a]	Placebo	37% (14/38)	5% (2/38)	11% (4/38)	5% (2/38)
	Eltrombopag 50mg	59% (45/76)	3% (2/76)	26% (20/76)	4% (3/76)
RAISE[b]	Placebo	92% (56/61)	18% (11/61)	30% (18/61)	7% (4/61)
	Eltrombopag 50mg	87% (118/135)	11% (15/135)	36% (48/135)	12% (9/135)

[a] six week intervention; [b] six month intervention

Details of adverse events in the three eltrombopag studies are reported in Tables B57, B58 and B60 of the manufacturer's submission. Most common adverse events (occurring in at least 10% of participants in a treatment group in at least one of the three trials) are shown in Table 12. Headache was the most common AE in all three trials. Other frequent adverse events were: fatigue, diarrhoea, nausea, nasopharyngitis, upper respiratory tract infection and pain in extremity.

Averse events of specific interest where assessed in the RAISE study and shown in Table B61 of the submission. Thromboembolic events and abnormal liver function measurements were observed more often in the eltrombopag group rather than in the placebo group, but no statistical comparisons were taken.

Table 12 Adverse events experienced by at least 10% of participants in one or more of the three eltrombopag RCTs

	TRA100773A[a]				TRA100773B[a]		RAISE[b]	
Event, n (%)	**Placebo**	**Eltrombopag**			**Placebo**	**Eltrombopag**	**Placebo**	**Eltrombopag**
	N = 29	**30 mg**	**50 mg**	**75 mg**	**N = 38**	**50mg**		**50mg**
		N = 30	**N = 30**	**N = 28**		**N =76**	**N=61**	**N=135**
Any AE	17 (59%)	14 (47%)	14 (47%)	17 (61%)	14 (37)	45 (59)	56 (92)	118 (87)
Headache	6 (21)	4 (13)	3 (10)	6 (21)	4 (11)	6 (8)	20 (33)	41 (30)
Fatigue	5 (17)	0	1 (3)	2 (7)	-	-	8 (13)	13 (10)
Diarrhoea	2 (7)	0	1 (3)	1 (4)	1 (3)	4 (5)	6 (10)	17 (13)
Nausea	-	-	-	-	0	6 (8)	4 (7)	16 (12)
Nasopharyngitis	-	-	-	-	3 (8)	5 (7)	8 (13)	14 (10)
Upper respiratory tract infection	-	-	-	-	-	-	7 (11)	14 (10)
Pain in extremity	1 (3)	2 (7)	0	0	-	-	6 (10)	9 (7)

[a] six week intervention; [b] six month intervention

Bleeding

Trials TRA100773A and B used the WHO bleeding scale with a bleeding event defined by grades 2-4 on this scale. RAISE also used the WHO bleeding scale with bleeding events defined by WHO grades 1-4 and clinically significant bleeds defined by WHO grades 2-4. The manufacturer's submission stated that, for TRA100773A, the proportion of participants with bleeding was reported to be lower in all eltrombopag treatment groups compared to placebo from day 15 to day 43 of treatment. The data were not provided in the manufacturer's submission but the ERG extracted relevant data in graphical form from the published article[68] and presented this in Table 13. The manufacturer states that six weeks after treatment finished, the bleeding rates had returned to baseline levels in all treatment groups. In TRA100773B, in the eltrombopag treatment group 20/51 (39%) had suffered bleeding by day 43 compared with 18/30 (60%) in the placebo group (OR: 0.27 (95% CI: 0.09-0.88), p=0.029), suggesting those receiving eltrombopag suffered fewer bleeds. Similarly, bleeding at any point during treatment (Table 14), occurred in fewer participants randomised to eltrombopag (46/76; 61%) compared with those randomised to placebo (30/38; 79%) (OR = 0.49, 95% CI (0.26, 0.89), p=0.021).

Bleeding information for RAISE was provided in detail in Appendix 2 of the manufacturer's submission. At the end of treatment, 57% of placebo participants had bleeding compared with 27% in the eltrombopag group. The odds ratio for bleed at end of treatment was 0.25 (95% CI: 0.12 to 0.51) for eltrombopag compared with placebo indicating a statistically significant reduction in bleeds for those receiving eltrombopag. Fewer eltrombopag participants experienced bleeding (79%) at any time during the study compared with placebo (93%) (OR = 0.21 95% CI (0.06, 0.71), p=0.12).

Table 13 Bleeding at end of treatment

		Eltrombopag		
	Placebo	30mg	50mg	75mg
TRA100773A (6 week intervention)[#]	50%	41%	25%	24%
TRA100773B (6 week intervention)	60% (18/30)	-	39% (20/51)	-
RAISE (six month intervention)	57% (34/62)	-	27% (37/165)	-

[#] estimated from graph in Bussel 2007

Table 14 Bleeding at any time during treatment

		Eltrombopag		
	Placebo	30mg	50mg	75mg
TRA100773A (6 week intervention)	14%	17%	7%	4%
TRA100773B (6 week intervention)	79% (30/38)	-	61% (46/76)	-
RAISE (six month intervention)	93% (56/60)	-	79% (106/135)	-

No information on bleeding split by splenectomy status was provided by the manufacturer for TRA100773A and B. Data were available for these two subgroups within RAISE for bleeding at any time during the six-month treatment period. Table 15 suggests that eltrombopag participants were less likely to suffer clinically significant bleeding at least once at any time during the study regardless of splenectomy status. Bleeding (defined by WHO grade 1-4) was less likely in the eltrombopag group compared to placebo for those non-splenectomised but not for those who underwent splenectomy.

Table 15 Odds of bleeding in splenectomised and non-splenectomised participants in the TRA 102537 RAISE study

	Non-splenectomised		**Splenectomised**	
	Placebo n=40	**Eltrombopag n=85**	**Placebo N=20**	**Eltrombopag n=50**
Any WHO grade (1-4), n (%)	38 (95)	65 (76)	18 (90)	41 (82)
OR [a]		0.10		0.87
95% CI		0.02, 0.53		0.12, 6.07
p-value		0.007		0.887
Clinically significant bleeding (Grade 2-4), n (%)	18 (45)	25 (29)	14 (70)	19 (38)
OR [a]		0.31		0.27
95% CI		0.11, 0.83		0.08, 0.95
p-value		0.020		0.041

a. From logistic regression, adjusted for baseline concomitant ITP treatment use, platelet count, and bleeding scales.

Source: Table 6, Appendix 2, manufacturer's submission

4.2.2 Comparison of eltrombopag and romiplostim

No head-to-head trials for eltrombopag versus romiplostim were identified and the manufacturer maintains that the sample size required may limit the feasibility of a non-inferiority trial in this orphan disease. Two RCTs comparing romiplostim and placebo were identified by the manufacturer, one in splenectomised participants and the other in non-splenectomised participants.[1] These two

studies were presented within the same published article and were combined for the purposes of the submission. In the absence of a head-to-head comparison between eltrombopag and romiplostim an indirect comparison analysis was undertaken using the RAISE study and the two romiplostim RCTs. The manufacturer considered two main outcomes, platelet response and bleeding, in the indirect comparison.

The following table (Table 16) describes the characteristics of the RAISE and Kuter 2008 trials.

Table 16 Comparison of characteristics of RAISE and Kuter RCTs

	RAISE	**Kuter 2008** splenectomised	**Kuter 2008** non-splenectomised
Main inclusion criteria	• Aged 18 years or older • Diagnosis of primary ITP of at least 6 months duration • Baseline platelet count < 30 000/µL • Had responded to one or more previous treatments for ITP	• Aged 18 years or older • Had undergone splenectomy 4 or more weeks previously • Mean platelet count < 30 000/µL • Creatinine < 176.8µmol/L • Bilirubin <1.5 times upper limit of normal • Haemoglobin >90g/L • In patients over 60: bone marrow biopsy consistent with ITP	• Aged 18 years or older • Not splenectomised • Mean platelet count < 30 000/µL • Creatinine < 176.8µmol/L • Bilirubin <1.5 times upper limit of normal • Haemoglobin >90g/L • In patients over 60: bone marrow biopsy consistent with ITP
Main exclusion criteria	• Participation in previous eltrombopag study • Evidence of HIV infection • Hepatitis B or C infection • Cardiovascular disease or arrhythmia • History of malignant disease, chemotherapy or radiotherapy • History of arterial or venous thrombosis and two or more thrombosis risk factors	• Active malignancy • History of stem cell disorder	• Active malignancy • History of stem cell disorder

	RAISE	**Kuter 2008** splenectomised	**Kuter 2008** non-splenectomised
Minimum time since other ITP therapy	• IVIg – 1 week • Splenectomy, rituximab and cyclophosphamide – 4 weeks • Romiplostim – 30 days	• IVIg and Anti-D – 2 weeks • Alkylating agents – 8 weeks • Rituximab – 14 weeks • All other treatments- 4 weeks	• IVIg and Anti-D – 2 weeks • Alkylating agents – 8 weeks • Rituximab – 14 weeks All other treatments- 4 weeks
Concurrent therapy criteria	Allowed as long as dose was stable for at least 4 weeks before randomisation (3 months for ciclosporin, mycophenolate and danazol) and remained unchanged during the last 6 weeks of the trial	Corticosteroids, azathioprine and danazol at a constant rate and schedule were all allowed.	Corticosteroids, azathioprine and danazol at a constant rate and schedule were all allowed.
Duration of treatment	Six months	24 weeks	24 weeks
Intervention and dosing schedule	Eltrombopag 50mg • Eltrombopag dose could be increased to a maximum of 75mg after 22 days if platelet count was <50 000/µL • Dose could be decreased to a minimum of 25mg if platelet count >200 000/µL • If platelet count >400 000/µL eltrombopag was interrupted and reintroduced at the next lowest dose once platelet count fell <150 000/µL	Romiplostim, initially 1µg/kg weekly, increased to a maximum of 15µg/kg according to response. • In order to achieve a target count of 50 000 -200 000/µL, dose was increased by 2 µg/kg every week if platelet count was <10 000/µL, and 2 µg/kg every two weeks if platelet count was 11 000-50 000/µL • During the first 12 weeks, concomitant therapies could be reduced if platelet count	Romiplostim, initially 1µg/kg, increased to a maximum of 15µg/kg according to response. • In order to achieve a target count of 50 000 -200 000/µL, dose was increased by 2 µg/kg every week if platelet count was <10 000/µL, and 2 µg/kg every two weeks if platelet count was 11 000-50 000/µL • During the first 12 weeks, concomitant therapies could be reduced if platelet count >100 000/µL. Concomitant

	RAISE	**Kuter 2008** splenectomised	**Kuter 2008** non-splenectomised
	• After 6 weeks of treatment, patients with a platelet count >100 000/μL could have their concomitant therapy reduced	>100 000/μL. Concomitant therapies could not be reduced in the final 12 weeks.	therapies could not be reduced in the final 12 weeks.
Primary outcome	Odds of achieving a platelet count 50 000 – 400 000/μL during the treatment period	Proportion of patients with a durable platelet response	Proportion of patients with a durable platelet response
Definition of durable (or sustained) response	Weekly platelet responses (platelet count 50 000-400 000/μL) during at least 6 of the last 8 weeks of treatment. Patients who received rescue treatment at any time during the study, or who withdrew early were not considered to have had a durable response.	Weekly platelet responses (platelet count ≥50 000/μL) during at least 6 of the last 8 weeks of treatment. Patients who received rescue treatment at any time during the study were not considered to have had a durable response.	Weekly platelet responses (platelet count ≥50 000/μL) during at least 6 of the last 8 weeks of treatment. Patients who received rescue treatment at any time during the study were not considered to have had a durable response.
Proportion who had ≥3 previous ITP treatments	54%	94%	42%
Proportion receiving concomitant ITP therapy	48%	29%	34%

The two romiplostim trials were first combined by the manufacturer using standard Mantel-Haenszel meta-analysis techniques. The indirect comparison of eltrombopag versus romiplostim was then performed using the Bucher method.[76] Separate indirect comparisons were also performed for splenectomised and non-splenectomised participants. For these analyses the manufacturer derived data from RAISE split by splenectomy status and combined the relevant RAISE data with the appropriate romiplostim trial.

Platelet response

Separate analyses were performed for two definitions of platelet response: durable response and overall response. Durable response was defined as a weekly platelet count $\geq 50x10^9$/L during six or more of the last eight weeks of treatment, excluding those who received rescue medication at any time during the study. Overall response was defined as durable plus transient response (four or more weekly responses $\geq 50x10^9$/L during the study without a durable response from week 2 to 25). Tables 17 and 18 show the results of the indirect comparison analyses - all results were checked and replicated by the ERG. The results of the indirect comparison were framed such that odds ratios greater than one favour eltrombopag. Although all point estimates favour romiplostim, each confidence interval for the odds ratio comparing eltrombopag with rompilostim includes one suggesting that there is no statistically significant differences between the two interventions. It is worth noting, however, that the confidence intervals are wide and that the odds ratio for overall response (including all participants) is of borderline statistical significance (OR 0.22: 95% CI: 0.05 to 1.02).

Table 17 Results of the indirect comparison between eltrombopag and romiplostim – durable response[a]

Eltrombopag vs. Placebo		Romiplostim vs. Placebo		Eltrombopag vs. Romiplostim
n/N	OR (95% CI)	n/N	OR (95% CI)[b]	OR 95% CI[c]
All participants				
63/135 vs 4/62	12.7 (4.4, 36.9)	41/83 vs 1/42	39.0 (5.1,297.5)	0.32 (0.03, 3.14)
Non-splenectomised				
43/85 vs 3/41	13.0 (3.7, 45.3)	25/41 vs 1/21	31.3 (3.8,256.3)	0.41 (0.04, 4.80)
Splenectomised				
20/50 vs 1/21	13.3 (1.7,107.4)	16/42 vs 0/21	26.8 (1.5,472.4)	0.50 (0.01, 17.3)

[a] defined as weekly platelet count $\geq 50x10^9$/L during six or more of the last eight weeks of treatment excluding those who received rescue medication at any time during the study
[b] Mantel-Haenszel meta-analysis (fixed effects model)
[c] Indirect comparison (Bucher)

Table 18 Results of the indirect comparison between eltrombopag and romiplostim – overall response[a]

Eltrombopag vs. Placebo		Romiplostim vs. Placebo		Eltrombopag vs. Romiplostim
n/N	OR (95% CI)	n/N	OR (95% CI)[b]	OR (95% CI)[c]
All participants				
91/135 vs 8/62	14.0 (6.1,31.9)	69/83 vs 3/42	64.1 (17.3, 236.8)	0.22 (0.05, 1.02)
Non-splenectomised				
61/85 vs 6/41	14.8 (5.5, 40.0)	36/41 vs 3/21	43.2 (9.3, 201.1)	0.34 (0.06, 2.14)
Splenectomised				
30/50 vs 2/21	14.3 (3.0, 68.0)	33/42 vs 0/21	151.6 (8.4, 2742.0)	0.09 (0.00, 2.52)

[a] defined as durable plus transient response (four or more weekly responses $\geq 50 \times 10^9$/L during the study without a durable response from week 2 to 25
[b] Mantel-Haenszel meta-analysis (fixed effects model)
[c] Indirect comparison (Bucher)

Bleeding

The manufacturer also conducted an indirect comparison of bleeding event data. In the romiplostim trials two definitions of bleeding were adopted: bleeding grades 2-5 and bleeding grades 3-5. For the purposes of the indirect comparison, the manufacturer grouped bleeding events in the same way for the RAISE trial using the common terminology criteria for adverse events (CTCAE). In the original manufacturer's submission, relative risks were presented where values less than one favoured eltrombopag. The ERG requested the comparison be presented consistently with the platelet response data. The revised analyses provided by the manufacturer were checked by the ERG and are presented in Tables 19 and 20. There were no statistically significant differences in the odds of bleeding between the eltrombopag and romiplostim treatments.

Table 19 Results of the indirect comparison between eltrombopag and romiplostim, grade 3-5 bleeds[a]

Eltrombopag vs. Placebo		Romiplostim vs. Placebo		Eltrombopag vs. Romiplostim
n/N	OR (95% CI)	n/N	OR (95% CI)[b]	OR 95% CI[c]
All participants				
3/135 vs 4/62	0.33 (0.07,1.52)	6/84 vs 5/41	0.55 (0.16, 1.93)	0.60 (0.08, 4.29)
Non-splenectomised				
3/85 vs 2/41	0.71 (0.12, 4.45)	2/42 vs 1/20	0.95 (0.08, 11.1)	0.75 (0.03, 16.1)
Splenectomised				
0/50 vs 2/21	0.08 (0.00, 1.68)	4/42 vs 4/1	0.45 (0.10, 2.00)	0.17 (0.01, 5.31)

[a] Common toxicity for adverse events for RAISE, 5 point scale for Kuter 2008
[b] Mantel-Haenszel meta-analysis (fixed effects model)
[c] Indirect comparison (Bucher)

Table 20 Results of the indirect comparison between eltrombopag and romiplostim, grade 2-5 bleeds[a]

Eltrombopag vs. Placebo		Romiplostim vs. Placebo		Eltrombopag vs. Romiplostim
n/N	OR (95% CI)	n/N	OR (95% CI)[b]	OR 95% CI[c]
All participants				
12/135 vs 9/62	0.57 (0.23, 1.45)	13/84 vs 14/41	0.35 (0.15, 0.85)	1.63 (0.46, 5.80)
Non-splenectomised				
8/85 vs 5/41	0.75 (0.23, 2.45)	4/42 vs 6/20	0.25 (0.06, 1.00)	3.05 (0.48, 19.2)
Splenectomised				
4/50 vs 4/21	0.37 (0.08, 1.65)	9/42 vs 8/21	0.44 (0.14, 1.40)	0.83 (0.13, 5.49)

[a] Common toxicity for adverse events for RAISE, 5 point scale for Kuter 2008
[b] Mantel-Haenszel meta-analysis (fixed effects model)
[c] Indirect comparison (Bucher)

Use of rescue medication

In both Kuter 2008 trials, there was a lower requirement for rescue medication in the romiplostim group (splenectomised: 11/42 (26%) vs 12/21 (57%); non-splenectomised: 7/42 (17%) vs 13/20 (62%). In RAISE 18% on those on eltrombopag required rescue medication compared with 40% placebo. No further analysis was undertaken by the manufacturer.

Discontinuation of concurrent ITP medication

The manufacturer reported that, in the Kuter 2008 trials, 31% of all participants were receiving concurrent ITP medication at baseline (27% of those on romiplostim, 39% on placebo). Dose decrease or discontinuation of concurrent ITP medications was allowed only during the first 12 weeks when platelet count was more than $100x10^9$/L. No decrease or discontinuation was allowed thereafter but increases were allowed at any time.

4.2.3 Comparison of eltrombopag with non-TPO-RA

The non-TPO-RA treatments under consideration were IVIg, Anti-D, rituximab, corticosteroids, vina alkaloids, mycophenolate mofetil, ciclosporin, cyclophosphamide, danazol and dapsone. Although a total of 113 studies were identified, including 20 RCTs (Table B40 in the submission), the manufacturer found relatively little high quality data to compare eltrombopag with the non-TPO-RA treatments. *Post hoc* exclusion criteria were applied which resulted in the majority of identified studies being excluded, including the majority of RCTs. The manufacturer chose to combine the results of the 37 included studies (of which only 6 RCTs) using a naive weighted average approach, weighted by the size of the study. Data were included regardless of the definition of response. Where sufficient data were identified by the manufacturer, they calculated weighted averages for response, time to response and duration of response. The manufacturer summarised the efficacy of each comparator using a simple average. They acknowledged that this is likely confounded by differences in patient characteristics and study design. The summary of the evidence provided by the manufacturer is presented in Table 21.

IVIg is commonly used as a rescue treatment, because while it produces a rapid increase in platelet count, the duration is short lived. In seven studies, responses were observed in 70-100% of patients with the weighted average calculated as 82%. Anti-D is not available in the UK for treatment of ITP but three studies were considered. Responses were observed in between 34% and 52.7% of participants, with weighted average 42%. In studies using rituximab, responses over $50x10^9$/L were observed for between 14% and 93% of patients, with an average time to response between 4 and 14 weeks with duration of response 12.5 to 65 months. The weighted average of response was 59%. Only one small study was identified for vinca alkaloids with response of over $50x10^9$/L reported in 59% of patients. One small study assessing Danazol[77] reported a response rate of 35% for two months and a sustained response of 21% over a 12- month period. Reiner[78] reported on cyclophosphamide treatment and gave response rate of 85%. Dapsone was used in two studies with response rates of 40% and 48% respectively, giving a weighted average of 45%. The use of mycophenolate mofetil was evaluated in three studies with response rates between 39% and 69%; weighted average

53%. In studies involving corticosteroid, response was observed in 35% to 86% participants with a weighted average of 54%.

Table 21 Weighted averages per treatment for response, time to response and duration of response

			Weighted Average	
	Total N	**Response (%)**	**Time to response (days)**	**Duration of response (days)**
Cyclophosphamide	20	85%	NR	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	285	82%	24.4	17.2
Rituximab	463	59%	6.6	748.4
Corticosteroids	154	54%	NR	NR
Vinca alkaloids	12	58%	NR	NR

Source: Table B49, manufacturer submission

The manufacturer also presented information on non-TPO-RA response from two other sources: an International Consensus Report[5] (Table 22) and Amgen's STA submission to NICE on romiplostim (TA221) (Table 23).

Table 22 Response outcomes per treatment as reported in the International Consensus Report[5]

	Response (%)	Time to response	Duration of sustained response
Ciclosporin	~50 - 80%	3 - 4 weeks	>50% or 2 years
Cyclophosphamide	24 - 85%	1 - 16 weeks	<50%
Danazol	67% complete/partial	3 - 6 months	46% remained in remission at median 119 months following 37 months treatment
Dapsone	<50%	3 weeks	sustained in up to two-thirds off therapy
Mycophenolate mofetil	up to 75%, complete in up to 45%	4 - 6 weeks	short term
Anti-D	initially up to 80%	4 - 5 days	typically 3 - 4 weeks, but can last longer
IVIg	initially up to 80%	2 - 4 days (can be as fast as 24h)	usually transient, lasting 2 - 4 weeks, but can last longer
Rituximab	60%, complete in 40%	1 - 8 weeks	>3-5 years in 15-20% of responders
Corticosteroids (reported as 1st line treatment)	70 - 90% in dexamethasone and prednis(ol)one	several days to several weeks	As high as 60 -80% in latter cycles of dexamethasone during 2-5 year follow-up. Remains uncertain, although estimated at 10 year disease free survival in 13-15%
Vinca alkaloids	1- 75%	5 - 7 days	average 10 months

Source: Table B50, manufacturer submission

Table 23 Response outcomes reported in Amgen romiplostim STA submission to NICE, TA221

	Response (%)		Time to response	Duration of sustained response
	Splenectomised	Non-Splenectomised		
Ciclosporin	63%	50%	8 weeks	16.2 months
Cyclophosphamide	61%	70%	8 weeks	27 months
Danazol	60%	45%	16 weeks	147.35 months
Dapsone	47%	50%	4 weeks	20.3 months
Mycophenolate mofetil	44%	57%	16 weeks	5.7 months
Anti-D	NA	46%	instant	1 month
IVIg	79%	81%	instant	1 month
Rituximab	58%	58%	8 weeks	18.9 months
Corticosteroids (assuming rescue use)	46%	46%	instant	1 month
Vinca alkaloids	53%	67%	4 weeks	1.4 months

Source: Table B51, manufacturer submission

The manufacturer concluded that compared with treatments typically used as rescue medications in ITP patients, such as IVIg and Anti-D, the response rate for eltrombopag was comparable.

4.3 Critique of submitted evidence

4.3.1 Eltrombopag versus placebo

The manufacturer identified four RCTs comparing eltrombopag and placebo but only three of these (TRA100773A, TRA100773B and RAISE) were considered further. These are described in the summary of evidence above. A fourth RCT conducted in Japan[2] was excluded. No additional relevant RCTs were identified by the ERG. The manufacturer also identified seven non-RCTs (published in nine reports), which are not discussed further in this section.

A major difference between the three eltrombopag trials was in the length of follow-up: six months for RAISE, but just six weeks for TRA100773A and TRA100773B. All three studies collected information on platelet response at multiple time points. The primary outcome in TRA100773A and TRA100773B was the proportion of responders, defined as participants

who had an increase in platelet count to ≥ 50x10 ^{9}/L at day 43 of the study, while in RAISE the primary outcome was the odds of achieving a platelet count of ≥ 50x10 ^{9}/L and ≤ 400x10^9/L during the 6-month treatment period. There were some differences between the studies in how missing data were handled. In TRA100773A and TRA100773B the last observation carried forward (LOCF) approach was applied to participants who withdrew early because of a platelet count > 200x10^9/L and thus they would be counted as responders. No imputation for intermittent missing data was undertaken in RAISE, which the ERG regarded as acceptable as the method of analysis used allows for intermittent missing data. For participants in RAISE who had a dose adjustment visit prior to a missed visit, the data from the dose-adjustment visit were used. This was regarded as acceptable by the ERG.

Participants who withdrew prematurely for reasons other than platelet count >200x10^9/L in the TRA100773A and B trials were counted as having had no response. In RAISE subjects who withdrew were classified as non-responders from the time of withdrawal and for subsequent visits. The manufacturer provided CONSORT flow diagrams describing the flow of participants through the included trials and describing the numbers of participants who were randomised, who completed treatment and who were included in the efficacy analyses. In TRA100773A, the numbers included in the efficacy analysis (n=109) were not the same as those randomised (n=118). Similarly in TRA100773B, only 112 of the 114 randomised participants were included in the efficacy analysis and only 110 were included in the meta-analysis of platelet response. For RAISE, all 197 participants were included in the efficacy analysis, but only 193 were included in the meta-analysis. The reasons for these small discrepancies were initially unclear. The ERG queried this with the manufacturer who provided a more detailed flow chart. The numbers included in the meta-analysis were lower than those randomised due to post randomisation exclusions (baseline platelet count > 30x10^9/L) or study withdrawals. The ERG was satisfied with the manufacturer's response.

Meta-analysis of eltrombopag RCTs

Meta-analysis of the three eltrombopag RCTs was carried out for response rate (platelet count ≥ 50x10^9/L) at day 43 (end of treatment for TRA100773A and B, and interim point for RAISE). It was not possible to examine longer term platelet response outcomes in a meta-analysis as only RAISE investigated the effect of continuing treatment beyond six weeks. Although there are some differences between trials in the handling of withdrawals, the ERG considered it appropriate to combine these three RCTs. As noted above the denominators included in the meta-analysis differed from the numbers randomised and are referred to as the numbers evaluable. The Mantel-Haenszel method of meta-analysis (using both fixed and

random effects models) was employed and this was considered appropriate. These analyses were checked and replicated by the ERG.

No summary or synthesis of quality of life outcomes was provided by the manufacturer. All three studies collected SF-36 data at six weeks, although raw data (in the form of mean group differences in change scores) are only given for RAISE in the published paper[79] and not the manufacturer's submission. No attempt was made to obtain data from the other studies and include this in a meta-analysis. The ERG queried this and the manufacturer maintained that it was unlikely that there would be an impact on patient quality of life within this six week period. The ERG agrees that this is reasonable.

Although all three trials reported information on bleeding during treatment, no attempt was made to conduct a meta-analysis or present a narrative summary of this information. The ERG noted that the trial reports for TRA100773A and TRA100773B[68,69] report the percentage with WHO bleeding grades 2-4 (clinically significant bleeding); RAISE reports bleeding rates over time (grades 2-4) as a figure and provides further information about those with any bleeding in the text.[79] While noting that a formal meta-analysis could have been attempted, the ERG agrees that there is relatively little value in conducting a meta-analysis of short-term bleeding.

ERG concern over the exclusion of Tomiyama 2009[2]

The manufacturer admitted that post hoc criteria were used to select studies that were considered more relevant to the decision problem. They explained that all-Japanese studies, and in particular the Tomiyama study, were not representative of UK patients mainly because they used a different starting dose to that approved by the EU. The ERG accepts that the Tomiyama study differs from the other study in important ways (it has a lower starting dose than the other studies - 12.5mg - and includes participants of solely East Asian origin). Nevertheless, the exclusion of studies based on *post hoc* criteria indicates a lack of methodological rigour. It should also be noted that each of the three eltrombopag RCTs (TRA100773A, TRA100773B and RAISE) enrolled approximately 17-18% participants of Asian origin. Therefore the ERG considered additional meta-analyses to investigate the inclusion of the Tomiyama study (see section 4.4 below).

The Tomiyama study was only available as a conference abstract[2] at the time of the manufacturer's search (February 2012) but has since been published as a journal article[35] - even though it did not make any difference whether the abstract or full paper was used. It was

possible to include the Tomiyama study data for the platelet response outcome at 43 days but no for the bleeding outcome (bleeding events were only presented for both arms combined).

4.3.2 Comparison of eltrombopag versus romiplostim

As no RCTs were identified that directly compared eltrombopag and romiplostim, the manufacturer conducted an indirect comparison analysis using placebo-controlled trials. The manufacturer presented an indirect comparison for two outcomes: platelet response (defined using both durable response and overall response) and bleeding rates (defined using grade 3-5 bleeds and grade 2-5 bleeds on the CTCAE scale). Analyses were presented for all subjects and by splenectomy status.

The manufacturer included only one eltrombopag RCT (RAISE) in the indirect comparison. They did not include the TRA100773A and B trials and explained that this was due to the fact that only shorter term (six week) data were collected for these studies. Romiplostim is known to take longer to evoke a response so to include these shorter term eltrombopag data would not be clinically comparable. Although indirect comparison meta-analyses of response and bleeding at six weeks could have been attempted, the ERG agrees that it is not particularly worthwhile to perform these analyses.

The manufacturer included two RCTs comparing romiplostim with placebo, one in splenectomised and one in non-splenectomised patients. These used exactly the same methodology and were presented within the same article.[1] The results of these two trials were first combined in a standard fixed effects meta-analysis. The ERG had some concerns over whether this was sensible as the two trials were in heterogeneous non-overlapping subgroups - this issue is discussed further below.

Three other romiplostim RCTs were identified but not considered in the analyses by the manufacturer. The largest of these[80] was excluded because it included participants with starting platelet counts up to $50x10^9$/L and those with persistent rather than chronic ITP. The ERG agrees that it was sensible to exclude this study. A phase II study[81] was also excluded because it was a small dose finding study. The ERG did not necessarily feel this was an adequate reason for exclusion but having read the article we agree that it was correctly excluded by the manufacturer. The study was in a small number of people, with several dose groups and it reported only peak platelet count. The period of observation (10 weeks) was significantly less than the six months follow-up in Kuter 2008[1] and as previously intimated 10 weeks is not long enough to observe a response from romiplostim. A third study[23] was excluded because it included only safety data and was based on a Japanese population. As

with the Tomiyama 2009[2] trial for eltrombopag, excluding for the sole reason of enrolling a Japanese population was not regarded as sufficient for exclusion by the ERG. However, the study was conducted with 12 weeks follow-up, and includes different definitions of response that cannot be compared directly with those in the Kuter 2008 trials.[1] Therefore the ERG deemed it appropriate to exclude this study.

The manufacturer highlighted a number of concerns over the conduct of the indirect comparison analyses. These are summarised below, along with a further concern raised by the ERG about the indirect comparison methodology used to combine the studies.

Heterogeneity of study populations

The manufacturer acknowledged that there are differences in the baseline characteristics of those recruited to RAISE and to the combined Kuter 2008 studies,[1] particularly in the duration of ITP, the prior use of ITP medications and the proportion receiving concomitant medication. These differences were driven by the proportion of splenectomised participants (36% in RAISE versus 50% in the combined Kuter 2008 study).[1]

Definitions of response and bleeding

The manufacturer's indirect comparison makes the assumption 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.

RAISE collected both WHO bleeding data and bleeding adverse events using the CTCAE scale, but Kuter 2008 only collected bleeding information through adverse event reporting using an unnamed scale, which was assumed to be equivalent.[1] For this reason the manufacturer urged caution when interpreting the results of the indirect comparison.

The ERG believes that it was reasonable to proceed with the indirect comparison analyses despite these differences in definitions, as long as these are treated extremely cautiously.

ERG concern over assuming equivalent efficacy of eltrombopag and romiplostim for the cost-effectiveness analysis

The manufacturer expresses caution about interpreting the indirect comparison analyses, a sentiment which is echoed by the ERG. There were different frequencies of assessments in RAISE and Kuter 2008, the studies had different policies for dose reduction and discontinuation and RAISE did not consider platelet counts above $400x10^9$/L as responses.

The proportion of participants in the romiplostim group (27%) within the Kuter 2008 trials receiving concurrent ITP medications was lower than that in the eltrombopag group of RAISE (47%). There were also different definitions of transient response and bleeding. Bleeding data were extracted from adverse event reporting and it is questionable whether the definitions used in RAISE and Kuter 2008 trials are comparable. The ERG therefore warns that the results of the indirect comparison analyses should only be interpreted with caution. This is particularly the case for the analyses split by splenectomy status, since they fail to preserve the randomisation in the RAISE trial.

Methodological approach to perform the indirect comparison analyses

The manufacturer used standard meta-analysis (a Mantel-Haenszel fixed effect approach) to combine the results of the two romiplostim studies and then used the Bucher method to conduct an indirect comparison analysis of eltrombopag and romiplostim.[76]

This is not the only possible approach for conducting this indirect analysis. In the manufacturer's previous eltrombopag submission in 2009, the romiplostim trials were instead pooled by summing numerators and denominators, and then the Bucher method was used to conduct the indirect comparison. After criticising this approach because of the failure to preserve the randomisation within each study, the ERG performed analyses using an alternative method using logistic regression in its 2009 report.

Five methodological approaches to conduct an indirect comparison of the data presented in the previous manufacturer's submission were discussed in a recent article sponsored by Amgen.[82] These included the manufacturer's current approach (Mantel-Haenszel meta-analysis followed by Bucher), the approach considered by the manufacturer in their previous eltrombopag submission (a simple pooling of the two Kuter studies followed by Bucher), a logistic regression approach (using both fixed and random effects) followed by Bucher and a new approach (Bayesian meta-regression). Cooper and colleagues conclude that the Bayesian method may be the most robust approach as it incorporates all trial data within a single model and accounts appropriately for parameter uncertainty.[82] The results obtained by each approach were similar. Except for the approach using Mantel-Haenszel, the results favoured romiplostim for overall platelet response for all other methodological approaches. There was no evidence of a difference between eltrombopag and romiplostim for durable platelet response . Results were not presented separately for splenectomised and non-splenectomised patients. The results of this paper should be treated with caution as they are based on data which differ slightly from those provided in the current manufacturer's submission.

ERG concern over manufacturer's approach to the indirect comparison

The ERG had concern over the manufacturer's method for the indirect comparison. While the ERG understand the rationale for the indirect comparison to be performed, the studies are clinically heterogeneous and any result must be treated with extreme caution. Two main methodological issues arise within the indirect comparison approach: modelling the heterogeneity between the eltrombopag and the romiplostim trials and whether it is appropriate to combine the two Kuter 2008 trials as if they were one trial. To overcome these issues the ERG decided to undertake analysis using a Bayesian approach to conduct the indirect comparison (network meta-analysis). This is described further in the additional analysis section (section 4.4). The manufacturer also presented the indirect comparison analysis split by splenectomy status. The ERG was also concerned by this as these analyses fail to preserve the randomisation within RAISE and are therefore essentially observational analyses. The ERG also attempted separate Bayesian analyses according to participants' splenectomy status. Many of the statistical models failed, however, to converge and the ERG decided not to pursue this further.

4.3.3 Eltrombopag versus non-TPO-RA

ERG Concern over non-TPO-RA data

The ERG has concerns over the methodological rigour of this section. Additional exclusion criteria were implemented *post hoc* and, according to these revised criteria,79 of the original identified 113 non randomised studies were subsequently excluded. Any definition of response was taken and pooled using a simple weighted average of treatment arms. Although the ERG accepts that the evidence base to compare eltrombopag with non-TPO-RA therapies is very limited, we believe that any results obtained by this approach may be subject to bias and consequently should be treated with extreme caution. Given the dearth of available data, the ERG was not able to perform any further analysis. The clinical effectiveness data for non-TPO-RA taken forward into the cost-effectiveness analysis was obtained within TA221 on romiplostim.

4.4 Additional work carried out by ERG

4.4.1 Meta-analysis of RCTs comparing eltrombopag versus placebo

The ERG repeated the meta-analysis comparing eltrombopag and placebo after adding data from the Tomiyama trial which was excluded by the manufacturer.[35] We chose to perform this analysis using the Mantel-Haenszel method and assuming both fixed and random effects. Incorporating the Tomiyama trial into the meta-analysis of platelet response at 43 days did not change the interpretation of the results (OR (fixed): 8.64, 95% CI: 4.97 to 15.04, OR (random): 8.47 (95%CI: 4.86 to 14.78) (Figures 3 and 4).

Figure 3 **Eltrombopag versus placebo: platelet response at 43 days (fixed effect analysis)**

Figure 4 **Eltrombopag versus placebo: platelet response at 43 days (random effects analysis)**

4.4.2 Bayesian meta-analysis for indirect comparison of eltrombopag and romiplostim

The ERG undertook a Bayesian network meta-analysis using random effects implemented in WinBUGS version 1.4.[83] A binomial likelihood function with a logit link function was used.[84]

In all the models, a burn in of 20,000 iterations was implemented and posterior distribution parameter estimates for the odds ratio were generated from a further 100,000 iterations to allow for convergence and thinning parameter of 5 to account for autocorrelation. The primary analysis was undertaken with a prior distribution for between study heterogeneity of uniform (0, 0.5). When a small number of studies are included in a network meta-analysis, the random effect is highly sensitive to the prior distribution,[85] so the ERG used lower and higher between study heterogeneity values (0.1 and 2 respectively) to act as a sensitivity. Unlike the manufacturer's analysis, this treats the two Kuter 2008 trials as separate studies.

Table 24 Indirect comparison results from WinBUGS – platelet response

	Eltrombopag versus romiplostim		
	OR	**95% CrI**	**Decision**
Durable platelet response			
Bucher (manufacturer reported)	*0.32*	*(0.03, 3.14)*	*no difference*
ERG (low heterogeneity)	0.22	(0.01, 2.07)	no difference
ERG (medium heterogeneity)	**0.20**	**(0.01, 2.13)**	**no difference**
ERG (high heterogeneity)	0.16	(0.00, 5.99)	no difference
Overall platelet response			
Bucher (manufacturer reported)	*0.22*	*(0.05, 1.02)*	*no difference*
ERG (low heterogeneity)	0.15	(0.02, 0.74)	Favours Romiplostim
ERG (medium heterogeneity)	**0.15**	**(0.02, 0.84)**	**Favours Romiplostim**
ERG (high heterogeneity)	0.11	(0.00, 3.20)	no difference

Table 25 Indirect comparison results from WinBUGS – bleeding outcomes

	Eltrombopag versus romiplostim		
	OR	**95% CrI**	**Decision**
Grade 3-5 bleeds			
Bucher (Manufacturer reported)	*0.60*	*(0.08, 4.29)*	*no difference*
ERG (low heterogeneity)	0.54	(0.06, 4.22)	no difference
ERG (medium heterogeneity)	**0.55**	**(0.06, 5.04)**	**no difference**
ERG (high heterogeneity)	0.53	(0.01, 15.3)	no difference
Grade 2-5 bleeds			
Bucher (Manufacturer reported)	*1.63*	*(0.46, 5.80)*	*no difference*
ERG (low heterogeneity)	1.73	(0.47, 6.66)	no difference
ERG (medium heterogeneity)	**1.72**	**(0.39, 7.72)**	**no difference**
ERG (high heterogeneity)	1.76	(0.10, 34.0)	no difference

Tables 24 and 25 show the results of this Bayesian approach for the four outcomes: durable platelet response, overall platelet response, bleeding (grades 3-5) and bleeding (grades 2-5) for all participants together (irrespective of splenectomy status). The odds ratio of eltrombopag versus romiplostin is provided alongside the 95% credible interval. Table 24 shows that for durable platelet response, the Bayesian approach gives similar results to those obtained by the manufacturer using the Bucher method. However, in the case of overall platelet response, when assuming moderate heterogeneity, the Bayesian approach finds in

favour of romiplostim as the credible interval for the odds ratio excludes one. The effect of this assumption is investigated further in the cost-effectiveness section. Table 25 shows that in all analyses for bleeding outcomes, there is no evidence of a difference between eltrombopag and romiplostim.

4.5 Conclusions of the clinical effectiveness section

Key points:

- Eltrombopag (compared with placebo) appears to be effective and safe for the short-term treatment of ITP
- Platelet count response rate and risk of bleeding appear to be similar between eltrombopag and romiplostim interventions (indirect comparison)
- There is no robust evidence on which to judge the effectiveness of eltrombopag compared with existing non-TPO therapies

The above summary conclusions should be weighed against the following ERG concerns with regard to the evidence synthesis:

- The differences in baseline characteristics of the participants within RAISE and the two romiplostin RCTs (this was also noted by the manufacturer).
- The different definitions of platelet response and bleeding within RAISE and the two Kuter studies and whether they can be regarded as clinically equivalent (this was also noted by the manufacturer).
- The methodology used by the manufacturer to undertake the indirect comparison of eltrombopag and romiplostim.
- The less rigorous methodology used to conduct the evidence synthesis of the non-TPO-RA comparators, particularly the *post hoc* revision of inclusion criteria.

In addition, the ERG has the following minor concern:

- The exclusion of the Tomiyama 2009[2] eltrombopag study from the original meta-analysis of the eltrombopag RCTs.

5 COST EFFECTIVENESS

5.1 ERG comment on manufacturer's review of cost-effectiveness evidence

5.1.1 Description of manufacturer's search strategies and critique

In section 7.1 of the submission the manufacturer stated that a systematic review was conducted in Feb 2012 in order to identify relevant cost-effectiveness and cost-utility studies for the treatment of ITP in adults.

The searches for cost-effectiveness data were undertaken in MEDLINE, MEDLINE In-process, EMBASE, Econlit, NHS EED and HEED on 6th February 2012 and are provided in full in Appendix 10 of the submission. The MEDLINE and EMBASE strategies combined the same ITP terms as was used for the clinical effectiveness combined with (AND) a variety of very broad cost and economic terms. As for CENTRAL, the NHS EED strategy also included methods search terms which again seems unnecessary since this is a database of economic evaluations so inclusion of such terms may reduce sensitivity.

Separate searches for utilities and quality of life information were undertaken in MEDLINE and EMBASE on 16th March 2012 using additional QoL terms to those included in the clinical effectiveness search. These searches are reproduced in full in Appendix 11 of the submission. The methods section of the searches used a comprehensive selection of both controlled vocabulary and text terms. All searches were limited to 2009 - onwards to update the systematic review conducted for the previous eltrombopag submission.

The ERG is satisfied with the cost-effectiveness search strategies developed by the manufacturer.

5.1.2 Inclusion and exclusion criteria

Studies were included if they enrolled adults with ITP as a primary diagnosis with a median/mean platelet counts $<30x10^9$/L at baseline. Studies where patients had a higher platelet count at baseline, were included only if a proportion of patients had a platelet count $<30x10^9$/L. Non-English language studies as well as studies published as conference abstracts were excluded.

5.1.3 Results and conclusions

The manufacturer did not identify any suitable study to be included in the cost-effectiveness systematic review.

In the light of the economics of the manufacturer submission as reviewed below, the conclusions of the romiplostim TA221 FAD may be relevant. Romiplostim was accepted for use -provided that the romiplostim PAS applied - for patients:

- refractory to standard therapies and rescue therapies; or,
- with severe disease and a high risk of bleeds that requires frequent courses of rescue therapies,

Only a haematologist should start and supervise romiplostim use. The Committee concluded that the ICERs would be under £20,000 per QALY gained for the treatment of splenectomised patients, and around £30,000 per QALY gained for the treatment of non-splenectomised patients. Romiplostim dosing might also tend to be lower in clinical practice than in the trial, which could improve cost effectiveness.

5.2 Summary and critique of manufacturer's submitted economic evaluation by the ERG

5.2.1 Comparison of economic submission with NICE reference case

Table 26 NICE reference case checklist

Attribute	**Reference case and TA Methods guidance**	**Does the *de novo* economic evaluation match the reference case**
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Rituximab is not considered as a comparator for the base case. As a consequence, the analysis appears to accept that TPO-RA should only be considered for patients who are refractory to rituximab. The base case considers a treatment sequence of 8 non-TPO-RA treatments as one comparator. This is compared with treatment sequences of: Eltrombopag followed by the treatment sequence of 8 non-

		TPO-RA treatments, and Romiplostim followed by the treatment sequence of 8 non-TPO-RA treatments.
Patient group	As per NICE scope. "Adults with immune (idiopathic) thrombocytopenic purpura, who have had a splenectomy and are refractory to other treatments (e.g. corticosteroids, immunoglobulins) Adults with immune (idiopathic) thrombocytopenic purpura, who have not had a splenectomy and for whom surgery is contraindicated, as second line treatment"	Broadly, yes though note that the RAISE inclusion criteria included a response to a previous ITP therapy. RAISE previous therapies at baseline among all patients: 100% had 1 previous, 79% had 2 previous and 54% had 3 or more previous. Whether those with fewer previous therapies are refractory to (all?) other treatments is debatable. There may be some uncertainty about whether all non-splenectomised patients in RAISE were contraindicated to surgery. The base case modelling may also assume that patients are refractory to rituximab because rituximab is not considered in the base case treatment sequence. This may in turn reflect the romiplostim FAD.
Perspective costs	NHS & Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-effectiveness analysis	Cost utility analysis.
Time horizon	Sufficient to capture differences in costs and outcomes	Lifetime.
Synthesis of evidence on outcomes	Systematic review	Not for the base case. A review is conducted, but the base case assumes that the TPO-RA are clinically equivalent.

Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	The base case mainly uses values drawn from a study using TTO among members of the general public evaluating CITP health states: i.e. patients are not involved in the enumeration. SF-6D data are available from the RAISE trial, and are presented as a sensitivity analysis.
Benefit valuation	Time-trade off or standard gamble	The base case uses TTO.
Source of preference data for valuation of changes in HRQL	Representative sample of the public	359 members of the public were involved in the disease specific TTO HRQoL study.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Probabilistic modelling	Probabilistic modelling	Yes.
Sensitivity analysis		A wide range of univariate sensitivity analyses are presented for the base case, though not for the alternative base case. An additional scenario analysis that attempts to replicate the analysis of the romiplostim TA221 as closely as possible is also presented.

Given the analysis of overall response rates for eltrombopag and placebo in RAISE, the overall response rates for romiplostim derived from Kuter 2008[1] and the indirect comparison presented in section 5.7 of the manufacturer submission, the manufacturer concludes that it is

appropriate for the base case to assume complete clinical equivalence between the two TPO-RA treatments. This is reviewed in greater detail in the preceding ERG review of the clinical effectiveness.

The manufacturer submission is unusual in that despite having a placebo controlled trial of eltrombopag, and having undertaken a literature review for other therapies, many of the base case data inputs that could be drawn from these sources are actually drawn from TA221 of romiplostim for the same indication. The choice of data inputs from the alternative sources could have been presented more clearly, to enable a comparison between sources.

In the light of this, the summary of the manufacturer submission that follows presents the data from the eltrombopag trials and manufacturer literature review alongside those of TA221, identifying which have been used for the manufacturer base case.

The manufacturer presents a scenario analysis that applies the input data estimated from the RAISE+EXTEND trials and the manufacturer literature review. This can be viewed as an alternative base case. It is presented as such in what follows within section 5.2.9 below, despite being considered as a scenario analysis within the manufacturer submission.

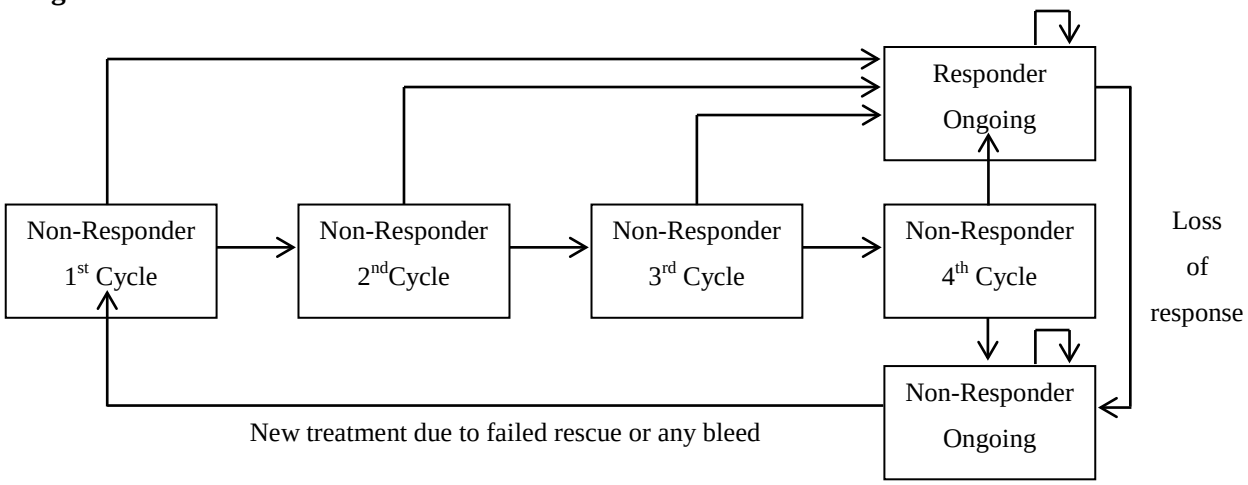
A further manufacturer analysis is presented which attempts to replicate the analysis of TA221 as closely as possible, the central estimates of which are presented within section 5.2.9.

The approach outlined above inevitably leads to a relative lengthy presentation of manufacturer modelling and results.

The ERG CIC mark-up has adopted a more precautionary approach than that of the manufacturer, viewing data that would enable the back calculation of the eltrombopag PAS, the romiplostim PAS or the ratio between these as being CIC.

5.2.2 Model structure

Figure 5 The model structure



The model structure adopts a 4 week cycle length. A cohort of patients starting a treatment may respond in the 1st, 2nd, 3rd or 4th 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 those in response to receive rescue therapy, though for these patients rescue therapy only incurs costs.

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 one 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 as outpatients and rates of severe bleeds treated as inpatients are differentiated by response status, with responders experiencing lower rates than non-responders. These lead on to differential mortality risks.

Definition of responder

The economic modelling and the derivation of many of the data inputs relies in large part upon the data being split into that relating to responders and that relating to non-responders. There are a number of definitions of responder, and assessment of the alignment of the modelling and data inputs requires that these be clearly referenced:

- Any response: Achieving a platelet count of $\geq 50 \times 10^9$/L but $\leq 400 \times 10^9$/L during at least one assessment point during RAISE. These responders will be referred to as "responder" since this definition underlies the base case and most of the economics of the submission.

- Overall response: Patients with either
  - Transient response: Achieving a platelet count of $\geq 50x10^9$/L but $\leq 400x10^9 l^{-1}$ for a minimum of four consecutive weeks of RAISE.
  - Sustained response: Achieving a platelet count of $\geq 50x10^9$/L but $\leq 400x10^9 l^{-1}$ for a minimum of six weeks out of the last eight weeks of RAISE.

These responders will be referred to as "responder (OR)".

It appears that many of the data inputs to the model split that trial data set by:

- assessments when patients were concurrently in response with a platelet count of $\geq 50x10^9$/L; and,
- assessments when patients were concurrently not in response with a platelet count of $<50x10^9$/L.

This will be referred to as "platelet count", with the first bullet being "platelet response" and the second being "platelet non-response".

For the bulk of the economics only the distinction between response and platelet response is required. Towards the end, sensitivity analyses are presented that apply the responder (OR) definition.

These distinctions are important to bear in mind. The proportion of time that a responder spends in platelet response is less than 100%. Applying bleed rates derived from a platelet response analysis within an overarching responder modelling framework underestimates the total number of bleeds among responders. This will tend to overstate the benefit of responder status and so artificially improve the ICER for the treatment sequence with the higher response rate.

5.2.3 Population

The patient population baseline characteristics are drawn from the RAISE trial:

- 48 years average age
- 69% female
- 74kg average weight
- $1.82m^2$ average body surface area

Due to the data inputs to the model being drawn from a mix of the RAISE trial and the romiplostim TA221, the clinical effectiveness estimates in some sense relate to a patient population that is a mix of the underlying trials' patient populations.

5.2.4 Interventions and comparators

The manufacturer base case considers the following three treatment sequences:

a. Azathioprine → mycophenolate mofetil → ciclosporin → danazol → dapsone → cyclophosphamide → vinblastine → vincristine

b. Eltrombopag followed by sequence 'a'

c. Romiplostim followed by sequence 'a'

Rituximab is not considered for the base case, the implicit assumption appearing to be that both splenectomised and non-splenectomised patients are refractory or contraindicated to rituximab.

Note that there is no consideration of the optimal sequencing of treatments; e.g. an additional comparator of:

- Sequence 'a' followed by eltrombopag.

Depending upon the time spent between treatments as non-responders, it might be anticipated that the most cost effective sequence would try a number of the cheaper treatments and only if a patient is refractory to these progress to more expensive treatments.

5.2.5 Perspective, time horizon and discounting

The perspective is the NHS for costs and the patient for benefits. The time horizon is effectively a lifetime horizon. Costs and benefits are discounted at an annual 3.5%.

5.2.6 Treatment effectiveness and extrapolation

Treatment effectiveness

Rates of TPO-RA and non-TPO-RA treatment

The base case assumes that for the TPO-RA containing treatment sequences 100% of patients receive the TPO-RA. The proportions receiving other treatments within a treatment sequence are drawn from the romiplostim TA221.

Table 27 Percentage of eligible receiving individual treatments

Treatment	Treated	Not treated
Eltrombopag	100.0%	0.0%
Romiplostim	100.0%	0.0%
Rituximab	100.0%	0.0%
Azathioprine	59.0%	41.0%
Mycophenolate mofetil	37.0%	63.0%
Ciclosporin	4.0%	96.0%
Dapsone	48.0%	52.0%
Danazol	7.0%	93.0%
Cyclophosphamide	2.0%	98.0%
Vincristine	2.5%	95.0%
Vinblastine	2.5%	97.5%

The base case assumes that rituximab does not form part of any treatment sequence. In effect, this appears to assume that both splenectomised patients and non-splenectomised patients are refractory to rituximab. This is on the basis of manufacturer expert opinion guidance from the Bedfordshire and Luton Joint Prescribing Committee and St. George's Healthcare NHS (see table 63 p166 of the manufacturer submission). Note that this differs from the romiplostim TA221 which apparently includes rituximab in the treatment sequence.

The rates of treatment and non-treatment are applied sequentially. For example, suppose that azathioprine is first in sequence, followed by mycophenolate mofetil. Of a cohort of 100 patients eligible for treatment in the first cycle, 59 patients are treated with azathioprine. Of the remaining 41, 37% or 15 patients are treated with mycophenolate mofetil. The remaining 26 patients are considered for treatments further down the sequence.

Note that unless at least one treatment in the sequence has a 100% treatment rate, some patients are modelled as receiving no treatment. Since the TPO-RA have 100% treatment rates, TPO-RA containing treatment sequences model all patients as receiving at least one treatment.

But in the manufacturer base case non-TPO-RA sequence around 11% of the initial cohort are modelled as receiving no treatment and spend the duration of the model as non-responders[1].

[1] These patients also immediately experience the doubling in the rate of fatal bleeds that is assumed for those at the end of the line.

There is the possibility of patients not responding to their current treatment. Subsequent to the first cycle there is also the possibility of patients losing response to their current treatment. For each cycle of the base case, 46% of non-splenectomised patients not in response are modelling as starting a new treatment, while 42% of splenectomised patients not in response are modelled as starting a new treatment. The patients starting a new treatment are distributed between the treatments further along the treatment sequence using a parallel arithmetic to that applied when calculating the patient distribution between first treatments. Again, this results in some patients receiving no further treatments. For instance, among those not in response from azathioprine treatment of those modelled as starting a new treatment 27% are modelling as receiving no further treatment.

TPO-RA response rates

Given the assumption of complete clinical equivalence between eltrombopag and romiplostim, the manufacturer draws the response rate for both treatments from the RAISE trial.

For the indirect comparison sensitivity analysis, the odds ratio is applied to the eltrombopag response rate to reverse calculate the romiplostim response rate:

Table 28 TPO-RA response rates

	RAISE Any response		RAISE Overall response		TA221	
	Splenect	Non-Splen	Splenect	Non-Splen	Splenect	Non-Splen
Responders	38	68	30	61	..	..
N	50	85	50	85	..	..
Eltrombopag	76%	80%	60%	72%	60%	72%
Odds ratio	..	..	..	..	0.094	0.340
Romiplostim	76%	80%	60%	72%	94%	88%

The base case applies the RAISE primary efficacy variable of any response.

TPO-RA time to assessment of response and cessation of treatment for non-responders

The mean time to response for eltrombopag is estimated from the RAISE trial as being 15 days, the standard error of which is 3.75 days. Possibly in the light of the standard error, the manufacturer assumes that all eltrombopag responses occur during the first cycle. This leads

to all eltrombopag non-responders being assumed to only receive one cycle of TPO-RA treatment.

The mean time to response for romiplostim is apparently drawn from TA221 and Kuter 2008,[1] which within the electronic copy of the model is given as 28 days, the standard error of which is 7.00 days. Despite the standard error, possibly to maintain the overall assumption of the TPO-RA being equivalent the manufacturer assumes that all romiplostim responses occur during the first cycle and that all romiplostim non-responders only receive one cycle of TPO-RA treatment.

TPO-RA probability of loss of response

The proportion of eltrombopag responders losing response is based upon the Kaplan-Meier curve of time to cessation of treatment as presented in figure B21 [p189] of the submission, and reproduced below, with an overlay of the log-normal fits of the Kaplan-Meier curves.

[redacted]

As summarised in appendix 15 of the manufacturer submission, the time to cessation of response was based upon an analysis of the eltrombopag arm of RAISE coupled with the EXTEND data for those patients in the eltrombopag arm of RAISE who continued into EXTEND. The definition of responder was as per the primary efficacy variable in RAISE, with response being required to have occurred during RAISE. The standard six parametric

distributions of exponential, Weibull, Gompertz, log-logistic, log-normal and gamma were fitted and examined by AIC, BIC, Cox-Snell residuals and visual inspection. Note that within this, separate fits were not estimated for splenectomised and non-splenectomised, but rather splenectomy status was included as a variable within a pooled analysis.

For the responder analysis this resulted in the following goodness of fit statistics.

Table 29 TPO-RA responders' time on treatment goodness of fit estimates

	AIC	**BIC**
Exponential	226.7362	232.0631
Weibull	228.6816	236.6719
Gompertz	228.1622	236.1525
Log-normal	225.7025	233.6928
Log-logistic	226.9506	234.9409
Gamma	227.6109	238.2646

The base case applies the log-normal fit, though the model also includes the facility to apply the log-logistic and the gamma fits.

[redacted]

There are only limited differences between the functional forms. The main distinction is the impact of the splenectomy variable, this moving the curves down and suggesting the splenectomised responders tend to spend less time on eltrombopag than non-splenectomised responders. Note that the analysis results in a long tail with a proportion of patients being extrapolated to remain on TPO-RA for a considerable time. [redacted], the tail of which has numbers at risk that are quite small.

Adopting an admittedly slightly arbitrary cut-off at [redacted], for the log-normal fit prior to the [redacted] point, the per cycle probability of ceasing treatment varies from 2.5% to 1.3% for the splenectomised, and from 1.3% to 0.9% for the non-splenectomised. For the extrapolation beyond the [redacted] point the cycle probability of ceasing treatment varies from 1.3% at [redacted] to 0.6% at the [redacted] point for the splenectomised and from 1.3% to 0.5% for the non-splenectomised.

A similar set of analyses are undertaken for all patients in the RAISE eltrombopag arm, with the model containing the facility to apply the Weibull, Gompertz and log-logistic fits from these analyses as sensitivity analyses.

Within the romiplostim TA221 manufacturer submission available on the NICE website, much of the clinical effectiveness section 6.3.4 is redacted. This redaction includes the Time to Failure analysis. The romiplostim mean response duration is also redacted from table 7.1 of the romiplostim TA221 manufacturer submission. But the current submission notes that the average time on treatment for romiplostim can be inferred from data within the publicly available documents. This is given as [redacted] for the splenctomised and [redacted] for the non-splenectomised. How these figures have been arrived at is not clear, but within the manufacturer model they appear to result in the following time on treatment curves, compared to those from RAISE[2].

[2] Implemented in the *Markov* worksheet by setting cell N18=Interim!G4, toggling the *Main* worksheet cell D32 and charting the *Markov* worksheet cells C23:C172. The implementation appears to be an exponential.

[redacted]

[redacted]

[redacted]

The ERG clarification question B1c requested "*Data from the RAISE and EXTEND trials for eltrombopag responders, some of which underlies the responder patient analysis of figure B21. This should report the data collected under RAISE and EXTEND; i.e. including the extension data, for the RAISE eltrombopag responders as defined in Appendix 15*". Appendix 15 of the manufacturer submission states that for the parametric analysis "*Responders in this instance… defined by achievement of a platelet count between 50 and 400 at least once during the treatment period in the RAISE trial …This analysis was restricted to patients randomised to eltrombopag in RAISE … as the response variable from RAISE … was not observed in EXTEND*".

The manufacturer response provides the following patient numbers for RAISE. Note that within the data there are a number of time points where not all patients on treatment had data on their platelet count. The data can be analysed without adjusting for this, implicitly assuming all missing platelet counts were not in platelet response, and adjusting for this, implicitly assuming that the missing platelet counts were in platelet response in the same proportion as the available platelet counts.

Table 30 RAISE eltrombopag responders platelet response: Splenectomised

	Day 0	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Wk 10	Wk 14	Wk 18	Wk 22	Wk 26
On treatment	38	38	38	38	38	38	38	35	35	35	32	32
In platelet response	[redacted]											
% platelet response	[redacted]											
No platelet data	0	0	0	0	1	0	0	6	4	4	4	1
Excluding observations with no platelet data												
On treatment	38	38	38	38	37	38	38	29	31	31	28	31
In platelet response	[redacted]											
% platelet response	[redacted]											

Table 31 RAISE eltrombopag responders platelet response: Non-splenectomised

	Day 0	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Wk 10	Wk 14	Wk 18	Wk 22	Wk 26
On treatment	68	68	67	67	67	67	67	67	67	66	65	65
In platelet response	[redacted]											
% platelet response	[redacted]											
No platelet data	0	0	1	1	1	1	0	15	13	17	15	0
Excluding observations with no platelet data												
On treatment	68	68	66	66	66	66	67	52	54	49	50	65
In platelet response	[redacted]											
% platelet response	[redacted]											

Table 32 EXTEND eltrombopag responders platelet response: Splenectomised

Month	0	3	6	9	12	15	18	21	24	27	30	33	36
On treatment	26	24	23	23	21	19	19	17	16	16	13	9	6
In platelet response	[redacted]												
% platelet response	[redacted]												

Table 33 EXTEND eltrombopag responders platelet response: Non-splenectomised

Month	0	3	6	9	12	15	18	21	24	27	30	33	36
On treatment	54	51	50	48	47	44	43	41	37	34	29	19	7
In platelet response	[redacted]												
% platelet response	[redacted]												

The above suggests that among eltrombopag responders remaining on eltrombopag treatment between [redacted] and [redacted] were in platelet response at a given time.

The parallel EXTEND data from the manufacturer response to ERG clarification question B1c provides the following patient numbers. There were no missing platelet count evaluations, and as a consequence the data do not have to be corrected for this.

Note that from month 24 the number discontinuing eltrombopag rises due to patients having completed EXTEND.

The reason for the low proportion reported as being in platelet response at entry to EXTEND is unclear. The ERG had initially thought this might be due to the reporting including those on placebo in RAISE but crossing over to eltrombopag during EXTEND, but this appears not to be the case.

The EXTEND data broadly mirror that of RAISE. The slightly higher percentages in EXTEND than in RAISE could be seen as good responders being the most likely to continue with treatment, but this is complicated by some quite small patient numbers in the final year that is reported.

Non-TPO-RA treatment response rates

The manufacturer undertakes a literature review to arrive at the average response rates for the non-TPO-RA treatments. Because these response rates apply to pooled patient populations of splenectomised patients and non-splenectomised patients, these rates are adjusted to arrive at estimates specific to splenectomised patients and non-splenectomised patients. This uses the response rate for splenectomised patients and the response rate for non-splenectomised patients to yield a relative risk of response for splenectomised patients compared to non-splenectomised patients. Depending upon the data source selected this relative risk is:

- 76% / 80% = 95% for the RAISE primary endpoint of responder
- 60% / 72% = 84% for the RAISE post-hoc analysis of responder (OR)

This is coupled with the 37% proportion of splenectomised patients in the RAISE trial to yield response rate estimates specific to splenectomised patients and non-splenectomised patients such that their weighted average is equal to the pooled patient response rates drawn from the literature.

The TA221 of romiplostim is viewed as an alternative source, with this specifying the response rate estimates specific to splenectomised patients and non-splenectomised patients.

This yields the following four sets of possible estimates.

Table 34 Non-TPO-RA treatment response rates

Data source	**Manufacturer literature review**					**TA221**	
RR Splen:NSplen		**95%**		**84%**		**n.a.**	
		Non		**Non**		**Non**	
	Pooled	**Splen**	**Splen**	**Splen**	**Splen**	**Splen**	**Splen**
Rituximab	59%	60%	57%	63%	53%	58%	58%
Azathioprine	45%	46%	44%	48%	40%	50%	63%
Mycophenolate mofetil	53%	54%	51%	56%	47%	57%	44%
Ciclosporin	42%	43%	41%	45%	37%	50%	63%
Dapsone	45%	46%	44%	48%	40%	50%	47%
Danazol	36%	37%	35%	38%	32%	45%	60%
Cyclophosphamide	85%	87%	82%	90%	76%	70%	61%
Vincristine	58%	59%	56%	62%	52%	67%	53%
Vinblastine	58%	59%	56%	62%	52%	67%	53%

For the base case, the manufacturer chooses to use the values from TA221, but these appear to be broadly in line with those of the manufacturer's own literature review.

Non-TPO-RA time to assessment of response and cessation of treatment for non-responders

The manufacturer literature review provides a set of estimates of the mean time to response for the non-TPO-RA treatments. Similar estimates are drawn from the romiplostim TA221. In line with the treatment of the TPO-RA, for the non-TPO-RA all responses are assumed to occur during the cycle in which the mean time to response falls. Those modelled as not responding by this point are assumed to cease their current treatment and move into the non-responder health state with the possibility of subsequent further treatment.

Table 35 Non-TPO-RA mean days to response

	Manufacturer review			TA221		
	mean	**s.e.**	**cycle**	**mean**	**s.e.**	**cycle**
Rituximab	24.4	6.1	1	56.0	14.0	2
Azathioprine	112.0	28.0	4	112.0	28.0	4
Mycophenolate mofetil	35.0	8.8	2	112.0	28.0	4
Ciclosporin	24.5	6.1	1	56.0	14.0	2
Dapsone	35.5	8.9	2	28.0	7.0	1
Danazol	126.0	31.5	4	112.0	28.0	4
Cyclophosphamide	59.5	14.9	3	56.0	14.0	2
Vincristine	13.7	3.4	1	28.0	7.0	1
Vinblastine	13.7	3.4	1	28.0	7.0	1

The base case applies the estimates from TA221. These are broadly similar to those of the manufacturer review, though the estimate for time to response for mycophenolate mofetil is slightly longer from TA221 than from the manufacturer review.

Non-TPO-RA probability of loss of response

Estimates of the times to treatment failure for the non-TPO-RA are drawn from the manufacturer literature review and the romiplostim TA221. The proportion of patients in response who lose response each cycle is based upon the mean duration of response.

Table 36 Non-TPO-RA mean duration of response

	Manufacturer literature review				TA221			
	Mean response (days)		Loss per cycle		Mean response (days)		Loss per cycle	
	Non Splen	Splenect	Non Splen	Splenect	Non Splen	Splenect	Non Splen	Splenect
Rituximab	748	748	3.7%	3.7%	575	575	4.8%	4.8%
Azathioprine	2,770	2,770	1.0%	1.0%	618	618	4.4%	4.4%
Mycophenolate mofetil	51	51	42.6%	42.6%	173	173	14.9%	14.9%
Ciclosporin	871	871	3.2%	3.2%	393	493	6.9%	5.5%
Dapsone	786	786	3.5%	3.5%	618	618	4.4%	4.4%
Danazol	4,413	4,413	0.6%	0.6%	4,426	4,485	0.6%	0.6%
Cyclophosphamide	1,269	1,269	2.2%	2.2%	822	822	3.3%	3.3%
Vincristine	1,269	1,269	2.2%	2.2%	43	43	48.2%	48.2%
Vinblastine	1,269	1,269	2.2%	2.2%	43	43	48.2%	48.2%

The base case applies the estimates drawn from TA221. With the exception of the estimate for mycophenolate mofetil these are typically somewhat higher than those of TA221. In particular, the estimate for azathioprine, which is 1st in line in the non-TPO-RA sequences, is very much larger in the manufacturer literature review and its 'per cycle probability' of loss of response is less than ¼ that drawn from TA221.

Probability of moving from being between treatments to starting a new treatment

The patients stopping treatment due to no response or loss of response enter the long-term non-responder health state. The likelihood of these patients moving onto another treatment is the sum of:

- The probability of rescue treatment which fails
- The probability of rescue treatment which succeeds but goes on to a bleed
- The probability of not receiving rescue therapy but bleeding

Note that these bleeds include both severe bleeds and non-severe bleeds. These inputs are summarised in later sections, and result in the following estimates for those not in platelet response who are between treatments. By definition, there are no estimates for those on treatment as 100% of these patients are assumed to be in platelet response.

Table 37 Probability of moving from being between treatments to starting a new treatment

	RAISE+EXTEND		TA221	
Platelet count	$< 50x10^9/L$	$\geq 50x10^9/L$	$< 50x10^9/L$	$\geq 50x10^9/L$
Splenectomised	38.1%	n.a.	46.0%	n.a.
Non-Splenectomised	24.3%	n.a.	41.7%	n.a.

The base case applies the estimates derived from the TA221 data.

Rates of rescue therapy by splenectomy and platelet response status

The rates of rescue therapy for the RAISE+EXTEND data are limited to countries with a minimum GDP per capita of $20,000 per annum. The justification for this subgroup analysis is that lower income countries are not able to afford the relatively expensive rescue therapies, and as a consequence it is more appropriate to limit the analysis to the wealthier countries within the RAISE+EXTEND trial. This results in data from 54 splenectomised patients and 47 non-splenectomised patients being used for the analysis, and excludes data from roughly half the RAISE+EXTEND trial recruited in: China, Czech Republic, Hong Kong, Peru, Poland, Russian Federation, Slovakia, Taiwan, Tunisia, Ukraine and Vietnam.

For the TA221 data, the rate of rescue therapies is reportedly drawn from the romiplostim manufacturer submission table 7.1 on page 114 of the romiplostim manufacturer submission. The balance between rescue therapies is drawn from the Amgen UK physician survey.

Table 38 Rates of rescue therapy: Splenectomised

	RAISE+EXTEND				TA221			
Platelet count	$< 50x10^9/L$		$\geq 50x10^9/L$		$< 50x10^9/L$		$\geq 50x10^9/L$	
	n	%	n	%	n	%	n	%
Immunoglobulin	78	51%	9	31%	..	64%	..	..
Anti-D	3	2%	0	0%	..	0%	..	..
IV Steroids	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%	

Table 39 Rates of rescue therapy: Non-splenectomised

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%	..	..
IV Steroids	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%	

The base case uses the values from the romiplostim TA221. For those in platelet non-response these are more than double those suggested by the individual patient data from RAISE+EXTEND. For those in platelet response, it appears that in the absence of data the manufacturer has assumed a zero rate of rescue.

Note that the ERG did not request at clarification the rescue rates for:

- RAISE+EXTEND as a whole; or,
- Western European RAISE+EXTEND patients; or,
- UK RAISE+EXTEND patients.

Depending upon patient numbers, these could have provided useful sensitivity analyses given the centrality of rescue rates and the costs of rescue within the cost effectiveness results.

But the data provided in response to the ERG clarification question F2 suggests that the rate of rescue for splenectomised patients in the high income countries was approximately 50% higher than for RAISE as a whole, while for non-splenectomised patients it was approximately 100% higher than for RAISE as a whole.

When assessing the justification for splitting the rescue data by country GDP, a distinction may need to be made between the rate of rescue and the balance between rescue therapies that are used, the latter being summarised in the costs section below. It seems reasonable for the use of rescue therapies with a high direct drug or ingredient cost to be lower in lower income countries, but it may be less reasonable to assume that the rate of rescue therapy will necessarily be lower.

Rescue therapy response rates

The response rates for rescue therapy are calculated in the same manner as the response rates for the non-TPO-RA treatments.

Table 40 Rescue therapy response rates

Data source	**Manufacturer literature review**					**TA221**	
RR Splen:NSplen		**95%**		**84%**		**n.a.**	
		Non		**Non**		**Non**	
	Pooled	**Splen**	**Splen**	**Splen**	**Splen**	**Splen**	**Splen**
Danazol	82%	84%	79%	87%	73%	81%	79%
Cyclophosphamide	42%	43%	41%	45%	37%	46%	0%
Vincristine	41%	42%	40%	44%	36%	46%	46%
Vinblastine	42%	43%	41%	45%	37%	43%	41%

As for the response rates for the non-TPO-RA treatments, in the base case the manufacturer chooses to use the values from TA221. The estimates from the two possible sources are broadly in line. The exception to this is the 0% response rate for Anti-D for splenectomised patients, but within the modelling this is not relevant since for the splenectomised when using TA221 as the source the rate of Anti-D therapy is also 0%.

Rate of non-severe bleeds by splenectomy and platelet response status

Non-severe bleeds that require non-admitted hospital case are based upon the ITP bleed classification as below.

Table 41 Definition of non-severe bleeds

ITP Bleed type	ITP severity requiring non-admitted hospital treatment
Skin petechiae code	Diffuse petechiae
Skin ecchymosis bleeding	>5 bruises with size >2 cm
Oral bleeding	Multiple blood blisters or gum bleeding >5 minutes
Epistaxis bleeding	Bleeding >5 mins (per episode)
Ocular bleeding score code	Retinal haemorrhage
GI bleeding score code	Streaks of blood or blood with wiping, Grossly bloody stool
Genitourinary bleeding score	Macroscopic
Gynecologic bleeding score	Spotting not at time of normal period, Bleeding >spotting not at time of period or very heavy period
Pulmonary bleeding score	Coughing up Blood, Pulmonary hemorrhage
Intracerebral haemorrhage	Yes

For the data drawn from RAISE + EXTEND these rates are differentiated by splenectomy status and by platelet response status. The romiplostim TA221 data are only differentiated by responder status.

Table 42 Non-severe bleeds by splenectomy and platelet count: Splenectomised

	RAISE+EXTEND		**TA221**	
Platelet count	$< 50x10^9/L$	$\geq 50x10^9/L$	$< 50x10^9/L$	$\geq 50x10^9/L$
Non severe bleeds	264	80	..	..
Patient years	65	78	..	..
Annual rate	4.087	1.028	..	..
4 wk cycle rate	0.341	0.086	0.455	0.071

Table 43 Non-severe bleeds by splenectomy and platelet count: Non-splenectomised

	RAISE+EXTEND		TA221	
Platelet count	$< 50x10^9/L$	$\geq 50x10^9/L$	$< 50x10^9/L$	$\geq 50x10^9/L$
Non severe bleeds	275	63	..	..
Patient years	107	190	..	..
Annual rate	2.570	0.332	..	..
4 wk cycle rate	0.214	0.028	0.455	0.071

The base case applies the rates derived from TA221. These are somewhat higher than those derived from the RAISE+EXTEND trial data. Also, the difference between the rates for those in platelet response and those not in platelet response is somewhat larger for the TA221 data, particularly for the non-splenectomised.

Rate of severe bleeds by platelet response status

Severe bleeds are defined as those which require inpatient care. The SAEs of RAISE+EXTEND categorised as severe bleeds are as below:

Table 44 Severe bleeds definition

SAEs classed as any of the following		
Brain stem haemorrhage[2]	Haemorrhage urinary tract	Respiratory tract haemorrhage
Cerebral haemorrhage[2]	Haemorrhagic anaemia	Retinal haemorrhage
Duodenal ulcer haemorrhage[1]	Haemorrhoidal haemorrhage[1]	Subarachnoid haemorrhage[2]
Epistaxis	Intra-abdominal haemorrhage	Urogenital haemorrhage
Gastrointestinal haemorrhage[1]	Intraventricular haemorrhage[2]	Vaginal haemorrhage
Gingival bleeding	Menorrhagia	Haematoma
Haematemesis[1]	Peritoneal haemorrhage	Mouth haemorrhage
Haemoptysis	Rectal haemorrhage[1]	Respiratory tract haemorrhage

[1] Classed as gastrointestinal haemorrhage; [2] Classed as intracranial haemorrhage.

These are further distinguished by whether the SAE bleed required hospitalisation, as outlined in table 36 of appendix 15 of the manufacturer submission. Note that this table also outlines whether the end result of the SAE was death.

Table 45 Severe bleeds requiring hospitalisation by platelet count

	RAISE+EXTEND				TA221	
Platelet count	< $50x10^9$/L		≥ $50x10^9$/L		<$50x10^9$/L	≥ $50x10^9$/L
Platelet count	n	%	n	%	<$50x10^9$/L	≥ $50x10^9$/L
Gastrointestinal	3	18.8%	2	29%	..	..
Cranial	3	18.8%	0	0%	..	..
Other	10	62.5%	5	71%	..	..
Total	16	100%	7	100%	..	..
Patient years	172		267		..	..
Per year	0.093		0.026		..	..
Per cycle	0.008		0.002		0.043	n.a.

The base case applies the rates derived from TA221, applying a zero rate for those in response. These are somewhat higher than those derived from the RAISE+EXTEND trial data, and the difference between the platelet response rate and the platelet non-response rate is somewhat larger for the TA221 data: 0.043 per cycle compared to 0.006 as derived from the RAISE+EXTEND trial data.

The modelling also assumes that the severe bleed rate doubles for those off treatment at the end of the line.

Rates of adverse events

The rates of adverse events for the both the TPO-RA and the non-TPO-RA are taken from TA221. Eltrombopag is assumed to have the same rate of adverse events as romiplostim.

Table 46 Adverse event rates: TPO-RA and non-TPO-RA

	SAE	Other AE
Eltrombopag	3.0%	31.0%
Romiplostim	3.0%	31.0%
Rituximab	3.3%	0.0%
Azathioprine	15.0%	24.0%
Mycophenolate mofetil	15.0%	24.0%
Ciclosporin	15.0%	24.0%
Dapsone	11.0%	24.0%
Danazol	16.0%	35.0%
Cyclophosphamide	21.0%	30.0%
Vincristine	21.0%	30.0%
Vinblastine	21.0%	30.0%

Platelet transfusion is assumed to have the same SAE rate as IV steroids.

Table 47 Adverse event rates: Rescue therapies

	SAE	Other AE
IVIg	2.1%	0.0%
Anti-D	2.8%	0.0%
IV steroid	3.0%	70.0%
Platelet transfusion	3.0%	0.0%

Mortality associated with severe bleeds

The modelling of additional CITP specific mortality as a function of severe bleeds differentiated by platelet response as drawn from RAISE+EXTEND is relatively straightforward, given a death rate per severe bleed. Table 36 of appendix 15 suggests that patient deaths associated with severe bleeds is recorded within the RAISE+EXTEND trial data. But for reasons that are not clear, the manufacturer uses a death rate per severe bleed drawn from Danese and colleagues.[86]

Table 48 Severe bleed deaths by platelet response status: RAISE+EXTEND

	RAISE+EXTEND				
Platelet count	< $50x10^9$/L		≥ $50x10^9$/L		
Platelet count	n	%	n	%	Death rate
Gastrointestinal	3	19%	2	29%	4.60%
Cranial	3	19%	0	0%	13.20%
Other	10	63%	5	71%	1.70%
Total bleeds	16	100%	7	100%	
Average bleed death rate	4.4%		2.5%		
Patient years	172		267		
Per year	9.3%		2.6%		
Bleeds per cycle	0.78%		0.22%		
Bleeds deaths per cycle	0.0342%		0.0055%		

For those remaining on treatment and so assumed to be in platelet response, the 0.0055% is applied unadjusted. For those having come off treatment and so not in platelet response, the fatality rate is a weighted average of:

- the proportion receiving rescue and responding to it during the cycle, who have the 0.0055% applied; and,
- the proportion not receiving rescue or not receiving rescue but not responding to it during the cycle, who have the 0.0342% applied.

For the splenectomised not in platelet response the rescue rate estimate from the RAISE+EXTEND data is 14%. Their average rate of response to rescue therapy is 65%. This results in a weighted average CITP mortality of 0.0287% per cycle.

For the non-splenectomised not in platelet response the rescue rate estimate from the RAISE+EXTEND data is 32%. Their average rate of response to rescue therapy is 60%. This results in a weighted average CITP mortality of 0.0315% per cycle.

The same approach can be adopted, only applying the bleed per cycle rate estimated under TA221 as below.

Table 49 Severe bleed deaths by platelet response status: TA221

Platelet count	**< $50x10^9$/L**	**≥ $50x10^9$/L**
Average bleed death rate	4.4%	2.5%
Bleeds per cycle	4.3%	..
Bleeds deaths per cycle	0.189%	0.000%

For the splenectomised not in platelet response the rescue rate estimate from the TA221 data is 33%. Their average rate of response to rescue therapy is 67%. This results in a weighted average CITP mortality of 0.1032% per cycle.

For the non-splenectomised not in platelet response the rescue rate estimate from the TA221 data is 68%. Their average rate of response to rescue therapy is 66%. This results in a weighted average CITP mortality of 0.1478% per cycle.

Table 50 Severe bleed deaths per cycle by platelet response status and splenectomy status

	RAISE+EXTEND		**TA221**	
Platelet count	< $50x10^9$/L	≥ $50x10^9$/L	< $50x10^9$/L	≥ $50x10^9$/L
Splenectomised	0.0287%	0.0055%	0.1032%	0.0000%
Non-Splenectomised	0.0315%	0.0055%	0.1478%	0.0000%

The base case applies the CITP specific mortality rates derived from TA221. These are three to four times as large as those derived from RAISE+EXTEND. Note also that for those at the end of the line of treatments because the inpatient bleed rate is assumed to double, the fatal bleed rate is also assumed to double. In the base case, this doubling of the fatal bleed rate applies from baseline to the 11% in the non-TPO-RA arm who received no treatment.

General Mortality

A general population mortality rate, weighted by gender, is included within the modelling. At baseline the cycle probability of general mortality is 0.0170%, while at the 5 and 10 year points it is 0.0272% and 0.0416% respectively.

Extrapolation

There are no additional assumptions made for extrapolation. The model structure is re-applied with patients progressing through the treatment sequences. Periods of time are spent off treatment, with the increase in event rates associated due to not being in platelet response.

Once patients reach the end of the line and are by definition not in platelet response: their severe bleed rate and CITP mortality is assumed to be double that of those not in platelet response elsewhere within the modelling.

5.2.7 Health related quality of life

The HRQoL values that are applied depart from the clinical effectiveness inputs that are applied. Values are available from RAISE+EXTEND SF-36 data as summarised in Table B72 of the submission. Values are also available from TA221, with those reported in the electronic copy of the manufacturer model for the current submission being reported below[3]. But for both the base case modelling and the alternative base case modelling, the main source of utility values is the Szende reference.[87]

Table 51 RAISE+EXTEND HRQoL values and those applied in the modelling

	RAISE	TA221	Applied	Source of applied values
Platelet response: no bleed	0.737	0.835	0.863	Szende[87]
Platelet response: OP bleed	0.693	0.734	0.734	
Platelet non-response: no bleed	0.712	0.800	0.841	
Platelet non-response: OP bleed	0.666	0.732	0.732	
IP bleed: Cranial	..	0.040	0.038	
IP bleed: GI	..	0.540	0.450	Leontiadis[88]
IP bleed: Other	..	0.540	0.450	Assumption
Steroid rescue treatment	..	0.758	0.758	Szende[87]
AE decrements				
TPO-RA and rituximab SAE	..	0.100	0.100	TA221
Non TPO-RA SAE	..	0.400	0.400	
Rescue SAE	..	0.100	0.100	
Other AE		0.100	0.100	

The RAISE+EXTEND SF-36 data were analysed as outlined within appendix 17 of the manufacturer submission. This analysis mapped the patient level SF-6D data onto utilities using the standard Brazier algorithm, with six alternative repeated measures models being tested. The non-severe categorisation of ITP bleeds, as previously described in Table 51 above, was used to define a dichotomous bleed variable. For SF-36 assessments where an ITP bleed score assessment was not available, the nearest within 14 days of the SF-36 assessment was used.

[3] Worksheet *Utilities_AEs* cells C17:C24

The values within the electronic model for TA221 do not appear to correspond with those of table 7.1 of the romiplostim submission. But as they are not much used within the current submission they are not particularly considered here. The only point to note is the somewhat higher value for inpatient gastrointestinal bleeds of 0.540 as drawn from Regier et al.[89] This was a Canadian study of the effects of oral anticoagulation therapy, with utility values being drawn from a further survey of the literature. Leontiadis et al,[88] an HTA monograph, was a systematic review of PPIs for acute upper gastrointestinal bleeding. Two utilities were used: 0.780 for being at home and 0.450 for being in hospital. These were based upon EQ-5D data from 57 patients surviving an upper gastrointestinal bleed at discharge and at a 4 week follow up.

Szende et al[87] developed 6 ITP related health states. These were evaluated by 359 members of the UK general public using TTO. Note that the 0.758 may have been for steroid treatment related adverse events, rather than for steroid treatment.

The RAISE +EXTEND SF-6D values for being in platelet response without a bleed and for not being in platelet response of 0.737 and 0.712 are somewhat below those of the 0.863 and 0.841 of Szende et al.[87] The RAISE +EXTEND SF-6D decrements for OP bleeds of 0.044 and 0.046 are also half to one third of the 0.129 and 0.109 of Szende et al.[87] The Szende et al utilities increase both the QALY gain from increased survival and the QALY gain from avoidance of OP bleeds compared to the RAISE +EXTEND SF-6D values.

The disutilities per SAE are drawn from TA221. There is no obvious explanation within section 7.2.8.3 of the TA221 manufacturer submission of how these values were arrived at. Based upon the published paper, they do not appear to have been part of the Szende et al TTO exercise.[87]

5.2.8 Resources and costs

Eltrombopag dose, direct drug cost and administration

Given the BNF list price of £770 for 700mg and the PAS of [redacted] this results in a price to the NHS of [redacted] per 700mg or [redacted] per mg.

The average doses are drawn directly from the RAISE trial for the first 6 cycles. Thereafter the average dose in EXTEND among patients previously within the RAISE trial is applied, this apparently including both those previously in the placebo arm of RAISE and those in the eltrombopag arm of RAISE. This results in the following daily dosing and 4 weekly direct drug costs for eltrombopag.

Table 52 Dosing and direct drug costs RAISE+EXTEND: Eltrombopag

	Splenctomised		Non-splenectomised	
Cycle	**Dose (mg)**	**Cycle cost**	**Dose (mg)**	**Cycle cost**
RAISE				
1	48.96	[redacted]	48.51	[redacted]
2	56.81	[redacted]	54.62	[redacted]
3	57.78	[redacted]	55.49	[redacted]
4	56.87	[redacted]	55.12	[redacted]
5	54.66	[redacted]	56.20	[redacted]
6	57.35	[redacted]	57.13	[redacted]
EXTEND				
7	52.63	[redacted]	49.32	[redacted]

Note that the manufacturer response to ERG clarification question D1 shows that there was minimal difference in the average dose during EXTEND between those previously treated with placebo and those previously treated with eltrombopag.

ERG clarification question D2 requested RAISE dosing information for eltrombopag split by patients of Asian origin and of non-Asian origin. The SPC notes a lower starting dose for those of Asian origin, and a significant proportion of RAISE patients were of Asian origin. Unfortunately, during the NICE revisions to the ERG clarification questions this inadvertently referred to the wrong table of appendix D of the clarification questions. As a consequence, the manufacturer declined to supply the requested data.

There are no administration costs for eltrombopag.

Romiplostim dose, direct drug costs, and administration

Given the BNF list price of £482 for 250mg and the PAS of [redacted] (personal communication to the manufacturer by Amgen), this results in a price to the NHS of [redacted] per 250mg or [redacted] per mg.

The distribution of patient weights from RAISE can be coupled with the average romiplostim doses per kilogram for splenectomised and non-splenectomised patients for the first 24 weeks of treatment as drawn from Kuter 2008,[1] averaged over the 4 weeks of each cycle, to derive the implied wastage rates. This assumes, in line with BNF, that only the 250mg vial is available. Bussel 2009[30] provides an alternative source of dose per kg over the first 144 weeks

of romiplostim treatment. This results in the following weekly dosing and 4 weekly direct drug costs for romiplostim.

Table 53 Dosing and direct drug costs: Romiplostim (Kuter 2008)[1]

	Splenctomised			Non-splenectomised		
Cycle	**mg/kg**	**Dose (mg)**	**Cycle cost**	**mg/kg**	**Dose (mg)**	**Cycle cost**
1	2.06	253	[redacted]	1.49	251	[redacted]
2	3.65	395	[redacted]	2.46	267	[redacted]
3	4.37	461	[redacted]	2.47	268	[redacted]
4	4.89	504	[redacted]	2.72	289	[redacted]
5	4.98	509	[redacted]	2.76	291	[redacted]
6	5.11	517	[redacted]	2.74	291	[redacted]

The dose required in cycle 6 is applied thereafter.

The Kuter ASH conference abstract noted that 82% of patients started home administration, and that 12% of these discontinued and resumed study site administration.[32] Home administration is assumed to be costless. The remaining administrations are assumed to be in hospital and are costed at £204.81, this being the weighted average of 2010-11 NHS reference costs[4] SB12Z simple parenteral chemotherapy 1st attendance. Given the rate of home administration, this results in an average administration cost of £56.54, or an additional £226.16 per cycle.

Non-TPO-RA doses, direct drug costs, administration

The direct drug and administration costs for the non-TPO-RA are as outlined below.

[4] Daycase £208, outpatient £231 and other £164. This compares with a follow up consultant led haematology outpatient appointment cost of £148.

Table 54 Non-TPO-RA drug and administration costs

	Per administration				Per cycle			
	Dose			£			Admi	
	mg	£ mg	£ dose	admin	Doses	Drug	n	Total
Rituximab	683	£1.75	£1,192	£331	4	£4,767	£1,322	£6,090
Azathioprine	111	£0.00	£0		56	£11		£11
Mycophenolate mofetil	1,000	£0.00	£1		49	£69		£69
Ciclosporin	371	£0.02	£7		28	£187		£187
Dapsone	88	£0.02	£2		28	£56		£56
Danazol	200	£0.00	£1		84	£46		£46
Cyclophosphamide	111	£0.01	£1		112	£87		£87
Vincristine	2	£14.03	£21	£205	4	£84	£819	£903
Vinblastine	10	£1.42	£14	£205	3	£42	£614	£657

The £331 administration cost for rituximab is based upon NHS reference cost: SB14Z Deliver complex Chemotherapy, including prolonged infusional treatment at first attendance, while the £205 for vincristine and vinblastine is based upon NHS reference cost: SB12Z Deliver simple Parenteral Chemotherapy at first attendance. These are weighted averages of the daycase, outpatient and others categories.

Rescue doses, direct drug and administration costs

The direct drug and administration costs for the rescue therapies are as outlined below.

Table 55 Rescue drug and administration costs

	Per administration				Per cycle			
	mg	£/mg	£/dose	£/admin	Doses	Drug	Admin	Total
IVIG	74,220	£0.05	£3,340	£1,235	1.5	£5,010	£1,853	£6,863
Anti-D	5	£155.00	£719	£1,235	2.0	£1,438	£2,471	£3,909
IV Steroid	93	£0.23	£21	£331	3.0	£64	£992	£1,056
Platelet		..	£461	£58	1.0	£461	£58	£518

The administration cost for IVIG and Anti-D are based upon NHS reference costs (high drug costs): Immunoglobins Band 1, while for IV steroids this is costed at the NHS reference cost: SB14Z Deliver complex Chemotherapy, including prolonged infusional treatment at first

attendance. Platelet therapy is assumed to require two units and be administered at an outpatient blood transfusion service cost.

As for the rates of rescue, the balance between treatments for the RAISE+EXTEND trial data is drawn from countries with a GDP of more than US$2,000. Given the balances between the rescue therapies and the rates of rescue therapy per cycle, this results in the following rescue costs per cycle.

Table 56 Rescue costs per cycle: Splenctomised

		RAISE+EXTEND		TA221	
	Unit cost	**<50bn**	**>50bn**	**<50bn**	**>50bn**
IVIG	£6,863	50.6%	31.0%	64.0%	..
Anti-D	£3,909	1.9%	0.0%	0.0%	..
IV Steroid	£1,056	11.0%	13.8%	36.0%	..
Platelet	£518	36.4%	55.2%	0.0%	..
Average rescue event cost		£3,857	£2,562	£4,772	..
Rescue rate per cycle		31.9%	4.6%	68.0%	0.0%
Rescue cost per cycle		£1,229	£117	£3,245	£0

Table 57 Rescue costs per cycle: Non-splenctomised

		RAISE+EXTEND		TA221	
	Unit cost	**<50bn**	**>50bn**	**<50bn**	**>50bn**
IVIG	£6,863	54.9%	50.0%	59.0%	..
Anti-D	£3,909	18.3%	14.3%	25.0%	..
IV Steroid	£1,056	7.0%	35.7%	16.0%	..
Platelet	£518	19.7%	0.0%	0.0%	..
Average rescue event cost		£4,662	£4,367	£5,195	..
Rescue rate per cycle		14.3%	1.4%	33.0%	0.0%
Rescue cost per cycle		£668	£60	£1,714	£0

The base case uses the estimates from TA221. For the splenectomised patients not in platelet response these rescue costs [redacted] the TPO-RA drug and administration cost of eltrombopag, while for the non-splenectomised they [redacted] the TPO-RA drug and administration cost of eltrombopag.

For both the splenectomised and the non-splenectomised the additional rescue costs from not being in platelet response compared to being in platelet response are around three times larger using the TA221 estimates than the RAISE+EXTEND estimates.

Monitoring costs

Monitoring is assumed to occur 4 weekly for the TPO-RA, for the non-TPO-RA and for those off treatment. This is costed using NHS reference costs as below.

Table 58 Monitoring costs per cycle

	ELTR Submission		**TA221**
	Code	**Cost**	
Clinical Haematology: consultant led non admitted FU apt.[5]	303	£147.53	
Haematology [Excluding Anti-Coagulant Services]	DAP823	£3.00	
Biochemistry	DAP841	£1.00	
Total		£151.53	£262.00

The TA221 value is only used in sensitivity analyses, with the base case applying the £151.53 monitoring cost.

Note that for those having romiplostim administered in hospital, it may be possible to combine a monthly monitoring visit with one of the weekly treatment visits. This is roughly equivalent to [redacted] of the direct drug costs for the splenectomised and [redacted] for the non-splenectomised. But given that only 28% of romiplostim patients are assumed to require hospital administration, the impact of this would be proportionately reduced.

Other costs

The cost of a non-severe bleed is assumed to be that of the NHS reference cost for a day-case haematological or splenic disorders without CC: £303. But note that there is some general confusion within the submission and the economic model between day-case bleeds and outpatient bleeds. It is not clear that all non-severe bleeds were treated as day-cases: a haematology outpatient appointment would be £207. It is also not clear from the submission that all non-severe bleeds were treated in hospital: a GP appointment would be of the order of £36.

[5] This is stated within the model as being the rate for a 1st attendance, but as noted later for the treatment of non-severe bleeds a 1st appointment would be £207.

The cost of a severe bleed is drawn from a weighted average of NHS reference costs for the inpatient costs of gastrointestinal bleeds, £1,553, and of haemorrhagic cerebrovascular disorders, £3,451, with the additional assumption that other severe bleeds would be the same cost as gastrointestinal bleeds.

5.2.9 Cost effectiveness results

The following table outlines the sources of the model inputs for the three main scenarios.

Table 59 Sources of model inputs for 3 main scenarios

	Base case	**Alternative base case**	**TA221 analysis**
TPO-RA treatment rates	100% assumption	100% assumption	100% assumption
TPO-RA response rates	RAISE	RAISE	TA221
TPO-RA time on treatment	RAISE	RAISE	TA221
TPO-RA AEs	TA221	TA221	TA221
Non-TPO-RA treatment rates	TA221	Man. lit review	TA221
Non-TPO-RA response rates	TA221	Man. lit review	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 2008[1]
Rescue treatment types	TA221	RAISE+EXTEND	TA221
Rescue response rates	TA221	RAISE+EXTEND	TA221
OP bleeds	TA221	RAISE+EXTEND	TA221
IP bleeds	TA221	RAISE+EXTEND	TA221
Mortality	TA221	RAISE+EXTEND	TA221
HRQoL	Szende et al[87]	Szende et al[87]	TA221
Eltrombopag dosing	RAISE+EXTEND	RAISE+EXTEND	RAISE+EXTEND
Romiplostim dosing	Kuter 2008[1] 2008	Kuter 2008[1]	TA221

Base case results: Splenectomised

For the splenectomised patient population, from a baseline age of 48 years the non-TPO-RA treatment sequence is estimated to result in an average 22.77 years undiscounted overall survival compared to 25.13 years for the TPO-RA containing sequences: a gain of 2.36 years overall survival.

The estimated costs are as follows.

Table 60 Deterministic costs for the base case: Splenectomised

	ELTR	**ROMI**		**Non-TPO-RA**	
	Total	**Total**	**net vs ELTR**	**Total**	**net vs ELTR**
TPO-RA acquisition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TPO-RA administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-TPO-RA acquisition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-TPO-RA administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rescue acquisition	£301,752	£301,752	£0	£370,832	£69,080
Rescue administration	£144,180	£144,180	£0	£177,187	£33,007
Bleeds	£24,954	£24,954	£0	£29,497	£4,543
Total	£556,089	£643,598	£87,508	£581,073	£24,984

The key elements to note here are;

- the relatively modest [redacted] total direct drug and administration cost for the non-TPO-RAcontaining sequence; and,
- the large additional net £102,087 rescue costs for the non-TPO-RA containing sequence compared to the eltrombopag containing sequence, which more than offset the [redacted] eltrombopag direct drug and administration costs.

The cost, QALY and costs effectiveness estimates are as below.

Table 61 Deterministic cost effectiveness base case: Splenectomised

	Cost	Δ Cost	QALYs	Δ QALYs	ICER
Eltrombopag	£556,089	..	12.22	0.00	..
Non-TPO-RA	£581,073	£24,984	10.95	-1.28	Dominated
Romiplostim	£643,598	£87,508	12.22	0.00	Dominated

Note that in the above the cost effectiveness of the romiplostim containing treatment sequence compared to the non-TPO-RA treatment sequence is estimated to be £48,914 per QALY.

Running the probabilistic model over 5,000 iterations results in the following central estimates and CEAF for the splenectomised[6].

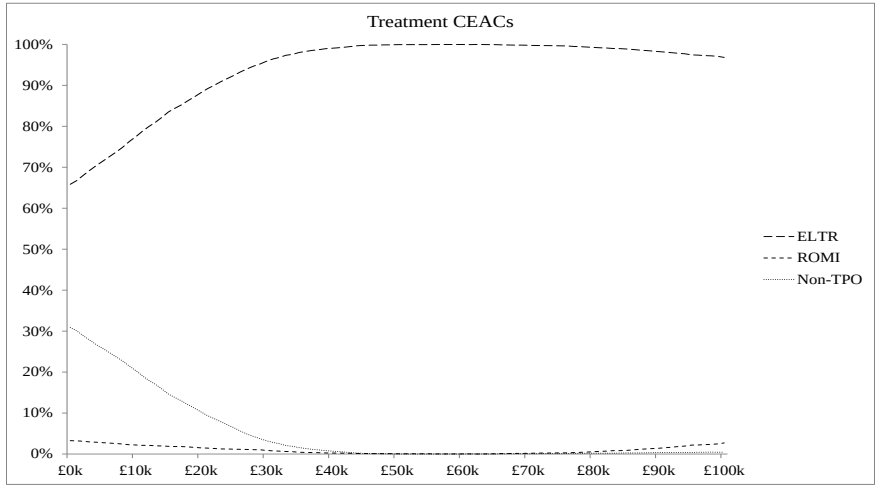
Table 62 Probabilistic cost effectiveness base case: Splenectomised

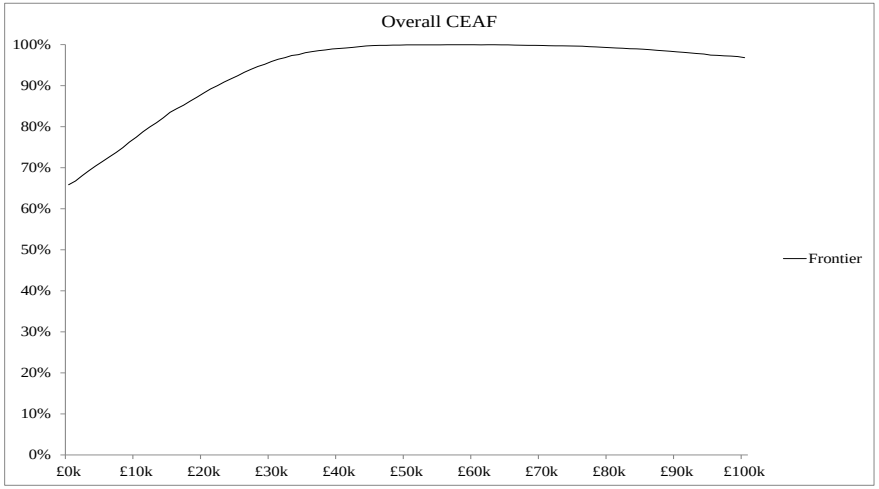
	Cost	Δ Cost	QALYs	Δ QALYs	ICER
Eltrombopag	£561,955	..	12.36		..
Non-TPO-RA	£589,996	£28,041	11.03	-1.33	Dominated
Romiplostim	£653,654	£91,699	12.31	-0.04	Dominated

In the above, the romiplostim containing sequence is modelled to confer slightly fewer QALYs than the eltrombopag containing sequence. This appears to arise due to the model implementation in effect running all the eltrombopag iterations and then running all the romiplostim iterations, and as a consequence not applying the same sequence of random drawings to the two treatment sequences.

[6] Note that these, and all other probabilistic results, CEACs and CEAFs are drawn from runs of the manufacturer model by the ERG rather than being drawn directly from the written submission of the manufacturer.

Figure 9 Base case CEACs and CEAF: Splenectomised





The CEAF follows the CEAC of the eltrombopag containing sequence over its entire length.

Base case results: Non-splenectomised

For the non-splenectomised patient population, the non-TPO-RA treatment sequence is estimated to result in 19.48 years undiscounted overall survival compared to 23.91 years for the TPO containing sequences: a gain of 4.43 years overall survival.

The estimated costs are as follows.

Table 63 Deterministic costs for the base case: Non-splenectomised

	ELTR	ROMI		Non-TPO-RA	
			net vs		net vs
	Total	Total	ELTR	Total	ELTR
[redacted]					
TPO-RA acquisition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TPO-RA administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-TPO-RA acquisition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-TPO-RA administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rescue acquisition	£119,178	£119,178	£0	£165,145	£45,968
Rescue administration	£67,003	£67,003	£0	£92,846	£25,843
Bleeds	£27,483	£27,483	£0	£36,060	£8,577
Total	£332,193	£372,744	£40,552	£297,292	-£34,900

The picture is similar for the non-splenectomised with:

- a relatively modest [redacted] total direct drug and administration cost for the non-TPO-RA containing sequence; and,
- a large additional net £71,811 rescue costs for the non-TPO-RA containing sequence compared to the eltrombopag containing sequence, though for the non-splenectomised this is not sufficient to offset the [redacted] eltrombopag direct drug and administration costs.

The cost, QALY and costs effectiveness estimates are as below.

Table 64 Deterministic cost effectiveness base case: Non-splenectomised

	Cost	Δ Cost	QALYs	Δ QALYs	ICER
Non-TPO-RA	£297,292	..	9.55	0.00	..
Eltrombopag	£332,193	£34,900	11.86	2.31	£15,105
Romiplostim	£372,744	£40,552	11.86	0.00	Dominated

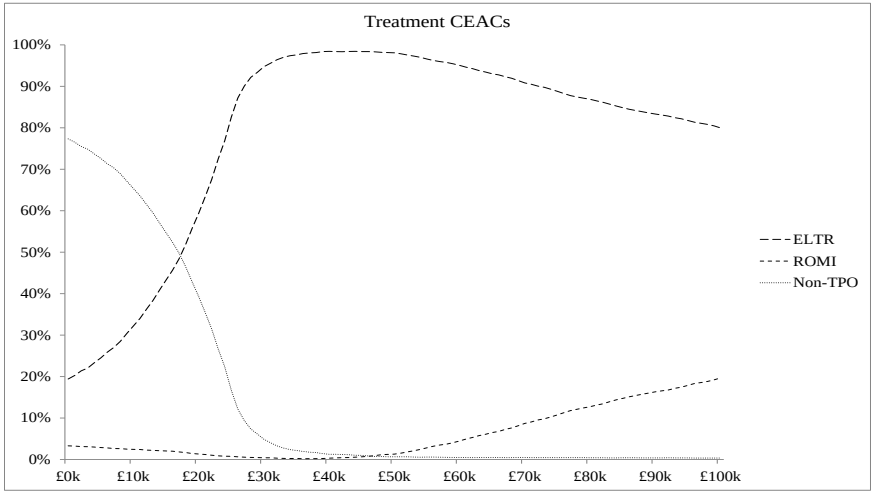
Note that in the above the cost effectiveness of the romiplostim containing treatment sequence compared to the non-TPO-RA treatment sequence is estimated to be £32,657 per QALY.

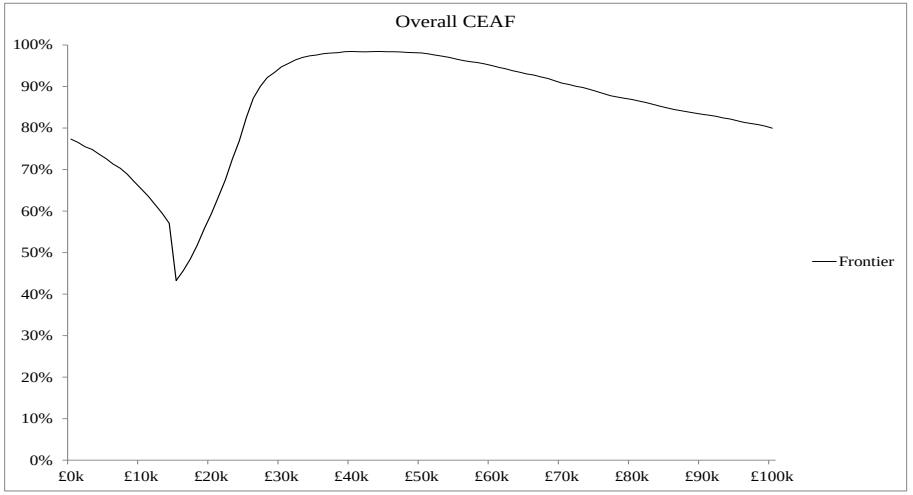
Running the probabilistic model over 5,000 iterations results in the following central estimates and CEAF for the non-splenectomised.

Table 65 Probabilistic cost effectiveness base case: Non-splenectomised

	Cost	Δ Cost	QALYs	Δ QALYs	ICER
Non-TPO-RA	£301,853	..	9.66		..
Eltrombopag	£334,975	£33,121	11.84	2.18	£15,214
Romiplostim	£376,549	£41,575	11.84	0.00	Dominated

Figure 10 Base case CEACs and CEAF: Non-splenectomised





The CEAF broadly follows the treatment sequence with the uppermost CEAC, but switches from the non-TPO-RA sequence to the eltrombopag containing sequence slightly before their CEACs cross over. For a short period of the CEAF, the eltrombopag containing sequence has the highest expected monetised health benefits despite not being the sequence with the highest probability of being cost effective.

As the willingness to pay increases, so the additional cost estimated for romiplostim wanes in importance and it has a greater likelihood of being cost effective, but this is never high. But the rise in the romiplostim CEAC may be illusory and more a function of the probabilistic modelling using sequential simulation rather than concurrent; e.g. while the HRQoL values are drawn from identical distributions, they are sampled separately for each of the comparators.

Alternative base case results: Splenectomised

For the splenectomised patient population, from a baseline age of 48 years the non-TPO treatment sequence is estimated to result in an average 30.49 years undiscounted overall survival compared to 31.22 years for the TPO-RA containing sequences: a gain of 0.74 years overall survival.

The estimated costs are as follows.

Table 66 Deterministic costs for the alternative base case: Splenectomised

	ELTR	**ROMI**		**Non-TPO-RA**	
	Total	**Total**	**net vs ELTR**	**Total**	**net vs ELTR**
		[redacted]			
TPO-RA acquisition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TPO-RA administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-TPO-RA acquisition	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-TPO-RA administration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	£148,085			£179,491	
Rescue acquisition		£148,085	£0		£31,406
Rescue administration	£60,384	£60,384	£0	£73,183	£12,799
Bleeds	£20,527	£20,527	£0	£23,807	£3,280
	£315,148			£281,654	
Total		£402,259	£87,111		-£33,495

Within the alternative base case, the additional net rescue costs for the non-TPO-RA containing sequence compared to the eltrombopag containing sequence are £44,205. This compares with £102,087 for the base case.

The cost, QALY and costs effectiveness estimates are as below.

Table 67 Deterministic cost effectiveness alternative base case: Splenectomised

	Cost	**Δ Cost**	**QALYs**	**Δ QALYs**	**ICER**
Non-TPO-RA	£281,654		13.94		
Eltrombopag	£315,148	£33,495	14.48	0.55	£61,337
Romiplostim	£402,259	£87,111	14.48	0.00	Dominated

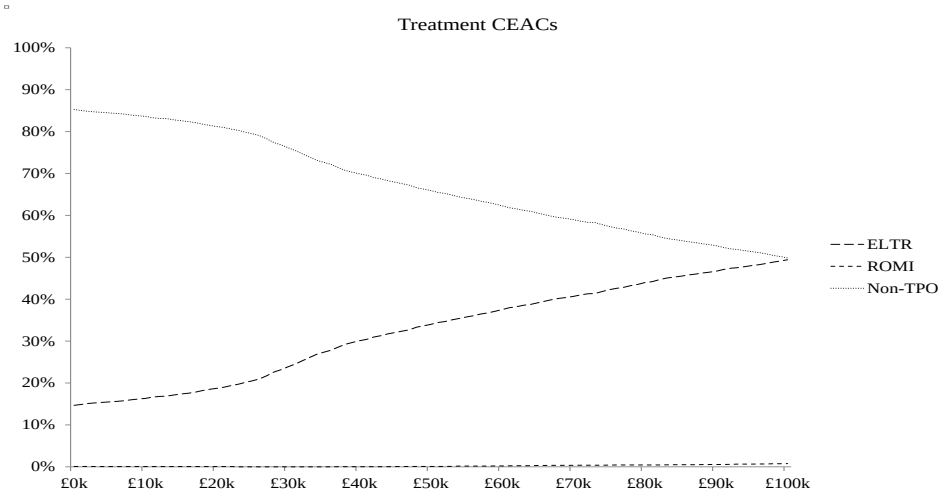
Note that in the above the cost effectiveness of the romiplostim containing treatment sequence compared to the non-TPO-RA treatment sequence estimate is £220,860 per QALY.

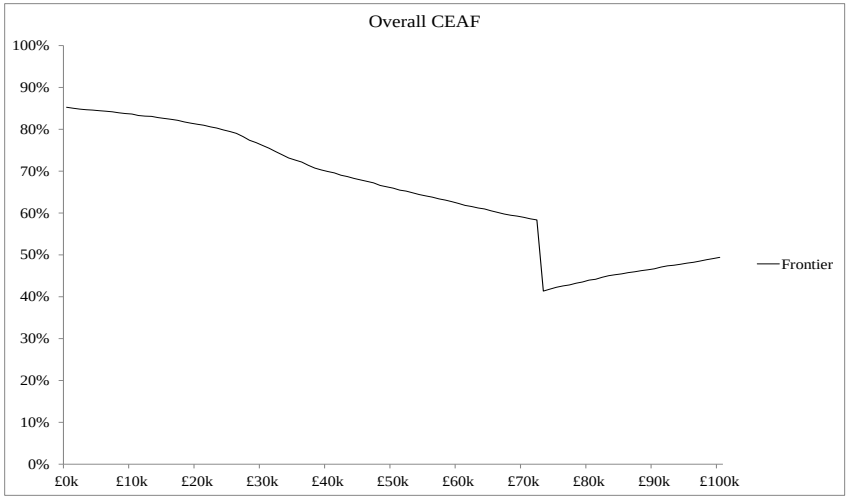
Running the probabilistic model over 5,000 iterations results in the following central estimates and CEAF for the splenectomised.

Table 68 Probabilistic cost effectiveness alternative base case: Splenectomised

	Cost	**Δ Cost**	**QALYs**	**Δ QALYs**	**ICER**
Non-TPO-RA	£290,328	..	14.38		..
Eltrombopag	£322,900	£32,572	14.83	0.45	£72,529
Romiplostim	£411,804	£88,904	14.81	-0.02	Dominated

Figure 11 Alternative base case CEACs and CEAF: Splenectomised





While the non-TPO-RA sequence remains the most likely to be cost effective up to a willingness to pay of £100k per QALY, beyond the willingness to pay of a little over £70k per QALY the eltrombopag containing sequence has the highest expected monetised health benefits.

Alternative base case results: Non-splenectomised

For the non-splenectomised patient population, the non-TPO-RA treatment sequence is estimated to result in 30.19 years undiscounted overall survival compared to 31.38 years for the TPO-RA containing sequences: a gain of 1.19 years overall survival.

The estimated costs are as follows.

Table 69 Deterministic costs for the alternative base case: Non-splenectomised

	ELTR	ROMI		Non-TPO-RA	
			net vs		net vs
	Total	Total	ELTR	Total	ELTR
[redacted]					
TPO-RA acquisition					
TPO-RA administration					
Non-TPO-RA acquisition					
Non-TPO-RA administration					
Rescue acquisition	£66,240	£66,240	£0	£90,245	£24,005
Rescue administration	£33,400	£33,400	£0	£45,126	£11,726
Bleeds	£13,222	£13,222	£0	£17,633	£4,411
Total	£232,335	£272,680	£40,345	£158,390	-£73,945

Within the alternative base case, the additional net rescue costs for the non-TPO-RA containing sequence compared to the eltrombopag containing sequence are £35,730. This compares with £71,811 for the base case.

The cost, QALY and costs effectiveness estimates are as below.

Table 70 Deterministic cost effectiveness alternative base case: Non-splenectomised

	Cost	Δ Cost	QALYs	Δ QALYs	ICER
Non-TPO-RA	£158,390		14.19		
Eltrombopag	£232,335	£73,945	14.96	0.77	£95,536
Romiplostim	£272,680	£40,345	14.96	0.00	Dominated

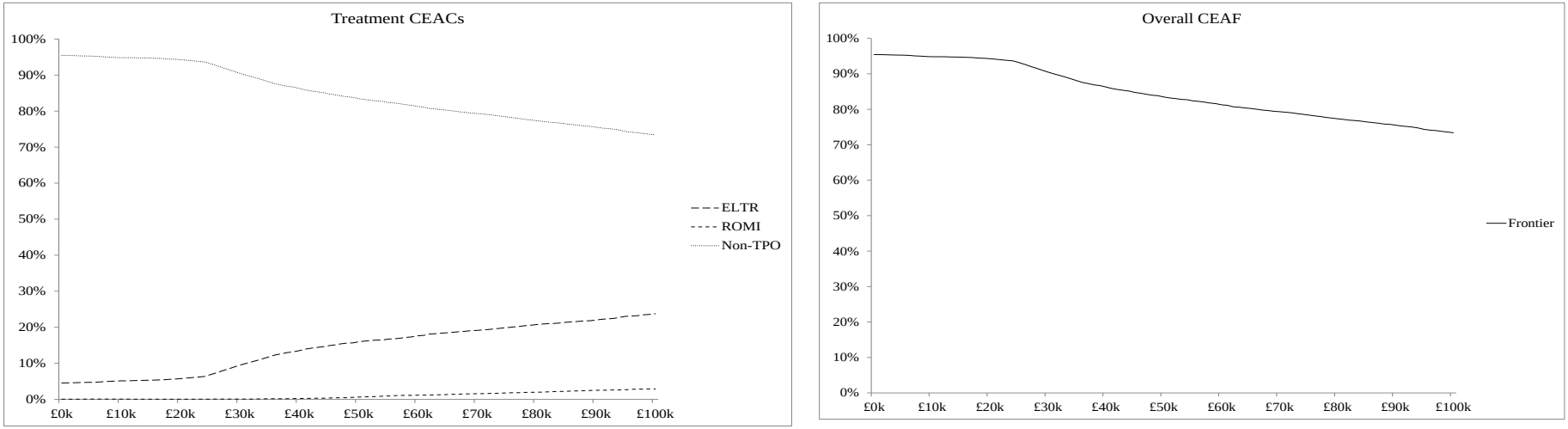
Note that in the above the cost effectiveness of the romiplostim containing treatment sequence compared to the non-TPO-RA treatment sequence is estimated to be £147,660 per QALY.

The probabilistic modelling and CEAF for the non-splenectomised are as below.

Table 71 Probabilistic cost effectiveness alternative base case: Non-splenectomised

	Cost	Δ Cost	QALYs	Δ QALYs	ICER
Non-TPO-RA	£163,902	..	14.77		..
Eltrombopag	£236,339	£72,437	15.33	0.56	£128,464
Romiplostim	£276,600	£40,261	15.31	-0.02	Dominated

Figure 12 Alternative base case CEACs and CEAF: Non-splenectomised



The CEAC for the non-TPO-RA sequence and the CEAF coincide over the range of willingness to pay values.

TA221 modelling results

For the splenectomised patient population, from a baseline age of 48 years the non-TPO-RA treatment sequence is estimated to result in an average 30.49 years undiscounted overall survival compared to 31.22 years for the TPO-RA containing sequences: a gain of 0.74 years overall survival.

The cost, QALY and costs effectiveness estimates are as below.

Table 72 Deterministic cost effectiveness alternative base case: Splenectomised

	Cost	Δ Cost	QALYs	Δ QALYs	ICER
Eltrombopag	£575,374		12.28		
Non-TPO-RA	£596,624	£21,250	11.09	-1.19	Dominated
Romiplostim	£633,714	£58,339	12.28	0.00	Dominated

Note that in the above the cost effectiveness of the romiplostim containing treatment sequence compared to the non-TPO-RA treatment sequence estimate is £31,062 per QALY.

For the non-splenectomised patient population, the non-TPO-RA treatment sequence is estimated to result in 30.19 years undiscounted overall survival compared to 31.38 years for the TPO-RA containing sequences: a gain of 1.19 years overall survival.

The cost, QALY and costs effectiveness estimates are as below.

Table 73 Deterministic cost effectiveness alternative base case: Non-splenectomised

	Cost	Δ Cost	QALYs	Δ QALYs	ICER
Non-TPO-RA	£472,641		12.08		
Eltrombopag	£475,646	£3,006	10.45	-1.62	Dominated
Romiplostim	£505,824	£33,184	12.08	0.00	Dominated

Note that in the above the cost effectiveness of the romiplostim containing treatment sequence compared to the non-TPO-RA treatment sequence is estimated to be £18,578 per QALY.

Section 10.6.10 of the submission does not make any reference to probabilistic modelling for the TA221 modelling, and the ERG has not performed any.

Summary of the 3 main scenarios' deterministic cost effectiveness results

The three main scenarios presented by the manufacturer have the following deterministic cost effectiveness results for splenectomised patients.

Table 74 3 main scenarios' deterministic ICERs: Splenectomised

	Base case vs Non-TPO-RA	vs ELTR	Alternative base case vs Non-TPO-RA	vs ELTR	TA221 analysis vs Non-TPO-RA	vs ELTR
Non-TPO-RA	..	Dominated	..	-£61,337	..	Dominated
Eltrombopag	Dominates	..	£61,337	..	Dominates	..
Romiplostim	£48,914	Dominated	£220,860	Dominated	£31,062	Dominated

The three main scenarios presented by the manufacturer have the following deterministic cost effectiveness results for non-splenectomised patients.

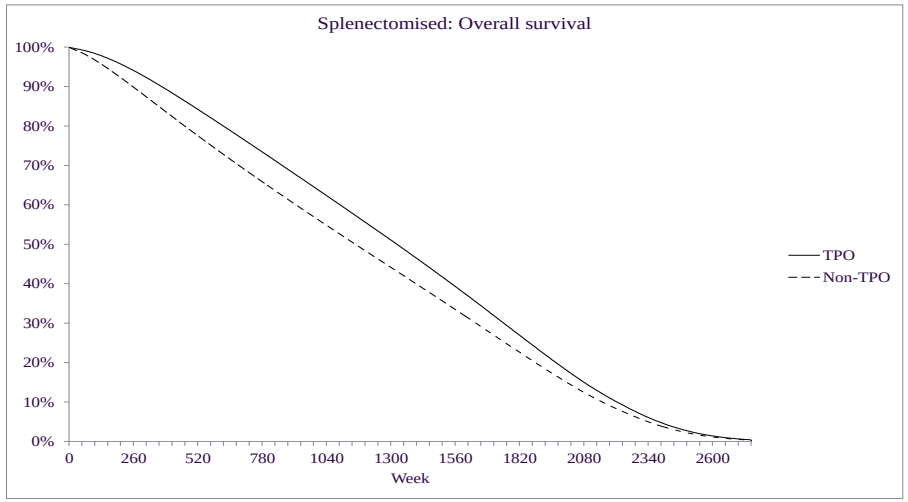
Table 75 3 main scenarios' deterministic ICERs: Non-splenectomised

	Base case vs Non-TPO-RA	vs ELTR	Alternative base case vs Non-TPO-RA	vs ELTR	TA221 analysis vs Non-TPO-RA	vs ELTR
Non-TPO-RA	..	Dominated	..	-£95,536	..	Dominated
Eltrombopag	£15,105	..	£95,536	..	Dominates	..
Romiplostim	£32,657	Dominated	£147,660	Dominated	£18,578	Dominated

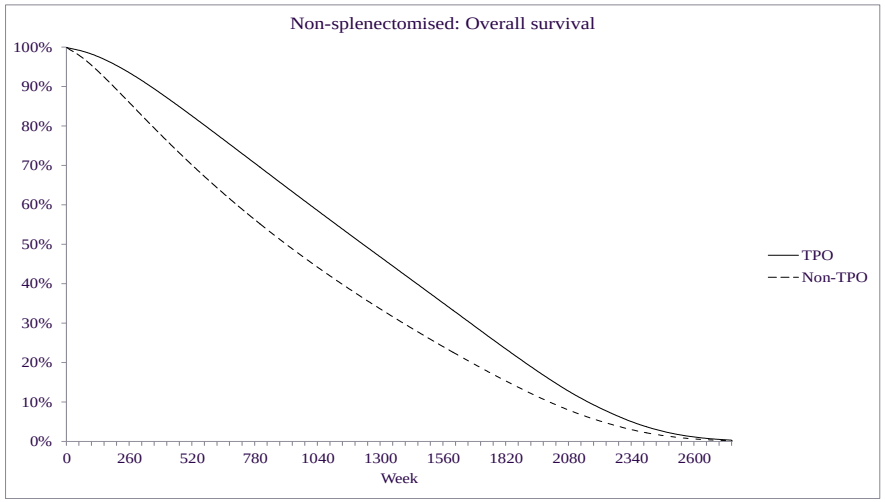
The survival curves and the cohort balances between those on TPO-RA treatment, on non-TPO-RA treatment, between treatments and at end of the line on no treatment for the base case and for the alternative base case are graphed overleaf.

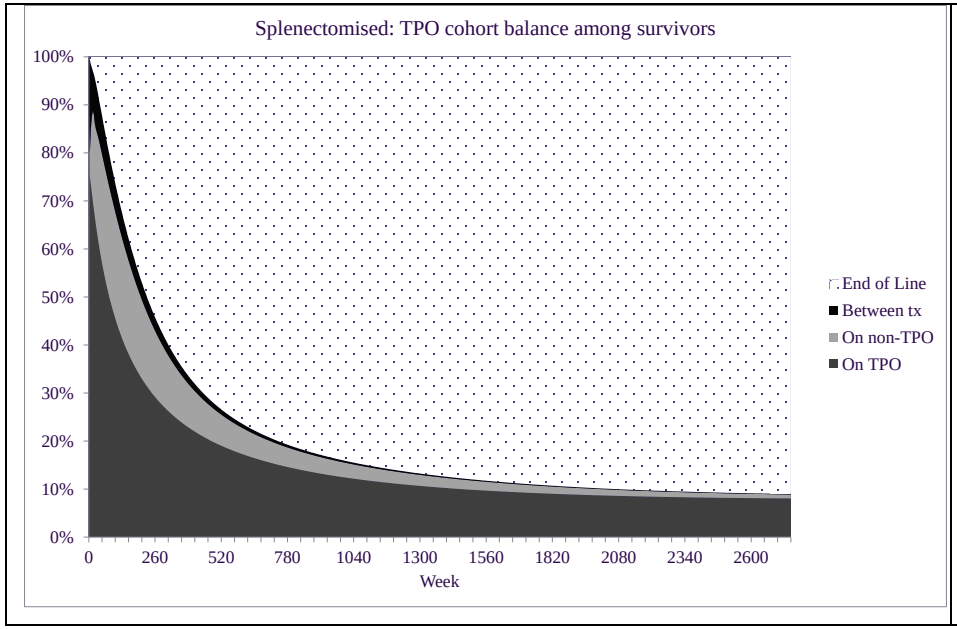
Figure 13 Base case survival and survivor cohort balance

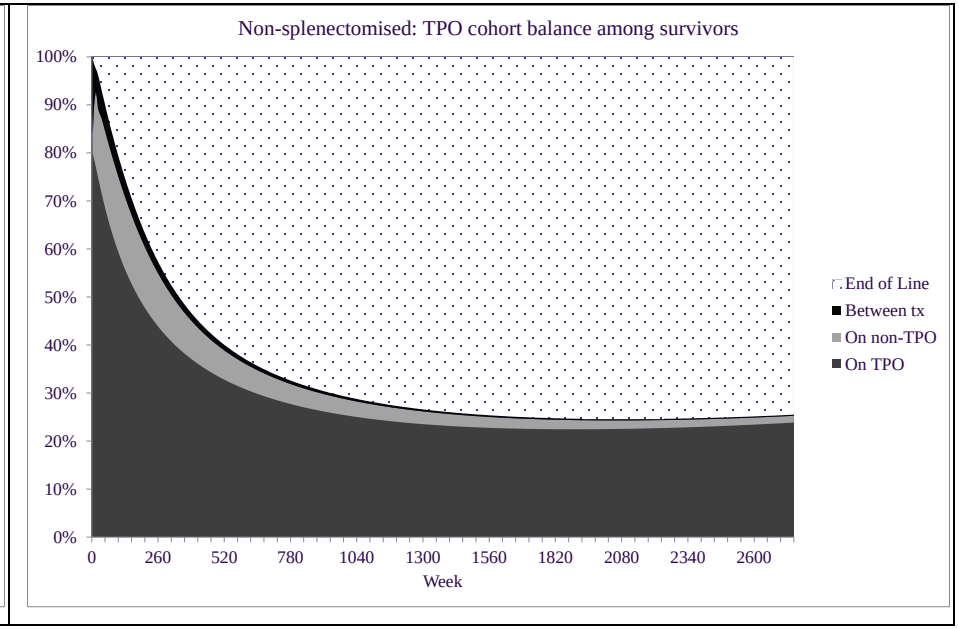
Splenectomised

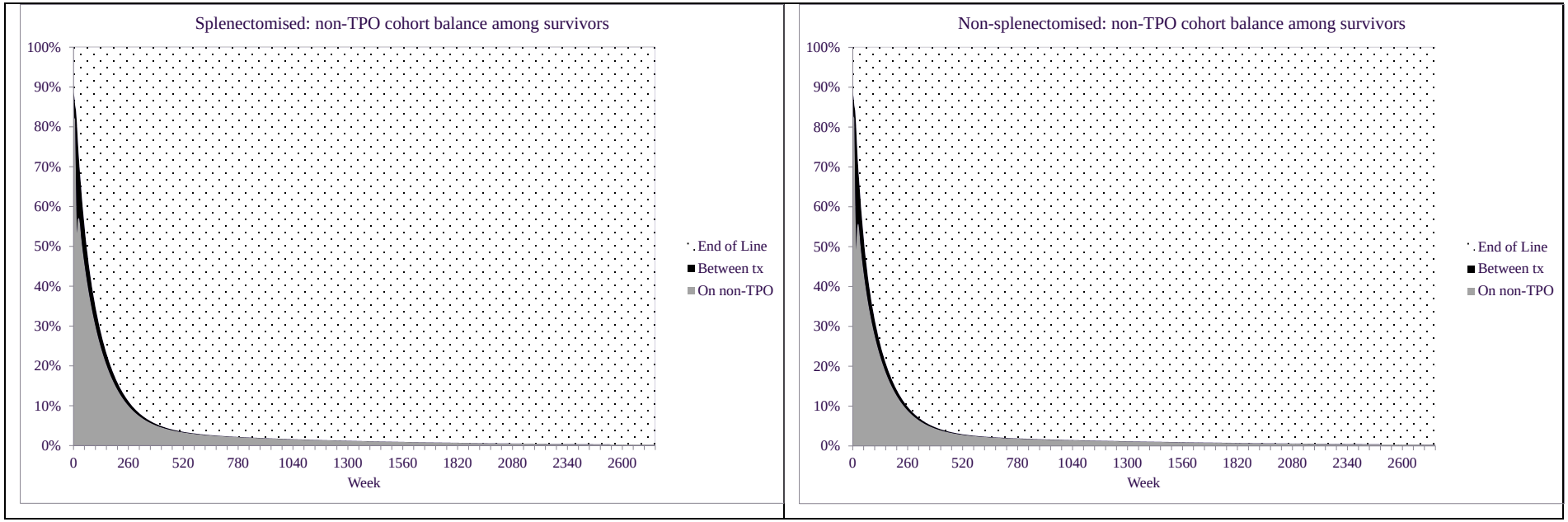


Non-splenectomised




Splenectomised: TPO cohort balance among survivors
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
260
520
780
1040
1300
1560
1820
2080
2340
2600
Week
End of Line
Between tx
On non-TPO
On TPO


Non-splenectomised: TPO cohort balance among survivors
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
260
520
780
1040
1300
1560
1820
2080
2340
2600
Week
End of Line
Between tx
On non-TPO
On TPO

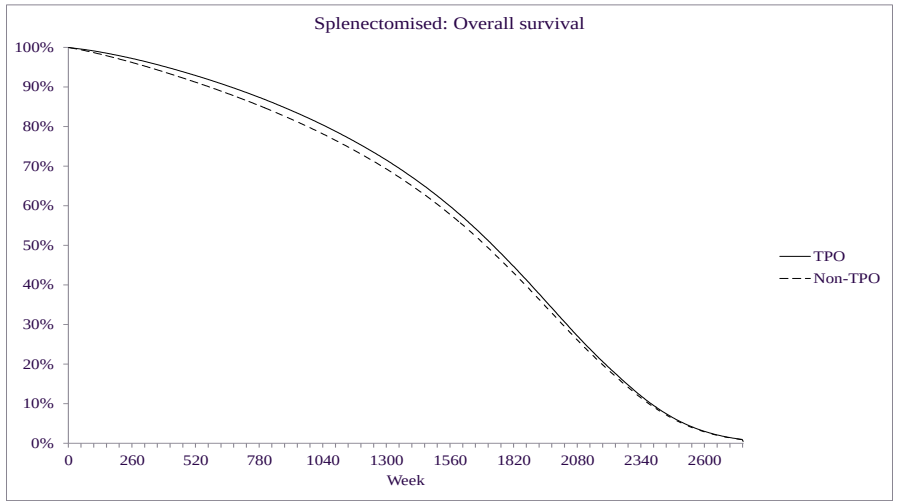


Among splenectomised patients, the base case suggests that at the 5 year point 94% will survive with the TPO-RA-sequence compared to only 90% with the non-TPO-RA sequence, with proportions of survivors on active treatment of 43% and 10%. At 10 years the corresponding survival figures are 84% and 77%, with proportions of survivors on active treatment of 26% and 3%.

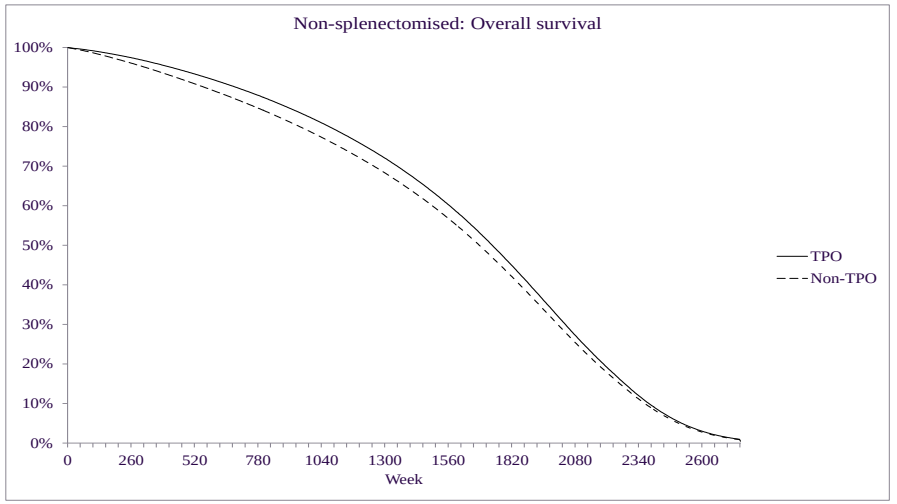
Among non-splenectomised patients, the base case suggests that at the 5 year point 93% will survive with the TPO-RA-sequence compared to only 86% with the non-TPO-RA sequence, with proportions of survivors on active treatment of 55% and 9%. At 10 years the corresponding survival figures are 82% and 70%, with proportions of survivors on active treatment of 39% and 3%.

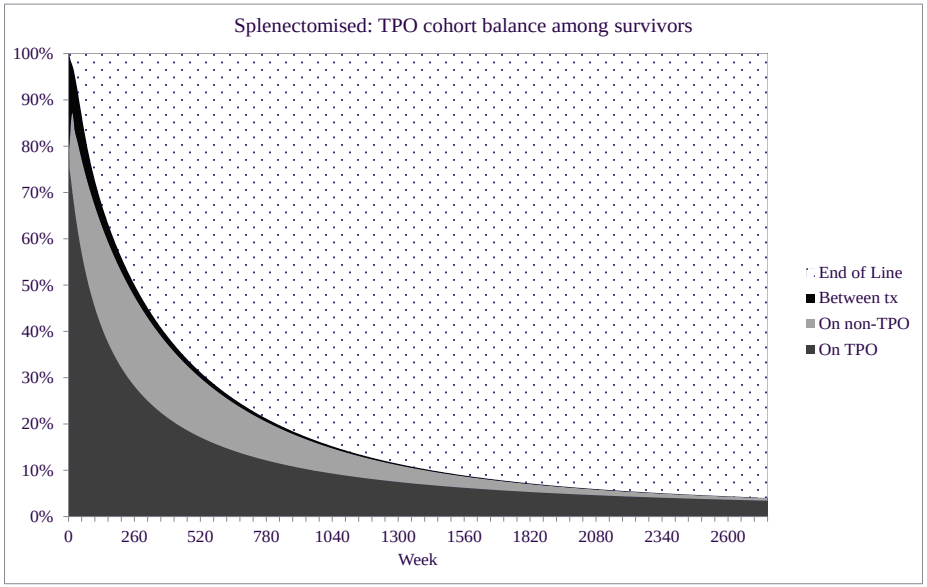
Figure 14 Alternative base case survival and survivor cohort balance

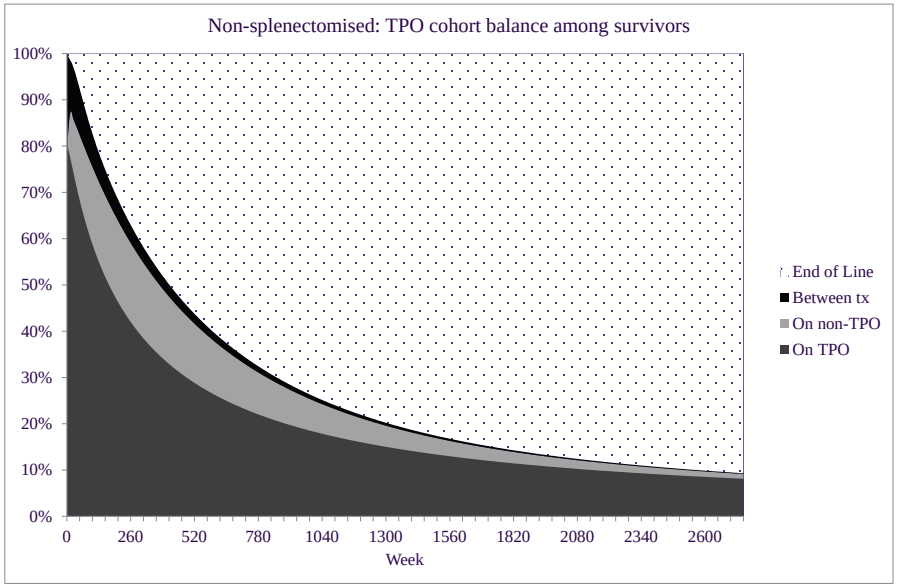
Splenectomised

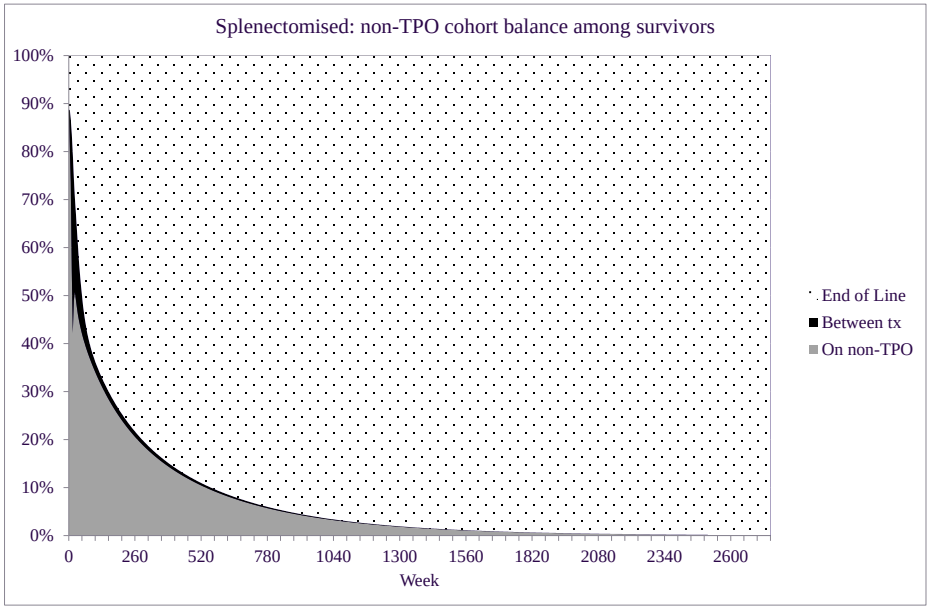


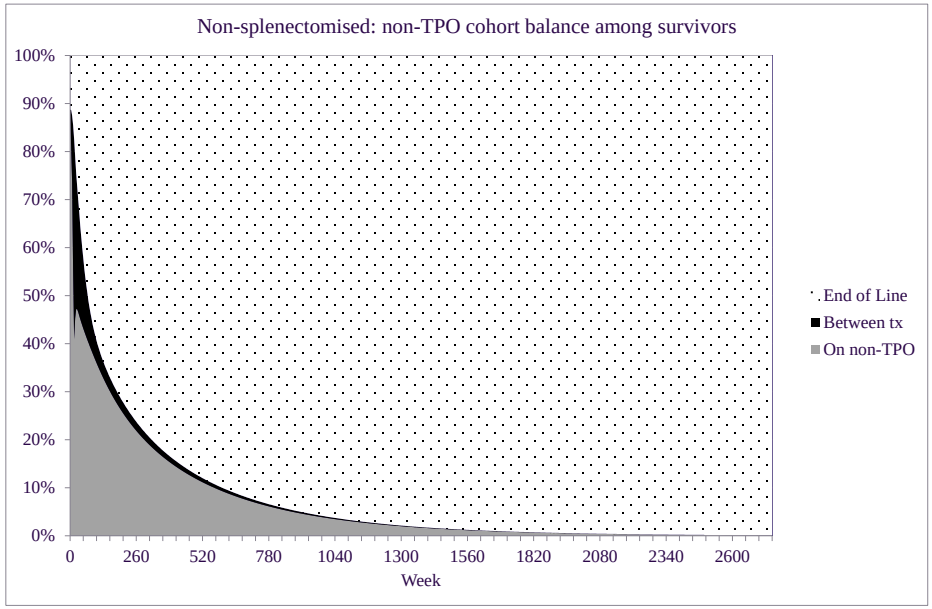
Non-splenectomised




Splenectomised: TPO cohort balance among survivors
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
260
520
780
1040
1300
1560
1820
2080
2340
2600
Week
End of Line
Between tx
On non-TPO
On TPO


Non-splenectomised: TPO cohort balance among survivors
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
260
520
780
1040
1300
1560
1820
2080
2340
2600
Week
End of Line
Between tx
On non-TPO
On TPO





Among splenectomised patients, the base case suggests that at the 5 year point 97% will survive with the TPO-RA-sequence compared to only 96% with the non-TPO-RA sequence, with proportions of survivors on active treatment of 48% and 21%. At 10 years the corresponding survival figures are 93% and 91%, with proportions of survivors on active treatment of 30% and 10%.

Among non-splenectomised patients, the base case suggests that at the 5 year point 97% will survive with the TPO-RA-sequence compared to only 96% with the non-TPO-RA sequence, with proportions of survivors on active treatment of 59% and 22%. At 10 years the corresponding survival figures are 93% and 91%, with proportions of survivors on active treatment of 42% and 11%.

5.2.10 Sensitivity analyses

The manufacturer presents a wide range of univariate sensitivity analyses:

- The treatment pathway.
  - SA01: Rituximab being 1st line of the non-TPO-RA treatment sequence, with the TPO-RA including treatment sequences placing the TPO-RA prior to the non-TPO-RA treatment sequence.
  - SA02: The TPO-RA in isolation compared to no active treatment, the latter presumably immediately including the doubling in the risk of fatal bleeds.
  - SA03: As per SA01, but with the TPO-RA including treatment sequences substituting the TPO-RA for rituximab in the non-TPO-RA treatment sequence.
- TPO-RA response rates.
  - SA04: Retaining equivalent efficacy for the TPO-RA but applying the responder (OR) rates of RAISE.
  - SA05: Applying the responder (OR) rate as in the previous bullet for eltrombopag, but applying the odds ratios of the indirect comparison to derive the romiplostim responder (OR) rate.
- TPO-RA time to loss of response.
  - SA06 & SA07: Applying the responders' log-logistic and the responders' gamma for time to loss of response.
  - SA08, SA09 & SA10: Applying the all patients' Gompertz, the all patients' log-logistic and the all patients' Weibull for the time to loss of response.
- Mortality.
  - SA11: Modelling CITP mortality as a function of the platelet count rather than as a function of bleeds.
- Rescue rates per cycle for patients in platelet non-response.
  - SA12: The RAISE+EXTEND data -25%
  - SA13: The RAISE+EXTEND data
  - SA14: The midpoint between the RAISE+EXTEND data and the TA221 data
  - SA15: The TA221 data
  - SA16: The TA221 data +25%
- Rescue that is IVIG
  - SA17 & SA18: ±25% from the base case
- Rates of serious bleeds for platelet non-responders
  - SA19: The RAISE+EXTEND data -25%
  - SA20: The RAISE+EXTEND data
  - SA21: The midpoint between the RAISE+EXTEND data and the TA221 data

  - SA22: The TA221 data
  - SA23: The TA221 data +25%
- Costs.
  - SA24: All romiplostim administered on an outpatient basis
  - SA25: Excluding the eltrombopag PAS
  - SA26: Basing romiplostim dosing upon Bussel rather than Kuter.
- Discount rates.
  - SA27 & 28: discount rates of 0% and 6%.
- Time horizons.
  - SA29, SA30, SA31 & SA32: Time horizons of 6 months, 5 years, 10 years and 20 years.
- Serious bleeds.
  - SA33: Assuming that the serious bleed rate for end of the line non-responders is that of long term non-responders who are between treatments.

Table B96 and table B97 of the submission present the impact of these sensitivity analyses' net costs and QALYs, using the eltrombopag treatment sequence as the referent when this is the least expensive and using the non-TPO-RA treatment sequence when this is the least expensive. These are replicated here for ease of reference. Within this ".." indicates the referent treatment sequence, which is either the eltrombopag containing sequence or the non-TPO-RA sequence; i.e. the cheapest sequence from which the net costs, net QALYs and ICERs for the other treatments are calculated. "*Dom.*" indicates a treatment which is dominated.

Table 76 Base case univariate sensitivity analyses: Splenectomised

	Costs			QALYs			ICERs		
	ELTR	ROMI	No-TPO-RA	ELTR	ROMI	No-TPO-RA	ELTR	ROMI	No-TPO-RA
Base case	£556,089	£643,598	£581,073	12.22	12.22	10.95			
Δ vs ELTR	..	£87,509	£24,984	..	0.00	-1.27	..	Dom.	Dom.
Δ vs no-TPO-RA	-£24,984	£62,525	..	1.27	1.27	..	Dom.	£48,914	..
	Δ cost			Δ QALY			ICERs		
	ELTR	ROMI	No-TPO-RA	ELTR	ROMI	No-TPO-RA	ELTR	ROMI	No-TPO-RA
Treatment pathway									
01: 1st rituximab	..	£87,508	£23,223	..	..	-1.21	..	Dom.	Dom.
02: vs no treatment	..	£87,508	£30,867	..	..	-1.38	..	Dom.	Dom.
03: TPO-RA no ritux.	..	£87,508	£12,228	..	..	-0.93	..	Dom.	Dom.
TPO response rates									
04: Overall	..	£69,183	£17,658	..	..	-0.96	..	Dom.	Dom.
05: Ind. comp.	..	£95,649	£19,075	..	0.56	-1.02	..	£171,156	Dom.
TPO time to loss of response									
06: Resp. log-log	..	£83,622	£23,543	..	..	-1.23	..	Dom.	Dom.
07: Resp. gamma	..	£93,305	£27,411	..	..	-1.35	..	Dom.	Dom.
08: All gompertz	..	£102,692	£33,099	..	..	-1.41	..	Dom.	Dom.
09: All log log	..	£80,300	£22,823	..	..	-1.17	..	Dom.	Dom.
10: All weibull	..	£57,558	£13,626	..	..	-0.9	..	Dom.	Dom.

Mortality									
11: Platelet mort.	..	£87,537	£38,927	..	..	-1.04	..	Dom.	Dom.
Rescue rates for platelet non-responders									
12: RAISE -25%	£45,829	£133,289	..	1.64	1.64	..	£27,957	Dom.	..
13: RAISE	£34,746	£122,214	..	1.58	1.58	..	£21,967	Dom.	..
14: RAISE&TA221	£7,076	£94,564	..	1.44	1.44	..	£4,914	Dom.	..
15: TA221	..	£87,508	£24,984	..	..	-1.28	..	Dom.	Dom.
16: TA221+25%	..	£87,527	£60,094	..	..	-1.1	..	Dom.	Dom.
IVIG rescue treatment									
17: RAISE +25%	..	£87,504	£54,886	..	..	-1.28	..	Dom.	Dom.
18: RAISE -25%	..	£87,476	£24,511	..	..	-1.51	..	Dom.	Dom.
Serious bleeds for platelet non-responders									
19: RAISE -25%	..	£87,595	£72,065	..	..	-0.36	..	Dom.	Dom.
20: RAISE	..	£87,594	£71,243	..	..	-0.37	..	Dom.	Dom.
21: RAISE&TA221	..	£87,551	£44,790	..	..	-0.89	..	Dom.	Dom.
22: TA221	..	£87,508	£24,984	..	..	-1.28	..	Dom.	Dom.
23: TA221+25%	..	£87,486	£16,540	..	..	-1.44	..	Dom.	Dom.
Costs									
24: ROMI OP	..	£117,132	£24,984	..	..	-1.28	..	Dom.	Dom.
25: No ELTR PAS	..	[redacted]	[redacted]	..	..	-1.28	..	Dom.	Dom.
26: ROMI dosing	..	£146,054	£24,984	..	..	-1.28	..	Dom.	Dom.

Discount rates									
27: 0%	..	£118,077	£9,560	..	..	-2.3	..	Dom.	Dom.
28: 6%	..	£74,447	£27,326	..	..	-0.92	..	Dom.	Dom.
Time horizon									
29: 6 months	..	£6,949	£1,877	..	..	-0.02	..	Dom.	Dom.
30: 5 years	..	£43,997	£20,965	..	..	-0.21	..	Dom.	Dom.
31: 10 years	..	£62,487	£35,432	..	..	-0.45	..	Dom.	Dom.
32: 20 years	..	£78,568	£36,987	..	..	-0.85	..	Dom.	Dom.
Non-responder fatal bleeds									
33: Equal FB	..	£58,339	£21,250	..	..	-1.19	..	Dom.	Dom.

Table 77 Base case univariate sensitivity analyses: Non-splenectomised

	Costs			QALYs			ICERs		
	ELTR	ROMI	No-TPO-RA	ELTR	ROMI	No-TPO-RA	ELTR	ROMI	No-TPO-RA
Base case	£332,193	£372,744	£297,292	11.86	11.86	9.55			
Δ vs ELTR	..	£40,551	-£34,901	..	0.00	-2.31	..	Dom.	..
Δ vs no-TPO-RA	£34,901	£75,452	..	2.31	2.31	..	£15,105	£32,657	..
	Δ cost			Δ QALY			ICERs		
	ELTR	ROMI	No-TPO-RA	ELTR	ROMI	No-TPO-RA	ELTR	ROMI	No-TPO-RA
Treatment pathway									
01: 1st rituximab	£35,001	£75,552	..	2.19	2.19	..	£15,996	Dom.	..
02: vs no treatment	£32,051	£72,603	..	2.48	2.48	..	£12,898	Dom.	..
03: TPO-RA no ritux.	£36,668	£77,220	..	1.88	1.88	..	£19,463	Dom.	..
TPO-RA response rates									
04: Overall	£31,710	£68,252	..	1.97	1.97	..	£16,073	Dom.	..
05: Ind. comp.	£31,619	£83,035	..	2.08	2.55	..	£15,177	£110,983	..
TPO-RA time to loss of response									
06: Resp. log-log	£33,552	£71,923	..	2.2	2.2	..	£15,235	Dom.	..
07: Resp. gamma	£35,852	£78,168	..	2.39	2.39	..	£14,987	Dom.	..
08: All gompertz	£37,588	£86,256	..	2.62	2.62	..	£14,347	Dom.	..
09: All log log	£30,455	£65,141	..	1.99	1.99	..	£15,305	Dom.	..
10: All weibull	£26,684	£54,511	..	1.67	1.67	..	£15,995	Dom.	..

Mortality									
11: Platelet mort.	£18,642	£59,216	..	1.84	1.84	..	£10,112	Dom.	..
Rescue rates for platelet non-responders									
12: RAISE -25%	£84,364	£124,904	..	2.55	2.55	..	£33,106	Dom.	..
13: RAISE	£76,936	£117,478	..	2.51	2.51	..	£30,623	Dom.	..
14: RAISE&TA221	£34,900	£75,452	..	2.31	2.31	..	£15,105	Dom.	..
15: TA221	£34,900	£75,452	..	2.31	2.31	..	£15,105	Dom.	..
16: TA221+25%	£14,367	£54,922	..	2.21	2.21	..	£6,492	Dom.	..
IVIG rescue treatment									
17: RAISE +25%	£26,035	£66,588	..	2.28	2.28	..	£11,439	Dom.	..
18: RAISE -25%	£43,911	£84,461	..	2.34	2.34	..	£18,726	Dom.	..
Serious bleeds for platelet non-responders									
19: RAISE -25%	..	£40,609	£10,705	..	..	-0.62	..	Dom.	Dom.
20: RAISE	..	£40,608	£9,833	..	..	-0.65	..	Dom.	Dom.
21: RAISE&TA221	£16,806	£57,385	..	1.65	1.65	..	£10,203	Dom.	..
22: TA221	£34,900	£75,452	..	2.31	2.31	..	£15,105	Dom.	..
23: TA221+25%	£42,125	£82,661	..	2.57	2.57	..	£16,381	Dom.	..
Costs									
24: ROMI OP	£34,900	£119,960	..	2.31	2.31	..	£15,105	Dom.	..
25: No ELTR PAS	[redacted]	£117,914	..	2.31	2.31	..	[redacted]	Dom.	..
26: ROMI dosing	£34,900	£160,173	..	2.31	2.31	..	£15,105	Dom.	

Discount rates									
27: 0%	£74,241	£132,010	..	4.22	4.22	..	£17,583	Dom.	..
28: 6%	£22,444	£55,948	..	1.64	1.64	..	£13,700	Dom.	..
Time horizon									
29: 6 months	£1,840	£4,259	..	0.02	0.02	..	£74,250	Dom.	..
30: 5 years	£4,324	£21,641	..	0.33	0.33	..	£13,022	Dom.	..
31: 10 years	£4,643	£30,866	..	0.76	0.76	..	£6,132	Dom.	..
32: 20 years	£15,694	£50,675	..	1.50	1.50	..	£10,467	Dom.	..
Non-responder fatal bleeds									
33: Equal FB	..	£33,184	£3,006	..	..	-1.62	..	Dom.	Dom.

As would be expected, of the variables explored in the manufacturer sensitivity analyses results are reasonably sensitive to:

- The assumption of TPO-RA equivalence
- The bleed rates
- The rescue rates
- The proportion of rescue that is IVIG
- The mortality associated with platelet response status
- Whether severe bleeds double when the patient is last in line
- The time horizon

Alternative base case and TA221 modelling univariate sensitivity analyses

The manufacturer submission does not present the univariate sensitivity analyses for the alternative base case or the TA221 modelling, viewing these as scenario analyses. It seems likely that the input variables that the base case net costs and/or net QALYs are sensitive to will also have an impact upon the results of the alternative base case and the TA221 modelling.

5.2.11 Model validation and face validity check

RAISE+EXTEND HRQoL values

As presented in the manufacturer response to ERG clarification question C2, the mean observed utility values from the patient level EQ-5D data and the mean utility values predicted by applying model 6 to the patient level data required for model 6 are as below.

Table 78 RAISE+EXTEND observed and predicted HRQoL values: All patients

Patients	Time points	N	Obs.	Pred.	Net Pred. – Obs.	
RAISE all	Baseline	187	0.715	0.748	0.033	4.6%
RAISE all	All RAISE excl baseline	509	0.716	0.748	0.032	4.5%
RAISE all	All EXTEND	1,300	0.722	0.749	0.027	3.7%
RAISE responder	All RAISE: in PR	242	0.739	0.764	0.025	3.4%
RAISE responder	All RAISE: not in PR	99	0.715	0.735	0.020	2.8%
RAISE responder	All EXTEND: in PR	632	0.744	0.772	0.028	3.8%
RAISE responder	All EXTEND: not in PR	233	0.712	0.753	0.041	5.8%
RAISE non-resp.	All RAISE excl baseline	167	0.685	0.726	0.041	6.0%

PR: platelet response

In the above the mean utilities among responders in platelet response are higher than those among responders not in platelet response. In general, there is roughly the same difference in mean utilities between responders in platelet response and responders not in platelet response as between responders not in platelet response and non-responders.

The above suggests that it may not be valid to apply the same utility value for responders in platelet response as to responders not in platelet response, with both the observed and the predicted values being higher for those in platelet response than for those not in platelet response. Whether and how much severe bleeds may be contributing to these discrepancies is not clear, but note that the predicted values for the modelled values take into account the non-severe bleeds.

Perhaps the more striking aspect of the above is the differences between the mean observed values and the mean predicted values. In all cases it appears that the predicted values are between 3% and 6% higher than the observed values. This seems peculiar, and it suggests that Model 6 of the utility analysis of the RAISE+EXTEND data may tend to have overvalued the modelled survival gain.

A similar picture occurs in the RAISE+EXTEND data when this is split into the splenectomised and the non-splenectomised subgroups.

Table 79 RAISE+EXTEND observed and predicted HRQoL values

		Splenectomised			**Non-Splenectomised**		
Patients	Time points	Obs.	Pred.	Net	Obs.	Pred.	Net
RAISE all	Baseline	0.696	0.721	3.6%	0.726	0.764	5.2%
RAISE all	All RAISE excl baseline	0.703	0.732	4.1%	0.724	0.757	4.6%
RAISE all	All EXTEND	0.708	0.730	3.1%	0.730	0.759	4.0%
RAISE resp. (any)	All RAISE: in PR	0.711	0.728	2.4%	0.752	0.784	4.3%
RAISE resp. (any)	All RAISE: not in PR	0.704	0.725	3.0%	0.722	0.741	2.6%
RAISE resp. (any)	All EXTEND: in PR	0.710	0.747	5.2%	0.758	0.785	3.6%
RAISE resp. (any)	All EXTEND: not in PR	0.722	0.724	0.3%	0.707	0.769	8.8%
RAISE non-resp. (any)	All RAISE excl baseline	0.696	0.734	5.5%	0.675	0.721	6.8%

The sensitivity analysis that applies the RAISE+EXTEND HRQoL data worsens the cost effectiveness estimate for the TPO-RA containing sequences compared to the non-TPO-RA containing sequences. Given this, the possibility that the RAISE+EXTEND model 6 appears

to overestimate the overall HRQoL and so the benefit of the additional survival is a further concern.

Model validation data

In response to ERG clarification question F2 the manufacturer provides the following validation data for the eltrombopag arm, comparing the modelled patient distribution and events with those observed in RAISE. Note that the ERG did not request this data for the comparator arm as there would be a lack of read across between the modelling and RAISE, due to the comparator arm of the model including a sequence of active treatments.

Table 80 Model validation data: Eltrombopag arm: Splenctomised

	On treatment											
	Platelet ≥ 50bn		Platelet < 50bn		Off treatment		Rescue events[7]		Severe bleeds		NSevere bleeds	
Mth	Model	RAISE	Model	RAISE	Model	RAISE	Model	RAISE	Model	RAISE	Model	RAISE
1	76%	42%	0%	56%	24%	2%	17%	10%	1%	0%	12%	46%
2	74%	44%	0%	50%	26%	6%	18%	3%	1%	0%	13%	16%
3	72%	44%	0%	48%	27%	8%	19%	13%	1%	0%	13%	12%
4	71%	42%	0%	46%	29%	12%	20%	19%	1%	0%	13%	12%
5	69%	42%	0%	42%	31%	16%	19%	13%	1%	0%	13%	8%
6	67%	47%	0%	37%	33%	16%	18%	19%	1%	0%	13%	10%

Due to the model anticipating patients coming off treatment if they do not respond in the first cycle, the proportion of patients that are off treatment is higher in the model than in RAISE. This would be anticipated to increase the number of rescue events and bleeds to be above that observed during the RAISE trial. It appears that this does not particularly occur. This may be due to the model assuming that all patients are in platelet response, when the proportion in RAISE was somewhat less than this.

[7] To the manufacturer's credit, the RAISE rescue rates for both high income countries and RAISE as a whole were reported in the response to ERG clarification question F2 despite the ERG not specifying this. The rates reported here are for the high income countries in order to maintain consistency with the modelling.

Table 81 Model validation data: Eltrombopag arm: Non-splenctomised

	On treatment											
	Platelet ≥ 50bn		Platelet < 50bn		Off treatment		Rescue events		Severe bleeds		NSevere bleeds	
Mth	Model	RAISE	Model	RAISE	Model	RAISE	Model	RAISE	Model	RAISE	Model	RAISE
1	80%	53%	0%	42%	20%	5%	7%	8%	1%	0%	13%	38%
2	79%	62%	0%	29%	21%	8%	7%	32%	1%	1%	13%	11%
3	78%	61%	0%	29%	21%	10%	7%	41%	1%	1%	13%	11%
4	77%	53%	0%	35%	22%	12%	7%	14%	1%	1%	14%	4%
5	76%	52%	0%	35%	23%	13%	7%	0%	1%	0%	13%	5%
6	75%	57%	0%	27%	24%	17%	6%	3%	1%	0%	13%	5%

The picture for the non-splenectomised is less clear, possibly due in part to the proportion in RAISE on treatment and in platelet response being that bit higher for the non-splenectomised than the splenectomised. Non-severe bleeds are higher in the model which is what should occur, though whether the extent of this is reasonable is difficult to gauge. But rescue rates in the early months are noticeably lower in the model than those observed during RAISE.

Note that the manufacturer also provides some aggregate validation data within the submission in tables B81 [p225] and B83 [p226]. These also include a comparison with the romiplostim trial.

Modelled survival and face validity of data inputs

The broadest face validity check of the modelling that can be presented it to compare the average undiscounted overall survivals modelled under the three scenarios[8]. These all relate to a baseline age of 48 years, for whom the approximate general population overall survival is around 33 years for men and 36 years for women[9].

Table 82 Modelled years overall survival: Splenectomised

	Non-TPO-RA	TPO-RA	Net gain
Base case	22.77	25.13	2.36
Alternative base case	30.49	31.22	0.74
TA221 modelling	23.32	25.61	2.29

Table 83 Modelled years overall survival: Non-splenectomised

	Non-TPO-RA	TPO-RA	Net gain
Base case	19.48	23.91	4.43
Alternative base case	30.19	31.38	1.19
TA221 modelling	21.54	24.73	3.19

The introduction section of the submission summarises the Danese et al study[86] as estimating an overall in-hospital fatality rate from ITP bleeds of 3.8% in the US. The model data suggest 2.5% for those in platelet response and 4.4% not in platelet response, though note that the base case modelling only applies the 4.4% for those not in platelet response.

The introduction section of the submission also summarises Cohen et al as estimating the annual fatal bleed rate for those with a platelet count persistently below $30x10^9$/L as between 1.62% and 3.89%.[16]

The RAISE+EXTEND data provide estimates of a 4 weekly fatal bleed rate for those with a platelet count below $50x10^9$/L of 0.0287% for the splenectomised and 0.0315% for the non-splenectomised. Ignoring general mortality, these translate into annual fatal bleed rates of 0.34% and 0.38% respectively.

[8]Implemented in the *Markov* worksheet with cell N8=SUM(BX23:OFFSET(BX23,Main!$AG$60,0))/(365/28)

[9] http://www.ons.gov.uk/ons/rel/lifetables/interim-life-tables/interim-life-tables/england-and-wales--interim-life-tables--1980-82-to-2007-09.xls though note that these do not project beyond age 100.

The TA221 data provide estimates of a 4 weekly fatal bleed rate for those with a platelet count below $50x10^9$/L of 0.1032% for the splenectomised and 0.1478% for the non-splenectomised. Ignoring general mortality, these translate into annual fatal bleed rates of 1.23% and 1.76% respectively.

The Cohen et al data applying only to those with a platelet count persistently below $30x10^9$/ L complicates any comparison with the figures used within the modelling. But the Portielje et al Norwegian study found that among those recently diagnosed with ITP the 2 year mortality risk was 1.3 times that of the general population.[90] Among those with platelet counts persistently below $30x10^9$/L it was 4.2 times that of the general population.

The balance between the platelet count categories within RAISE is presented below for the subgroup of eltrombopag responders and for the placebo arm as a whole. Note that 16% of patients had discontinued in the eltrombopag arm for both the splenectomised and the non-splenectomised, while discontinuations in the placebo arms were 5% and 12%.

Table 84 Platelet counts eltrombopag responders and placebo: Splenectomised

	Day 0	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Wk 10	Wk 14	Wk 18	Wk 22	Wk 26
Eltrombopag arm: responders												
N with platelet count (PC)	38	38	38	38	37	38	38	29	31	31	28	31
% $50x10^9$/L<= PC	0%	45%	53%	58%	57%	68%	63%	69%	71%	74%	82%	68%
% $30x10^9$/L<= PC <$50x10^9$/L	3%	21%	24%	18%	22%	13%	16%	10%	16%	13%	4%	19%
% PC <30bn	97%	34%	24%	24%	22%	18%	21%	21%	13%	13%	14%	13%
Placebo arm: all patients												
N with platelet count	21	20	20	20	20	20	19	16	16	15	15	19
% $50x10^9$/L <= PC	5%	5%	5%	5%	5%	5%	16%	19%	13%	20%	27%	16%
% $30x10^9$/L <= PC <$50x10^9$/L	0%	10%	10%	0%	15%	15%	5%	13%	6%	7%	13%	26%
% PC <$30x10^9$/L	95%	85%	85%	95%	80%	80%	79%	69%	81%	73%	60%	58%

Table 85 Platelet counts eltrombopag responders and placebo: Non-splenectomised

	Day 0	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Wk 10	Wk 14	Wk 18	Wk 22	Wk 26
Eltrombopag arm: responders												
N with platelet count (PC)	68	68	67	66	66	66	67	52	54	49	50	65
% $50x10^9$/L <= PC	1%	49%	70%	74%	65%	76%	76%	77%	69%	69%	74%	83%
% $30x10^9$/L <= PC <$50x10^9$/L	0%	22%	19%	8%	18%	12%	13%	15%	19%	22%	6%	5%
% PC <$30x10^9$/L	99%	29%	10%	18%	17%	12%	10%	8%	13%	8%	20%	12%
Placebo arm: all patients												
N with platelet count	40	40	39	38	39	39	38	27	30	30	29	36
% $50x10^9$/L <= PC	0%	8%	10%	11%	13%	10%	16%	26%	23%	20%	21%	22%
% $30x10^9$/L <= PC <$50x10^9$/L	0%	13%	21%	18%	10%	23%	18%	7%	3%	13%	17%	8%
% PC <$30x10^9$/L	100%	80%	69%	71%	77%	67%	66%	67%	73%	67%	62%	69%

Towards the end of RAISE, compared to baseline the proportion of those with a platelet count of <$30x10^9$/L in the placebo arm was around an absolute 50% higher than that among eltrombopag responders.

5.3 ERG cross check and critique

The ERG has rebuilt the deterministic model structure. The results from this broadly cross check with those of the manufacturer model, is reviewed in more detail in Appendix 2. The main exception to this is the QALY decrements from the TPO SAEs and AEs. The manufacturer model assumes these events occur only during the first cycle of TPO treatment. It may be more reasonable to assume that they occur on an ongoing basis among those remaining on TPO treatment.

5.3.1 Base case results

The base case results, the alternative base case results and the TA221 modelling results cross check with those of the submission.

5.3.2 Data Inputs: Correspondence between written submission and sources cited

Romiplostim dose

The romiplostim doses are drawn from Kuter 2008.[1] The final romiplostim doses applied within the modelling are 0.00511mg/kg for the splenectomised and 0.00274mg/kg for the non-splenectomised. These appear to cross check with figure 2 of Kuter 2008.[1]

But Kuter 2008[1] also noted that the median [range] dose during the last eight weeks of the trial for those achieving a durable response was somewhat lower than for those not achieving a durable response: 0.0030mg/kg [0.0000-0.0070mg/kg] compared to 0.0053mg/kg [0.0005-0.0150mg/kg] for the splenectomised and 0.0010mg/kg [0.0003-0.0070mg/kg] compared to 0.0030mg/kg [0.0010-0.0150mg/kg] for the non-splenectomised. The application of this data within the modelling is complicated by only the medians being reported. The ranges for those not achieving a durable response also suggest that some of these patients may have been titrated to a somewhat a higher dose.

The ranges for those achieving a durable response may be more symmetric, at least for the splenectomised. In the light of this, bearing in mind that the modelling assumes that only responders continue TPO therapy, it may have been more reasonable to apply the median romiplostim dose from the last eight weeks of the trial among those achieving a durable response. This would significantly reduce the TPO-RA costs within the romiplostim sequence: perhaps by around 40% for the splenectomised and by around 60% for the non-splenectomised.

This is complicated by the dosing from the romiplostim extension study as reported in Bussel 2009,[30] which shows overall average dose of around 0.0060mg/kg pooled across

splenectomised and non-splenectomised. But this also has to be read in the context of a model structure which assumes that non-responders cease treatment after the first month, and only responders continue therapy beyond this point.

Non-TPO-RA duration of response

There may be some minor errors of transcription from the romiplostim TA221 manufacturer submission table 7.1 and those cited as being from TA221 that underlie the eltrombopag submission base case. The mean durations of response for the non-TPO-RA treatments are outlined below.

Table 86 Non-TPO-RA duration of response cross check

	Romiplostim TA221 table 7.1				**Manufacturer**	
	28 day cycles		**Days**		**Days**	
	Non-		**Non-**		**Non-**	
	Splen	**Splenect**	**Splen**	**Splenect**	**Splen**	**Splenect**
Rituximab	18.90	18.90	529	529	575	575
Azathioprine	20.30	20.30	568	568	618	618
Mycophenolate mofetil	5.70	5.70	160	160	173	173
Ciclosporin	16.20	12.91	454	361	393	493
Dapsone	20.30	20.30	568	568	618	618
Danazol	147.35	145.40	4126	4071	4426	4485
Cyclophosphamide	27.00	27.00	756	756	822	822
Vincristine	1.40	1.40	39	39	43	43
Vinblastine	1.40	1.40	39	39	43	43

It is unlikely that these errors will have a major impact upon the cost effectiveness estimates. The main discrepancies are for ciclosporin where the non-splenectomised and splenectomised values may have been confused. But in general the mean number of days of response for the non-TPO-RA treatments may tend to have been overestimated within the eltrombopag submission, and may be based upon assuming a 31 day cycle rather than a 28 day cycle.

It might also be noted that table 7.1 of the romiplostim TA221 gives the mean duration of response as being measured from treatment initiation. This could suggest subtracting the mean time to response from the above to arrive at an approximate average duration of response.

Table 87 Non-TPO-RA duration of response from TA221

	TA221 Days	
	Non-Splen	**Splenect**
Rituximab	473	473
Azathioprine	456	456
Mycophenolate mofetil	48	48
Ciclosporin	398	305
Dapsone	540	540
Danazol	4014	3959
Cyclophosphamide	700	700
Vincristine	11	11
Vinblastine	11	11

Rescue rates and therapies from TA221

The 33% and 68% rescue rates cited by the manufacturer as being drawn from the romiplostim TA221 cross check. But TA221 also provides details on the balance between rescue therapies, where minor discrepancies occur.

Table 88 TA221 rescue rates and rescue therapies

	Splenectomised		**Non-splenectomised**	
	Applied	**TA221**	**Applied**	**TA221**
Immunoglobulin	64%	63%	59%	61%
Anti-D	0%	0%	25%	21%
IV Steroids	36%	37%	16%	18%
Platelet transfusion	0%	0%	0%	0%

Severe bleeds mortality risk

Danese et al report the following mortality rates for ITP inpatients by discharge code.[86]

Table 89 ITP inpatients' mortality risks

Discharge code	Mortality risk
All	3.8%
Splenectomy	1.5%
Coagulation disorder	1.7%
GI haemorrhage	4.6%
Cranial haemorrhage	13.2%
Septicaemia	14.4%
Epistaxis	2.3%
All other	4.3%

It is unclear how these mortality risks have been translated into mortality risks from inpatient bleeds of 4.4% for CITP inpatients not in platelet response and 2.5% for CITP inpatients in platelet response.

HRQoL values from TA221

The HRQoL values reported in the electronic model do not entirely cross check with those of table 7.1 of the manufacturer submission for TA221. As these are not used for either the base case or the alternative base case, this has no impact upon the main results of interest. The TA221 analysis may be affected, to the detriment of the TPO-RA. But note that the values from Szended et al[87] do cross check with the current submission, and as a consequence it may be that it is the HRQoL values within TA221 which are out of line.

5.3.3 Data Inputs: Correspondence between written submission and electronic model

Most of the data inputs to the model outlined above have been drawn from the electronic copy of the model. The inputs that are specified within the economics of the written submission cross check with those outlined above.

Adverse events rates

The adverse event rates for the modelling are drawn from TA221 and for the TPO-RA this suggests a 4 weekly SAE rate of 3% and a 4 weekly AE rate of 31%.

Table B59 of the submission outlines that during RAISE there were 21 SAEs among 135 eltrombopag patients. This suggests a 4 weekly SAE rate of around 2.6%, which given that not all remained on eltrombopag for the duration of RAISE is broadly in line with the estimate taken from TA221.

Table B59 also outlines 158 AEs related to study medication, which translates into an approximate 4 weekly AE rate of around 19.5%. While this differs from the 31% applied within the modelling, given eltrombopag discontinuations the value applied within the modelling seems reasonable.

5.3.4 ERG commentary on model assumptions, model structure and data inputs

Model Assumptions

TPO complete clinical equivalence

The data underlying this assumption are reviewed in greater detail in the clinical effectiveness section. But it is worth recalling that the clinical equivalence that is assumed is wider than just response rates and relates to all clinical aspects of the TPO-RA, for both the splenectomised and the non-splenectomised:

- Response rates
- Responders' duration of TPO therapy
- Responders' duration of TPO therapy spent in platelet response
- Adverse event rates

Treatment sequences considered

The modelling presented does not consider the optimal sequencing of treatments. Since the base case presented by the manufacturer does not consider rituximab it appears that the manufacturer may implicitly accept that patients should be refractory to rituximab before trying TPO-RA. But this still leaves open the question of the optimal positioning of the TPO-RA within the treatment sequence. Whether other non-TPO-RA with an acceptable adverse event profile should be tried for a response prior to moving on to the rather more expensive TPO-RA has not been addressed.

There may also be a question around the optimal sequencing of the TPO-RA if they are not assumed to be clinically equivalent. If this assumption is not made, eltrombopag will be seen as being less effective than romiplostim, but probably also cheaper than it. It may be reasonable to trial patients on the cheaper TPO-RA. Those that respond within four weeks could be maintained on the cheaper TPO-RA, with only non-responders moving on to try the more expensive TPO-RA.

Response and platelet response

The modelling assumes that responders; i.e. those experiencing a platelet response at least once during RAISE, are in continuous platelet response while on treatment.[10] This is not the case. Most of the relationships within the model are derived from platelet response data. Confusing response and platelet response is likely to have biased the analysis in favour of the TPO-RA.

Addressing this within the current model structure would require the relationships to be based upon responder status rather than platelet response status. An approximation to this within the current model structure might be to estimate responder event rates as averages of the platelet response event rates and the platelet non-response event rates, weighted by the proportion of time responders spend in platelet response.

Model structure

Event rates and the annual number of cycles

Within the model, it appears that a range of inputs relating to the number of events per cycle are based upon the annual number of events divided by 12. Given the 4 week cycle length it would be more appropriate to divide the annual number of events by 13. Dividing by 12 will have tended to overstate the number of events by around 8%. These events are typically adverse events such as bleeds, which are estimated to be higher for non-responders than for responders. As a consequence, cycle event rates based upon dividing the annual rate by 12 rather than by 13 will tend to favour the treatment, or treatment sequence, with the higher response rate.

Direct drug and drug administration costs: half cycle correction

A previous version of the model apparently applied half cycle correction to the non-TPO-RA drug and administration costs. As noted in the manufacturer commissioned PAI validation study supplied in response to ERG clarification question F1: "*for the costs of non-TPO-RA medication and administration costs for the SOC arm, the method used for the half-cycle correction in the two models may lead to a modest underestimate of these costs … The net effect of this underestimate is not material, because of the low cost associated with azothioprine, although the effect might be greater if it the initial therapy was more expensive*". The submitted model removes half cycle correction from the non-TPO-RA drug and administration costs.

[10] See manufacturer response to ERG clarification question E4.

The model retains half cycle correction to the direct drug and drug administration costs for the TPO-RA. Since eltrombopag is dispensed in packs of 28, half cycle correction is not appropriate for the eltrombopag direct drug costs. Half cycle correction tends to reduce the eltrombopag direct drug costs. This applies with particular force between the first and second cycle of the model due to the proportion of patients modelled as discontinuing eltrombopag therapy due to lack of response.

The situation is slightly more convoluted for romiplostim due to it being a weekly injection. With a four week cycle length, it can be argued that it may be appropriate to apply half cycle correction for romiplostim that is administered in a hospital or GP setting. But this is complicated by the base case 72% rate of home administration. On the assumption that unused vials prescribed for home administration are thrown away, it seems more reasonable not to apply half cycle correction to the direct drug costs for romiplostim that is administered at home.

As a consequence, for the base case it seems appropriate to remove the half cycle correction from the TPO drug and administration costs.

Monitoring

ERG expert opinion suggests that the frequency of non-TPO-RA monitoring is likely to be less than that for the TPO-RA. Rather than monthly, quarterly monitoring is more reasonable to assume for non-TPO-RA. Quarterly monitoring is apparently also reasonable to assume for those off treatment, whether this is being modelled as being off treatment but between treatments or off treatment and end of line.

Data Inputs

Main source of data inputs

There is a manufacturer sponsored RCT of eltrombopag, complete with an extension phase. The eltrombopag RCT is that bit larger than the romiplostim RCT. The manufacturer has direct access to IPD data from the eltrombopag trial programme. The manufacturer has only partial access to some data from the romiplostim trial as summarised in TA221, and the data definitions underlying these data are often not particularly clear.

In the opinion of the ERG the natural approach would have been for the manufacturer to rely upon its own data for the base case. The possibility of some form of meta-analysis of its own data and the data from TA221 where the data definitions for the TA221 data are clear also

exists. But it seems rather odd for the manufacturer to choose data inputs from TA221 in preference to its own data for many of the key inputs to the base case modelling.

TPO dosing

The doses for the TPO-RA are drawn from the relevant trial averages. But these are averages across responders and non-responders. Only responders are assumed to continue with TPO treatment.

The evidence from Kuter 2008[1] suggests that responders had a somewhat lower median dose than non-responders during the romiplostim trial. A similar argument may hold for eltrombopag. Incorporating this will improve the overall cost effectiveness of the TPO containing sequences against the non-TPO-RA containing sequence. But given the quite dramatically lower median dosing for those experiencing a durable response with romiplostim, there could be a quite marked change in the cost effectiveness of eltrombopag compared to romiplostim.

Rescue rates

The base case applies 4 weekly rescue rates for non-responders of 68% for the splenectomised and 33% for the non-splenectomised. This is equivalent to a little under 9 rescue events per year for splenectomised patients, and a little over 4 rescue events per year for the non-splenectomised. About 60% of these rescue events are assumed to be IVIG, and even taking into account the cheaper rescue therapies the average cost applied per rescue is between £4,700 and £5,200. Given these event costs, the rescue rate is one, if not the, key variable of the analysis. ERG expert opinion views the rescue rates as being surprisingly high.

Severe bleed rates

The base case applies 4 weekly rescue rates for non-responders of 4.3%. This suggests that among non-responders half will experience a severe bleed that leads to inpatient treatment each year. Again, ERG expert opinion suggests this rate of severe bleeds leading to inpatient treatment seems surprisingly high.

Classification of non-severe bleeds

The classification of events requiring “non-admitted” hospital treatment appears questionable. ERG expert opinion suggests that some will be sufficiently minor to probably only require an outpatient appointment while others are more likely to be major and to possibly require inpatient treatment.

Table 90 Possible reclassification of "non-admitted" hospital treatment events

ITP Bleed type	ITP severity	OT	IP
Skin petechiae code	Diffuse petechiae	✓	
Skin ecchymosis bleeding	>5 bruises with size >2 cm	✓	
Oral bleeding	Multiple blood blisters or gum bleeding >5 minutes	✓	
Epistaxis bleeding	Bleeding >5 mins (per episode)	✓	
Ocular bleeding score code	Retinal hemorrhage		✓
GI bleeding score code	Streaks of blood or blood with wiping	✓	
GI bleeding score code	Grossly bloody stool		✓
Genitourinary bleeding score	Macroscopic	✓	
Gynecologic bleeding score	Spotting not at time of normal period	✓	
Gynecologic bleeding score	Bleeding >spotting not at time of period or very heavy period	✓	
Pulmonary bleeding score	Coughing up Blood, Pulmonary hemorrhage		✓
Intracerebral hemorrhage	Yes		✓

OT: outpatient; IP: inpatient

The impact of this upon the average cost per event is cannot be estimated with accuracy by the ERG, but given the balance between the classifications and a probable balance of numbers underlying the classifications it could argue for applying the outpatient cost of £207 to the non-severe bleed event.

Perhaps more significant might be the overall impact upon the manufacturer analysis of the RAISE+EXTEND SF-6D data. The inclusion of what appear to be severe bleeds may tend to overstate the impact of non-severe bleeds upon HRQoL. That said, in analyses that consistently apply the RAISE+EXTEND data, these HRQoL data will relate to the "non-severe" bleed rates as applied within the modelling.

5.4 Exploratory and sensitivity analyses undertaken by the ERG

ERG revisions to the manufacturer base case and alternative base case are minor:

- Amending the model to correct the doubling of inpatient bleeds for those having reached last in line as outlined in Appendix E of the manufacturer response to the ERG clarification questions
- Remove the half cycle correction from TPO-RA drug and drug administration costs[11]

[11] Implemented within the *Markov* worksheet in cell CB23 and cell CC23 by revising the half cycle correction element of the cell formulae from (SUM(M23:Q23)+SUM(M24:Q24))/2 to SUM(M23:Q23), and copying the resulting formulae into cells CB24:CC712.

- Only applying 1/3rd of the TPO-RA monthly monitoring costs to the non-TPO-RA treatments[12]

These have little to no real impact upon results.

In the move from the base case, which relies mainly upon TA221 data, to the alternative base case, which relies mainly upon RAISE+EXTEND data, the following inputs are changed.

1. The non-TPO-RA response rates, using the manufacturer literature review.
2. The non-TPO-RA response durations, using the manufacturer literature review.
3. The rate of rescue, using the RAISE+EXTEND data.
4. The balance between rescue treatments, using the RAISE+EXTEND data.
5. The probability of bleeding by platelet count, using the RAISE+EXTEND data.

The above changes can be applied individually to explore their individual impact. Additional analysis can be performed that individually apply:

6. The RAISE+EXTEND utility values.
7. The overall response rates drawn directly from the trials[13]:
   - Splenectomised 30/50=60% for eltrombopag and 33/42=79% for romiplostim.
   - Non-splenectomised 61/85=72% for eltrombopag and 36/41=88% for romiplostim.
8. Overall response rates drawn from the manufacturer indirect comparison:
   - Splenectomised 60% for eltrombopag and 94% for romiplostim.
   - Non-splenectomised 72% for eltrombopag and 88% for romiplostim.
9. A reduction in the romiplostim dosing to reflect [1] 2008 median estimates[14]
   - Splenectomised 40% reduction
   - Non-splenectomised 60% reduction
10. The same fatal bleed rate for all non-responders whether last in line or not.
11. Removing adverse events from the analysis[15].
12. Outpatient rather than daycase costs for non-severe bleeds[16].

The sensitivity analyses 6 to 12 are performed for the base case and the alternative base case.

Note that the following does not adjust the TPO SAE rates to be in line with the possible model error in the manufacturer model as outlined in appendix 2.

[12]Implemented within the *Markov* worksheet in cells CE23:CE712 by revising the element of the cell formulae from 'Other Costs'!$C$30 to 'Other Costs'!$C$30/3.

[13] Implemented in the *Transition_Probabilities* worksheet by entering the values directly in cells C74:C75

[14] Implemented within the *Vial_Wastage_Calculations* worksheet by inputting these values in cells C11:I11 directly. Note that the ERG report sent to the manufacturer for cross checking incorrectly amended the *Drug_Costs* worksheet by multiplying C8 by the relevant percentage.

[15] Implemented in the *Utilities_AEs* worksheet by setting cells C76:D92 to zero

[16] Implemented in the *Other_Costs* worksheet by entering the value directly into cell H18

Table 91 ERG sensitivity analyses: Base Case: Splenectomised

	Costs			QALYs			ICERs		
	ELTR	ROMI	No-TPO-RA	ELTR	ROMI	No-TPO-RA	ELTR	ROMI	No-TPO-RA
Base case	£554,871	£643,026	£578,756	12.28	12.28	11.02			
Δ vs ELTR	..	£88,155	£23,885	..	0.00	-1.26	..	Dom.	Dom.
Δ vs No-TPO-RA	-£23,885	£64,270	..	1.26	1.26	..	..	£50,985	..
	Δ cost			Δ QALY			ICERs		
	ELTR	ROMI	No-TPO-RA	ELTR	ROMI	No-TPO-RA	ELTR	ROMI	No-TPO-RA
Non-TPO-RA resp.	..	£88,153	£24,632	..	0.00	-1.30	..	Dom.	Dom.
Non-TPO-RA resp. dur.	..	£88,155	£16,013	..	0.00	-1.14	..	Dom.	Dom.
Rescue rate	£41,579	£129,694	..	1.57	1.57	..	£26,526	£82,740	..
Rescue treatments	..	£88,147	£2,014	..	0.00	-1.31	..	Dom.	Dom.
Bleed probability	..	£87,765	£60,864	..	0.00	-0.40	..	Dom.	Dom.
Utility values	..	£88,155	£23,885	..	0.00	-1.07	..	Dom.	Dom.
Trial TPO resp. rate	..	£84,325	£18,043	..	0.25	-0.85	..	£331,179	Dom.
IC TPO resp. rates	..	£96,481	£18,043	..	0.55	-1.00	..	£174,503	Dom.
Romi dose reduced	..	[redacted]	£23,885	..	0.00	-1.26	..	Dom.	Dom.
Fatal bleed rate	..	£88,155	£45,281	..	0.00	-0.80	..	Dom.	Dom.
Adverse events	..	£88,155	£23,885	..	0.00	-1.22	..	Dom.	Dom.
OP bleed cost	..	£88,155	£23,361	..	0.00	-1.26	..	Dom.	Dom.

Table 92 ERG sensitivity analyses: Base Case: Non-splenectomised

	Costs			QALYs			ICERs		
	ELTR	ROMI	No-TPO-RA	ELTR	ROMI	No-TPO-RA	ELTR	ROMI	No-TPO-RA
Base case	£331,255	£372,056	£295,188	11.89	11.89	9.59			
Δ vs ELTR	..	£40,802	-£36,067	..	0.00	-2.29	..	Dom.	Check
Δ vs No-TPO-RA	£36,067	£76,869	..	2.29	2.29	..	£15,730	£33,526	..
	Δ cost			Δ QALY			ICERs		
	ELTR	ROMI	No-TPO-RA	ELTR	ROMI	No-TPO-RA	ELTR	ROMI	No-TPO-RA
Non-TPO-RA resp.	£35,658	£76,460	..	2.31	2.31	..	£15,464	£33,158	..
Non-TPO-RA resp. dur.	£40,629	£81,430	..	2.12	2.12	..	£19,193	£38,467	..
Rescue rate	£82,360	£123,152	..	2.50	2.50	..	£33,003	£49,349	..
Rescue treatments	£43,643	£84,444	..	2.30	2.30	..	£18,989	£36,741	..
Bleed probability	£2,155	£42,751	..	0.69	0.69	..	£3,141	£62,312	..
Utility values	£36,067	£76,869	..	1.95	1.95	..	£18,489	£39,404	..
Trial TPO resp. rate	£32,649	£83,998	..	1.75	2.14	..	£18,622	£39,288	..
IC TPO resp. rates	£32,747	£84,470	..	2.07	2.53	..	£15,843	£33,418	..
Romi dose reduced	£36,067	[redacted]	..	2.29	2.29	..	£15,731	[redacted]	..
Fatal bleed rate	£16,763	£57,564	..	1.50	1.50	..	£11,141	£38,260	..
Adverse events	£36,067	£76,869	..	2.28	2.28	..	£15,820	£33,716	..
OP bleed cost	£37,071	£77,872	..	2.29	2.29	..	£16,168	£33,964	..

Table 93 ERG sensitivity analyses: Alternative Base Case: Splenectomised

	Costs			QALYs			ICERs		
	ELTR	ROMI	No-TPO-RA	ELTR	ROMI	No-TPO-RA	ELTR	ROMI	No-TPO-RA
Base case	£313,050	£400,808	£278,253	14.78	14.78	14.32			
Δ vs ELTR	..	£87,758	-£34,797	..	0.00	-0.46	..	Dom.	Check
Δ vs n No-TPO-RA	£34,797	£122,555	..	0.46	0.46	..	£75,297	£265,196	..
	Δ cost			Δ QALY			ICERs		
	ELTR	ROMI	No-TPO-RA	ELTR	ROMI	No-TPO-RA	ELTR	ROMI	No-TPO-RA
Utility values	£34,797	£122,555	..	0.38	0.38	..	£90,753	£319,631	..
Trial TPO resp. rate	£27,912	£126,600	..	0.30	0.40	..	£91,854	£319,525	..
IC TPO resp. rates	£27,597	£150,556	..	0.38	0.59	..	£73,335	£256,881	..
Romi dose reduced	£34,797	[redacted]	..	0.46	0.46	..	£75,297	[redacted]	..
Fatal bleed rate	£31,997	£119,756	..	0.29	0.29	..	£110,905	£415,079	..
Adverse events	£34,797	£122,555	..	0.46	0.46	..	£76,245	£268,536	..
OP bleed cost	£35,554	£123,312	..	0.46	0.46	..	£76,935	£266,834	..

Table 94 ERG sensitivity analyses: Alternative Base Case: Non-splenectomised

	Costs			QALYs			ICERs		
	ELTR	ROMI	No-TPO-RA	ELTR	ROMI	No-TPO-RA	ELTR	ROMI	No-TPO-RA
Base case	£230,375	£270,970	£154,845	15.10	15.10	14.39			
Δ vs ELTR	..	£40,595	-£75,531	..	0.00	-0.71	..	Dom.	Check
Δ vs No-TPO-RA	£75,531	£116,125	..	0.71	0.71	..	£106,800	£164,201	..
	Δ cost			Δ QALY			ICERs		
	ELTR	ROMI	No-TPO-RA	ELTR	ROMI	No-TPO-RA	ELTR	ROMI	No-TPO-RA
Utility values	£75,531	£116,125	..	0.57	0.57	..	£133,508	£205,263	..
Trial TPO resp. rate	£67,956	£127,174	..	0.51	0.62	..	£133,592	£205,181	..
IC TPO resp. rates	£68,358	£128,130	..	0.63	0.77	..	£108,336	£166,150	..
Romi dose reduced	£75,531	[redacted]	..	0.71	0.71	..	£106,800	[redacted]	..
Fatal bleed rate	£73,524	£114,119	..	0.44	0.44	..	£168,129	£260,957	..
Adverse events	£75,531	£116,125	..	0.71	0.71	..	£107,008	£164,521	..
OP bleed cost	£76,474	£117,069	..	0.71	0.71	..	£108,135	£165,535	..

In terms of moving from the base case to the alternative base case, the duration of the non-TPO-RA response has some impact. This is due to the manufacturer literature review estimating a somewhat longer duration of response for azathioprine. But the main driver is rescue rates, which affect both costs and QALYs. Bleed rates also have an impact, but note that applying the RAISE+EXTEND data reduces the net gain in both inpatient and outpatient bleeds from being a responder. Casual intuition would suggest that this should worsen the ICER for the TPOs compared to the non-TPO but the reverse happens. The net QALY gain is much reduced but given the absolute change in the net costs, the proportionate reduction in the net costs for eltrombopag is somewhat larger and the ICER improves markedly.

Applying the RAISE+EXTEND utility values also has quite a large impact upon results, reducing the net QALY gains by around 20%, but this change is not included in the move from the base case to the alternative base case.

The impact of the alternative possible estimates for the response rates for the TPO-RA is felt mainly in the comparison between eltrombopag and romiplostim. But by itself it is not sufficient to make romiplostim cost effective compared to eltrombopag.

Reducing the romiplostim dose by 40% for the splenectomised reduces costs in the romiplostim containing sequence, but by itself this is not sufficient for romiplostim to be cost effective. [redacted]. Due to indivisibilities the 4 weekly drug cost of romiplostim for the non-splenectomised is only reduced from [redacted] to [redacted], and while the dominance of eltrombopag over romiplostim is lessened it remains.

Dropping the assumption of a doubling in the fatal bleed rate for those last in line has a large impact upon the net QALY gain over the non-TPO-RA sequence. As with most of the sensitivity analyses, by itself it is not sufficient to change conclusions. But it has a surprisingly large impact upon results, and as a pure assumption it warrants more discussion and justification by the manufacturer.

The impact of assuming the lower rate of bleeds from RAISE+EXTEND increases the costs in the non-TPO-RA arm. It appears that this may be due to the reduced mortality impact. But as would be expected, the difference in QALYs falls and the cost effectiveness of the TPO sequences compared to the non-TPO-RA sequence worsens.

Adverse events have little impact upon the model results. Altering the cost of non-severe bleeds from day-case to outpatient has some impact upon costs, but it is also relatively minor.

5.5 Conclusions of the cost effectiveness section

The manufacturer model structure appears to be reasonable and is broadly the same model structure as applied within the romiplostim TA221. Eltrombopag appears to be a more cost-effective option than romiplostim. However, there are a number of serious concerns which should be considered when interpreting the current cost effectiveness data.

The main concerns are:

- Which set of data inputs is it most reasonable for the manufacturer to use: those from the romiplostin TA221 which underlie the base case, or those that the manufacturer estimates from the eltrombopag trial programme which underlie the alternative base case?
- Is the assumption of complete clinical equivalence between the TPO-RA reasonable?
- Which definition of response is most reasonable to apply within the modelling?
- Should the modelling consider the optimal positioning of the TPO-RA in the therapy sequence?
- Response and platelet response status are not synonymous. Responders only spend a proportion of their time in platelet response. Applying platelet response event rates to responders underestimates the number of events responders will experience.
- The extrapolation of TPO responders' time on treatment has a long tail which flattens out considerably during the extrapolation period.
- Azathioprine responders' time on treatment in the base case is considerably less than that suggested by the manufacturer's own literature review.
- The average TPO dose among responders may be less than the average TPO dose across the trial as a whole. There is the suggestion of a considerably lower romiplostim median dose among romiplostim durable responders, perhaps as much as 40% to 60% less. No data have been presented for eltrombopag responders' dose compared to the trial average dose. If these differences are taken into account, both the cost effectiveness of the TPO-RA compared to the non-TPO-RA and the cost effectiveness of eltrombopag compared to romiplostim will change.
- The eltrombopag trials contained a high proportion of patients of Asian descent, who may manage on a lower dose of eltrombopag. Whether the average dosing of RAISE+EXTEND is representative of the probable UK average is unclear.
- The manufacturer eltrombopag SF-6D analysis worsens the costs effectiveness estimates. There is also the suggestion that this SF-6D analysis may itself overstate the benefit of the modelled additional survival from the TPO-RA.

- Both the rates of rescue and the rates of severe bleeds applied within the modelling appear quite high to ERG expert opinion.
- The doubling in the severe bleed rate for those last in line is an assumption with little to no discussion or justification by the manufacturer.

More minor concerns are:

- Whether it is reasonable to assume that all TPO responses will occur during the 1st cycle and as a consequence TPO non-responders only incur one month's TPO treatment costs. For romiplostim the SPC suggests increasing the dose by 1mcg/kg per week to a maximum dose of 10mcg/kg, hence over 10 weeks.
- Eleven per cent of patients in the non-TPO-RA containing sequence immediately being last in line and receiving no further treatment.
- Dividing annual rates by 12 rather than by 13 to estimate event rates. This exaggerates the event rate cost and HRQoL impact by around 8%.
- The severe inpatient bleed mortality rates of RAISE+EXTEND are not reported or considered within the economics.
- The derivation of the severe inpatient bleed mortality rates is not immediately clear, though the percentages are of a similar magnitude to those of the cited reference.
- It is unclear whether the modelled non-TPO-RA containing sequence is itself cost effective compared to no further treatment. If it is not, this could lead to some perverse effects within the modelling and could exaggerate the cost effectiveness of the TPO-RA.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

The ERG views the alternative base case as the natural starting point for the analysis. Within this eltrombopag dominates romiplostim due to its lower acquisition cost. But the cost effectiveness of eltrombopag compared to the non-TPO-RA sequence is poor: £75,297 per QALY for the splenectomised and £106,800 per QALY for the non-splenectomised. These results are presented in more detail in Section 5.4 above.

These results are reasonably sensitive to the application of the RAISE+EXTEND SF-6D analysis and dropping the assumption of a doubling in severe bleeds for those beyond last in line, both of which worsen the cost effectiveness of eltrombopag. Applying the overall response rates of the trials rather than the response rate of RAISE also tends to worsen the cost effectiveness of eltrombopag.

There is evidence that towards the end of the romiplostim trial the average responder dose of romiplostim was considerably less than the average all patient dose of romiplostim. Adjusting for this worsens the cost effectiveness of eltrombopag compared to romiplostim. But this sensitivity analysis is partial, and the ERG has no access to data on the average eltrombopag responder dose.

The ERG has not performed all these sensitivity analyses simultaneously because considerable uncertainty remains as to which are most reasonable for the base case, and they cannot all be applied equally across the comparators.

The above may also be conditioned by any amalgamation of TA221 data for which the data definition is clear with the corresponding RAISE+EXTEND data. Amalgamation of the TA221 data into the analyses would tend to improve the cost effectiveness estimates. It should be borne in mind that the manufacturer base case estimates eltrombopag to dominate the non-TPO-RA sequence for the splenectomised, and to have a cost effectiveness of £15,105 per QALY for the non-splenectomised.

The major concerns summarised in more detail at the end of Section 5 remain.

- Are the TPO-RA clinically equivalent?
- The responder event rates need to be adjusted for responder time spent in platelet response.
- Is the tail of the TPO responder time on treatment curve a reasonable extrapolation?
- What is the most reasonable estimate for azathioprine duration of response?
- The TPO doses need to be specific to TPO responders.
- Are severe bleed rates doubled for those last in line?

Note that both the rates of rescue and the rates of severe bleeds appear quite high to ERG expert opinion.

7 OVERALL CONCLUSIONS

The manufacturer included in the current assessment 10 eltrombopag studies (of which 3 RCTs); 4 romiplostim studies (of which 2 RCTs); and 37 non-TPO-RA studies (of which 6 RCTs). Overall, the quality of the eltrombopag and romiplostim RCTs was deemed good. On the contrary, little could be concluded about the overall quality of non-TPO-RA studies as only the quality of the six included RCTs was formally appraised, whilst no attempt was made to assess the remaining 31 non-randomised studies.

Eltrombopag versus placebo

The manufacturer was able to combine the platelet response at 43 days (six weeks) from the three included RCTs (TRA100773A, TRA100773B and RAISE) in a meta-analysis. Although the ERG was somewhat concerned about the exclusion of an additional trial (i.e. the Tomiyama trial),[2] sensitivity analyses including this study did not change the overall interpretation. Eltrombopag was statistically significantly more effective than placebo in achieving a platelet count $>50x10^9$/L at 6 weeks of treatment.

As only one trial with longer term follow-up was identified, further meta-analyses of outcomes beyond six weeks could not be conducted.

Individual results of TRA100773B and RAISE indicate that eltrombopag is more effective than placebo at 6 weeks with regard to:

- Platelet response at any time during treatment
- Need for rescue medication
- Reduction of concomitant ITP medication

Eltrombopag versus romiplostim

No head-to-head RCTs comparing eltrombopag and romiplostim were identified by the manufacturer; therefore an indirect comparison of placebo-controlled trials was attempted. The manufacturer identified two romiplostim trials, one in splenectomised and one in non-splenectomised participants,[1] and included these in an indirect comparison with RAISE. No meta-analyses of short-term outcomes were attempted but the ERG thought this was reasonable.

The indirect comparison did not show any significant difference between the two treatments.

It is worth noting, however, that even though the RAISE and the Kuter 2008 trials recruited roughly the same population, there were considerable differences in terms of study design and baseline characteristics of patients. These include:

- Differences in response definitions (50-400x10^9/L in RAISE versus $\geq$50x10^9/L in the Kuter 2008 trials)
- Differences in the assessment of bleeding events
- Differences in the number of prior ITP therapies
- Differences in the proportion of baseline concomitant medications
- Difference in the timing of platelet count
- Difference in the timeframes in which participants were allowed to reduce concomitant ITP medications

Because of the substantial clinical heterogeneity as well as the statistical heterogeneity between RAISE and the Kuter 2008 trials, the ERG maintains that the results of any indirect comparison analyses ought to be interpreted with extreme caution.

The ERG also had concerns that the methodology used to conduct the indirect treatment comparison was not necessarily optimal. The two Kuter 2008 trials were first combined using a Mantel-Haenszel meta-analysis, despite the fact these were in non-overlapping patient subgroups. Meta-analyses of platelet response and bleeding were then performed using the Bucher method.[76] The ERG attempted indirect comparisons using a Bayesian (mixed treatment comparison) approach.[84] The results of the indirect comparison odds ratios were very similar to the manufacturer's analyses, except that the result for overall platelet response (using medium heterogeneity) now favoured romiplostim (OR 0.15 [95% CrI (0.02 to 0.84)]), whereas in the manufacturer's analysis the 95% confidence interval included one (OR 0.22 [95% CI (0.05 to 1.02)]).

The manufacturer also conducted separate indirect comparisons for splenectomised and non-splenectomised participants but the ERG was concerned that these analyses fail to preserve the randomisation within RAISE. The ERG attempted to repeat these analyses using the Bayesian approach but this did not prove possible because most of the models failed to converge.

Summary of cost-effectiveness issues

The ERG views the analysis of the alternative base case as the natural starting point for the eltrombopag submission. It does not seem tenable for the manufacturer to discard its own trial data in favour of whatever the manufacturer can glean from the publicly available TA221 documents. The cost effectiveness of eltrombopag compared to the non-TPO-RA sequence is poor: £75,297 per QALY for the splenectomised and £106,800 per QALY for the non-splenectomised. These estimates worsen when the SF-6D data from RAISE+EXTEND are applied.

It is questionable to in effect assume that those who responded during RAISE and remained on treatment were in continual response. Only between 60% and 80% of their assessments showed a platelet count of more than $50x10^9$/L. The relationships derived for those with a platelet count of more than $50x10^9$/L need to be adjusted before they can be applied to the RAISE responders.

The duration of response extrapolated for the TPO-RA may also be optimistic, though standard statistical methods have been applied. The parametric curves fitted to the Kaplan-Meier curves flatten considerable during the period of extrapolation, and it is not clear that their tails are reasonable.

Given the responder analysis of the modelling the TPO-RA doses should be responder specific. There is evidence that the responder dose in the romiplostim trial was somewhat below the all patient dose in the romiplostim trial. This could improve the cost effectiveness of the TPO-RA against the non-TPO-RA containing sequence. It may improve or worsen the cost effectiveness of eltrombopag compared to romiplostim.

Differentiating the TPO-RA response rates seems unlikely to alter the conclusions as to their relative effectiveness unless other elements are also differentiated. These might include the average responder dose as above, or the average duration of treatment among responders.

All the above may be quite significantly altered if the TA221 data are amalgamated with the RAISE+EXTEND data. But this would be complicated by some lack of clarity around the TA221 data definitions within the publicly available documents.

ERG expert opinion is that the rates of rescue and the rates of bleeds appear quite high. Lower rates would worsen the cost effectiveness estimates.

There is a concern that the modelling should have considered additional treatment sequences in order to explore the optimal placement of the TPO-RA within the treatment sequence. This has to some extent been informally addressed by the manufacturer base case and alternative base case modelling, given the apparent implicit assumption that patients should be refractory to rituximab before being considered for TPO-RA treatments. The assumption of previous treatment with rituximab is not in the original scope from NICE.

7.1 Implications for research

There is currently limited evidence on the efficacy of eltrombopag in patients with chronic ITP. In particular, there are no studies which compare eltrombopag with romiplostim or rituximab directly. The important clinical questions that need to be addressed are:

- What is the best drug to use as third line treatment? This would require large well-designed RCTs comparing eltrombopag, romiplostim and possibly rituximab with each other (direct comparisons). Ideally such trials should include an economic evaluation and a long enough follow-up to capture the most relevant economic differences.
- What is the risk of bleeding or death if a patient has a specific platelet count? This would allow patients and clinicians to individually balance the risk of treatment to raise the platelet count against the risk of bleeding.
- Should eltrombopag, romiplostim and possibly rituximab be considered as first line therapy for the treatment of ITP? Due to the dearth of current evidence, large well-designed trials addressing this question would provide important clinical findings. These trials should also include proper economic evaluations.

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9 APPENDICES

Appendix 1 Searching undertaken by ERG

MEDLINE/EMBASE search for Eltrombopag

Database: Ovid MEDLINE(R) (1966- Aug wk 2 2012), Ovid MEDLINE(R) In-Process (15th Aug 2012), EMBASE (1980- wk 32 2012)

Search Strategy:

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1 purpura, thrombocytopenic, idiopathic/ use mesz
2 idiopathic thrombocytopenic purpura/ use emez
3 idiopathic thrombocytop?enic purpura.tw.
4 immune thrombocytop?enic purpura.tw.
5 autoimmune thrombocytop?enic purpura.tw
6 idiopathic thrombocytop?enia.tw.
8 autoimmune thrombocytop?enia.tw.
9 itp.tw
10 aitp.tw.
11 or/1-10
12 eltrombopag.tw,rn.
13 promacta.tw,rn.
14 revolade.tw,rn
15 (sb-497115$ or sb497115$).tw,rn.
16 or/12-15
17 11 and 16
18 limit 17 to yr =”2009 - Current”
19 remove duplicates from 18

MEDLINE/EMBASE search for clinical effectiveness of comparators

Database: Ovid MEDLINE(R) (1966- Aug wk 2 2012), Ovid MEDLINE(R) In-Process (15th Aug 2012), EMBASE (1980- wk 32 2012)

Search Strategy:

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1. idiopathic thrombocytop?enic purpura.tw.
2. immune thrombocytop?enic purpura.tw.
3. autoimmune thrombocytop?enic purpura.tw.
4. idiopathic thrombocytop?enia.tw.
5. immune thrombocytop?enia.tw.
6. autoimmune thrombocytop?enia.tw.
7. (itp or aitp).tw.
8. purpura, thrombocytopenic, idiopathic/ use mesz
9. idiopathic thrombocytopenic purpura/ use emez
10. or/1-9
11. exp steroid/ use emez
12. exp steroids/
13. immunoglobulins, intravenous/ use mesz
14. exp immunoglobulin/iv use emez
15. (ivig or igiv or ivigg or igv).tw.
16. (gammaglobulin$ or gamma globulin$).tw.
17. (intravenous adj (immunoglobulin$ or immune globulin$ or ig)).tw.
18. (iv immunoglobulin$ or intravenous antibod$).tw.
19. (sandoglobulin or gamunex or flebogamma or gammagard or octagam or vigam).tw.
20. "RHo(D) Immune Globulin"/
21. Rhesus D Antibody/ use emez
22. Anti D.tw.
23. Anti Rh$.tw.
24. (rh$ adj3 (immune globulin$ or immunoglobulin$)).tw.
25. (winrho or rhophylac).tw.
26. rituximab/
27. antigens, CD20/
28. rituximab.tw,rn.
29. ritux?n.tw,rn.
30. mabthera.tw,rn.
31. anti-CD20.tw,rn.

32. danazol/
33. danazol.tw,rn.
34. danol.tw,rn.
35. (danatrol or danocrine).tw,rn.
36. dapsone/
37. dapsone.tw,rn.
38. azathioprine/
39. azathioprine.tw,rn.
40. (im?uran or immurel or azamum or azamune).tw,rn.
41. Mycophenolic Acid 2 Morpholinoethyl Ester/
42. myfortic.tw,rn.
43. cellcept.tw,rn.
44. mycophenolate mofetil.tw,rn.
45. mmf.tw.
46. cyclosporine/
47. c?closporin$.tw,rn.
48. (neoral or sandimmun$).tw,rn.
49. cyclophosphamide/
50. (endoxan$ or se?doxan$ or neosar$ or cytoxan$ or procytox$).tw,rn.
51. exp vinca alkaloids/
52. vinblastine/ or vinc alkaloid/ or vincristine/ or vindesine/
53. (vinblastine or vincristine or vindesine or vinorelbine).tw,rn.
54. romiplostim.tw,rn.
55. remiplistim.tw,rn.
56. nplate.tw,rn.
57. (amg 531 or amg531).tw.
58. or/11-57
59. 10 and 58
60. exp clinical trial/
61. randomized controlled trial.pt.
62. controlled clinical trial.pt.
63. randomization/ use emez
64. randomi?ed.ab.
65. placebo.ab.
66. drug therapy.fs.
67. randomly.ab.
68. trial.ab.

69. groups.ab.
70. comparative study/ use mesz
71. follow-up studies/ use mesz
72. time factors/ use mesz
73. Treatment outcome/ use emez
74. major clinical study/ use emez
75. controlled study/ use emez
76. clinical trial/ use emez
77. (chang$ or evaluat$ or reviewed or baseline).tw.
78. (prospective$ or retrospective$).tw. use mesz
79. (cohort$ or case series).tw. use mesz
80. (compare$ or compara$).tw. use emez
81 or/60-80
82 59 and 81
83. case report/ use emez
84. case reports.pt.
85. 82 not (83 or 84)
86. exp child/ or exp infant/
87. exp adult/
88. 86 not 87
89 85 not 88
90. limit 89 to english language
91 limit 90 to yr=”2009 – Current”
92 remove duplicates from 91

Appendix 2 ERG model rebuild cross check

The ERG cross check rebuild of the deterministic model results in a generally very good correspondence with the corrected manufacturer model: correcting the doubling of bleeds for those at the end of the line is made and removing half cycle correction for the TPO costs.

The exception to this good correspondence is in the QALY impacts from SAEs and AEs. It appears that the manufacturer model inadvertently assumes that adverse events for the TPOs only occur during the first cycle. In the opinion of the ERG within the *Markov* worksheet the formula for cell CP23 should have the element relating to this revised from:

VLOOKUP(trt_1,AE_implications,2,0)*AVERAGE(M23,M24)

to

VLOOKUP(trt_1,AE_implications,2,0)*if(OR(trt_1="eltrombopag",trt_1="romiplostim"),AVERAGE(M23,M24)+AVERAGE(Q23,Q24), AVERAGE(M23,M24))

with the corollary of this being copied to the cells below.

Due to time constraints it has not been possible to incorporate this into the main body of the ERG report. But applying this correction within the manufacturer model results in the TPO sequences' adverse event QALY impacts increasing from -0.207 QALYs to -0.340 QALYs for the splenectomised and from -0.046 QALYs to -0.244 QALYs for the non-splenectomised.

Comparing the results with the ERG cross check model rebuild results in the following. Note that due to model constructions, the monitoring costs within the manufacturer model cannot be easily separated from the drug administration costs.

Appendix 2 Table 01: Manufacturer model and ERG cross check rebuild model correspondence: Splenectomised

	TPO		Non-TPO		Rescue		Monitor	Bleeds	Total	vs nonTPO	Base	Bleeds	AEs	Total	vs nonTPO
	Drug	Admin	Drug	Admin	Drug	Admin									
Manufacturer															
Eltrombopag	[redacted]	[redacted]	[redacted]	[redacted]	£301,752	£144,180		£24,954	£556,780	-£24,293	13.299	-0.814	-0.340	12.145	1.128
Romiplostim	[redacted]	[redacted]	[redacted]	[redacted]	£301,752	£144,180		£24,954	£644,935	£63,862	13.299	-0.814	-0.340	12.145	1.128
Non TPO	[redacted]	[redacted]	[redacted]	[redacted]	£370,832	£177,187		£29,497	£581,073		12.230	-0.963	-0.250	11.017	
ERG															
Eltrombopag	[redacted]	[redacted]	[redacted]	[redacted]	£302,005	£144,300	[redacted]	£24,991	£557,418	-£24,457	13.315	-0.815	-0.339	12.161	1.131
Romiplostim	[redacted]	[redacted]	[redacted]	[redacted]	£302,005	£144,300	[redacted]	£24,991	£645,183	£63,308	13.315	-0.815	-0.339	12.161	1.131
Non TPO	[redacted]	[redacted]	[redacted]	[redacted]	£371,336	£177,426	[redacted]	£29,550	£581,875		12.245	-0.964	-0.251	11.030	

Appendix 2 Table 02: Manufacturer model and ERG cross check rebuild model correspondence: Non-splenectomised

	TPO		Non-TPO		Rescue		Monitor	Bleeds	Total	vs nonTPO	Base	Bleeds	AEs	Total	vs nonTPO
	Drug	Admin	Drug	Admin	Drug	Admin									
Manufacturer															
Eltrombopag	[redacted]	[redacted]	[redacted]	[redacted]	£119,178	£67,003		£27,483	£332,802	£35,510	12.830	-0.897	-0.244	11.689	2.095
Romiplostim	[redacted]	[redacted]	[redacted]	[redacted]	£119,178	£67,003		£27,483	£373,604	£76,311	12.830	-0.897	-0.244	11.689	2.095
Non TPO	[redacted]	[redacted]	[redacted]	[redacted]	£165,145	£92,846		£36,060	£297,292		10.831	-1.177	-0.059	9.594	
ERG															
Eltrombopag	[redacted]	[redacted]	[redacted]	[redacted]	£116,228	£65,344	[redacted]	£26,966	£335,429	£37,622	12.976	-0.879	-0.255	11.841	2.233
Romiplostim	[redacted]	[redacted]	[redacted]	[redacted]	£116,228	£65,344	[redacted]	£26,966	£378,276	£80,469	12.976	-0.879	-0.255	11.841	2.233
Non TPO	[redacted]	[redacted]	[redacted]	[redacted]	£165,423	£93,002	[redacted]	£36,137	£297,808		10.847	-1.179	-0.059	9.609	

The models for the splenectomised show a reasonable degree of correspondence. The ICER for romiplostim compared to the non-TPO containing sequence is £56,608 per QALY using the corrected manufacturer model, and £55,990 per QALY using the ERG cross check rebuild.

The models for the non-splenectomised show a slightly worse correspondence, with slightly higher net costs for the TPO containing sequences but also slightly higher net QALYs. These effects almost exactly cancel: the ICER for eltrombopag compared to the non-TPO containing sequence is £16,952 per QALY using the corrected manufacturer model and £16,851 per QALY using the ERG cross check rebuild. Those for romiplostin are £36,430 per QALY and £36,043 per QALY.

It should be noted that the QALY totals differ by a reasonable amount depending upon whether the number of cycles being assumed per year is 12, 52/4 or 365/28, as these are all possible divisors that have been used within the modelling at various points. The ERG has tried to adopt the manufacturer approach throughout.

Some minor additional aspects arose during the ERG cross check rebuild of the model that were not clear within the submission and have not been summarised in the main body of the submission.

- Those in the long term non-responder health state between treatments are assumed not to be monitored. The ERG views this as possibly being too low, and it may be more reasonable to assume quarterly monitoring for these patients.
- SAEs and AEs appear not to be associated with any costs.
- The duration of a cranial IP bleed is assumed to be 4 months. For non-responders given the duration of a cranial IP bleed the total QALY decrement is 0.268 QALYs, compared to 0.033 QALYs for gastrointestinal and other IP bleeds.
- It remains unclear to the ERG whether rescue steroid has an adverse quality of life impact within the modelling.