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

Produced by: Aberdeen Health Technology Assessment Group

Authors: [1]Dwayne Boyers
[2]Xueli Jia
[3]Mark Crowther
[2]David Jenkinson
[2]Cynthia Fraser
[2]Graham Mowatt

[1] Health Economics Research Unit
Institute of Applied Health Sciences
University of Aberdeen

[2]Health Services Research Unit
Institute of Applied Health Sciences
University of Aberdeen

[3]Department of Haematology
Aberdeen Royal Infirmary

Correspondence to: Graham Mowatt
Health Services Research Unit
University of Aberdeen
Health Sciences Building
Foresterhill
Aberdeen AB25 2ZD

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Contributions of authors

Dwayne Boyers conducted the critique of the manufacturer's economic evaluation. Xueli Jia critiqued the manufacturer's submission of effectiveness evidence. Mark Crowther provided clinical advice and drafted the background and critique of the manufacturer's decision problem. David Jenkinson critiqued the statistical methods used and conducted additional analysis on the indirect comparison. Cynthia Fraser conducted the literature searches and critiqued the methods

used for identifying relevant literature. Graham Mowatt advised and commented on work throughout the project.

Conflicts of interest

None

SUMMARY

Scope of the submission

The submitted evidence related to the use of eltrombopag for the treatment of chronic idiopathic (immune) thrombocytopenic purpura (ITP) in adults who have a platelet count <30 x 10^9/L and are:

- Refractory to splenectomy; or are
- Inadequate responders to corticosteroids and have medical contraindications to splenectomy.

Summary of submitted clinical effectiveness evidence

Evidence on clinical effectiveness of eltrombopag came from three RCTs.

Efficacy

Platelet response rates (≥ 50 x 10^9/L) after 6-week treatment ranged from 27% (8/29, 30mg/day) to 80% (21/26, 75mg/day). 58% (44/76) of participants had a platelet count ≥ 50 x 10^9/L and at least twice the baseline count. Median cumulative duration of platelet response after 6-month eltrombopag treatment was 13.4 weeks amongst non-splenectomised, and 6.0 weeks amongst splenectomised. 22% [11/50] of those splenectomised required rescue medication. The percentage amongst those not splenectomised was 17% [14/85]. Overall 44% (12/27) reduced dose/frequency of concomitant ITP medications compared with baseline.

The efficacy of administration of eltrombopag plus standard care was significantly better than placebo plus standard care in the above outcomes except for: platelet response (≥ 50 x 10^9/L) after 6-week 30mg/day eltrombopag treatment (27% vs. 11%, p=0.070); the need for rescue medication during 6-month treatment in splenectomised participants (48% vs. 22%, p=0.055); and the reduction in dose/frequency of concomitant ITP medications taken at baseline in splenectomised participants during 6-month treatment (39% vs. 44%, p=0.714). It is unclear for duration of platelet response during 6-month treatment, whether rescue treatment was taken into account.

Safety

Risk of any grade of bleeding (WHO grade 1-4) during 6-month eltrombopag treatment was 76% (65/85) amongst non-splenectomised participants and 82% (41/50) amongst splenectomised

participants. Risks of clinically significant bleeding (WHO grade 2-4) was 29% (25/85) amongst non-splenectomised participants and 38% (19/50) amongst splenectomised participants. Conflicting information on bleeding of 13% overall was also reported. It is unclear which data are most relevant to this review.

Risks of any adverse events were also inconsistently reported as either 47% or 57%-87% at six months. Risks of serious adverse events (not defined) ranged from 3% (2/76, 6-week) to 20% (6/30, 6-week). Risks and types of adverse events appeared to be similar between the eltrombopag group and placebo group.

The risk of liver function disturbances for eltrombopag was higher (8% to 13%) compared with placebo (3% to 7%). No cases of bone marrow fibrosis, phototoxicity, cardio- or renal- toxicity occurred during the intervention.

Comparing efficacy between eltrombopag and romiplostim

Overall, for durable response eltrombopag may be less effective than romiplostim (manufacturer reported OR 0.26 [95% CI 0.03 to 2.62], ERG OR 1.04 [95% CI 0.32 to 3.44]) and overall response (manufacturer reported OR 0.17 [95% CI 0.03 to 0.82], ERG OR 0.26 [95% CI 0.07, 0.97]). In the manufacturer's analysis, all participants withdrawing prematurely or lost to follow-up were counted as non-responders (worst scenario). In the ERG's further analysis, all such participants were counted as responders (best scenario). As data were not available on the splenectomy status of withdrawals in the eltrombopag trial, a breakdown by splenectomy status was not possible in the further analysis conducted by the ERG.

Comparator treatments

No attempt was made to statistically or narratively synthesise data on effectiveness of comparators. The manufacturer stated that best available evidence was used to generate values for the long-term economic model. However, alternative evidence could have been used.

Summary of submitted cost-effectiveness evidence

The manufacturer submitted two economic evaluations and models analysing the cost-effectiveness of eltrombopag for the treatment of adult ITP.

Watch and Rescue model:

The watch and rescue model, compares eltrombopag plus standard care with standard care alone, where standard care is where patients received rescue medication in response to clinical need. The model was based on the double blinded RAISE RCT with uptake rates of the drug determined from an internal GlaxoSmithKline study.

The incremental cost per QALY for the base case analyses for splenectomised and non–splenectomised patients are £78,253 and £90,471 respectively. Sensitivity analyses varying the risk of death, target platelet counts, and use of concomitant medications did not reduce the incremental cost per QALY greatly. A probabilistic analysis showed that there is little or no chance of eltrombopag being cost-effective at a threshold of £30,000 per QALY. Substantial reductions in the price of eltrombopag would be required to obtain a cost per QALY of £30,000.

The ERG conducted additional sensitivity analyses around the source of cost data for managing bleeds, discount rate, and the annual risk of bleeding. Only by combining these changes into an optimistic multivariate sensitivity analysis did the incremental cost per QALY begin to approach £30,000.

Long term care model:

The manufacturer provided a second model to assess the cost-effectiveness of a smaller patient group with more severe ITP requiring long-term continuous treatment. The Markov model provided aimed to assess the most cost-effective sequence of treatments (rituximab, romiplostim, IVIg, Anti-D [only those with a spleen] and eltrombopag). Given the input parameters used, the model was very similar for the two patient groups.

In the analyses conducted by the manufacturer a treatment sequence of rituximab, eltrombopag, romiplostim and IVIg was the least costly but least effective. No other sequences had an incremental cost per QALY approaching £30,000. The manufacturer reported that treatment sequences including eltrombopag dominated the same sequences without eltrombopag when patients have received prior treatment with rituximab. The manufacturer's deterministic sensitivity analysis varied the response rate used in the model and the model time horizon. These did not greatly change the results.

The ERG's further univariant analyses (varying the discount rate, changing response rates of eltrombopag in line with the meta-analysis, allowing romiplostim to respond over a 12 week period and varying the assumption of a fatal bleeding event between 0%-100%) did not greatly alter the results. Plausible combinations of changes could change which treatment sequence was least costly but least effective but again no other sequence had an ICER approaching £30,000. Introducing a standard of care sequence where patients only received rescue medication resulted in the no active treatment sequence being associated with an ICER below £50,000.

Commentary on robustness of submitted evidence

The overall quality of the RCTs used to support the watch and rescue model appear reasonable and the ERG found no evidence that any data of consequence were omitted from the submission. Only indirect evidence relating to relatively short follow-ups was used in the long-term model and the use of these data introduces a bias of unknown direction and magnitude. Due to the lack of other suitable data, two different measures of utilities were used (the SF-6D and the EQ-5D). Furthermore, apart from bleeding no other utility decrements e.g. for other adverse events, were included in the models. Information on other parameters for both models can be questioned but even when assumptions were varied the incremental costs per QALYs remained well above £30,000.

Key issues

Overall, the key issues for a decision maker to note are as follows:

Effectiveness

- Eltrombopag appears to be a safe treatment for ITP.
- Eltrombopag has short term efficacy for the treatment of ITP.
- There is no robust evidence on long-term efficacy of eltrombopag.
- Eltrombopag appears to be less effective in achieving an overall response rate than romiplostim in a 6-month intervention period.
- There is no robust evidence on the effectiveness of eltrombopag compared to other relevant comparators.

Watch and Rescue model

- Substantial reductions in the cost of eltrombopag are needed before the incremental cost per QALY is less than £30,000.

- If the chance of dying from a bleeding event increases towards the upper boundary considered by the manufacturer, and the price of eltrombopag is reduced then it is plausible that the cost per QALY could be reduced to less than £30,000.
- Other than bleeding no adverse events are modelled. The bias this causes is unknown.

Long term treatment model

- Using non-randomised non-comparative data may result in biased estimates. The magnitude and direction of these biases is uncertain.
- Inclusion of the *indirect treatment* comparison of eltrombopag with romiplostim along with other plausible changes in the effectiveness of romiplostim substantially alters the order of treatments in terms of cost-effectiveness. A decision is needed as to whether such data are sufficiently robust.
- Inclusion of the standard of care sequence results in no active treatment sequence having an ICER below £30,000. It is unclear whether such a standard of care sequence is plausible.
- When excluding a standard of care sequence, a sequence where eltrombopag is used after rituximab is the least costly but least effective sequence. None of the other sequences have an ICER below £30,000.
- Restricting the time horizon to 2 years then a treatment sequence where eltrombopag is given after rituximab is most likely to be cost-effective. A 50 year time horizon favours a sequence involving romiplostim.
- Many assumptions are used to estimate the target patient population and the numbers of patients who will require long-term treatments. It is unclear how applicable these are.

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LIST OF ABBREVIATIONS

AE	Adverse event
ASH	American Society for Hematology
BCSH	British Committee for Standards in Haematology
CEACs	Cost-effectiveness acceptability curves
CRD	Centre for Reviews and Dissemination
EBAG	Eltrombopag
ERG	Evidence Review Group
FACT-Th	FACT-Thrombocytopenia Subscale
GI	Gastrointestinal
GSK	GlaxoSmithKline
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratio
ICH	Intracranial haemorrhage
ITP	Idiopathic thrombocytopenic purpura
ITT	Intention to treat
IVIg	Intravenous immunoglobulin
LOCF	Last observation carried forward
MeSH	Medical subject headings
PSA	Probabalistic Sensitivity Analysis
PSSRU	Personal Social Services Research Unit
RCT	Randomised Controlled Trial
STA	Single Technology Appraisal
QALY	Quality Adjusted Life Year
WHO	World Health Organization

1 INTRODUCTION TO ERG REPORT

The remit of the evidence review group (ERG) is to comment on the clinical and cost-effectiveness evidence submitted to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology review process. Evidence has been submitted to NICE by GlaxoSmithKline (GSK) UK. The information considered by the ERG related to a main submission report, a systematic review report, a response report, and a CD with results of the eltrombopag trials. The ERG also conducted further analysis on the indirect comparison of eltrombopag and romiplostim and further economic modelling.

The submitted evidence related to the use of eltrombopag for the treatment of chronic immune or idiopathic thrombocytopenic purpura (ITP). Two patient populations were considered:

1. Splenectomised patients who are refractory to other treatments.
2. Non-splenectomised patients who have inadequate response to first-line treatment and for whom splenectomy is contraindicated.

In the economic model, two distinct care pathways were considered:

1. Watch and rescue management.
2. Long-term continuous management.

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 140-400 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. Diagnosis of chronic ITP remains one of exclusion of other causes of thrombocytopenia.

No large registry data exist from the UK on the incidence of adult ITP but a case series from Newcastle[1] suggested an incidence of 1.13 per 100,000 per year which is lower than a Danish study which reported an incidence of 3.2 per 100,000 per year[2] and the British Committee for Standards in Haematology (BCSH)[3] which quotes an American review[4] which in turn quotes two American papers[5,6] for its incidence in the UK of 5.8-6.6 per 100,000 per year.

Spontaneous remission of adult ITP is rare. Both BCSH[3] and the American Society for Hematology (ASH)[7] 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 new International Consensus Report, 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). The BCSH

guidelines quote a response rate of 66% with 33% achieving long term remission with steroids and a response rate of 75% with IVIg, but response to IVIg is not long lasting.

Splenectomy, a surgical treatment, is possibly curative in 66% of patients[8] but carries mortality 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 has been licensed in Europe for the treatment of ITP and was 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.[9] Romiplostim has undergone a single technology assessment by NICE, the outcome of which is awaited.

Retrospective cohorts have demonstrated variable mortality from refractory ITP while the largest pooled case series[10] demonstrated age-adjusted mortality rates from bleeding of 0.004, 0.012, and 0.130 deaths per patient-year for age groups younger than 40, 40 to 60, and older than 60 years, respectively. However, there was wide variation in the quality of the data and the case series went as far back as 1954, raising the question whether these data can be applied to modern practice. More recent case series have demonstrated lower mortality but considerable treatment related mortality and morbidity.[11]

2.1 Critique of manufacturer's description of underlying health problem

The manufacturer's submission clearly details the problem of treating chronic refractory ITP and the need for new safe treatments.

2.2 Critique of manufacturer's overview of current service provision

The manufacturer acknowledges the lack of good quality evidence in the area of chronic ITP and the absence of NICE guidelines. They correctly identify that the best clinical guidance

available are guidelines from the ASH and the BCSH. Both the BCSH and ASH guidelines are from expert groups who prepare 'best evidence' guidelines which are peer reviewed prior to publication. Unfortunately these guidelines were published in 1996 and 2003 respectively and may be out of date and much of the evidence is expert opinion. As noted above the new international consensus guidelines[12] were published after the manufacturer's submission had been made. The guideline recommendations do not differ greatly from the previously published UK[3] and USA[7] guidelines except recommending the thrombopoietin agonists (romiplostim and eltrombopag) be used as possible second line agents after the failure, or unacceptable side-effects, of steroids, IVIg and anti-D. They list other possible second line treatments as splenectomy, vinca-alkaloids, rituximab, mycophenolate mofetil, dapsone, danazol, cyclophosphamide, ciclosporin and azathioprine but list them alphabetically rather than giving any preferences.

Because of the lack of licensed second and third line therapies and good quality evidence for the treatment of ITP the manufacturer contacted seven UK experts to determine current UK practice. It is unclear the extent to which these expert opinions mirror current UK practice, which may lead to potential bias in the submission. However the experts' views on current practice were similar to the above guidelines. The manufacturer was requested to provide information on any conflict of interests these experts may have and whether they were remunerated. In response they stated that the experts were paid using British Medical Association guidelines but did not discuss conflicts of interest.

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

3.1 Population

The manufacturer's submission states that the drug is to be used for adult patients with ITP requiring treatment who are:

- Splenectomised and refractory to other treatments; or as
- Second line treatment to those who have medical contraindications to splenectomy.

Due to the lack of good registry data the prevalence of the above patients in the UK can only be estimated, as acknowledged by the manufacturer. The manufacturer uses the prevalence (23.6 per 100,000) calculated from a USA database[13] to estimate the prevalence in the UK. They consulted an epidemiologist who runs a UK ITP database and he confirmed by personal communication that the prevalence in the UK was similar to the USA. As with the incidence, the reported prevalence varies considerably. A study not mentioned by the manufacturer had determined the prevalence of ITP using the UK general practice database of between 2.1 to 8.1 per 100,000,[14] while Segal and colleagues estimate a prevalence rate of 9.5 per 100,000.[15]

A GSK funded survey (DEMAND) of 50 UK haematologists then determined the proportion of patients that would likely be suitable for treatment with eltrombopag (8.6% of total ITP population). From this it was estimated that there were approximately 850 patients with chronic ITP who were suitable for eltrombopag treatment. There is no way of determining if the manufacturer's assumptions about the numbers of patients are correct and there is likely to be considerable uncertainty surrounding this estimate.

The manufacturer's expert opinion also claims that the RCTs' participants, of whom only a small proportion was from the UK (22/433), were similar to the UK ITP population. The patients who entered into the RCTs were heavily pre-treated, probably more so than the average UK patient who would be eligible for eltrombopag, with 37.9% having received three or more treatments. It is also unclear as to the reasons why those non-splenectomised participants in the trials had not received a splenectomy, whether it was because they were medically unfit, as in the proposed indication, or had not had the procedure for other reasons.

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 [reason for lower dose unclear]), aiming for a platelet count of between 50 and 200 x 10^9/L (normal range 140-400 x 10^9/L).

3.3 Comparators

The manufacturer's panel of experts split the type of ITP patient into two groups and suggested the following comparators:

- Those undergoing 'watch and rescue' management, where the comparators were corticosteroids, IVIg, rituximab, immunosuppressant agents, romiplostim and, in those who have not had a splenectomy, anti-D.
- Those requiring long-term treatment, where the comparators were romiplostim, IVIg, rituximab and anti-D.

These are all the reasonable comparators as described for second-line treatment in the latest international consensus document.[12] They are all available in the UK with the current exception of the licensed preparation of anti-D. The only drugs licensed for the treatment of ITP are steroids, anti-D, IVIg and romiplostim.

Both romiplostim and eltrombopag are thrombopoietin agonists, with romiplostim being delivered by weekly subcutaneous injection during a hospital out-patient visit while eltrombopag is a daily oral preparation.

3.4 Outcomes

The outcomes included by the manufacturer are appropriate. They include mortality, reduction in symptoms, adverse effects of treatment, quality of life and need for rescue therapies. The greatest emphasis, however, is on platelet count, response rate and duration of response, which may not be appropriate. As the international consensus document[12] states there is no set platelet count below which a patient should be treated, instead treatment should be based on bleeding risk and side-effects of treatments. Therefore platelet count is less important than symptoms, adverse effects and quality of life. All three of the eltrombopag RCTs (TRA100773A, TRA100773B and TRA102537 RAISE) include bleeding symptoms, quality of life and drug side-effects as secondary outomes.

3.5 Time frame

ITP is a chronic condition with patients often requiring multiple courses of one or more treatments over their lifetime, with spontaneous remissions outwith the first few weeks rare. Any economic analysis must therefore look at long-term outcomes and the requirement for prolonged treatments. This can be illustrated by the cohort presented by Stasi and colleagues.[16] One hundred and twenty-one patients were treated with prednisolone (1 mg/kg for 1 month); refractory or relapsed cases then underwent splenectomy and/or other

therapeutic modalities. At last follow-up (between 48 and 151 months) 43 patients were in complete remission and free from therapy, 52 were still on therapy, 11 had died (5 due to ITP) with the remainder (15) having ITP but not requiring treatment.

3.6 Relevant factors

It should also be considered that the economic model considers patients who are taking unlicensed products (immunosuppresants, including rituximab) before the licensed products (romiplostim and possibly eltrombopag), and hence going against their licensed and proposed licensed indications.

4 CLINICAL EFFECTIVENESS

4.1 Critique of manufacturer's approach

4.1.1 Description of manufacturer's search strategy and critique

Details of the literature searches undertaken on 16th June 2009 are reported in Appendix 2 of the manufacturer's submission. MEDLINE, EMBASE and the Cochrane Library were searched. These searches were supplemented by hand searching of the proceedings of the European Haematology Association and American Society of Hematology for the years 2004-2009. The authors state that reference lists were also screened for additional studies. While other databases such as Science Citation Index, CINAHL and Biosis would have been appropriate to search, the included sources are the most important ones and as such should have provided adequate coverage of the literature.

The search strategies that were used are reproduced in full and are 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, and (c) methodology terms. These were correctly combined using the Boolean operator OR for each set of terms. Then the summaries 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. For example, free text searching did not always include common variations. Most notable omissions were variation for "thrombocytopenic" (thrombocytopaenic and thrombocytopenia) and "romiplstim" (nplate, AMG 532, AMG531 and remiplistim).

The methodology parts 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 terms comparative study/ quality of life/ and quality adjusted life years/ and EMTREE terms controlled study/, major clinical study/ and exp quality of life/. The strategy would also have benefited from additional methodology – related text terms.

The search strategy used in the Cochrane Library also included a methodology section. This seemed unnecessary since each database has already been filtered for trials (CENTRAL) or

systematic reviews (DARE and CDSR) or HTA assessments (HTA database) and risked compromising the sensitivity of the search.

No details were provided on the separate searches that were undertaken for clinical information for the long-term economic model. It is unclear why this was done because the systematic review should have identified all relevant studies.

Due to concerns over the sensitivity of the manufacturer's searches, the ERG undertook independent searches for eltrombopag and the clinical effectiveness of the comparators. MEDLINE, MEDLINE In-Process, EMBASE CDSR, DARE and HTA 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 manufacturer's 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 the Centre for Reviews and Dissemination (CRD) systematic review filter.[17] Details are provided in Appendix 1.

4.1.2 Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate

The inclusion criteria used in the study selection for the systematic review are tabulated in Table 4.1.

Table 4.1 Details of the inclusion criteria for the systematic review

Population	Adults (≥ 18 years) with ITP (mean/median 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 • Immuosuppressive agents (azathioprine, ciclosporin, mycophenolate mofetil) • Cytotoxic agents (vincristine, cyclophosphamide) • Splenectomy • Autologous stem cell transplantation or • Any combination of the above treatments.
Outcomes	***Efficacy outcomes included:*** • Platelet count - Median platelet count - Response rate - Durability of response • Need for rescue treatment or concurrent treatment • Symptom reduction ***Safety outcomes included:*** • Headache • Nausea • Nasopharyngitis • Diarrhoea and vomiting • Bleeding (incidence, severity and outcome) • Mortality ***Health related quality of life outcomes*** ***Economic outcomes included:*** • Total costs • Total effectiveness • Life years gained • Quality adjusted life years (QALYs) gained • Cost per life year gained • Cost per QALY
Study design	Prospective clinical studies (RCTs, non-randomised comparative studies, case series) with a sample size of≥ 10 patients, and cost -effectiveness and cost-utility studies of agents used to treat ITP.

For population, the decision problem specified that one group of patients considered should be non-splenectomised patients who have inadequate response to first-line treatment and for whom splenectomy is contraindicated. However, no definition on contraindication to splenectomy was set and evidence from studies that included patients who may be suitable for splenectomy was subsequently included in the review. The manufacturer stated that this was the case and the licensed use of eltrombopag is indeed more restrictive.

In terms of study design, only evidence from prospective studies was considered by the manufacturer. As a consequence only a limited amount of data was identified for some interventions, for example cyclophosphamide (one study) and mycophenolate mofetil (two studies). Retrospective studies for these interventions might have been considered and indeed, contrary to the inclusion criteria, were included for some comparators in the submission.

With regard to the additional review conducted for the economic evaluation, the inclusion criteria were limited to large RCTs or published meta-analyses reporting IVIg, anti-D, rituximab, or romiplostim in adult chronic ITP patients. Studies of these designs should have formed a subset of the systematic review described above. However, this was not the case.

4.1.3 Table of identified studies

The manufacturer identified 20 RCTs and 93 non-randomised comparative studies or case series, of which three RCTs (TRA100773A,[18] TRA100773B,[19] RAISE[20]), one case series (REPEAT),[21] and two ongoing studies (EXTEND,[22] TRA108132LENS[23]) reported on eltrombopag. Table 4.2 summarises the characteristics of the studies reporting eltrombopag, all of which were funded by the manufacturer. The ERG did not identify any additional studies reporting eltrombopag.

Table 4.2 Studies reporting eltrombopag

Study, design, links with other studies	N, Population, baseline platelet count, spleen status	Intervention, duration	Publication status
TRA100773A, RCT	117 participants with chronic ITP who had relapsed or were refractory to ≥ 1 prior ITP therapies, < 30 $x10^9$/L, a mixture of splenectomised and non-splenectomised patients.	A, eltrombopag 30, 50 or 75 mg/day orally, 6 weeks B, placebo, 6 weeks	Published
TRA100773B, RCT	114 participants. Other characteristics as above.	A, eltrombopag 50 mg/day orally, 6 weeks B, placebo, 6 weeks	Published
TRA102537RAISE, RCT	197 participants. Other characteristics as above.	A, eltrombopag 50 mg/day orally, 6 months B, placebo, 6 month	Conference abstracts
TRA108057REPEAT, Case series	66 with chronic ITP who had ≥ 1 prior ITP therapies, ≥ 20 $x10^9$/L and ≤ 50 $x10^9$/L, a mixture of splenectomised and non-splenectomised patients.	Eltrombopag 50 mg/day in 3 cycles (up to 6 weeks) of repeated intermittent dosing	Conference abstracts
On-going studies			
TRA105325EXTEND, case series, an extension of eltrombopag intervention in adults who were previously enrolled in an eltrombopag study (not specified which study)	207 by 07 Jan 2008, 88% ≤ 50 $x10^9$/L.	Eltrombopag 50 mg/day orally as starting dose, 15 months	Due to complete in June 2012; conference abstracts
TRA108132LENS, long-term follow up of adults who were previously enrolled in a phase II or III eltrombopag study (not specified which study).	Not reported	Eltrombopag, no other information reported	Due to complete in April 2013; unpublished.

For comparator treatments, 36/113 (32%) studies including children or adolescents (< 18 years old), i.e. not meeting the review's stated inclusion criteria, were also included (Table 4.3). Another two retrospective studies reporting on dapsone were also included although the inclusion criteria stated that for case series only prospective studies were considered.

Table 4.3 Studies included inappropriately in the systematic review[1]

Study ID	Reason
Dexamethasone	
Arruda 1996[24] Borst 2004[25] Cheng 2003[26] Stasi 2000[27]	Included patients < 18 years old
IVIg	
Newland 2001[28] Pacetti 1997[29] Salama 2008[30] Reding1988[31](Cited as Sautter 1998 in manufacturer's report)	Included patients < 18 years old
Anti-D	
Bussel 1991[32] Rodeghiero 1992[33] Unsal 2004[34]	Included patients < 18 years old
Splenectomy	
Badea 2004[35] Bourgeois 2003[36] Cascavilla 2009[37] Fenaux 1989[38] Gadenstatter 2002[39] Houwerzijl 2008[40] Ismet 2004[41] Kwon 2005[42] Mazzuconi 1999[43] Syed 2007[44] Szold 2002[45] Winde 1996[46] Zamir 1996[47]	Included patients < 18 years old
Rituximab	
Alasfoor 2009[48] Arnold 2007[49] Garcia–Chavez 2007[50] Stasi 2001[51] Zaja 2008[52]	Included patients < 18 years old
Peňalver 2006[53]	Included patients < 18 years old, also a retrospective study
Danazol	
Kondo 1992[54] Nalli 1988[55]	Included patients < 18 years old
Dapsone	
Hernandez 1995[56]	Included patients < 18 years old
Godeau 1997[57] Godeau 1993[58]	Retrospective study
Mycophenolate mofetil	
Provan 2006[59]	Included patients < 18 years old
Vinca alkaloid	
Kueh 1982[60] Szczepanik 2007[61]	Included patients < 18 years old

4.1.4 Relevant studies not included in the submission

The ERG conducted independent literature searches to identify additional studies. The manufacturer did not mention the ASH guidance on IVIg and corticosteroids[7] and a systematic review reporting on IVIg (Table 4.4).[62]

Table 4.4 Relevant studies/reviews missed in the systematic review

Study ID	Study design
IVIg	
George 1996 (ASH guideline)[7]	Summary of 14 case series
Chen 2008[62]	Systematic review consisting of 28 RCTs
~~**Danazol**~~	
~~Mylvaganam 1989[63]~~	~~Prospective case series, n=15~~
~~**Ciclosporin**~~	
~~Emilia 2002[64]~~	~~Prospective case series, n=12~~
~~Kappers-Klunne 2001[65]~~	~~Prospective case series, n=20~~

4.1.5 Description and critique of the manufacturer's approach to validity assessment

Only the methodological quality of the included RCTs was assessed. A 13-item checklist (recommended by NICE in the guidance to manufacturers for the submission of evidence) was used to assess the three eltrombopag RCTs. A separate 7-item checklist (recommended in the Cochrane Reviewer's handbook version 4.2.6) was used to assess the 17 RCTs reporting on the effectiveness of comparator treatments. Two reviewers assessed study quality independently.

The ERG considered the quality assessment tools appropriate for appraising RCTs, although it is unclear why separate instruments were used for the eltrombopag and comparator RCTs. Ideally the same tool should have been used for all RCTs. In addition, the latest version of the Cochrane Handbook for Systematic Reviews of Interventions (version 5.0.2) recommends using a new quality assessment tool for RCTs (Cochrane risk of bias tool).[66]

The manufacturer's submission did not critically appraise non-randomised comparative studies or case series included in the review. The manufacturer did not explain why non-randomised studies were not quality assessed in their response to the ERG's clarification queries (Clarification response: C34).

An interactive voice response system was used to conceal the treatment allocation in the eltrombopag RCTs. In each RCT the randomisation was stratified according to concomitant

ITP medication, splenectomy, and baseline platelet count, with a block size of 4 within each stratum. The ERG considered the randomisation procedure to be appropriate.

The participants and outcome assessors were blinded. Matching placebo was used to blind participants, who were identified by a unique subject number during the study. The ERG queried how the blinding was maintained in the three eltrombopag RCTs other than using placebo and what the criteria for unblinding were. The manufacturer clarified that an investigator or other physician managing the patient could have unblinded the participant's treatment code when there was a medical emergency or in the event of a serious medical condition, when knowledge of the investigational product was essential for the clinical management and welfare of the subject (clarification response: C7). However, the manufacturer did not provide information on whether any participants were unblinded and, if so, whether their treatment continued after unblinding. It is unclear to what extent, if any, this introduced a potential bias into the analysis. It must also be considered that, as participants in the treatment arm with chronically low platelet counts significantly improved their platelet counts compared with placebo, then knowledge of the platelet count may lead to knowledge of the randomisation.

4.1.6 Description and critique of the manufacturer's outcome selection

The three eltrombopag RCTs used slightly different outcomes. Table 4.5 summarises the outcomes used in each RCT, their validity and appropriateness. The ERG considered that all outcomes were appropriate. The outcomes were either objective or well accepted in ITP practice and research, with some validated in ITP patients.

Table 4.5 Appropriateness of outcome selection in the three eltrombopag RCTs

Outcome and definition	Validity	Appropriate Y/N	Trial(s) used the outcome
Primary outcome			
Proportion or odds of participants with a platelet count of $\geq 50 \times 10^9$/L at the end of the intervention	Well accepted	Y	All three RCTs
Secondary outcomes			
Efficacy			
Proportion of participants with at least 75% of assessments $\geq 50 \times 10^9$/L and $\leq 400 \times 10^9$/L	Objective measure	Y	TRA102537RAISE
Odds of participants with a platelet count of 50×10^9/L during the intervention period	Well accepted	Y	TRA100773B TRA102537RAISE
Proportion of participants with platelet count of 50×10^9/L and at least x 2 the baseline amount	Objective measure	Y	TRA100773B
Maximum duration of response	Objective measure	Y	TRA102537RAISE
Proportion of participants with a reduction in use of concomitant ITP medications from baseline	Objective measure	Y	TRA102537RAISE
Safety			
Incidence and severity of bleeding, measured using WHO criteria	Well accepted	Y	All three RCTs
Proportion of participants receiving a rescue treatment (new ITP medication, increased dose of a concomitant ITP medication from baseline, platelet transfusion, and/or splenectomy) during the intervention period	Objective measure	Y	TRA102537RAISE
Safety and tolerability	Clinician reported (well accepted)	Y	TRA100773A TRA100773B
Safety and tolerability, adverse events graded according to the National Cancer Institute (NCI) Common Toxicity Criteria for adverse events.	Well accepted	Y	TRA102537RAISE
Outcomes of participants incurring a haemostatic challenge (collected retrospectively)	Clinician reported (well accepted)	Y	All three RCTs
Quality of life			
Health-related quality of life (HR-QoL), measured using SF-36v2 tool	Validated in ITP patients	Y	All three RCTs
HR-QoL measured using FACT-Th subscale measuring the impact of thrombocytopenia on daily activities and mental health	Validated in cancer patients with thrombocytopenia	Y	TRA102537RAISE
Other outcomes			
Serum thrombopoietin level, measured using immunosorbent assay	Well accepted	Y	TRA100773A

4.1.7 Description and critique of the statistical approach used

4.1.7.1 Eltrombopag

The statistical approaches used for the three eltrombopag RCTs were reported in detail and they were very similar across studies.

Patient baseline characteristics were tabulated by treatment group. Information on age, sex, race, splenectomy status, concomitant ITP medication, platelet counts, and number of prior therapies were described. Logistic-regression was then used for primary outcomes with adjustment for stratification variables, i.e. use of concomitant ITP medications, splenectomy status, and baseline platelet count. If the null hypothesis was rejected by logistic regression, the odds of the response rate between placebo group and eltrombopag group were compared.

All RCTs were adequately powered for their statistical purpose. Assuming 60% of participants would respond to eltrombopag and 25% to placebo, each trial had a 90% statistical power at the 5% level (1% for RAISE trial) of significance (2-sided) to detect a 30% difference in platelet response rate between eltrombopag group and placebo group.

The manufacturer stated that an ITT analysis was used, i.e. all participants were analysed in the group to which they were randomised. However, a small number of randomised patients (8/109 [7.3%] in TRA100773A, 2/102 [2%] in TRA100773B) were excluded from the efficacy analysis because of a baseline platelet count $\geq$ 30 x 10^9/L or because a baseline platelet count was not available (Clarification response: C10, C11). Excluding already randomised patients who did not meet inclusion criteria is a pragmatic practice but not including them in the final analysis contravenes the principles of ITT analysis. Any degree of exclusion following randomisation may break the balance of the baseline patient characteristics achieved by randomisation.

In studies TRA100773A and B (6-week trials), when participants withdrew prematurely because of a platelet count reaching more than 200 x 10^9/L, the last-observation-carried-forward (LOCF) imputation was applied and participants were classified as responders in the final analysis. The ERG considered such a way of dealing with missing data here is appropriate.

4.1.7.2 Comparators

The characteristics and results of studies reporting on comparator treatments were tabulated in the systematic review report but no statistical synthesis was undertaken.

Information on the response rates for IVIg, anti-D, rituximab, and romiplostim was needed for the long-term economic model. The manufacturer reported that they aimed to use the data from the highest available level of evidence. For example meta-analysis and RCTs, as well as large case series (Clarification response: B6). However, evidence from only one or two studies/reviews was used for each comparator treatment. Although the manufacturer consulted two ITP experts in the UK (Dr Drew Provan, Dr Adrian Newland) to help clinically validate the assumptions made in the cost-effectiveness approaches, the ERG nevertheless considered the way of generating values for comparator treatments in the long-term economic model as representing a potentially biased selection of evidence. As the manufacturer has identified a considerable amount of evidence for these comparators in the systematic review, descriptive statistics might have been considered such as the median and range of results across studies as an alternative source of values.

4.1.7.3 Meta-analysis

Meta-analysis of the three eltrombopag RCTs was carried out for response rates (50-400 x 10^9/L) at day 43 of the RCTs (end point of TRA100773A&B, midpoint of the RAISE trial). The response rates for the three eltrombopag groups in the TRA100773A trial were summed for this purpose. The ERG considered the use of meta-analysis here as appropriate.

4.1.7.4 Indirect comparison

No RCTs identified in the manufacturer's systematic review directly compared eltrombopag with any of the comparator treatments. Two RCTs reported by Kuter and colleagues[67] reporting romiplostim which also used placebo-plus-standard-care in the control group were compared with the RAISE eltrombopag RCT using a mixed treatment comparison. None of the other included RCTs used placebo as a comparator treatment.

Data were available for two outcomes in the mixed treatment analysis: durable platelet response rate and overall platelet response rate. The platelet response rate in the RAISE study was calculated post hoc so that the criteria for platelet response were the same for the eltrombopag and romiplostim RCTs. Durable platelet response was defined as a weekly platelet count $\geq 50 \times 10^9$/L during six or more weeks of the last eight weeks of treatment excluding those who received rescue medication at any time during the study. Overall platelet response was defined as durable plus transient response (four or more weekly responses $\geq 50 \times 10^9$/L during the study without a durable platelet response from week 2 to 25).

- ***Concerns on combining the two romiplostim trials***

The results in Figures 6.10 and 6.12 in the manufacturer's report are confusing. There is no acknowledgement in them that "Kuter 2008" refers to, technically, two separate RCTs and that the odds ratio calculations for "all subjects" are from a Mantel-Haenszel fixed effects meta-analysis, and not the odds ratio estimate and confidence interval that would be calculated from the data given for "all subjects", i.e. the totals of the two trials.

The question of how to combine the two trials by Kuter and colleagues[67] to get an estimate for the odds ratio for all subjects is not straightforward. However, in our opinion a Mantel-Haenszel meta-analysis is inappropriate. In most meta-analyses an important issue is whether the populations used in the different trials are homogeneous. In this case it is clear that the two populations being meta-analysed are heterogeneous: one considered splenectomised patients and the other considered non-splenectomised patients. Analysis exploring other methods of amalgamation is shown in Section 7.3.1.

- ***Concerns on assuming participants who did not complete the trials are non-responders***

In the RAISE trial and the two romiplostim RCTs (all 6-month trials), participants who did not complete the trials, i.e. withdrew prematurely due to adverse effects, lack of efficacy, non-compliance, protocol violation, patient choice, or loss to follow-up were counted as non-responders. However, the distributions of, and reasons for, not completing the intervention amongst the eltrombopag group and romiplostim groups were uneven. More participants withdrew prematurely in the RAISE trial than in the romiplostim trials (Table 4.6). Assuming all participants who withdrew were non-responders is an extreme scenario (worst scenario). It is unclear whether this introduces a bias for or against eltrombopag and further analysis, reported in Section 7.3.2, has been conducted by the ERG to explore this issue further.

Table 4.6 Number and reasons of premature withdrawals in RAISE trial and romiplostim RCTs

Reasons	**Eltrombopag**		**Romiplostim (non-splenectomised)**		**Romiplostim (splenectomised)**	
	Eltr.	**Placebo**	**Romi.**	**Placebo**	**Romi.**	**Placebo**
	23/135 (17%)	7/62 (11%)	2/41 (5%)	4/21 (19%)	2/42 (5%)	2/21 (10%)
Adverse events	13	4	2	1	1	0
Withdrew consent	4	2	0	2	1	0
Deaths	0	0	0	0	0	2
Pregnancy	0	0	0	1	0	0
Other	1	1	0	0	0	0
Loss to follow-up	3	0	0	0	0	0
Lack of efficacy	1	0	0	0	0	0
Non-compliance	1	0	0	0	0	0

4.1.8 Summary statement of manufacturer's approach

The ERG's main concerns with regard to the manufacturer's approach were:

- Intention to treat analysis was not applied in TRA100773A & B trials as the manufacturer stated, in that not all participants who were randomised were included in the analysis.
- Participants who withdrew from the RAISE trial and romiplostim trials were counted as non-responders. As there were more such participants in the eltrombopag group than in the romiplostim groups, the indirect comparison results might have favoured romiplostim.
- Highly selective data (from one or two studies/reviews) were used for comparator treatments in the long-term economic model.

Other concerns:

- The characteristics of the non-splenectomised participants in the eltrombopag RCTs were not in line with the licensed use for eltrombopag (i.e. such participants should be contraindicated for splenectomy).
- There may have been participants or clinicians who were unblinded to the intervention during the eltrombopag RCTs.
- In the manufacturer's systematic review, 32% (36/113) of studies not meeting the inclusion/exclusion criteria were included and two reviews were missed.
- The methodological quality of included non-randomised comparative studies and case series was not assessed.

4.2 Summary of submitted evidence

4.2.1 Eltrombopag

The manufacturer reported the results from three eltrombopag RCTs. The ERG has summarised the results by outcome in order to allow comparison across studies.

A. Efficacy

A1. Platelet response ($\geq 50 \times 10^9$/L) at the end of the intervention

Platelet response, defined as $\geq 50 \times 10^9$/L at the end of the intervention, was reported for studies TRA100773A and B. Platelet response rates after 6-week eltrombopag treatment ranged from 26.6% (8/29, 30mg/day) to 80.0% (21/26, 75mg/day). Statistically significantly more participants in the eltrombopag group responded to treatment compared with the placebo group ($p<0.001$), apart from the 30mg/day eltrombopag group ($p=0.070$) (Table 4.7).

Table 4.7 Platelet response (≥ 50 x 10^9/L) at the end of intervention

	Placebo	**Eltrombopag 30mg**	**Eltrombopag 50mg**	**Eltrombopag 75mg**
TRA100773A (6-week intervention)				
Responders, n/N (%)	3/27 (11.1%)	8/29 (26.6%)	19/27 (70.4%)	21/26 (80.8%)
Odds ratio (relative to placebo), 95% CI	Not available	3.1 (0.7, 13.8)	22.0 (4.7, 102.2)	38.8 (7.6, 197.7)
p-value	Not available	0.070	< 0.001	< 0.001
TRA100773B (6-week intervention)[a]				
Responders, n/N (%)	6/37[b] (16.2%)	-	43/73[b] (58.9%)	
Odds ratio (relative to placebo), 95% CI	Not available	-	9.6 (3.3, 27.9)	
p-value	Not available	-	< 0.001	

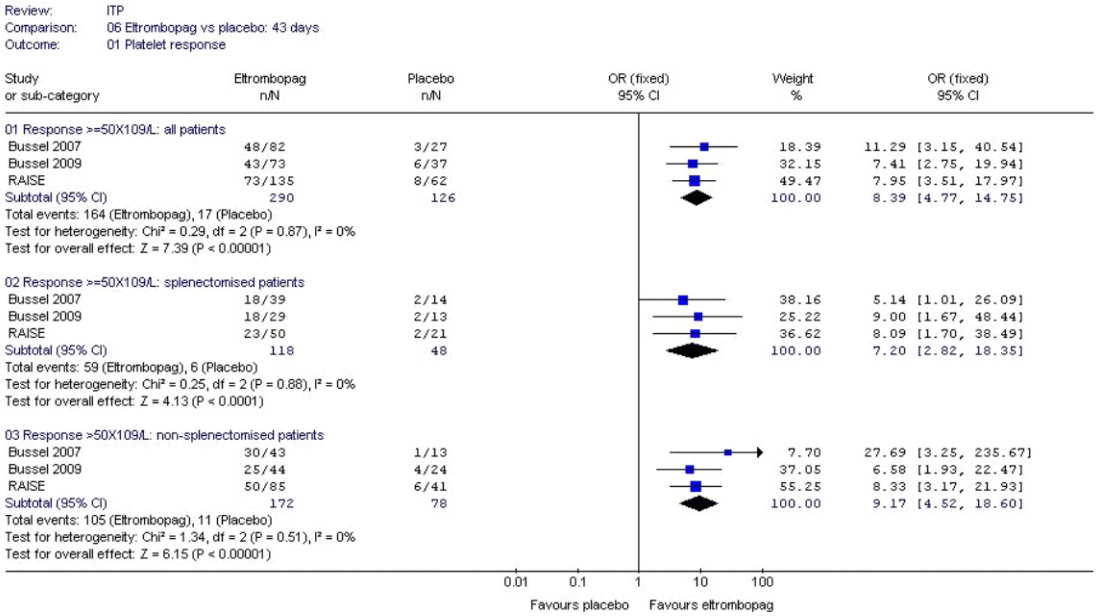
[a]Initial dose used was 50mg/day, adjusted to 75mg/day during treatment in some participants.

[b]One patient was not evaluable and was not included in the analysis.

Results were presented separately by splenectomy status for TRA100773B. Amongst the non-splenectomised, 56.8% (20/35) of participants in the eltrombopag group had a platelet response ≥ 50 x 10^9/L at the end of the intervention compared with 16.7% (4/24) in the placebo group. The results for splenectomised participants were similar (62.1% [19/31] vs. 15.4% [2/14]).

Meta-analysis was carried out to combine response rates (50-400 x 10^9/L) between eltrombopag and placebo at day 43 of the three RCTs (end point of TRA100773A and B, mid point of the RAISE trial) (Figure 4.1). The results show that statistically significantly more participants responded to eltrombopag than to placebo overall (164/290 vs. 17/126, OR 8.39, 95% CI 4.77 to 14.75). The results were similar amongst non-splenectomised and splenectomised participants.

Figure 4.1 Response rates (50-400 x 10^9/L) for eltrombopag and placebo at day 43



Source: Clarification report, A3.

A2. Platelet response (≥ 50 x 10^9/L) at any point during the intervention

The odds ratio of a platelet response (≥ 50 x 10^9/L) at any point during the intervention for eltrombopag and placebo was reported for the TRA100773B and RAISE trials. The actual numbers of participants who responded were not reported. In the TRA100773B trial (6-week intervention) statistically significantly more participants responded to eltrombopag than to placebo (OR 8.8, 95% CI 3.5 to 21.9, p<0.0001). Results were similar in the RAISE trial (6-month intervention) (OR 8.2, 95% CI 3.6 to 18.7, p<0.001).

A3. Platelet response (≥ 50 x 10^9/L) and at least 2x baseline count at the end of the intervention

A platelet count ≥ 50 x 10^9/L and at least 2x the baseline count was reported for the TRA100773B trial at the end of the intervention. Statistically significantly more participants in the eltrombopag group met this criterion compared with the placebo group (58% [44/76] vs. 14% [5/38], p<0.001).

A4. Median platelet counts at each point of assessment

Median platelet counts at each point of assessment were reported for the RAISE trial. The median platelet counts for the eltrombopag arm began to rise after one week of treatment and remained above 50 x 10^9/L throughout the 6-month treatment period. The median platelet counts for the placebo arm did not rise above 30 x 10^9/L throughout the study.

A5. Duration of platelet response

Duration of platelet response (continuous and cumulative number of weeks of response) was reported for the RAISE trial. However, it was not clear whether rescue treatments were taken into account when reporting this information.

The median duration of the maximum continuous response in the eltrombopag group was 8.1 weeks compared with 0 weeks in the placebo group.

The median cumulative weeks of response in the eltrombopag group was 10.9 weeks compared with 0 weeks in the placebo group. Amongst non-splenectomised participants, this was 13.4 weeks (range 0 to 26.1 weeks) in the eltrombopag group compared with 0 weeks (range 0 to 23.7 weeks) in the placebo group. Amongst splenectomised participants, it was 6.0 weeks (range 0 to 23.7 weeks) in the eltrombopag group compared with 0 weeks (range 0 to 19.7 weeks) in the placebo group.

A6. Need for rescue medication during treatment

The need for rescue medication was reported by the RAISE trial. Rescue medication was defined as a composite of new ITP medication, increased dose of concomitant ITP medication, platelet transfusion, and/or splenectomy during the intervention. Overall, 40% (25/62) of participants in the placebo group required rescue medication compared with 18% (25/135) in the eltrombopag group ($p < 0.001$). Similar results were observed for placebo compared with eltrombopag amongst non-splenectomised participants (15/41 [36.6%] vs. 14/85 [16.5%], OR 0.34, 95% CI 0.14 to 0.79, p=0.013). The same direction of effect was observed for placebo compared with splenectomised participants although the difference was not statistically significant (10/21 [47.6%] vs. 11/50 [22.0%], OR 0.33, p=0.055).

A7. Reduction in dose/frequency of concomitant ITP medications taken at baseline

The manufacturer provided evidence on the reduction of concomitant ITP treatments for the RAISE trial in their response to the ERG clarification queries (Clarification report, Appendix 1). There was a statistically significant reduction in concomitant treatments amongst those not splenectomised who received eltrombopag compared with the placebo group (placebo 5/18 [27.8%] vs. eltrombopag 25/36 [69.4%], OR 5.87, 95% CI 1.67 to 20.59, p=0.006). The difference between eltrombopag and placebo amongst splenectomised participants was not statistically significant (placebo 5/13 [38.5%] vs. eltrombopag 12/27 [44.4%], OR 1.29, 95% CI 0.33 to 5.04, p=0.714).

A8. Results of haemostatic challenge during or after the intervention

There were a small number of participants in the TRA100773A and B trials who needed surgery or in one case was involved in a car accident during treatment. None of the participants (0/4) from the eltrombopag arms needed rescue treatment compared with all of those (3/3) from the placebo arms (Table 4.8). Similarly, in the RAISE trial fewer participants in the eltrombopag arm needed rescue treatment as a result of haemostatic challenge compared with the placebo arm (28.6% [4/14] vs. 50.0% [2/4]). The ERG was not able to compare the severity of bleeding between the eltrombopag and placebo group as the event occurred too rarely. In addition, the types of surgery experienced by the participants in the placebo group were not reported in detail.

Table 4.8 Results of haemostatic challenge during or after intervention

Outcome reported	Placebo	Eltrombopag 30mg/day	Eltrombopag 50mg/day	Eltrombopag 75mg/day
TRA100773A (6-week intervention)				
Number of participants facing a haemostatic challenge, n/N (%)	1/27 (3.7%)	0/29	3/27 (11.1%)	0/26
Type of challenge	Surgery	-	2 surgeries, 1 car accident.	-
Need for rescue treatment to prevent bleeding	Needed	-	Not needed and no bleeding complications	-
TRA100773B (6-week intervention)[a]				
Number of participants facing a haemostatic challenge, n/N (%)	2/38 (5.3%)	-	1/74 (1.4%)	
Type of challenge	Not reported	-	Teeth extraction 1week after intervention.	
Need for rescue treatment to prevent bleeding	Needed for both	-	Not needed and no bleeding complications	
TRA102537RAISE (6-month intervention)[b]				
Number of participants facing a haemostatic challenge, n/N	4/62 (6.5%)	14/135 (10.4%)		
Type of challenge	Minor surgery	Various from dental prosthetic work to open heart surgery		
Need for rescue treatment to prevent bleeding	Needed by the 2/4 (50.0%) who underwent dental procedures	Needed by 4/14 (28.6%) participants who underwent tooth extraction, tooth extraction and skin biopsy, open heart surgery, and colonoscopy and hemicolectomia respectively.		

[a]Initial dose of eltrombopag was 50mg/day, adjusted to 75mg/day during treatment in some participants.

[b]Initial dose of eltrombopag was 50mg/day, adjusted to between 25mg and 75mg/day during treatment.

B. Safety

B1. Death

One participant in the 50 mg/day eltrombopag treatment group in the TRA100773A trial died during the study. At baseline this participant had chronic obstructive pulmonary disease,

asthma, and peripheral oedema. Following 21 days of treatment he developed pneumonia, hepatitis, and renal insufficiency and after 25 days he died from cardiopulmonary failure.

B2. Incidence and severity of bleeding

Although detailed data on the number of bleeding events and data by splenectomy status were requested from the manufacturer in the ERG clarification queries, such data from only the RAISE trial were provided.

In non-splenectomised participants, 76% (65/85) of participants in the eltrombopag group experienced bleeding (any grade [1-4]) during treatment. This was statistically significantly less than that in the placebo group (95%, 38/40, p=0.007) (Table 4.9). Amongst splenectomised participants, 82% (41/50) of participants in the eltrombopag group experienced bleeding (any grade [1-4]) during treatment. This was lower than in the placebo group (90%, 18/20) but the difference was not statistically significant (p=0.887).

The manufacturer also reported odds ratios for clinically significant bleeding (WHO grade 2-4). Statistically significantly fewer participants experienced a clinically significant bleed in the eltrombopag group compared with the placebo group, for both non-splenectomised (18/40 [45%] vs. 25/85 [29%], p=0.020) and splenectomised participants (14/20 [70%] vs. 19/50 [38%], p=0.041) (Table 4.9).

Table 4.9 Incidence of bleeding any time from day 8 to end of treatment

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

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

EBAG, eltrombopag.

The manufacturer also provided the total number of bleeding events that occurred during treatment, in its response to ERG clarification queries. A similar proportion of WHO grade 3 or 4 bleeding events occurred in the eltrombopag and placebo groups for both non-splenectomised and splenectomised participants (Table 4.10). Fewer grade 1 or 2 bleeding

events occurred in the eltrombopag group compared with the placebo group regardless of splenectomy status. Brain stem haemorrhage that led to the death of one participant in the placebo group of the RAISE trial was not classified as a WHO grade 4 bleeding event since it was directly reported as an adverse event captured by CTCAE 3.0 criteria. While this may fit with the trial protocol it does however lead to under-reporting of bleeding risk and represents a bias against eltrombopag.

Table 4.10 Total number of bleeding events during treatment

	Non-splenectomised participants		**Splenectomised participants**	
	Placebo, n=41	**Eltrombopag, n=85**	**Placebo, n=21**	**Eltrombopag, n=50**
Total number of assessments	631	1393	364	862
Grade 1	257 (41%)	242 (17%)	142 (39%)	216 (25%)
Grade 2	87 (14%)	77 (6%)	72 (20%)	64 (7%)
Grade 3	6 (<1%)	16 (1%)	4 (1%)	5 (<1%)
Grade 4	0	0	0	0

B3. Adverse events

In the three eltrombopag RCTs, the risk of any adverse event ranged from 57% to 87%, the risk of a serious adverse event (not defined) ranged from 3% to 20%, the proportion of adverse events related to study medication ranged from 27% to 36%, and the proportion of adverse events leading to withdrawal of treatment ranged from 0 to 9% (Table 4.11). For each category, the risk of an adverse event appeared to be similar between the eltrombopag and placebo group in each RCT; however, no statistical comparisons were undertaken.

Table 4.11 Summary of adverse events (AEs) during intervention, number of participants (%)

	Placebo	Eltrombopag 30mg/day	Eltrombopag 50mg/day	Eltrombopag 75mg/day
TRA100773A (6-week intervention)				
Any AE	18/29 (62%)	20/30 (67%)	17/30 (57%)	19/28 (68%)
Any serious AE	4/29 (14%)	1/30 (3%)	6/30 (20%)	2/28 (7%)
AEs related to study medication	11/29 (38%)	10/30 (33%)	8/30 (27%)	10/28 (36%)
AEs leading to withdrawal	3/29 (10%)	0	2/30 (7%)	1/28 (4%)
TRA100773B (6-week intervention)				
Any AE	14/38 (37%)	-	45/76 (59%)	
Any serious AE	2/38 (5%)	-	2/76 (3%)[1]	
AEs related to study medication	4/38 (11%)	-	20/76 (26%)	
AEs leading to withdrawal	2/38 (5%)	-	3/76 (4%)	
TRA102537RAISE (6-month intervention)				
Any AE	56/61 (92%)	118/135 (87%)		
Any serious AE	11/61 (18%)	15/135 (11%)		
AEs related to study medication	18/61 (30%)	48/135 (36%)		
AEs leading to withdrawal	4/61 (7%)	12/135 (9%)		

Table 4.12 lists the most common adverse events (5% or greater in any group) that occurred in the three eltrombopag RCTs. The manufacturer repeated the information on the numbers of participants who experienced any adverse event that was included in Table 4.11, however, different numbers were reported for Trial TRA100773A. The numbers reported in Table 4.11 were 18 (62%) for placebo group, 20 (67%), 17 (57%) and 19 (68%) for eltrombopag groups, while the numbers reported in Table 4.12 were 17 (59 %), 14 (47%), 14 (47%) and 17 (61%) respectively, i.e. the rates in Table 4.11 were higher than those reported in Table 4.12 for placebo and eltrombopag groups.

According to the description in Table 4.12, the most common adverse events (10% or greater in any of the RCTs) in the eltrombopag groups were headache (range 8% to 30%), diarrhoea (0 to 13%), nausea (8% to 12%), nasopharyngitis (7% to 10%), upper respiratory tract infection (10% in the RAISE trial), and fatigue (7% to 10%). Other common adverse events (range 5% to 10% in any of the eltrombopag groups) were pain in extremity (0 to 7%), alanine transaminase increase (7%), vomiting (5% to 7%), urinary tract infection (7%), arthralgia (0 to 7%), pharyngolaryngeal pain (7%), rash (0 to 7%), aspirate aminotranferase level increase (0 to 7%), myalgia (6%), pharyngitis (6%), and constipation (0 to 7%) (Table 4.12).

Table 4.12 Adverse events in 5% or more participants in any study group, number of participants (%)

Event	TRA100773A				TRA100773B		TRA102537RAISE	
	Placebo, n=29	EBAG 30mg/d n=30	EBAG 50mg/d n=30	EBAG 75mg/d n=28	Placebo, n=38	EBAG ≥50mg/d n=76	Placebo, n=61	EBAG ≥25mg/d n=135
Any AE	17 (59)	14 (47)	14 (47)	17 (61)	14/38 (37)	45/76 (59)	56 (92)	118 (87)
Headache	6 (21)	4 (13)	3 (10)	6 (21)	4 (11)	6 (8)	20 (33)	41 (30)
Diarrhoea	2 (7)	0	0	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)
Fatigue	5 (17)	0	1 (3)	2 (7)	-	-	8 (13)	13 (10)
Pain in extremity	1 (3)	2 (7)	0	0	-	-	6 (10)	9 (7)
Alanine transaminase increased	-	-	-	-	-	-	4 (7)	10 (7)
Vomiting	-	-	-	-	0	4 (5)	1 (2)	10 (7)
Urinary tract infection	-	-	-	-	-	-	4 (7)	9 (7)
Arthralgia	3 (10)	1 (3)	0	0	-	-	3 (5)	9 (7)
Pharyngolaryngeal pain	-	-	-	-	-	-	3 (5)	9 (7)
Rash	1 (3)	1 (3)	0	2 (7)	-	-	-	-
AST increased	0	1 (3)	0	2 (7)	-	-	-	-
Myalgia	-	-	-	-	-	-	2 (3)	8 (6)
Pharyngitis	-	-	-	-	-	-	1 (2)	8 (6)
Aspirate aminotranferase increased	-	-	-	-	-	-	2 (3)	7 (5)
Epistaxis	0	4 (13)	0	0	-	-	6 (10)	7 (5)
Back pain	-	-	-	-	-	-	3 (5)	7 (5)
Influenza	-	-	-	-	-	-	3 (5)	7 (5)
Cough	-	-	-	-	-	-	4 (7)	6 (4)
Upper abdominal pain	-	-	-	-	-	-	5 (8)	6 (4)
Constipation	2 (7)	1 (3)	0	2 (7)	-	-	5 (8)	6 (4)
Dizziness	-	-	-	-	-	-	6 (10)	5 (4)
Anaemia	2 (7)	1 (3)	1 (3)	1 (4)	-	-	-	-
Taste disturbance	2 (7)	0	0	1 (4)	-	-	-	-

Table 4.12 Cont'd Adverse events in 5% or more participants in any study group, number of participants (%)

Event	TRA100773A				TRA100773B		TRA102537RAISE	
	Placebo, n=29	EBAG 30mg, n=30	EBAG 50mg, n=30	EBAG 75mg, n=28	Placebo, n=38	EBAG ≥50mg, n=76	Placebo, n=61	EBAG ≥25mg, n=135
Pruritus	-	-	-	-	-	-	5 (8)	4 (3)
Cataract	-	-	-	-	-	-	4 (7)	4 (3)
Hypertension	-	-	-	-	-	-	3 (5)	4 (3)
Oedema peripheral	2 (7)	0	1 (3)	1 (4)	-	-	6 (10)	2 (1)
Dyspepsia	-	-	-	-	-	-	4 (7)	2 (1)
Ecchymosis	-	-	-	-	-	-	4 (7)	2 (1)
Insomnia	-	-	-	-	-	-	4 (7)	2 (1)
Anxiety	-	-	-	-	-	-	3 (5)	2 (1)
Conjunctival haemorrhage	-	-	-	-	-	-	3 (5)	2 (1)
Contusion	-	-	-	-	-	-	3 (5)	2 (1)
Neck pain	-	-	-	-	-	-	3 (5)	2 (1)
Non-cardiac chest pain	-	-	-	-	-	-	3 (5)	2 (1)
Abdominal distension	2 (7)	1 (3)	0	0	-	-	3 (5)	1 (<1)
Conjunctivitis	-	-	-	-	-	-	4 (7)	1 (<1)
Fall	-	-	-	-	-	-	3 (5)	1 (<1)
Swelling face	-	-	-	-	-	-	3 (5)	1 (<1)
Cellulitis	-	-	-	-	-	-	4 (7)	0
Eye swelling	-	-	-	-	-	-	3 (5)	0
Haemorrhoids	2 (7)	0	0	0	-	-	-	-
Gingival bleeding	-	-	-	-	3 (8)	0	-	-

Source: manufacturer's submission, pages 85, 86, 88.

EBAG, eltrombopag.

B4. Specific adverse events highlighted by the manufacturer

The manufacturer highlighted adverse events relating to the eyes, liver function, bleeding, thromboembolism, malignancies, bone marrow fibrosis, phototoxicity, and cardio- or renal-toxicity (Table 4.13).

A higher proportion of participants in the eltrombopag groups developed cataracts compared with placebo groups (1 vs. 0 in TRA100773A trial, 3/74 [4.1%] vs. 1/38 [2.6%] in TRA100773B trial). Similarly, more participants in the eltrombopag group suffered a deterioration of an existing cataract (3/74 [4.1%] vs. 1/38 [2.6%] in TRA100773B). The manufacturer stated that most of the incidence or progression of cataract in the eltrombopag groups were due to the concomitant use of corticosteroids, which is a known risk factor for cataract. However, a similar proportion of participants in the placebo group also received corticosteroids during the study (90% vs. 88% in the eltrombopag group, response to ERG clarification queries, A6).

A higher proportion of participants in the eltrombopag groups experienced disturbance of liver function (8.1% [6/74] in TRA100773B, 13% [number of participants not reported] in RAISE trial) compared with placebo (2.6% [1/38] in TRA100773B, 7% [number not reported] in the RAISE trial).

The manufacturer repeated the information on bleeding adverse events in this section of the submission for the RAISE study but the numbers differed from those reported previously (Table 4.9), due to the two sources of data reporting different bleeding events captured by two different criteria (WHO and CTAE) (as stated by the manufacturer in their comments dated 6 January 2009 on the version of the ERG report submitted to NICE on 17 December 2009). It was previously reported that 76% of non-splenectomised participants and 82% of splenectomised participants in the eltrombopag group had any degree of bleeding, and 29% of non-splenectomised participants and 38% of splenectomised participants in the eltrombopag group had clinically significant bleeding (WHO grade 2-4). This was higher than that reported in this section of the manufacturer's submission (19% overall).

Two (2%) participants in the eltrombopag group in the RAISE trial developed venous thromboembolism, both of whom had risk factors for this condition at baseline.

One participant in the eltrombopag group in the RAISE trial developed rectosigmoid colon cancer, identified 91 days after the treatment began. No cases of bone marrow fibrosis, phototoxicity, cardio- or renal- toxicity occurred during the intervention.

Table 4.13 Specific adverse events highlighted by the manufacturer

	TRA100773A	TRA100773B	TRA102537RAISE
Ocular-related adverse effects	Cataract progression: (1) placebo, n= 0. (2) 75mg/day eltrombopag, n=1. Reported 181 days after intervention in a 60y female smoker.	Cataract: (1) placebo, n=1/38 (2.6%). (2) eltrombopag, n=3/74 (4.1%). Cataract progression: (1) placebo, n=1/38 (2.6%). (2) eltrombopag, n=3/73 (4.1%).	None.
Hepatobiliary events	-	Transaminase concentration to 2x upper limit normal: (1) placebo, n=1/38 (2.6%). (2) eltrombopag, n=6/74 (8.1%) with 1 withdrawal	Elevated transaminases and/or bilirubin level: (1) placebo, 7%; (2) eltrombopag, 13%; all returned to normal level either on-treatment or following discontinuation of treatment.
Bleeding adverse events/transient decrease in platelet count	-	Platelet count less than baseline value in 4wk after intervention: (1) placebo, n=5 (13%). (2) eltrombopag, n=8 (11%), of whom 2 had bleeding problem (menorrhagia, gingival bleeding).	Bleeding adverse events during intervention: (1) placebo: 31%. (2) eltrombopag: 19%. Serious bleeding events during intervention: (1) placebo: 7%. (2) eltrombopag: <1% (p=0.033). Transient decrease in platelet count after stopping intervention: (1) placebo: 7%. (2) eltrombopag: 7%, of whom one had bleeding problem (mouth haemorrhage, petechiae)
Thromboembolic events	-	-	Venous thromboembolic events: (1) placebo: 0. (2) eltrombopag: 2 (2%); both had risk factor(s) for thrmboembolism, resolved after discontinuing the treatment.
Malignancies	-	-	(1) placebo: n=1, acute leukaemia. (2) eltrombopag: n=1, rectosigmoid colon cancer. Identified 91day after the start of eltrombopag treatment.
Bone marrow fibrosis	-	-	None
Phototoxicity, cardiotoxicity, renal toxicity	-	-	None

y = year; wk = week

C. Health-related quality of life

The SF-36 instrument, consisting of eight sub-domains (physical functioning, physical role, body pain, general health, vitality, social functioning, emotional role, mental health) and two component summary scores (physical health summary, mental health summary), were used in all three eltrombopag RCTs. The FACT fatigue assessment subscale for thrombocytopenia (FACT-Th) was also used in the RAISE trial. The manufacturer did not report quality of life data in detail. In response to the ERG clarification queries the manufacturer provided data for the RAISE trial but not for trials TRA100773A and B. Data comparing eltrombopag with placebo at the end of the follow-up rather than change from baseline were not provided despite being requested.

In TRA100773A and B, the SF-36 scores in the eltrombopag group at the end of the intervention (6 weeks) were not statistically significantly different from baseline except that in TRA100773A there was a statistically significant decrease from baseline in the mean emotional-role score for the group receiving 75mg/day of eltrombopag ($p = 0.02$).

In the RAISE trial, the scores in all SF-36 sub-domains in the eltrombopag group were increased at the end of the study (6 months) compared with baseline (Table 4.14). The changes in scores were statistically significant in favour of the eltrombopag group for physical role ($p = 0.030$), vitality ($p = 0.045$), emotional role ($p = 0.023$), and the mental health component summary ($p = 0.030$). The changes in other sub-domains were not statistically significant. The manufacturer also provided data for non-splenectomised and splenectomised participants separately in its response to ERG clarification queries, however no statistical comparison between the eltrombopag and placebo groups was made.

Table 4.14 Health-related quality of life in RAISE trial: SF-36, mean (SD)

	Placebo		Eltrombopag		p-value[a]
	Baseline n=58	End of study[b] n=57 or 58	Baseline n=131	End of study[b] n=121 or 123	
Physical functioning	75 (22)	76 (23)	73 (27)	81 (22)	0.154
Physical role	65 (27)	68 (27)	65 (30)	74 (25)	0.030
Body pain	70 (23)	69 (25)	75 (28)	76 (27)	NS[c]
General health	54 (22)	53 (25)	56 (21)	57 (23)	0.243
Vitality	57 (20)	58 (22)	55 (26)	60 (23)	0.045
Social functioning	76 (22)	75 (26)	73 (28)	79 (24)	NS[c]
Emotional role	73 (25)	72 (27)	69 (31)	77 (25)	0.023
Mental health	70 (19)	69 (23)	68 (21)	70 (22)	0.154
Physical health summary	46 (8)	46 (8)	47 (10)	49 (9)	NS[c]
Mental health summary	46 (10)	45 (12)	44 (13)	47 (12)	0.030

[a]Comparing the changes of scores from baseline between eltrobompag group and placebo group.

[b]Including some of those who withdrew from the study.

[c]p value not reported.

NS, not statistically significant.

For FACT-Th scores reported in the RAISE trial, participants in the eltrombopag group had a statistically significant improvement in the activities and concerns or attitudes associated with thrombocytopenia and ITP, compared with the placebo group (p= 0.004). More detailed data were not reported.

4.2.2 Comparison of eltrombopag with romiplostim

In the mixed treatment analysis, the data were presented in such a way that an odds ratio greater than 1 favoured eltrombopag. The results, as shown in Table 4.15 and 4.16, suggest that eltrombopag may be less effective than romiplostim, with the difference in overall response rate statistically significant (OR 0.17, 95% CI 0.03, 0.82). Further analysis was conducted by the ERG to explore this finding (see Section 7.3).

Table 4.15 Comparison between eltrombopag and romiplostim: durable response rate[a]

Eltrombopag vs. placebo		Romiplostim vs. placebo		OR (95% CI) [c]
n/N	OR (95% CI) [b]	n/N	OR (95% CI) [b]	
All participants				
57/135 vs. 4/62	10.60 (3.64, 30.87)	41/83 vs. 1/42	40.02 (5.26, 304.70)	0.26 (0.03, 2.62)
Non-splenectomised				
38/95 vs. 3/41	10.24 (2.93, 35.77)	25/41 vs. 1/21	31.25 (3.81, 256.24)	0.33 (0.03, 3.79)
Splenectomised				
19/50 vs. 1/21	12.26 (1.52, 98.90)	16/42 vs. 0/21	26.77 (1.52, 472.41)	0.46 (0.01, 15.91)

[a]Defined as weekly platelet count ≥ 50 x 10^9/L during six or more weeks of the last eight weeks of treatment excluding those who received rescue medication at any time during the study.

[b]Meta-analysis (fixed effect model).

[c]Mixed treatment analysis (fixed effect model).

Source: manufacturer's submission.

Table 4.16 Comparison between eltrombopag and romiplostim: overall response rate[a]

Eltrombopag vs. placebo		Romiplostim vs. placebo		OR (95% CI) [c]
n/N	OR (95% CI) [b]	n/N	OR (95% CI)[b]	
All participants				
72/135 vs. 6/62	10.67 (4.31, 26.43)	69/83 vs. 3/42	64.07 (17.33, 236.82)	0.17 (0.03, 0.82)
Non-splenectomised				
49/85 vs. 4/41	12.59 (4.12, 38.50)	36/41 vs. 3/21	43.20 (9.27, 2741.84)	0.29 (0.04, 1.95)
Splenectomised				
23/50 vs. 2/21	8.09 (1.70, 38.49)	33/42 vs. 0/21	151.63 (8.39, 201.33)	0.05 (0, 1.43)

[a]Defined as durable plus transient response (four or more weekly responses ≥ 50 x 10^9/L during the study without a durable platelet response from week 2 to 25).

[b]Meta-analysis (fixed effect model).

[c]Mixed treatment analysis (fixed effect model).

Source: manufacturer's submission

4.2.3 Comparator treatments

The manufacturer's systematic review presented the characteristics and results from each study but no statistical synthesis of the results was undertaken.

Although the decision problem section listed a comprehensive list of treatment comparators, not all were considered as comparators in the economic models developed by the manufacturer. Efficacy data on the maximum time that a platelet response was achieved and data on platelet response at different time points during treatment were required and provided for the long-term economic model for anti-D (non-splenectomised patients only), IVIg,

rituximab, and romiplostim. Table 4.17 lists the sources of such data that the manufacturer used.

Only one or two studies/reviews were used for each comparator to provide the efficacy data that were used in the economic model. Although the manufacturer stated that the best available evidence was used, the ERG identified other potentially reliable data for some of the comparators from other studies/reviews that were included in the manufacturer's systematic review.

For eltrombopag, the data from the RAISE trial were recalculated by excluding those participants who withdrew prematurely, i.e. per protocol analyses were used (Clarification B10-12). The platelet response rates were therefore much higher than those from the ITT analysis (Table 4.17). For example, if ITT analysis is used, the response rate ($\geq 50 \times 10^9$/L) at 4 weeks since treatment started was reduced to 52.4% from 65.5% for non-splenectomised patients, and reduced to 42.9% from 61.2% for splenectomised patients.

For romiplostim, response rates using ITT analysis were used. Participants who prematurely withdrew were considered as non-platelet-respondents.

For platelet response rate for IVIg, the manufacturer used the evidence from a RCT consisting of 116 participants.[68] The ERG identified the ASH guideline where 14 case series on IVIg and anti-D were reported and a high quality systematic review where 28 RCTs on IVIg were reported (identified in HTA database).[62] The platelet response rate ($\geq 50 \times 10^9$/L) reported by the ASH guideline and the HTA review is higher than that used by the manufacturer: 75% vs. 62.5%.

For anti-D, the manufacturer used the evidence from a prospective case series consisting of 96 participants.[69] The ASH guideline reported a lower platelet response rate ($\geq 50 \times 10^9$/L) than that used by the manufacturer: 50% vs. 65.6%.

The evidence for rituximab was from two systematic reviews[49,70] and a case series.[53] The youngest participants in the primary studies included in the two systematic reviews were both 16 years old. The range of age of the participants in the case series was 4 to 98 years old; in addition, this was a retrospective study. Considering that the quality of the two systematic reviews is relatively high and assuming that the majority of people included were 18 years old or more, the ERG considered that the use of evidence from the two systematic reviews was appropriate, but not the use of evidence from the Penalver study. Removing the Penalver study, however, did not affect the values used in the economic model.

Table 4.17 Validity of efficacy data used in long-term economic model

	Data source, type of study	Alternative data source	Non-splenectomised		Splenectomised	
			Values used	Alternative values	Values used	Alternative values
Eltrombopag	**RAISE trial**, 6 month RCT, n=197	No	≥ 50 x 10^9/L: 4 week: 65.5% 8 week: 70.2%	≥ 50 x 10^9/L: 4 week: 52.4% 8 week: 59.5%	≥ 50 x 10^9/L: 4 week: 61.2% 8 week: 69.4%	≥ 50 x 10^9/L: 4 week: 42.9% 8 week: 46.0%
Romiplostim	**Kuter 2008[67],** two 6-month RCTs, n=125 in total	No	≥ 50 x 10^9/L: 4 week: 50% 8 week: 68.9% 12 week: 87.8%	No	≥ 50 x 10^9/L: 4 week: 50% 8 week: 64.3% 12 week: 78.6%	No
IVIg	**Godeau 1993[68,71]**, 2-day RCT, n=18; **Godeau 2002[68]**, 3-week RCT, n=116	**George 1996[7] (ASH guideline)**, consisting 14 case series; **Chen 2008[62]**, systematic review consisting 28 RCTs.	≥ 30 x 10^9/L: 71.4% ≥ 50 x 10^9/L: 62.5%	≥ 30 x 10^9/L: no data available, assumed to be 75% to 100%. ≥ 50 x 10^9/L: 75%	Same as non-splenectomised.	Assumed to be the same as non-splenectomised patients.
Anti-D	**Aledort 2007[69]**, Prospective case series, n=96	**ASH guideline 1996[7]** , consisting 14 case series;	-	-	≥ 30 x 10^9/L: 52.7% ≥ 50 x 10^9/L: 65.6%	≥ 30 x 10^9/L: no data available. ≥ 50 x 10^9/L: 50%
Rituximab	**Arnold 2007[49]**, Systematic review consisting of 19 case series. **Penalver 2006[53]**, case series, n=89. **Vesely 2004[70],** systematic review consisting of 8 case series.	Removing Penalver study.	≥ 30 x 10^9/L: 67.6% ≥ 50 x 10^9/L: 62.5%	No	≥ 30 x 10^9/L: 65.7% ≥ 50 x 10^9/L: 58.5%	No

4.2.4 Critique of submitted evidence synthesis

Quality of reporting in the manufacturer's submission

The manufacturer submitted a substantial amount of evidence (more than 200 pages for the main submission, nearly 200 pages for a systematic review report and a CD with more than 5000 pages reporting the results of the eltrombopag trials). The ERG did not go through the full clinical study reports except for those parts that were specifically referred to in the response to ERG clarification queries.

Some outcomes (e.g. bleeding events, quality of life) relating to the eltrombopag RCTs were poorly reported. The ERG in its clarification queries requested more detailed data and a breakdown by splenectomy status (Clarification response: A2).

Quality of the manufacturer's review

The ERG assessed the clinical effectiveness part of the manufacturer's submission for its methodological quality as a systematic review using the questions contained in CRD report 4 (Table 4.18). The methodological quality of the manufacturer's systematic review was variable.

Table 4.18 Quality assessment (CRD criteria) of the manufacturer's review

CRD Quality Item; score Yes/No/Uncertain with comments	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes except: • No criteria set for defining patients who are medically contraindicated to splenectomy.
2. Is there evidence of a substantial effort to search for all relevant research?	Partially • Only major sources searched.
3. Is the validity of included studies adequately assessed?	Partially • 20 included RCTs were adequately assessed; • 96 included non-RCTs were not assessed.
4. Are sufficient details of the individual studies presented?	Yes. Characteristics and results of all primary studies were reported in detail.
5. Are the primary studies summarised appropriately?	Partially. • Only evidence from RCTs on eltrombopag were summarised adequately; • No synthesis undertaken of the primary studies reporting comparator treatments.

Representativeness of participants in the eltrombopag trials to UK chronic ITP patients

Only 3/109 (2.8%), 10/114 (8.8%) and 9/197 (4.7%) participants in the three eltrombopag trials were from the UK (Clarification response: A5). The profile of UK chronic ITP patients is not available, so the extent to which the RCTs' participants were representative of adult chronic ITP patients in the UK is unclear.

The manufacturer argued that the participants in the three trials were comparable to the UK chronic ITP patients in terms of the baseline platelet count and bleeding symptoms. Table 4.19 shows the baseline characteristics of participants in the three trials. The manufacturer added that two ITP experts in the UK (Professor Adrian Newland and Dr. Drew Provan approached by the manufacturer) had commented that the previous concomitant medications received by participants in the RAISE trial were reflective of UK clinical practise, and the populations in the TRA100773A and B trials were also reflective of the ITP 'watch and rescue' population managed within UK clinical practice.

Table 4.19 Baseline characteristics of participants in eltrombopag groups in RCTs

	TRA100773A[a], n= 88	**TRA100773B, n=76**	**RAISE, n=135**
Age, median (range), years	18 - 81	47 (19 – 84)	47 (18 – 85)
Men (%)	31 (35%)	33 (43%)	42 (31%)
Previous treatment			
≥ 2	66 (75%)	56 (74%)	105 (78%)
≥ 3	46 (52%)	42 (55%)	75 (56%)
≥ 4	30 (34%)	30 (39%)	51 (38%)
≥ 5	-	16 (21%)	35 (26%)
Splenectomy	45 (51%)	31 (41%)	50 (37%)
Bleeding symptoms			
Any grade	-	-	73%
Clinically significant (WHO grade 2-4)	-	-	About a quarter
Duration of disease	-	47 (41%) over 5 years	-
Platelet count at baseline			
≤ 15 x 10^9/L	48%	38 (50%)	67 (50%)
Median	-	-	16 x 10^9/L
Concomitant treatment at randomisation	32%	32 (42%)	63 (47%)

[a]The three eltrombopag groups were summed.

Efficacy of eltrombopag

Efficacy evidence on eltrombopag was based on three eltrombopag RCTs. In general, the evidence showed that eltrombopag was statistically significantly more efficacious than placebo in terms of all outcomes other than:

- Platelet response ($\geq 50 \times 10^9$/L) at the end of the intervention for 30mg/day eltrombopag (27% vs. 11%, p=0.070; TRA100773A);
- Need for rescue medication during treatment in splenectomised participants (48% vs. 22%, p=0.055; RAISE trial); and
- Reduction in dose/frequency of concomitant ITP medications taken at baseline in splenectomised participants (39% vs. 44%, p=0.714; RAISE trial).

For duration of platelet response, it was unclear whether rescue treatment was taken into account (RAISE trial).

However, there were slight imbalances in patient baseline characteristics between the eltrombopag and placebo groups in studies TRA10077B and RAISE. In study TRA100773B there were more women in the placebo group (71%, 27/38) than in the eltrombopag group (57%, 43/76) (Table 6.9 in the manufacturer's submission). In study TRA102537RAISE participants in the placebo group were older than those in the eltrombopag group (median 52.5 vs. 47.0 years old) (Table 6.10 in the manufacturer's submission). If women or older people were to have a poorer prognosis in relation to ITP treatments then the results might have favoured the eltrombopag group. The manufacturer did not conduct sensitivity analyses to explore the impact that these baseline imbalances might have had on the results.

In addition, there were relatively large proportions of participants who withdrew or were lost to follow-up in the eltrombopag RCTs. In study TRA100773A there were more such participants in the placebo group (21%, 6/29) than the eltrombopag groups (10% [3/30], 30mg/day; 7% [2/30], 50mg/day; 14% [4/28], 75mg/day), as there also were for study TRA100773B (18% [7/38] in the placebo group; 8% [6/76] in the eltrombopag group). In study TRA102537RAISE there were fewer such participants in the placebo group (11%, 7/62) than the eltrombopag group (17%, 23/135). Nearly half of these withdrawals were due to adverse effects. Other reasons for withdrawal included lack of efficacy, protocol violation, or participant choice. As participants who withdrew or were lost to follow-up were all considered as non-responders, and there were more such participants in the placebo group in TRA100773A and B, the results on platelet response from these two studies might have

favoured eltrombopag. For TRA102537RAISE, as there were more such participants in the eltrombopag group, the results on platelet response might have favoured placebo.

Safety of eltrombopag

Two participants in the eltrombopag group died during the intervention. One participant had a severe illness at baseline (TRA100773B) while the other had a baseline platelet count of only 2×10^9/L (RAISE trial).

The risk of adverse events appeared to be similar between the eltrombopag group and the placebo group in each RCT. However, no statistical comparisons were undertaken. There were differences in TRA100773A but not in TRA100773B or RAISE in the figures reported for total numbers of any adverse events (Table 4.11) and any adverse events in 5% or more participants (Table 4.12). There were relatively large differences in the figures reported for bleeding adverse events for the RAISE trial (Tables 4.9 and 4.13) due to the two sources of data reporting different bleeding events captured by two different criteria (WHO and CTAE).

Quality of life

In the RAISE trial, baseline data on health-related quality of life were not available for a small number of participants who received treatment (4/135 [3.0%] in the eltrombopag group, 4/62 [6.5%] in the placebo group). Also, data were not available for a small number of participants (10/135 [7.4%] in the eltrombopag group, 1/62 [1.6%] in the placebo group) who withdrew during the study. If assuming that the most ill people did not return to provide data at the end of the study, the results might have favoured eltrombopag. If assuming that the healthier people did not return, the results might have favoured placebo.

Comparator treatments

The ERG considered that the efficacy data used for comparator treatments in the long-term economic model were highly selective. Alternative methods, e.g. median and range, could have been explored. Even based on the best available evidence, the manufacturer failed to identify the best evidence for IVIg and anti-D (Table 4.17).

Comparison of eltrombopag with romiplostim

The manufacturer stated that the RAISE trial and the two romiplostim RCTs were comparable in terms of baseline participant characteristics, trial methodology, and follow-up (all 6 months). However more participants in the RAISE study received concomitant medication (eltrombopag 55%, placebo 69%) than those in the romiplostim trials (romiplostim 28%, placebo 38%). Concomitant medication may have positive effects on treatment, but on the

other hand patients receiving concomitant medication may have more severe ITP. Therefore, the direction of bias caused by the baseline imbalance in concomitant medication is uncertain. There is an error in the "Conclusion of the meta-analysis / indirect comparison" section (see page 83 of the manufacturer's submission). It states:

"In particular, the fact that there is no significant between-treatment difference when the splenectomised and non-splenectomised participants are considered separately casts doubt on the robustness of the indirect comparison reported for the combined population."

The widths of the confidence intervals for the between-treatment odds ratios are dependent upon the amount of data available from which to calculate them. All other things being equal, a larger sample size will produce a smaller confidence interval. It can be seen from the formula used to calculate an approximation to the variance of the log odds ratio that fewer participants in a trial will produce a larger variance. Bucher's method[72] of indirect comparison involves adding together the variances of the log odds ratios, so this maintains the larger variance, hence wider confidence intervals.

For this reason and despite the discussion about the best way to combine the two Kuter 2008 trials,[67] once that is done it is erroneous to claim that the lack of statistical significance in the subgroup analyses casts doubt over the significant result for all subjects. The authors themselves suggest that with only one study for each drug (allowing a synthesis of the two Kuter 2008 trials) comparing them "is far from ideal and negates the possibility of exploring possible subgroups" (page 84, first bullet point). Therefore, subgroup results should not detract from the all patient results.

4.2.5 Summary

The ERG's main concerns with regard to evidence synthesis were:

- Representativeness of participants in the eltrombopag trials to UK chronic ITP patients is uncertain (see Table 4.19).
- There were some discrepancies in the figures reporting on total number of adverse events for TRA100773A (see Table 4.11 and 4.12), and relative large discrepancies in the figures reporting bleeding events (see Table 4.9 and 4.13). It is unclear which figures were correct.
- More participants in the RAISE trial (eltrombopag) received concomitant ITP treatments than in the romiplostim trials. The effect that this imbalance might have had on the indirect comparison results is uncertain.

- In the indirect comparison between eltrombopag and romiplostim, participants who prematurely withdrew were considered as non-responders. As there were more such participants in the eltrombopag study, the results might have favoured romiplostim. The ERG conducted further analysis to explore this (see Section 7.3).

Minor concerns:

- More reliable sources of evidence might have been sought to generate values for comparator treatments IVIg and anti-D in the economic model.

5 ECONOMIC EVALUATION: Cost effectiveness comparison of chronic ITP `Watch and Rescue` consisting of active management and/or rescue medication, with or without Eltrombopag

As part of the manufacturer's submission, 2 de novo economic evaluations were conducted by GlaxoSmithKline and are as follows:

- ***De novo economic evaluation 1****: Cost effectiveness comparison of chronic ITP `Watch and Rescue` consisting of active management and/or rescue medication, with or without eltrombopag*

- ***De novo economic evaluation 2****: Cost-effectiveness evaluation of chronic ITP long-term continuous treatments as part of a treatment sequence with and without eltrombopag*

In Chapter 5 we address the first of these analyses. Chapter 6 addresses the second long term evaluation model for eltrombopag. In each economic evaluation, the analysis was split for splenectomised and non splenectomised patients.

GlaxoSmithKline found an error in their original watch and rescue model. An addendum and revised economic model was provided on October 23rd 2009 by the manufacturer detailing the corrections made to the model together with the corresponding analysis, figures and tables. The critique presented here refers to the main submission document and is supplemented by information from the addendum where appropriate

5.1 Introduction and overview of manufacturer's economic evaluation

The economic evaluation of eltrombopag for the treatment of chronic immune or idiopathic thrombocytopenic purpura (ITP) included:

- A systematic literature review to identify all relevant cost-effectiveness or cost-utility studies in relation to the relative efficiency of eltrombopag for the treatment of chronic adult ITP. Section 7.1 of the GlaxoSmithKline report details the processes used to identify the relevant studies and Appendix 3 provides further detail on the search strategy used.
- A report on the de novo economic evaluation for watch and rescue care plan conducted by GlaxoSmithKline (p104 – 155). Patient characteristics including inclusion and exclusion criteria for the trial based model were presented (p110 – 112). A description of

the model (including a model schematic) can be found on page 114. A table of the key assumptions used is given in table 7.3 (p117).

- Tables 7.4 and 7.5 of the manufacturer's submission provide information in relation to the costing approach used in the watch and rescue model. Costs are estimated using a macro and micro costing approach. Macro costing is used in the base case and micro costing as a sensitivity analysis.
- Results of the analysis are provided separately for splenectomised and non-splenectomised patients (Section 7.3 of the original manufacturer's submission). The base case analysis (pp 131-133); subgroup analysis (pp134-138) and sensitivity analysis (pp 139-153) can be found on the pages quoted.
- The manufacturer also provided a Microsoft Excel based electronic copy of the model used.

Following receipt of the submission, the ERG responded by requesting a number of points for clarification from GlaxoSmithKline. Specifically in relation to the de novo economic evaluation 1, the following points for clarification were sought:

- Whether eltrombopag is always used within its licensed indication within the model and if not to provide information as to why this was the case.
- What relevance US rates of ITP have in relation to predicting the UK rates of the disease?
- In relation to the use of the clinical expert opinion used for parameters and assumptions, the manufacturer was asked to clarify how these opinions were elicited and to confirm that they were indeed representative of general UK practice.
- Further information was sought in relation to a survey (DEMAND) conducted by GlaxoSmithKline of 50 UK clinicians to determine the number of patients tho may be treated with eltrombopag in the UK.
- Further in depth information was sought in relation to the reported SF-6D scores used in the submission and the differences between treatment arms. Also, clarification in relation to how mortality was incorporated into these scores was requested.
- Further information in relation to quality of life measurement was sought in particular in relation to a breakdown of how QALYs were calculated.
- The manufacturer was asked to provide a within trial economic evaluation which would be superior if the patient group truly represented the UK population as it would more fully reflect differences between patients.
- Further clarification and information in relation to adverse events was sought as the submission only reported adverse events in relation to bleeding.

- The manufacturer was asked to conduct an analysis for drug prices and specifically to estimate the price required for eltrombopag to be cost-effective at various different ICER thresholds.

The following section will focus on the manufacturer's submission using updated information and addendums as provided by GSK where appropriate.

5.2 Cost-effectiveness analysis methods

As per Section 7.1 of the manufacturer's submission, a systematic review was conducted to identify any cost-effectiveness or cost-utility studies relating to the cost-effectiveness of eltrombopag for the treatment of chronic adult ITP. The company developed their search strategy specifying the inclusion/exclusion criteria with no limit on the date of publication. Searches were conducted on June 16th 2009, using the same databases as were used for the clinical effectiveness review. These searches were also supplemented by hand searching of the proceedings of the European Haematology Association and the American Society of Haematology.

The full search strategies are detailed in Appendix 10.3 of the manufacturer's submission and are reproducible. The searches comprised MeSH and keyword terms relating to ITP and combined, using the Boolean operator AND, with several cost- and economic - related terms. While the search was broad, as the manufacturer stated, it did not fully utilise the indexing features available in MEDLINE and EMBASE; in particular specifically searching with MeSH or Emtree terms such as exp "costs and cost analysis"/ or exp economic evaluation/ or for MEDLINE, using the economics subheading.

The following section provides an overview of the cost-effectiveness analysis methods used by GlaxoSmithKline, including an overview of: natural history; treatment effectiveness; health related quality of life; resources and costs; discounting; sensitivity analysis; model validation and the results of cost-effectiveness analysis. A detailed critique of the model, the submission and the assumptions underpinning the results will follow this overview.

5.2.1 Natural history

The manufacturer split the Chronic ITP population into two main sub-categories: (A) Splenectomised patients and (B) Non Splenectomised patients (where having a splenectomy was assumed to be medically contra indicated). The economic "Watch and Rescue" model evaluation explores two pathways of care: (i) A standard of care approach plus placebo and (ii) standard of care plus eltrombopag. Patients were assumed to have had previous ITP

treatment, may be on concurrant medication and are given rescue medication as required over the time horizon of the model. As the treatment pathway for chronic ITP patients is ill defined, a trial based model using data from the RAISE trial was used for the submission. The RAISE trial is a placebo controlled double blinded RCT with patients randomised to either placebo or eltrombopag. A schematic of the model structure is represented in Figure 7.2 (p114) of the manufacturer's submission.

In the trial based model, adult patients enter the study on the basis that they have platelet counts $<30 \times 10^9$/L. It is assumed that the patients entering the model are representative of the UK ITP patient population and the clinical opinion of ITP experts is used to support this assumption.

The analysis refers to two biologically identifiable groups (splenectomised and non-splenectomised patients) and the analysis is presented separately for each group. Further sub groups considered included:

- Individuals with a platelet count $<15 \times 10^9$/L
- patients on concomitant medication.

Due to a limited number of subjects, the subgroups were not analysed on the basis of splenectomy status.

5.2.2 Treatment effectiveness

The effectiveness of eltrombopag came from the eltrombopag arms of the three RCT trials identified in the manufacturer's submission (Studies TRA100773A, TRA 100773B and RAISE). With regard to the modelling approach undertaken, the RAISE study was the primary reference point. Data in relation to comparator treatments were confined to those used in the control arm of the RAISE trial. Data in relation to alternative treatments for direct comparison to eltrombopag are non existent and so no data for relative comparators specified in the NICE scope has been included in the model aside from those used as part of standard of care.

5.2.3 Health related quality of life

The impact of health related quality of life on patients with ITP was measured using the Short Form 36 Item Version 2 (SF-36v2) questionnaire. As part of TRA102537 RAISE, SF-36 assessments were administered to all patients at weeks 0, 6, 14 and 26. The results of this were then translated using the Brazier and colleagues algorithm to preference based utility

scores in the form of the SF-6D.[73] The overall HRQoL benefit on each arm was calculated using 'method two` described in Manca and colleagues to adjust for differences in baseline characteristics between the two arms.[74,74] This approach is discussed and critiqued in a later section.

Utility values reflected two components, namely the utility gained from reduced risk of death/bleeding and the improvement in quality of life generated as a result of the treatment administered. Appendix 4 (Table 10.4) details the utility values used for placebo and eltrombopag at weeks 0 (baseline), 6, 14 and 26 for each subgroup of the population analysed. Utility scores were recorded and transformed as described at each point estimate stage for both the placebo and eltrombopag arms of the study and QALY gains through the use of eltrombopag were thus calculated.

The utility values used by the manufacturer are reproduced in Table 5.1 below:

Table 5.1: Utility values used in the model for each subgroup based on SF-36 data from the RAISE trial mapped to SF-6D scores using Brazier, 2002

Subgroup	**Week 0**		**Week 6**		**Week 14**		**Week 26**	
	Placebo	*EPAG*	*Placebo*	*EPAG*	*Placebo*	*EPAG*	*Placebo*	*EPAG*
Splenectomised	0.699	0.699	0.687	0.703	0.709	0.705	0.691	0.708
Non-Splenectomised	0.687	0.707	0.700	0.745	0.68	0.725	0.698	0.745
Baseline <15 $x10^9$/L	0.672	0.714	0.679	0.731	0.687	0.713	0.673	0.735
Patients receiving concomitant medication at baseline	0.701	0.686	0.687	0.706	0.681	0.692	0.694	0.717

EPAG = Eltrombopag

Further details in relation to the calculation of QALYs were requested in the matters for clarification from GlaxoSmithKline specifically asking them to give details in relation to life years gained and incremental life years gained. This information has been provided in the base case for each subgroup and is presented in Table 27 of the response to ERG clarification queries document. Further information was requested in relation to how the estimation of utilities was actually conducted and also in relation to mortality. Annual risk of having a fatal bleed[10] was used to calculate the relative risk of mortality as described in figure 5, page 124

of the submission document. No additional information in relation to the utility estimation process was provided.

QALYs were for both arms of the study and both treatment groups. QALY estimates related to the 26 week follow-up period except for the loss of QALYs over an estimated patient lifetime caused by death in the 26 week follow–up period.

5.2.4 Resources and costs

Section 7.2.9 of the manufacturer's submission describes the identification measurement and valuation of resource use. Two alternative approaches to the costing process were presented in the submission and are as follows:

- Micro costing approach: Clinical expert opinion was used to estimate resource consumption for each grade of bleed severity.

- Macro costing approach: Clinical expert opinion was once again used. Analogous costs were used as ITP cost and resource data were limited for each grade of bleed. Grade of bleeding was as classified on the World Health Organisation bleeding scale.

Details of the estimated costs of bleeding as calculated using expert opinion are presented in Table 7.5 of the submission and reproduced in Table 5.2. The manufacturer has taken the macro costing approach as default in the model and has explored the associated uncertainty by conducting a sensitivity analysis using the micro costing approach in Section 7.3.3.1 of their submission. One point on which the ERG requested further clarification was whether or not the expert opinion used was likely to be truly representative of expert opinion in the UK. The manufacturers provided the details of all expert opinion used to inform the model, stating that they were widely accepted experts in the field of ITP and were responsible for the treatment of a large number of ITP patients from throughout the UK. Further detail is presented in point A.10, page 10 of the clarification document. However, it remains unclear which clinical experts were used to inform which valuations or indeed if all experts had an input into each assumption/value identified through consultation with ITP experts.

Table 5.2 Costing approaches used through out the model

Bleeding grade	Micro-costing	Macro-costing
Grade 1	£12.50	£3.99
Grade 2	£98.60	£125
Grade 3	£431.47	£1,056.25
Grade 4	£2,582.00	£8,277.09
Grade 5	£2,582.00	£8,277.09

One may question whether or not it is appropriate that the resource costs are similar for both a grade 4 and a grade 5 bleed in both approaches. It would seem plausible to argue that perhaps the cost of treating a grade 5 bleed would in reality be greater than the cost of treating a grade 4 bleed.

Resource use and cost data were not taken directly from the RAISE trial with the exception of ITP medication consumption. Resource consumption used for the costing approaches were estimated using clinical expert opinion as stated in section 7.2.9.1 of the main submission document. All costs were estimated from NHS Reference costs/eBNF and further validated through discussion with a clinical expert. The anticipated prices of eltrombopag for use in chronic adult ITP patients in the UK market are £27.50 for a 25 mg tablet and £55.00 for a 50mg tablet. The consequences for variation in the quoted prices are explored in a sensitivity analysis, the results of which are presented in Section 5.2.8 of this report.

The total cost of eltrombopag taken from the trial based model is a function of the total dose of eltrombopag administered and the price per mg of dosage over the period of administration. Administration costs directly related to the administration of eltrombopag were not captured by the analysis nor are any routine management costs. As it is an oral medication, taken un-supervised at home by the patient, these costs are unlikely to be significant. Product wastage was not considered for any treatments. The overall cost per patient over the 26 week trial period for both splenectomised and non-splenectomised patients and both treatment arms is shown in Table 5.4. Costs beyond 26 weeks were not estimated.

The costs of drugs used as concomitant medication were taken from the NHS reference costs 2007-2008 wherever possible as well as the Personal Social Services Research Unit (PSSRU) and were further confirmed through informal clinical expert consultation. Drug resource use data has been extracted directly from the RAISE trial.

5.2.5 Discounting

Only the loss of QALYs over an assumed lifetime of those estimated to have died during the 26 week follow-up period were discounted. These were discounted at a rate of 3.5% in accordance with NICE guidelines.

5.2.6 Sensitivity analysis

A number of deterministic and probabilistic sensitivity analyses were conducted and these are detailed in Section 7.3.3 of the manufacturer's submission. A summary of the analyses conducted is given here and the results of each analysis undertaken are summarised in Section 5.2.8.

Price of Eltrombopag

At the time of submission, the price of Eltrombopag was given as a guide only. Therefore, the acquisition cost of £55 was varied to a lower limit of £50 and an upper limit of £60 for a 50 mg tablet.

Utility

Values for utility are varied at each assessment point to the upper and lower bounds of their confidence intervals at a 5% level of significance.

Micro and Macro costing procedures

The results of the micro costing approach were used in the sensitivity analysis to reflect the uncertainty surrounding the costs of bleeding events.

Relative risk of a fatal bleed

The base case analysis uses the relative risk of clinically significant bleeds (WHO grades 2-5) as a proxy for the relative risk of a fatal bleed. In a sensitivity analysis of the uncertainty surrounding the risk of bleeding, relative risk of any bleeding event was used as a proxy for a fatal bleed. Perhaps the manufacturer could have also conducted analysis at the other end of the scale, taking the risk of a serious grade 4 or grade 5 bleed as a proxy for a fatal bleed.

The impact of varying the annual rate of fatal bleed on the ICER

A one way sensitivity analysis was conducted on this figure given that fatal bleeds were one of the main determinants of QALYs and hence played a pivotal role in the estimation of ICERs.

A probabilistic sensitivity analysis was also conducted to inform the uncertainty around the point estimates presented in the base case. One thousand iterations of the model were used and the results are presented in Section 7.3.3 (pp 139 – 142) of the manufacturer's submission and in Appendix 10.5 for distributions used of the manufacturer's submission.

The ERG requested that GlaxoSmithKline conduct a wider sensitivity analysis around price and in particular to estimate the price at which Eltrombopag would comply with cost effectiveness thresholds of £10,000, £20,000 and £30,000. This information is provided in Tables 22 and 23 of the response to ERG clarification queries document and reproduced in Table 5.3.

Table 5.3 Acquisition cost required to achieve key ICERs in the base case analysis.

	Acquisition cost for achieving key ICERs		
	£10,000	**£20,000**	**£30,000**
Splenectomised	£13.91	£20.11	£26.31
Non Splenectomised	£10.23	£15.89	£21.55

5.2.7 Model validation

The economic model used as part of this submission was validated through internal quality control checks. In addition to this, the model was reviewed by Abacus International (an independent provider of health economics services). It is stated in the submission that Abacus checks involved literature searches, and a quality check of the model (including cell inputs, calculations etc). It was stated that this quality control process was conducted in line with the University of York Centre for Health Economics checklist.[75] However, in spite of the quality control checks conducted both internally and by Abacus, a number of minor discrepancies were identified by the ERG. These are discussed in section 5.4.2 below.

5.2.8 Results

Results for the base case analysis are presented separately for splenectomised and non-splenectomised patient groups. Non-splenectomised subjects are assumed by the manufacturer to be representative of the patient groups who are contra-indicated to having a splenectomy. The revised results are presented in the addendum provided by GlaxoSmithKline to their original submission. The base case analysis for both patient groups is presented in Table 5.4.

Table 5.4 Summary of base case results of the manufacturer's model

Group of Patients	Results						
	Placebo		Eltrombopag		Incremental		ICER (£ per QALY)
	Cost (£)	QALYs	Cost (£)	QALYs	Cost (£)	QALYs	
Splenectomised	3380	0.197	12,835	0.075	9455	0.122	77,496
Non Splenectomised	1894	0.193	11,917.	0.082	10,024	0.111	90,471
Concomitant meds at baseline	2832	0.193	11,951	0.067	9119	0.126	72,331
Platelet count <15 $x10^9$**/L**	3607	0.195	13,977	0.088	10,370	0.107	96,749
<15 $x10^9$**/L & death risk of 4.03%**	3607	0.285	13,977	0.130	10,371	0.155	66,880

Sensitivity analysis results:

GlaxoSmithKline provided probabilistic and deterministic sensitivity analyses for both splenectomised and non splenectomised patients, the findings of which are detailed in Section 7.3.3 of the manufacturer's submission.

Table 5.5 details the results of the deterministic sensitivity analyses carried out by the manufacturer as part of its submission.

Table 5.5 Summary of sensitivity analysis results

Sensitivity analysis	Group of Patients	Submission finding					
		Cost (£)		QALY		ICER	
		Default	Sensitivity Analysis	Default	Sensitivity Analysis	Default	Sensitivity Analysis
Micro costing	Splenectomised	9,455	10,069	0.122	0.122	77,496	82,527
	Non Splenectomised	10,024	10,101	0.111	0.111	90,471	91,175
All Bleed events	Splenectomised	9,455	9,455	.122	0.095	77,496	99,379
	Non Splenectomised	10,024	10,024	.111	.112	90,471	89,850
Price £50 not £55	Splenectomised	9,455	8,455	.122	.122	77,496	69,301
	Non Splenectomised	10,024	9,030	.111	.111	90,471	81,501
Price £60 not £55	Splenectomised	9,455	9,030	.122	.122	77,496	85,690
	Non Splenectomised	10,024	11,017	.111	.111	90,471	99,441
Utilities at lower bound of CI	Splenectomised	9,455	9,455	.122	.121	77,496	78,307
	Non Splenectomised	10,024	10,024	.111	.111	90,471	90,691
Utilities at upper bound of CI	Splenectomised	9,455	9,455	.122	.123	77,496	76,820
	Non Splenectomised	10,024	10,024	.111	.111	90,471	90,299

All figures produced in Table 5.5 have been checked and are reproducible from the economic model as presented by GlaxoSmithKline.

With regard to the probabilistic sensitivity analysis results, these are presented in Figures 7.10–7.15 on pages 139–142 of the manufacturer's submission. For both the splenectomised and non-splenectomised groups there is little or no chance of eltrombopag being cost-effective at the threshold of £30,000 per QALY. The exact percentage, while given in the main submission document is omitted in the addendum to Section 7. Similar results are indicated for each of the alternative subgroups which have been analysed throughout the submission document.

5.3 Critical appraisal of the manufacturer's submitted economic evaluation

The ERG has critically appraised the manufacturer's evaluation using the critical appraisal questions as outlined in Table 5.6. The methods have also been compared with the criteria set out in the reference case. The critical appraisal of the model refers to the addendum presented by the company in addition to its main submission document unless otherwise stated.

Table 5.6: Structured critical appraisal of manufacturer's economic model

Item	Critical Appraisal	Reviewer Comment
Is there a well defined question	Yes	The economic model and submission assessed the cost-effectiveness of eltrombopag as part of a watch and rescue care programme for adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP)
Is there a comprehensive description of alternatives?	Yes	The modelled alternatives followed 2 pathways as part of a watch and rescue care programme. (i) Standard of care; (ii) Standard of care plus eltrombopag. As this is a trial based model, only these two options that corresponded to the randomised groups were considered.
Is the perspective of the analysis clearly stated	Yes	According to the submission document, the analysis was performed from the perspective of the NHS and PSS.
Is the perspective employed appropriate?	Unclear	While the perspective is stated as being that of the NHS and PSS, there is limited evidence of costs falling onto the PSS in the submission. Section 8 clearly deals with the financial impact for the NHS but there is no mention of the impact on PSSs..
Has the correct patient group / population of interest been clearly stated	Partly	Two groups of adult chronic ITP patients are modelled as part of the Watch and Rescue care plan: (i) Patients who have previously had a splenectomy and are refractory to that splenectomy

Item	Critical Appraisal	Reviewer Comment
		(ii) Non–splenectomised patients who are assumed to be contra-indicated to having a splenectomy. It is unclear how similar the trial population is to this group.
Is the correct comparator used?	Yes	As this was a double blinded placebo controlled study, the comparator used was placebo. Due to a lack of sound comparable data, no other comparators were considered. Elsewhere in the submission a meta-analysis indirectly comparing romiplostim with eltrombopag was reported. These data were not used in this model.
Is the study type reasonable?	Yes	A cost–utility study is used to estimate relative efficiency. The model used is a trial-based model linked to the RAISE study.
Is effectiveness of the intervention established?	Possibly	The only information in relation to Eltrombopag came from the 3 RCTs as previously mentioned. However, the study period was short and UK participant numbers were small. Furthermore, the patient populations within the trials did not wholly match the population to be modelled. It is assumed that those who have not had a splenectomy are the same as those that are contraindicated for splenectomy as stipulated for this STA.

Item	Critical Appraisal	Reviewer Comment
Has a lifetime horizon been used for analysis (has a shorter horizon been justified)?	No	A lifetime horizon has not been used. The only extrapolation has been for the QALY loss for those who died during the 26 week follow-up. It was assumed that life expectancy of those who died was the same as the general population at the same age.
Are the costs and consequences consistent with the perspective employed?	Yes	Yes, costs are attributed from an NHS viewpoint and a budget impact statement supports this perspective. Consequences are measured in QALYs which is standard procedure. However, QALY measurements do not account for adverse events apart from bleeding events. Therefore no adverse events attributable to eltrombopag or other treatments are modelled.
Is differential timing considered?	Yes	As the model only covers a time period of 26 weeks, discounting was not necessary for the most part. However QALYs lost due to death during the 26 week follow-up period are discounted at 3.5%, as per NICE guidelines.
Is incremental analysis performed?	Yes	The results of the model were presented as incremental cost effectiveness ratios (ICERs).
Is the sensitivity analysis undertaken and presented clearly?	Yes	A number of sensitivity analyses were carried out as part of the manufacturer's submission, the results of which are described above. Further sensitivity analyses could have been done to explore the impact of varying and/or relaxing a number of assumptions used (such as

Item	Critical Appraisal	Reviewer Comment
		considering a percentage of non-splenectomised patients to be contra-indicated as opposed to 100%; patient numbers; response rates to treatment; wider price analysis, etc.

Table 5.7 Comparison of economics submission with NICE reference case

Attribute	Reference Case	Included in Submission	Comment on whether de novo evaluation meets requirements of NICE reference case
Comparator(s)	Alternative therapies including those used routinely in the NHS	Partly	Evidence on the effectiveness of comparators is not formally incorporated into the analysis. It is assumed that the outcomes of standard of care of the RAISE trial, which involved the use of interventions used in the NHS is representative of NHS practice in the absence of eltrombopag
Perspective – costs	NHS & PSS	Partly	NHS cost perspective is clearly described. No PSS costs were included. It is unclear if there are any PSS costs which were relevant.
Perspective – benefits	All health effects on individuals	Yes	QALY benefits to treatment with eltrombopag relative to standard care. Differences in QALYs between treatments relate primarily to differences in bleeding events and death between the groups.
Time Horizon	Sufficient to capture differences in costs and outcomes	No	The economic model considered costs and benefits over the 26 week time period, the time period considered by RAISE. Differences in outcomes apart from the loss of lifetime QALYs caused by death in the 26 weeks were excluded. No disease progression was assumed or incorporated into the economic model.

Attribute	Reference Case	Included in Submission	Comment on whether de novo evaluation meets requirements of NICE reference case
Synthesis of evidence	Literature Review and indirect comparisons	Partly	A comprehensive literature review was carried out to identify evidence on eltrombopag. A review for comparator evidence, which is very limited, was conducted but not used in the model.
Outcome Measure	QALYs	Yes	The manufacturer's submission generated QALYs from 2 different sources: (i) Utility change from baseline (using the SF-36 collected during the trial). (ii) Utility benefit through reduction in mortality was calculated using the Cohen study using the mean annualised risk of fatal bleeding,[10] QALY at baseline and UK average life expectancy.
Health States for QALY measurement	Described using a standardized and validated instrument	Yes	Health utility data were collected as part of the RAISE trial and are incorporated in the results of the model. Utility data were collected using the SF-36 questionnaire and transformed to the SF-6D using the Brazier 2002 algorithm. NICE recommends the use of EQ-5D wherever possible. No justification for not using the EQ-5D was provided.
Benefit Valuation	Time trade off or standard gamble	Standard Gamble	Benefits have been tranformed into the SF-6D from SF-36 using Brazier 2002 which is based on the standard gamble approach.

Attribute	Reference Case	Included in Submission	Comment on whether de novo evaluation meets requirements of NICE reference case
Source of preference data	Sample of Public	Yes	The preference data used in utility calculation were derived from a sample of the UK general public and used to value the responses to the SF-36 provided by participants of the RAISE trial which had centres in various international locations. In response to the ERG clarification queries, the manufacturer stated that only 9 of the patients in the RAISE trial were from the UK. This raises questions in relation to the applicability of the results as the responses to the SF-36 may not be representative of UK patients.
Discount rate	Health Benefits and costs	Yes where appropriate	Discounting was only applied to QALYs lost by death. These are discounted at 3.5%.
Equity	No special weighting	No	No special weighting in relation to equity was undertaken.
Sensitivity Analysis	Probabilistic sensitivity analysis	Yes	Probabilistic sensitivity analysis was undertaken and is presented in the form of various scatter plots and cost effectiveness acceptability curves.

5.3.1 Critical appraisal of economic evaluation methods

The model presented appears to be quite transparent and most, if not all calculations are traceable and referenced. Many key assumptions are clearly stated and their incorporation into the model is traceable and modifiable where necessary. However, there are a number of points of uncertainty which are less clear from the model and these are addressed below.

Decision Problem, description of alternatives and perspective

The decision problem is detailed in section 2 of the manufacturer's submission (pp 8-9). Table 2 of the manufacturer's submission describes the alternatives in the NICE scope as well as how the submission plans to deal with these.

The scope states that the indication for eltrombopag is those patients who have previously had a splenectomy and are refractory to that splenectomy and non–splenectomised patients who are contra-indicated for splenectomy. It is unclear whether any of the data used are actually relevant to the second patient group. It should be noted that little of the existing data for any treatment appears to be precisely for this group.

In the economic model the comparison is eltrombopag plus standard care versus standard care alone. Standard care is based upon treatments provided in the RAISE trial and may not represent standard NHS practice or what might be described as current best practice.

The perspective taken in the submission is that of NHS / PSS although information from the perspective of the PSS is not presented nor discussed.

5.4 Modelling methods

5.4.1 Modelling approach / model structure

Type of Model used: Is it justified for the purpose

The submission made by the manufacturer was based around a trial-based model developed in Microsoft Excel. It has a very simple structure that arguably may be biased as it assumes that differences between treatments arise primarily due to death and bleeding events. This potentially assumes away other outcomes e.g. side effects of treatments, etc, which may also influence costs and outcomes. As a consequence it might be argued that such an approach will produce biased results. However, a counter argument can be advanced that the modelling 'adds power' to (for economic outcomes) an under powered study. The ERG did ask that GlaxoSmithKline produce a within-trial analysis as this information would most likely lead to more accurate results. GlaxoSmithKline provided further disaggregated costs and QALYs but further extra information from the trials was not provided.

Rationale of the structure

The model does not provide any facility to directly compare treatments. While the model presented estimates eltrombopag's cost-effectiveness against standard of care, it is unclear as to whether eltrombopag is more or less cost-effective than some other comparator treatments.

Structural assumptions

Transparent and justified?

Many of the assumptions used justified using clinical expert opinion. However a lack of transparency into this method of evaluation for so many parameters raises questions as to how the expert opinion was obtained, whether it is accurate and whether it is representative of expert opinion in the UK. The validity of some of these assumptions is questionable. For example, the model assumes that all patients who have not undergone a splenectomy are contra-indicated to splenectomy. The use of this assumption does not seem to reflect a real world situation. The impact of this assumption on the cost-effectiveness of eltrombopag is unclear.

Time horizon and cycle length?

The model time horizon is for 26 weeks, the period of the RAISE trial. The model does not include the continuing costs of survivors. Given the data used within the model this represents a bias in favour of eltrombopag.

Duration of treatment:

Duration of treatment was for the 26 week period of the trial. However, a number of participants dropped out of the trials for various reasons and these are detailed in Figure 6.4 of the manufacturer's submission. A number of participants in the RAISE study entered the EXTEND long term trial and this data has been used for the second economic evaluation model which will be assessed in the next chapter.

5.4.2 Data

Data identification process clear?

Generally, a clear description of the source of effectiveness data was provided. In all cases, the data in the model matched the data in the submission report and no discrepancies were found here. However, what was rather unclear was the source of some data used in the model taken from the RAISE reanalysis pdf files. A number of typographical errors were identified, specifically in relation to the dosage of certain ITP medications administered during the trial as rescue medication (on both the eltrombopag and placebo arms of the trial). These errors appear to be genuine mistakes but all create a bias (admittedly small) in favour of eltrombopag.

Secondly, in relation to figures presented by subgroups for the number of bleeding events, the source for this data was given as table 49 (RAISE CSR). However, this table only details

bleeding events for all patients and not separately for each subgroup. Therefore, the source of this data remains unclear and while it may be accurate was unable to be checked.

Further issues in relation to model cell calculations

In relation to certain cell calculations used in the model, there is uncertainty surrounding their accuracy. For example, the method used to calculate incremental utilities over the 26 week period for both the placebo and eltrombopag arms seems to show inconsistencies in the calculation method used at each incremental stage of utility estimation. The formulae used to calculate utilities for the placebo arm (weeks 14 – 26) and eltrombopag (weeks 14 – 26) seem to be inconsistent. The eltrombopag calculation references the baseline as opposed to the placebo calculation which references the previous time point estimate.

[a]This yields a utility value of 0.0031 over that period. However, when one looks at the placebo arm for the same time increment, the point estimate at week 26 is referenced to week 14, (the previous point estimate). It appears as if two separate methods have been employed here and it is unclear as to which method is being used and how the calculations are arrived at. Further, the method used is method 2 from the Manca and colleagues' paper,[74] which recommends that in order to calculate correct utilities incrementally that one should adjust for baseline imbalances in utility. However, the paper referenced states that this method is flawed and an alternative method 3 is suggested. The submission document does not mention this method at all. It is unclear as to why the recommended approach for the calculation has not been adopted. Also, it is interesting to note that the method 2 used gives the lowest ICER value of all 3 methods identified by Manca and colleagues.

A further issue arises in relation to the weighting of bleeding events in order to adjust for numbers of assessments in the placebo and eltrombopag arms. The bleeding events are adjusted to reflect the fact that the eltrombopag arm of the trial has almost twice the number of patients by adjusting for the number of regular assessments. However, in relation to spontaneous reporting, no adjustment is made. The text of the submission suggests that it has been inflated but the formulae do not ascribe to this. This represents a potential small bias against eltrombopag.

[a] For example, when calculating incremental utility for the Eltrombopag arm between weeks 14 and 26, Cell H56 takes the point estimate at week 26 and compares it with the point estimate at base line.

Is the pre model data analyses methodology based on justifiable statistical and epidemiological techniques?

A number of assumptions are made throughout the model which may lead to questions about their justification. For example, one patient in the placebo arm of the trial died as a result of ITP. Therefore, data from other sources was used to justify a difference in mortality. It is unclear whether any differences in mortality exist and if they do what is their magnitude and direction. It is assumed that a difference in clinically significant bleeds is a legitimate proxy for differences in mortality rates. A sensitivity analysis is however conducted to look at all bleeding events; unfortunately the sensitivity analysis is one way and does not explore the use of more serious bleeds as a proxy for mortality rates. Given the mortality risk has a pivotal role in the model; such a sensitivity analysis would be useful.

The model also assumes that mortality risk is the same for all patients, both splenectomised and non-splenectomised. Little or no data are available about this and the net impact on the analysis is unknown.

5.4.3 Quality of life / Utilities

Are the utilities incorporated into the model appropriate? Are methods used to derive utility weights justified?

Throughout the model, QALYs are used to estimate the impact of ITP on Health. QALYs are estimated using the SF-36 questionnaire and are transformed into SF-6D using the Brazier 2002 algorithm.[73] This is a reasonable measure of health status utilities but it is not the method as recommended by NICE for use in the STA process. NICE recommends the use of EQ-5D where possible. The manufacturer has however stated that both measures are widely accepted methods of preference based utility measurement. In their response to clarification, question B16, the manufacturer acknowledged that each method had its own merits but presented no evidence to suggest that the measures were interchangeable. Both measures are none the less used interchangeably in the report. The ERG notes that it is unclear whether or not this introduces a bias in the calculation of overall QALYs. However, no reference to any studies comparing the measures has been made. For example, Seymour and McNamee have completed some work in this field in an effort to compare the two methods using a quantile regression approach.[76] Further work completed by Brunenberg[77] concludes that it is incorrect to compare the two methods. The main point to note here is that the non-comparison of the methods adds uncertainty as to the accuracy of combining the two measures to derive an overall QALY measurement.

5.4.4 Data incorporation

Is the process of data incorporation transparent?

The process of data incorporation into the model was clear and transparent and the use of data between sections is clear and logical in the most part. The only section in which data has not been traceable is in relation to subgroup bleeding events, and potential errors in data entry as detailed previously.

5.5 Comment on the validity of the results presented with reference to the methodology used?

Apart from the points raised above the results appear valid in terms of the methods used.

5.6 Summary of uncertainties and issues

Were methodological, structural, heterogeneity, parameter uncertainties addressed?

There are some concerns with regard to methodological uncertainties in the model. Issues also arise in relation to uncertainty surrounding the costing assumptions used to inform the model. There are large differences between macro and micro costing approaches. It is likely that the true values lie somewhere between these two points. Also, costing has been estimated largely with the use of clinical expert opinion, which may not be adequately representative of the wider UK population under consideration. The effects and/or biases generated as a result of this uncertainty are unclear; however the ERG does feel that some bias will exist but the magnitude and direction is unclear.

Also, in relation to the cost of eltrombopag, the ERG requested that the manufacturer estimate the price at which eltrombopag would have to be cost-effective at various cost effectiveness thresholds (for example £30,000/QALY). This information was presented in response to ERG clarification queries document, the results of which are summarised in Table 5.3 above.

The impact of the variation of certain structural assumptions on cost effectiveness will be explored in Chapter 7 of this report.

6 ECONOMIC EVALUATION: De novo economic evaluation 2 Cost-effectiveness evaluation of chronic ITP long-term continuous treatments as part of a treatment sequence with and without eltrombopag

The manufacturer did not identify any significant errors in this model and therefore the relevant results are those presented in a second Section 7 included as a separate document to the main submission document and in the response to ERG clarification queries document. All page numbers, sections, tables and figures referred to in this section of the ERG report come from this second Section 7 unless otherwise stated.

6.1 Introduction and overview of manufacturer's economic evaluation

This second de novo economic evaluation used a Markov model to assess the cost-effectiveness of eltrombopag as part of a long term continuous treatment strategy to treat chronic adult ITP patients who have been unresponsive to or intolerant of non-selective immunosuppressive agents. The model presents eltrombopag as part of a treatment sequence that may also include treatment with rituximab, IVIg, anti-D and romiplostim.

The submission for the second de novo economic evaluation included:

- A systematic literature review of any studies assessing the cost-effectiveness of eltrombopag in a long term continuous care setting.
- Inclusion and exclusion criteria (Section 7.2.2), detailed description of comparator technology (7.2.3). A schematic of the model and the Markov health states used are detailed in Figures 7.1 a & b. Movement through the model and each treatment sequence considered is illustrated in Figure 7.1 c.
- A list of model assumptions and justification for their inclusion are detailed in Table 7.2.
- Results of the model are detailed in Section 7.3 (pp31 – 36). Various sensitivity analyses were conducted on the assumptions and uncertainties within the model as identified by the manufacturer and these are presented between pages 37 and 52 of the second Chapter 7.
- Two separate Microsoft Excel copies were included (one for each population group: splenectomised and non-splenectomised).
- Budget impact is detailed in Section 8

As part of the review process, the ERG requested a number of points of clarification from the manufacturers in relation to uncertainties or discrepancies which were identified at an early

review stage of the model. The issues on which the group required further clarification are as follows:

- The manufacturer was asked to clarify a discrepancy in the modelling and reporting of disease progress and those reported in the source RAISE trial.
- More detail was requested in relation to the pooling of the SF-36 data and the manufacturer was requested to elaborate on the calculations used. Also, they were asked to clarify as to why two differing methods of utility estimation were used in the model and how accurate this mix and match approach was. Further tables relating to SF-36 data are included in an appendix to the clarification document.
- The manufacturer was asked to justify the assumption that that 80% of grade 4 bleeds are fatal.
- Evidence that the data used in the model was in fact relevant to the study question was requested.
- Estimates of life years as well as QALYs were requested i.e. full and complete tables for every analysis and every treatment.
- Also a number of further non priority points were flagged for clarification.

The manufacturer responded in detail to the requests made by the ERG and this evidence will be used where appropriate throughout the report. It appears from the manufacturer's response that a number of points are mentioned but are not discussed in any detail. For example, the assumption of 80% of grade 4 bleeds being fatal is not adequately justified in the response document. While information on life years is presented in selected treatment sequences, it is only available for the first two (not all) sequences on the cost-effectiveness frontier. Further information is only presented comparing treatment sequences with and without eltrombopag for the lead sequence on the frontier. This fails to account for the fact that the lead sequence may not always be the most relevant to UK practice. There is however little or no guidance available to dictate the order in which treatments are received. One may however question the use of rituximab as first line treatment given that it is not licensed for the treatment of ITP.

6.2 Cost-effectiveness analysis methods

The identification of appropriate studies evaluating eltrombopag and the systematic review process is as described in section 5.1 above. As reported in this section no relevant studies assessing the cost-effectiveness of Eltrombopag as part of a long-term continuous treatment programme were found. As no economic evaluation was identified, the manufacturer based its evaluation on a Markov model to evaluate the cost-effectiveness of eltrombopag as part of a treatment sequence in the long term continuous management of chronic adult ITP for

patients who had previously received and been refractory to treatment using non-selective immuno-suppressive agents. The following sections of this report summarise treatment background, HRQOL, resources, costs, results and sensitivity analyses as reported in the manufacturer's submission and the subsequent clarification document.

6.2.1 Natural history

The submission addressed a small sub-group of patients with more severe chronic adult ITP who will require long-term treatment and who are not adequately responsive to treatment in a watch and rescue scenario. The model addresses a hypothetical cohort of 25 patients given a regular stable dose of eltrombopag of 50 mg daily.

One point on which the ERG requested further clarification was as to what patients actually entered the model as it is assumed that only a very small number of patients would be eligible for this treatment per year (in Table 8.2 of the manufacturer's submission it is estimated that only between 22 and 23 patients will be eligible for treatment each year).

The model framework is a simple repeated decision tree framework which supports a Markov (health state transition) structure, repeated per treatment within a treatment sequence (Figure 7.1(a-b) of the manufacturer's submission and are reproduced in Figure 6.1 below for completeness). Figure 6.2 further illustrates the treatment sequence approach used in the economic model.

Figure 6.1 Markov health states

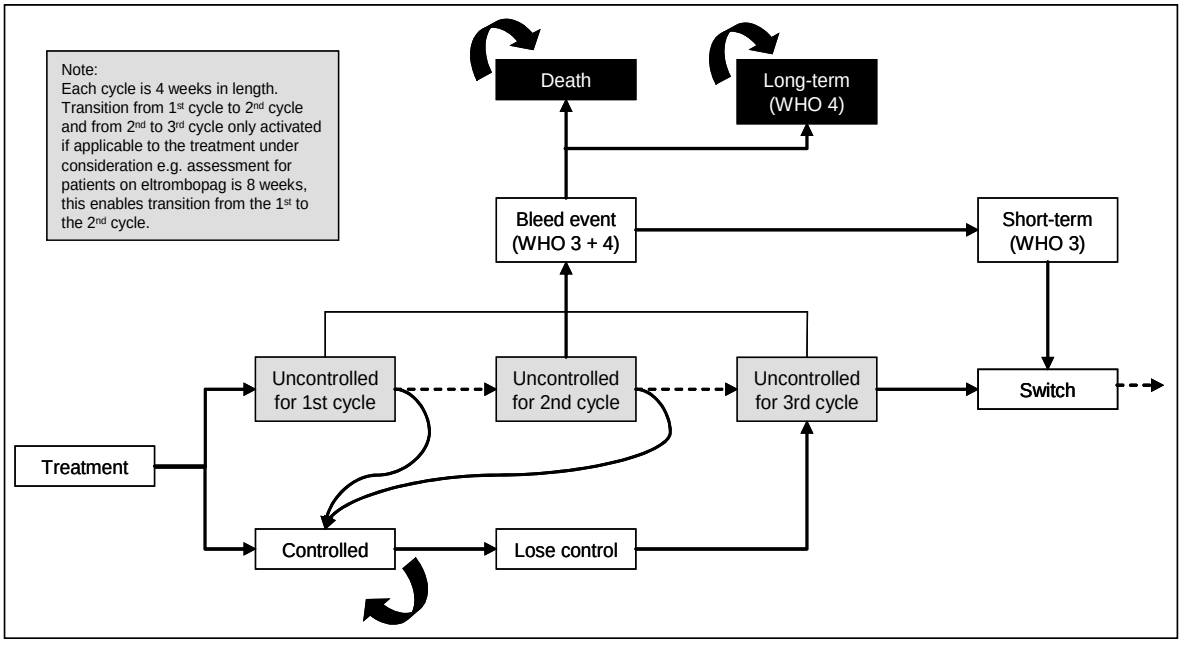
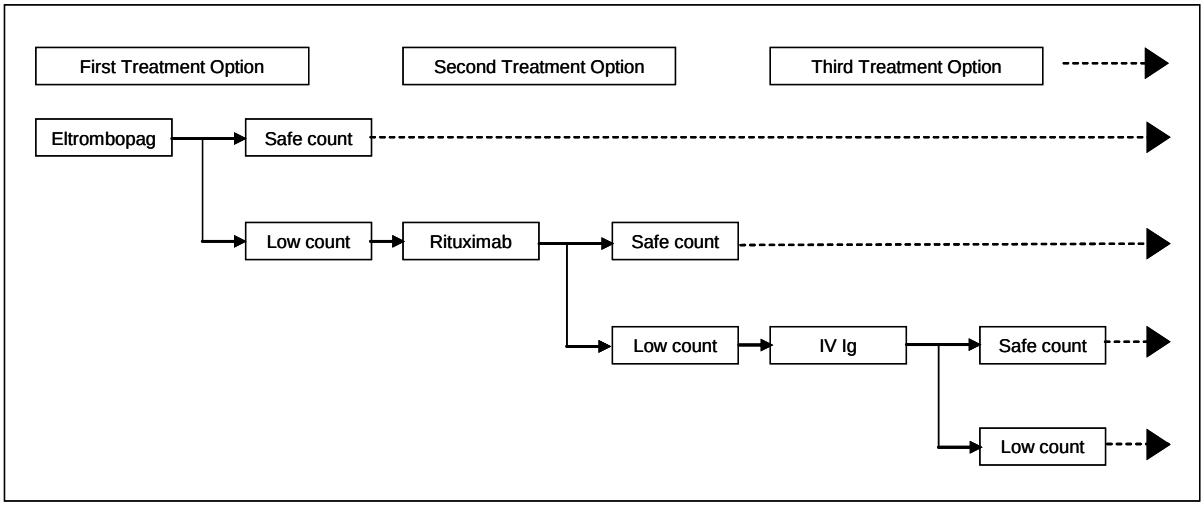


Figure 6.2 Treatment sequence approach to modelling



Patients (over 18 years old) enter the model with a platelet count of <30 $x10^9$/L and who have had previous ITP therapy to which they are assumed to have had an inadequate response. Long-term treatment is assumed to be required until the patient reaches a platelet level of >50 $x10^9$/L. Patients who fail to a platelet count of 50 $x10^9$/L enter a sink state i.e. these patients will have failed to respond to all treatments within a sequence or will have survived a non fatal grade 4 bleed. They remain in this state until the end of the model. Patients with a fatal WHO grade 4 bleed exit the model as a result of death. This model was considered by the manufacturer to be the most appropriate option in order to deal with the lack of evidence in relation to comparator treatments. Also as the population group remains ill defined and there is no evidence to inform the most appropriate treatment course. It was felt by the manufacturer that the Markov model used would therefore be the most appropriate in the circumstances.

6.2.2 Treatment effectiveness

Time to treatment switch is detailed in table 7.3 of the manufacturer's submission and is based upon clinical expert opinion. The manufacturer has provided details of clinical expert opinion used to assist the development of assumptions and parameters in response to question A.10 in the matters for clarification. However, it is unclear which experts detailed provided information in this regard. Patients enter the model in the first line of treatment and move through various treatment sequences. The decision to move between treatment stages within the sequence is based on assessment of response and the occurrence, or not, of a significant bleeding event. Efficacy data are taken from pooled SF-36 data obtained from the RAISE and EXTEND trial data. Health effects in the model are measured in terms of life years and QALYs gained.

6.2.3 Health related quality of life

Health related quality of life measurements are detailed in Section 7.2.8 of the manufacturer's submission and are reported in terms of QALYs gained. Measured health effects in the model include (utility weights applied to controlled and uncontrolled) platelet counts and the duration of a bleeding event. Utility data for controlled and uncontrolled platelet counts are measured from pooled data in the RAISE and EXTEND trials and mapped to SF-6D using the Brazier and colleagues' algorithm. Utility measures of impact following a significant bleed event are measured using various indexes mapped to the EQ-5D measurement. In response to an ERG clarification query, the manufacturer stated that both measures are widely accepted methods of measuring preference based utility scores. While each method is acknowledged to have its own merits, the manufacturer presents no evidence to suggest that the measures are interchangeable. They are none the less used interchangeably in the report. The ERG notes that it is unclear whether or not this introduces a bias in the calculation of overall QALYs.

Adverse events other than bleeding events are not modelled and this is justified by the manufacturer on the grounds that they wanted to avoid double counting of effects captured in the SF-36 data. However, there is no data provided that the utility differ between treatments other than because of response rates and bleeding events. Numbers of bleeding events are reported in Tables 13-18 of the matters for clarification document. Utility scores following a significant bleed are detailed in Table 7.6 of the main submission document.

6.2.4 Resources and costs

Section 7.2.9 of the manufacturer's submission states that resource and cost measurements were detailed from a NHS and PSS perspective. Within the model, it is assumed that all patients requiring a treatment switch will consult with a haematologist, the cost of which is estimated using the national schedule of reference costs to be £124.86. Tables 7.8 and 7.9 further estimate the resource use associated with grade 3 or grade 4 bleeding events. These are macro costing assumptions analogous to GI bleeds and ICH bleeding respectively. A four weekly liver function test for eltrombopag patients is also included and costed at £1.34 per test. It is likely that a visit to a haematologist or a GP would be required for each liver test. This additional cost associated with obtaining getting a liver test does not appear to be included in the analysis and would likely result in a bias towards eltrombopag although the size of this bias in the context of the model is not likely to be significant. Given that the cycle length is 8 weeks and liver test is required every 4 weeks for eltrombopag, it would appear plausible to assume an extra GP visit would need to be incorporated into the Eltrombopag treatment calculation.

Treatment costs are outlined in Table 7.10, while Table 7.11 and 7.12 detail the estimated short and long-term costs of WHO grade 3 and 4 bleeds. All costs and resource usage estimates were informally validated through discussion with clinical experts. Details of 7 clinical experts used during the submission development are given in response to Q A.10 in the matters for clarification document but it is not specified which experts valued which resources or if all contributed to the valuation of each resource. While resource use was not measured in RAISE directly, estimates were based on trial based events. However, no adjustment of resource use over future periods was made. The manufacturer took this step due to co morbidities and the uncertainty which would arise from making such an assumption. Some extrapolation to the future may have been appropriate to fully value the costs and resources which may be incurred over a longer time horizon due to varying treatment options.

NHS reference costs were used to value costs and resources wherever possible. However, the long term costs used for a grade 4 bleeding event were sourced from the literature based on an ICH bleeding event.

The cost of eltrombopag is assumed to be similar to the watch and rescue model at £55 per 50 mg tablet. Costs are reported in 2008 prices and indexed to 2008 prices where necessary, however no details of where such indexing has occurred are provided.

6.2.5 Discounting

Both costs and benefits are discounted in the Manufacturer's submission at the rate of 3.5% in accordance with NICE guidelines.

6.2.6 Sensitivity analysis

The manufacturer has conducted a number of sensitivity analyses in the model in order to explore various uncertainties surrounding certain assumptions made (Section 7.2.11 of the manufacturer's submission). The main sensitivity analyses undertaken in the model are as follows:

- Varying the response rate in the model from >50 $x10^9$/L (base case) to >30 $x10^9$/L.
- The impact on cost effectiveness of varying the price per day from £50 to £60.
- Changing the time horizon of the model to the patient's lifetime as opposed to a 2 year time horizon used in the base case.
- A probabilistic sensitivity analysis was reported in Section 7.3.3 of the document for both splenectomised and non splenectomised patient groups over a 2 year time horizon and a response rate of >50 $x10^9$/L.

The ERG presents further sensitivity analyses that it feels are relevant later in this report.

6.2.7 Model validation

An independent supplier of health economic services (RTI) was used to develop the model. Two clinical experts were consulted independently through informal discussion to verify assumptions made and the patient population addressed in the modeling approach. One point on which the ERG required further information was in relation to how clinical expert opinion was obtained. This information is provided in response to Question A.10 in the matters for clarification document. Abacus Healthcare also checked the model for quality and robustness using the checklist of quality criteria developed by the Centre for Health Economics at the University of York.

6.2.8 Results

The results of the model and analysis are presented in Section 7.3 of the manufacturer's submission and are summarised here for completeness. These results are critiqued in Section 6.3 of this report; further analysis conducted by the ERG is reported in section 7.5.

Treatment sequences with eltrombopag are dominant over the same sequences without eltrombopag in cases where there has been prior treatment with rituximab (see Tables 7.15 and 7.18 of the manufacturer's submission for comparisons showing that the lead sequence with the inclusion of eltrombopag dominates the same sequence without eltrombopag for both splenectomised and non-splenectomised patient groups). Detailed results are available in the manufacturer's response to ERG clarification queries (Tables 31 – 54).

The base case results for splenectomised and non-splenectomised patients are presented on pages 33 – 36 of the manufacturer's submission and shown in Tables 6.1 and 6.2 below. No further subgroup analyses were conducted due to the small number of patients passing through the model.

Table 6.1 Splenectomised population: Base case results

Sequence	**RI-EP-RO-IV**	**RI-EP-IV-RO**	**RI-IV-EP-RO**	**IV-RI-EP-RO**
Cost:				
Drug	18315.04	20925.32	25380.86	60419.09
Bleed	128.19	124.99	119.81	127.31
Treatment Switch	83.89	82.82	83.81	80.03
Total Cost (£)	**18,527**	**21,133**	**25,584**	**50,644**
Life Years				
Controlled platelet count	1.873	1.877	1.884	1.359
Uncontrolled platelet count	0.008	0.008	0.007	0.004
Bleed Related	0.105	0.101	0.094	0.065
	1.986	**1.986**	**1.986**	**1.986**
QALY				
Controlled platelet count	1.351	1.354	1.874	1.352
Uncontrolled platelet count	0.005	0.005	0.008	0.005
Bleed Related	0.073	0.070	0.104	0.072
Total QALY	**1.428**	**1.429**	**1.429**	**1.429**
ICER (relative to previous sequence)	**----------**	**11,235,680**	**11,711,779**	**150,959,104**

RI = Rituximab; EP = Eltrombopag; RO = Romiplostim; IV = Intravenous immunoglobulin

Table 6.2 Non – splenectomised population: Base case results

Sequence	**RI-EP-RO-IV-AD**	**RI-EP-IV-AD-RO**	**RI-IV-EP-AD-RO**	**RI-IV-AD-EP-RO**
Cost:				
Drug	17,404.09	19,812.38	23,807	26,751
Bleed	105.92	102.82	102	99
Treatment Switch	77.06	76.97	80	82
Total Cost (£)	**17,587**	**19,992**	**23,986**	**26,932**
Life Years				
Controlled platelet count	1.907	1.912	1.917	1.917
Uncontrolled platelet count	0.007	0.006	0.006	0.006
Bleed Related	0.072	0.068	0.064	0.063
	1.986	**1.986**	**1.986**	**1.986**
QALY				
Controlled platelet count	1.376	1.379	1.383	1.383
Uncontrolled platelet count	0.004	0.004	0.004	0.004
Bleed Related	0.050	0.047	0.044	0.044
Total QALY	**1.43**	**1.43**	**1.43**	**1.43**
ICER (relative to previous sequence)	**----------**	**10,749,060**	**15,402,007**	**164,623,320**

RI = Rituximab; EP = Eltrombopag; RO = Romiplostim; IV = Intravenous immunoglobulin; AD = Anti D

For both patient groups, the ICERs for one treatment sequence over another are driven mainly by changes in drug related costs and show that eltrombopag is most cost-effective within a treatment sequence when used as second line treatment after a patient has previously received rituximab. There is little difference in QALYs between treatments on the cost-effectiveness frontier as is evident from the above tables.

Sensitivity analysis results:

Tables 6.3 and 6.4 summarise the deterministic sensitivity analyses as conducted by the manufacturer.

Table 6.3 Response rate >50x10^9/L, time horizon: life time: Splenectomised

Sequence				
	Cost (£)	Life years	QALY	ICER
RI-EP-RO-IV	£252,519.3	42.308	15.692	-
RI-IV-EP-RO	£323,979.9	42.314	15.694	24,554,474
IV-RI-EP-RO	£469,238	42.314	15.694	29715911

RI = Rituximab; EP = Eltrombopag; RO = Romiplostim; IV = Intravenous immunoglobulin

Table 6.4 Response rate >50 x10^9/L, time horizon: life time: Non-splenectomised

Sequence				
	Cost (£)	Life years	QALY	ICER
RI – EP – RO – IV – AD	£260,119	42.64	15.82	-
RI – IV – EP – AD - RO	£325,257	42.65	15.82	24,727,254
RI – IV –AD - EP - RO	£386,796	42.65	15.82	545,565,480

RI = Rituximab; EP = Eltrombopag; RO = Romiplostim; IV = Intravenous immunoglobulin; AD = Anti D

Taking the lead sequence in each case and comparing it with the same sequence without eltrombopag, the sequence including eltrombopag is reported as being dominant for both population groups.

The analysis in this case reports the lead sequence against the same sequence without eltrombopag for each price level and shows that in each case the sequence with eltrombopag is dominant over the sequence without it (Tables 6.5 and 6.6).

Table 6.5 Varying price of eltrombopag between £50 and £60: Splenectomised

Sequence	**(£50)**			
	Cost	Life years	QALY	ICER
RI – RO –IV	21,544	1.985	1.425	-
RI – EP – RO - IV	17,571	1.986	1.428	Dominant
Sequence	**(£55)**			
	Cost	Life years	QALY	ICER
RI – RO –IV	21,544	1.985	1.425	-
RI – EP – RO - IV	18,527	1.986	1.428	Dominant
Sequence	**(£60)**			
	Cost	Life years	QALY	ICER
RI – RO –IV	21,544	1.985	1.425	-
RI – EP – RO - IV	19,484	1.986	1.428	Dominant

RI = Rituximab; EP = Eltrombopag; RO = Romiplostim; IV = Intravenous immunoglobulin

Table 6.6 Varying price of Eltrombopag between £50 and £60: Non-Splenectomised

Sequence	**(£50)**			
	Cost	Life years	QALY	ICER
RI – RO –IV – AD	21,910	1.986	1.428	-
RI – EP – RO – IV -AD	16,685	1.986	1.430	Dominant
Sequence	**(£55)**			
	Cost	Life years	QALY	ICER
RI – RO –IV – AD	21,910	1.986	1.428	-
RI – EP – RO – IV -AD	17,587	1.986	1.430	Dominant
Sequence	**(£60)**			
	Cost	Life years	QALY	ICER
RI – RO –IV – AD	21,910	1.986	1.428	-
RI – EP – RO – IV -AD	18,490	1.986	1.430	Dominant

RI = Rituximab; EP = Eltrombopag; RO = Romiplostim; IV = Intravenous immunoglobulin; AD = Anti D

The variation in price does not change the resulting sequences in the long-term care model. However, it does lead to notable differences in cost value driven changes in drug related costs. In all three cases in Tables 6.5 and 6.6, the inclusion of eltrombopag in a post Rituximab treatment sequence is dominant over the same lead sequence without the inclusion of eltrombopag.

The impact of rerunning the model when the target platelet level was changed to >30 $x10^9$/L is detailed in Tables 6.7 and 6.8. Once again the lead sequence with eltrombopag included dominates the treatment sequence without eltrombopag for both the splenectomised and non-splenectomised patient populations (Tables 51 and 54 of the matters for clarification document).

Table 6.7 Response Rate: >30 $x10^9$/L: Splenectomised

Sequence				
	Cost (£)	Life Years	QALY	ICER
RI – EP – RO – IV	16,400.24	1.986	1.428	
RI – EP – IV – RO	18,285.44	1.986	1.429	6,798.229
RI – IV – EP – RO	23,408.02	1.986	1.429	13,565,519
IV – RI – EP - RO	54,336.58	1.986	1.429	106,979,580

RI = Rituximab; EP = Eltrombopag; RO = Romiplostim; IV = Intravenous immunoglobulin; AD = Anti D

Table 6.8 Response Rate: >30 $x10^9$/L: Non- splenectomised

Sequence				
	Cost (£)	Life Years	QALY	ICER
RI – EP – RO – IV – AD	15,869.95	1.986	1.43	
RI – EP – IV –AD - RO	17,233.26	1.986	1.43	6,040,665
RI – IV – EP – AD - RO	22,714.95	1.986	1.43	99,227,335
IV – RI – EP – AD – RO	54,482.72	1.986	1.43	164,090,976
IV – EP – RI – AD - RO	59,574.40	1.986	1.43	219,607,583

RI = Rituximab; EP = Eltrombopag; RO = Romiplostim; IV = Intravenous immunoglobulin; AD = Anti D

Finally, a probabilistic sensitivity analysis is conducted for the sequences including eltrombopag in a post rituximab treatment sequence for each patient group. The results of the analysis are reported on pages 51 and 52 of the manufacturer's submission. Substantial variation in cost between the sequences is evident but there is very little variation in effectiveness. This suggests that the results which favour Eltrombopag are very much cost driven in the model, thus confirming the details of the deterministic analysis presented. Unfortunately, the submission does not provide any cost-effectiveness plots or cost effectiveness acceptability curves (CEACs). The manufacturer justifies this by stating that

because of the magnitude of the ICERs between sequences, CEACs would be uninformative. Further probabilistic analyses including such graphical illustrations are explored in Section 7.6 of the ERG report.

6.3 Critical appraisal of the manufacturer's submitted economic evaluation

Table 6.9 Structured critical appraisal of the manufacturer's economic model

Item	Critical Appraisal	Reviewer Comment
Is there a well defined question	Yes	The economic model and submission assessed the cost-effectiveness of eltrombopag as part of a treatment sequence for long-term chronic ITP patients who have failed to respond adequately to non-selective immuno suppressive agents.
Is there a comprehensive description of alternatives?	Yes	The alternatives presented for use in the model are detailed in Table 7.1 of the manufacturer's submission. Non-selective immunosuppressive agents and corticosteroids are not included as it is assumed they have previously been used and have failed to control platelet counts. Any treatment rules are identified and the number of possible treatment sequences for splenectomised and non-splenectomised patients are clearly defined.
Is the perspective of the analysis clearly stated	Yes	The analysis was stated to be performed from the perspective of the NHS and PSS.

Item	Critical Appraisal	Reviewer Comment
Is the perspective employed appropriate?	Unclear	While the perspective is stated as being that of the NHS and PSS, there is no detail of costs from a PSS perspective in the report.
Has the correct patient group/population of interest been clearly stated	Yes	Two biologically identifiable groups are discussed in the models: - Patients who have previously had a splenectomy and are refractory to that splenectomy - Non–splenectomised patients who are assumed to be contra indicated to splenectomy This is in line with the NICE scope.
Is the correct comparator used?	Yes	The list of comparators included in the model is broadly in line with the NICE scope. Any omitted medications are justified in the submission and any relevant treatment rules are followed. Due to the population split, splenectomy has not been included as a treatment option in the model for non-splenectomised patients as splenectomy is contraindicated in these patients.
Is the study type reasonable?	Yes	A Markov model is used to evaluate the cost-effectiveness of eltrombopag within a sequence of treatments for long term chronic ITP patients who fail to respond to other commonly prescribed treatments, using a cohort of 25 patients. Given the lack of comparable data for comparator drugs, this seems a reasonable way to proceed.

Item	Critical Appraisal	Reviewer Comment
Is effectiveness of the intervention established?	Yes, given the available evidence	The only information in relation to eltrombopag comes from the 3 RCTs Effectiveness of the other treatments comes from generally small studies, none of which are comparative. The relative performance of eltrombopag is therefore unclear. The effectiveness of each treatment sequence in the model presented for long-term care is calculated on the basis of response rates over various treatment cycles depending on the drug / treatment used at a particular point in time. Better comparative data between eltrombopag and the alternatives would undoubtedly improve the accuracy of conclusions.
Has a lifetime horizon been used for analysis (has a shorter horizon been justified)?	Yes	A longer time horizon has been estimated over 50 years in order to predict model results over an average life time.
Are the costs and consequences consistent with the perspective employed?	Costs – Yes Consequences - Partly	Costs are attributed from an NHS view point and a budget impact statement supports this perspective. Consequences are measured in QALYs obtained using valuations from the RAISE and EXTEND trials together with studies from the literature where QALY information was not available through the trial data. No adverse events other than bleeding are modelled.

Item	Critical Appraisal	Reviewer Comment
Is differential timing considered?	Yes	All costs and benefits are discounted where appropriate using the discount rate of 3.5% as recommended by NICE. No sensitivity analysis has been conducted around discount rates.
Is incremental analysis performed?	Yes	The results of the model were presented as incremental cost effectiveness ratios (ICERs) measuring the incremental cost effectiveness between each sequence identified on the cost effectiveness frontier. Detailed results are only presented for non-dominated options. The manufacturer also compares ICERs of the lead treatment sequence with eltrombopag compared to the same sequence without eltrombopag.
Is the sensitivity analysis undertaken and presented clearly?	Yes	A number of sensitivity analyses are carried out. The results of these are clearly presented and easily interpretable. Probabilistic sensitivity analyses are limited in there usefulness due to the manner presented and there is no multivariant analysis undertaken. A range of further univariant and multivariant sensitivity analyses are explored in Section 7.5.

Table 6.10 Comparison of economics submission with NICE reference case

Attribute	Reference Case	Included in Submission	Comment on whether de novo evaluation meets requirements of NICE reference case
Comparator(s)	Alternative therapies including those used routinely in the NHS	Yes	The main comparators as indicated in the NICE scope document are included. All omissions are justified above. At the time of the manufacturer's submission, romiplostim had been launched in the UK; however the Appraisal Committee's preliminary recommendations had not been made. However, romiplostim was still considered within the model as a comparator technology.
Perspective – costs	NHS & PSS	Possibly	NHS cost perspective is clearly detailed in Section 8 of manufacturer's submission. It is unclear as to whether PSS costs were included.
Perspective – benefits	All health effects on individuals	NO	QALY benefits are measured from the RAISE and EXTEND trials. There is no utility decrement due to adverse events. This is likely to have created some bias in the results, the direction of which is unclear. Further, two different tools are used to measure utility gain from different effects. The impact of using two different measures is unclear.
Time Horizon	Sufficient to capture differences in costs and outcomes	Unclear	The base case time horizon is 2 years, extended to 50 years in a sensitivity analysis. The economic model considered costs and benefits over 4 and 8 week cycles in a treatment sequence. This may not be a long enough period to gain the full

Attribute	Reference Case	Included in Submission	Comment on whether de novo evaluation meets requirements of NICE reference case
			benefits of certain treatments. For example, romiplostim performs much better when response rates are measured at 12 weeks.
Synthesis of evidence	Literature Review and indirect comparisons	Yes	A literature review was carried out for this submission. Studies were selected for comparator treatments on the basis that they provided the 'best' data.
Outcome Measure	QALYs	Yes	QALY estimates in the manufacturer's submission are derived from: (i) Utility levels associated with various platelet level responses. (ii) The short and long term impact on utility from a significant WHO grade 3 or 4 bleed event. They do not include other adverse events.
Health States for QALY measurement	Described using a standardized and validated instrument	Yes	Health status was collected as part of the RAISE and EXTEND trials using the SF-36 converted into SF-6D scores using the Brazier 2002 algorithm. Response utilities are measured using the SF-6D while impact of bleed events are measured using the EQ-5D. NICE recommends the use of EQ-5D where possible.
Benefit Valuation	Time trade off or standard gamble	Standard Gamble	The SF-6D scores are based upon valuations from a standard gamble exercise. The EQ-5D scores are based upon mapping of the Barthel index on to the EQ-5D to measure the long and

Attribute	Reference Case	Included in Submission	Comment on whether de novo evaluation meets requirements of NICE reference case
			short term impact of a significant bleed event.
Source of preference data	Sample of Public	Yes	The SF-6D and EQ-5D scores are derived from samples of the UK general population. SF-36 scores used to convert to SF-6D are based on the RAISE and EXTEND trials. It is important to note that only 9 patients on the RAISE trial were from the UK.
Discount rate	Health Benefits and costs	Yes where appropriate	Discounting for costs and benefits was at the rate of 3.5% as recommended by NICE.
Equity	No special weighting	No	No special weighting in relation to equity was undertaken.
Sensitivity Analysis	Probabilistic sensitivity analysis	Yes	Probabilistic sensitivity analysis was undertaken for rituximab lead sequences and the iterations are plotted on pages 50 and 51 of the manufacturer's submission.

6.3.1 Critical appraisal of economic evaluation methods

As a general point, the model presented here is usable; however there are a large number of data sheets which are traceable but also quite cumbersome. This makes it difficult to trace where certain figures originate from.

Decision problem, description of alternatives and perspective

The decision problem for this section is clearly defined as addressing the question of what is the most cost-effective sequence of treatments for long term continuous care of adult ITP patients who require treatment and have been unresponsive to or intolerant of non-selective immunosuppressive agents. Section 2 of the manufacturer's submission further presents the decision problem and this is discussed in Section 5.3.1 above.

The alternative treatments mentioned are romiplostim, IVIg, Anti D and rituximab. This discussion seems to be broadly in line with the NICE scope. Treatments mentioned in the scope and not dealt with in the model are identified and justified on the basis described in the second point in Table 6.9. Section 7.2.3 of the manufacturer's submission describes each alternative, its response rates in improving platelet count and its justification for inclusion as a comparator. Treatment rules include not administering Anti-D to splenectomised patients and using IVIg in practice before Anti-D. Both of these treatment rules are acknowledged and adhered to in the model. The ERG is not aware of any other treatment administration rules which have been omitted from the submission. However it should be noted that the licensed Anti-D preparation has been withdrawn from the market in the UK by its manufacturer due to safety concerns.

The perspective taken for this evaluation is again that of the NHS and the PSS. While Section 8 of the manufacturer's submission deals comprehensively with the budget impact for the NHS, there is no mention of the impact from a PSS viewpoint.

6.4 Modelling methods

6.4.1 Modelling approach / model structure

Type of model used: Is it justified for the purpose

The type of model used in this case appears to be justified. An alternative simulation model was considered by the manufacturer but due to a lack of available data, the Markov model was adopted. Within the model patients pass through a series of treatment sequences, all of which include eltrombopag. As one treatment fails to elicit a response, the subject moves to the next treatment phase and so on. Should a patient fail to respond to any treatments in a sequence it is stated that the patient would be treated in an experimental way. The impact of this on costs and effects is excluded from the model. Therefore, given the limited data the approach used appears reasonable.

Rationale of the structure

The model is quite sensitive to the treatment sequence. In the main, sequences appearing on the cost-effectiveness frontier only find eltrombopag to be conclusively more effective and less costly on average than other treatment sequences when the sequence involves prior treatment with rituximab, which is not licensed in the UK for this use.[78] This begs the question as to whether rituximab is always likely to be administered before eltrombopag in clinical practice.

A number of the model assumptions rely heavily on clinical expert opinion, both in the estimation of the population group, uptake rates and other important assumptions. The ERG requested further information with regards to who the clinical experts were and how they were remunerated. It is important to note that while information in relation to clinical experts contacted by GSK is provided, no further information is available in relation to which experts contributed to which areas of the analysis. Perhaps all clinicians had an input into each and every point which is referenced to clinical expert opinion; however there is no evidence to support this from the Manufacturer's submission.

It is also assumed that a response is measured as reaching a platelet threshold of > 50 $x10^9$/L. Within the UK a platelet threshold of 30 $x10^9$/L is more commonly adopted. However a sensitivity analysis did consider a platelet threshold of 30 $x10^9$/L.

A number of structural assumptions are also made which give rise to some questions as to their source and their relevance. For example, it is assumed that 80% of grade 4 bleeds are fatal in the model. The ERG requested in its queries for clarification that a reference for this be provided. However, the manufacturer's response was that the figure of 80% was assumed in the absence of any available data on the issue. This is one area in which further sensitivity analysis is provided in Section 7.5 of the ERG report.

The model only allows romiplostim to work over 8 weeks while the available evidence suggests that a maximum response is achieved at 12 weeks. The effects of extending the time over which Romiplostim is given to 12 weeks is explored in further sensitivity analysis reported in Section 7.5 of the ERG report. There are also further discrepancies between the response rates in the model and for the indirect treatment comparison described in Section 6 of the manufacturer's submission and critiqued in Chapter 4 of this report. The response rates estimated as part of the indirect treatment comparison are much more favourable to romiplostim that the values used in the economic model. The impact of incorporating this relative effectiveness data into the review is explored further in Chapter 7 of the ERG report.

6.4.2 Structural assumptions

Transparent and justified?

A series of assumptions are made by the manufacturer and these are detailed in Table 7.2 of the manufacturer's submission together with a justification for each assumption used in the model. The assumptions are transparent, and justifications are provided and referenced as appropriate.

As mentioned above, some of the assumptions used may lead to biases for or against eltrombopag. For example, it is assumed that patients who have not undergone a splenectomy are contra-indicated for splenectomy. This is in accordance with the scope but there is no evidence from the RAISE trial on how many, if any, of the non-splenectomised patients were indeed refractory to such a treatment option. Further sensitivity analysis may have addressed some of these uncertainties. Perhaps splenectomy should have been included as a treatment option within the sequences for those who are non-splenectomised as in clinical practice.

It is also assumed that patient's in the treatment sequence are treated using one therapy only. No possibility of treatment interactions and possible combinations is allowed and this may be possible in practice for this group of patients. Neither is there evidence that the treatment sequences appearing on the frontier will be those which are actually used in practice. For example, a clinician may decide not to treat with rituximab first, a plausible option given that it is not licensed in the UK for the treatment of ITP.

It is assumed that patients maintain their response rates through the model and no attenuation of response occurs. This is unlikely to be a realistic assumption and it would have been interesting to see the effects of which treatments maintain response levels over time and which do not. Inevitably, this assumption will have caused a bias in the results; however it is unclear whether this is in favour of or against eltrombopag.

For simplicity, it was assumed that no risk of mortality associated with ITP was included apart from the risk of mortality from all causes. This will undoubtedly boost life expectancy and HRQOL values in the model for all treatments in the sequence. It is unclear if any treatment would affect mortality in other ways.

Finally, adverse events are not modelled, with the exception of bleeding events. The justification for this is that adverse events in the placebo and eltrombopag arms in the RAISE trial are quite similar. However, it is unclear whether this would be the case for the treatments and the group of patients considered in the long-term model.

Time horizon and cycle length?

The model is run over two years in the base case and over 50 years in a sensitivity analysis. The longer term time horizon should capture all of the relevant costs and effects associated with each treatment sequence.

While varying the time horizon does not have an effect on sequence results in the univariant analysis, it is shown in Sections 7.5 that in a multivariant analysis longer time horizons tend to favour romiplostim over eltrombopag in the treatment sequences.

Duration of treatment

Treatment effectiveness was measured based on response rates indicated. Cycle lengths of 4, 6 and 8 weeks were selected based on the treatment used as this was assumed to be representative of clinical practice. The time on each treatment is the time before a treatment can be changed if an adequate response has not been achieved. It is important to note that specifically for romiplosim that response appears to increase by 12 weeks, and a shorter cycle of 8 weeks as used in the model may be a bias against this treatment. This is acknowledged in the submission but has not been provided for in the economic model. The implications of this for cost-effectiveness are explored in Section 7.5. Further questions may be raised in relation to how response rates for rituximab are modelled given that the treatment would need to be repeated every 8-9 months on average in order to maintain a satisfactory response.

6.4.3 Data

Data identification process clear?

Most of the data are clearly identified and referenced where required. While the model is difficult to navigate through all of the relevant data, it is none the less traceable and calculations presented are referenced where appropriate.

One issue that did arise was that the costs and QALYs as reported did not match those as were calculated in the model. This point was acknowledged by the manufacturer in the matters for clarification and correct tables were provided. While costs and QALYs were incorrectly reported, ICERs were not and so the error made no real impact on the cost-effectiveness outcomes.

The ERG has not identified any further errors in data incorporation and all results presented in the response to ERG clarification queries are true reflections of those provided in the models.

Is the pre model data analyses methodology based on justifiable statistical and epidemiological techniques?

Assumptions linking the splenectomised and non-splenectomised groups together are quite similar and one may wish to question whether or not there may be a difference between the patient groups in reality. Further statistical methods and observations are critiqued in Chapter 4 of this report. However, no parameter differences between the two patient groups are

identified. It is assumed that all of the assumptions made are the same for splenectomised and for non-splenectomised patient groups. This introduces an element of uncertainty and it is unclear whether or not the resulting impact on cost–effectiveness would favour eltrombopag.

6.4.4 Quality of life / Utilities

Are the utilities incorporated into the model appropriate? Are methods used to derive utility weights justified?

Methods for deriving SF-6D are described in Section 5.2.3 above. The utility decrement is also measured by changes in EQ-5D scores in relation to significant WHO grade 3 and 4 bleeding events and was identified through the literature (Table 7.6 of the manufacturer's submission). A point of clarification was why two different utility measurements were used. The manufacturer's response was that both were widely accepted preference measures. However, as stated previously, there is no evidence cited in the report to suggest that these measures can be used interchangeably, a point which is in fact acknowledged by the manufacturer in their clarification document (B.16, clarification document, page 42).

The health effects of any further adverse events are also not modelled and this may or may not impact on the results of the model. Furthermore, there is no information in relation to how surveys were conducted, what setting they were conducted in or how responses were elicited or recorded. This is unlikely to significantly change treatment sequences, but does introduce further uncertainty.

6.4.5 Data Incorporation

Is the process of data incorporation transparent?

Generally speaking, the process of data incorporation is clear and transparent as well as accurate in most cases. However, a number of discrepancies arise. Firstly, in relation to response rates, it appears that romiplostim response rates are similar in achieving a platelet count of >50 $x10^9$/L as they are to achieving a platelet count of >30 $x10^9$/L. As only response rates for platelet counts >50 $x10^9$/L were available from the romiplostim study, this submission assumes their responses to be the same over 30 $x10^9$/L as for over 50 $x10^9$/L. It is plausible that romiplostim will have a higher response rate at 30 $x10^9$/L. On balance this assumption probably represents a bias against eltrombopag.

Further discrepancies appear in the response measures of romiplostim and eltrombopag between the meta-analysis and the economic model. These have been discussed above and are explored further in Chapter 7.

6.4.6 Comment on the validity of the results presented with reference to the methodology used?

With reference to the methodology and assumptions employed, the ERG has found that the results appear to be valid in the context presented. However, what is of concern is that some of the assumptions used do not seem entirely plausible, as noted above.

Summary of uncertainties and issues

Were methodological, structural, heterogeneity, parameter uncertainties addressed?

It appears that the assumptions used to estimate the patient population which would be treated under this approach are unclear and may or may not be valid. Much information was derived from an internal GlaxoSmithKline survey together with expert opinion which may or may not be reflective of UK clinical practice. Patient numbers may increase to a greater level than GlaxoSmithKline predicts as eltrombopag represents a more convenient, less invasive method of administration than the intravenous medications e.g. IVIg, rituximab. Also, as the second model deals with patients who are intolerant of the non-specific immune-suppressants then patients who wish to start eltrombopag may become `intolerant` of their current medication. The estimation of a small predicted patient population is based on a number of assumptions which are subject to a considerable amount of uncertainty. The cost of eltrombopag to the NHS may be significantly greater than that suggested if the assumptions on patient numbers are incorrect.

More importantly, however, is that while all of the issues discussed above may not be individually important to the results, taken together they lead to further uncertainty in the analysis. The combination of uncertainties within multivariant sensitivity analyses was not explored in the manufacturer's submission. This and further probabilistic sensitivity analysis are reported in Chapter 7.

The applicability of the analysis is also uncertain, as a judgement is required as to which patients will actually receive this drug and whether the model is entirely reflective of the relevant patient population.

A further concern in relation to structural uncertainty is how patients move through the sequences and if the sequences are reflective of UK clinical practice. Cost-effectiveness is very sensitive to patients entering the first line of treatment with rituximab. It is however not entirely clear as to whether rituximab is likely to be prescribed as a first line treatment in practice, indeed would clinicians be comfortable prescribing an unlicensed drug (rituximab)

before a licensed drug (eltrombopag, romiplostim, IVIg) If not, eltrombopag may be significantly less cost-effective as a result, when compared to alternative sequences.

Finally, the manufacturer's submission assumes many of the assumptions apply to splenectomised and non–splenectomised patient groups. It may be argued that in reality, some of these assumptions and costs may vary depending on a patient's splenectomy status. This has not been incorporated into the model and the resulting impact for cost–effectiveness results is unclear.

7 ADDITIONAL WORK UNDERTAKEN

7.1 Independent literature searchers to identify additional studies

7.1.1 Search strategy

Due to concerns over the sensitivity of the manufacturer's searches, the ERG undertook independent searches for eltrombopag and the clinical effectiveness of the comparators. The independent search strategies that were used are reported in Appendix 1. Inclusion and exclusion criteria used are the same as those listed in the final scope issued by NICE.

7.1.2 Comparing results from additional studies and those in the submission

The ASH guideline consisting of 14 case series reporting on IVIg or anti-D was identified, and a systematic review consisting of 28 RCTs reporting on IVIg (identified from the HTA Database search).

For IVIg and anti-D, lower platelet response rates were reported in the ASH guidance and the HTA systematic review (see Table 4.17). It is unlikely that these data would have greatly affected the results of the long-term economic model.

7.2 Screening included studies in the systematic review against inclusion criteria

By screening of the 113 included studies in the manufacturer's systematic review we identified a total of 36 (32%) studies that included children or adolescents, i.e. less than 18 years old (see Table 4.3).

7.3 Additional analysis for indirect comparison between eltrombopag and romiplostim

7.3.1 Combining the two romiplostim trials

In the manufacturer's submission they combined the two romiplostim trials[67] by using Mantel-Haenszel fixed effects meta-analysis. Since the populations from which each trial drew its participants are heterogeneous a different method of combining the trials is required to produce an odds ratio for all participants.

The method chosen here is to estimate the odds ratio of romiplostim compared to a placebo from a logistic regression model. The data from all of the participants in both trials was put together, modelling the success of each patient against two binary variables: whether the participant received romiplostim or placebo, and whether the participant was splenectomised or not. The odds ratios shown for romiplostim versus placebo in the all participants sections, worst and best scenarios (see Section 7.3.2) of Tables 7.1 and 7.2 were calculated using this method.

7.3.2 Dealing with participants who did not complete eltrombopag or romiplostim treatment in trials

In the manufacturer's submission, participants who did not complete eltrombopag or romiplostim treatment in the trials, i.e. withdrew prematurely or were lost to follow-up, were counted as non-responders. As there were more of these participants in the eltrombopag trial than in the romiplostim trials (Table 4.10), assuming such participants were non-responders (worst scenario) might have led the indirect comparison results to favour romiplostim.

To explore the impact of assuming participants who did not complete studies were non-responders on the indirect comparison results, we did further analysis assuming all such participants were responders (best scenario). The indirect comparisons shown were calculated using Bucher's method.[72]

7.3.3 Results of the additional analysis

The results of the comparison between eltrombopag and romiplostim are presented for durable response in Table 7.1 and overall response in Table 7.2.

For durable response the additional analysis using the logistic regression method produced an indirect comparison between eltrombopag and romiplostim that is similar to that given in the manufacturer's submission. Using the "best scenario" for handling participants who did not complete their treatment produced smaller estimates of the odds ratio than in the "worst scenario", with the indirect comparison between eltrombopag and romiplostim having a point estimate that slightly favours eltrombopag. Therefore, the results of this analysis appear to be sensitive to the method used for handling those who do not complete their treatment.

For overall response, the all participant indirect comparisons between eltrombopag and romiplostim show a significant (5% level) result in the manufacturer's submission and in both additional analyses. This suggests that these results are not sensitive to the method used to handle those that did not complete their treatment.

Table 7.1 Comparison between eltrombopag and romiplostim: durable response rate[a]

	Eltrombopag vs. placebo		Romiplostim vs. placebo		Indirect comparison
	n/N	**OR (95% CI)**	**n/N**	**OR (95% CI)**	**OR (95% CI)**
All participants					
Worst scenario[b]	57/135 vs. 4/62	10.60 (3.64, 30.87)	41/83 vs. 1/42	40.02 (5.26, 304.70)	0.26 (0.03, 2.62)
Worst scenario[c]	57/135 vs. 4/62	10.60 (3.64, 30.87)	41/83 vs. 1/42	44.99 (5.81, 348.4)	0.24 (0.02, 2.37)
Best scenario[c]	80/135 vs. 11/62	6.74 (3.23 ,14.09)	45/83 vs. 7/42	6.51 (2.52, 16.80)	1.04 (0.32, 3.44)
Non-splenectomised					
Worst scenario[b]	38/85 vs. 3/41	10.24 (2.93, 35.77)	25/41 vs. 1/21	31.25 (3.81, 256.24)	0.33 (0.03, 3.79)
Best scenario[c]	-	-	27/41 vs. 5/21	6.17 (1.87, 20.36)	-
Splenectomised					
Worst scenario[b]	19/50 vs. 1/21	12.26 (1.52, 98.90)	16/42 vs. 0/21	26.77 (1.52, 472.41)	0.46 (0.01, 15.91)
Best scenario[c]	-	-	18/42 vs. 2/21	7.13 (1.47, 34.59)	-

[a]Defined as weekly platelet $\geq 50 \times 10^9$/l during six or more weeks of the last eight weeks of treatment excluding those who received rescue medication at any time during the study

[b]Manufacturer reported.

[c]ERG calculated (combining romiplostim trials using a logistic regression model).

Table 7.2 Comparison between eltrombopag and romiplostim: overall response rate[a]

	Eltrombopag vs. placebo		Romiplostim vs. placebo		Indirect comparison
	n/N	**OR (95% CI)**	**n/N**	**OR (95% CI)**	**OR (95% CI)**
All participants					
Worst scenario[b]	72/135 vs. 6/62	10.67 (4.31, 26.43)	69/83 vs. 3/42	64.07 (17.33, 236.82)	**0.17 (0.03, 0.82)**
Worst scenario[c]	72/135 vs. 6/62	10.67 (4.31, 26.43)	69/83 vs. 3/42	77.68 (19.47, 309.9)	**0.14 (0.03, 0.72)**
Best scenario[c]	95/135 vs. 13/62	8.95 (4.38, 18.29)	73/83 vs. 9/42	34.19 (11.36, 102.9)	**0.26 (0.07, 0.97)**
Non-splenectomised					
Worst scenario[b]	49/85 vs. 4/41	12.59 (4.12, 38.50)	36/41 vs. 3/21	43.20 (9.27, 2741.84)	0.29 (0.04, 1.95)
Best scenario[c]	-	-	38/41 vs. 7/21	25.33 (5.74, 111.83)	-
Splenectomised					
Worst scenario[b]	23/50 vs. 2/21	8.09 (1.70, 38.50)	33/42 vs. 0/21	151.63 (8.39, 201.33)	0.05 (0.002, 1.43)
Best scenario[c]	-	-	35/42 vs. 2/21	47.50 (8.96, 251.77)	-

[a]Defined as durable plus transient response (four or more weekly response $\geq 50 \times 10^9$/l during the study without a durable platelet response from week 2 to 25)

[b]Manufacturer reported.

[c]ERG calculated (combining romiplostim trials using logistic regression model).

7.4 Additional cost-effectiveness sensitivity analysis conducted by the ERG

A number of further sensitivity analyses have been conducted by the ERG for both economic models to explore the impact on the cost-effectiveness results of uncertainties raised in Chapters 5 and 6 of this report. Details of all changes made to the models to achieve these results can be found in Appendix 2 of this report.

7.4.1 Additional sensitivity analysis: Watch and Rescue model

Additional sensitivity analyses were conducted in the following areas in relation to the Watch and Rescue model. Analysis point 2 includes details of a typing error which was identified in the analysis. This has been incorporated into all other sensitivity analyses results presented.

- **Variation of discount rates:** The ERG explored the possible impact of varying the discount rate used for costs and benefits in the model from 0% to 6% (base case 3.5%) to highlight the impact of uncertainty surrounding society's true rate of time preference.
- **Correction of typing errors in the model:** A number of typing errors were identified in the Microsoft Excel based copy of the model and have been included as discussed in Chapter 5.
- **Variation of annual risk of a fatal bleeding event:** The manufacturer's submission uses an annual risk of a fatal bleed taken from Cohen 2000[10] for use within their model. The impact of varying this value within the bounds of its confidence interval is estimated in the probabilistic analysis. The ERG has however incorporated it as an additional deterministic analysis (Table 7.3).
- **Multivariate analysis:** As detailed in Table 7.3, the manufacturer has conducted some sensitivity analyses which have also been reported for completeness. These analyses and those detailed above have been combined in a multivariate sensitivity analysis. Analyses 9 and 10 in Table 7.3 (splenectomised) and 7.4 (non-splenectomised) combine manufacturer and ERG analyses into best and worst case scenarios.

Table 7.3 Watch & Rescue model – (Splenectomised patients)

Scenario	Cost (£)	QALY	ICER
1. Baseline Results	9455	0.122	77,496
2. Typo Correction	9547	0.122	78,253
3. Micro Cost	10,161	0.122	83,284
4. All Bleeding events	9547	0.095	100,350
5. 0% Discount Rate	9547	0.2	47,712
6. 6% Discount Rate	9547	0.092	103,500
7. Annual Risk of fatal Bleed Cohen 2000[10] – lower bound	9547	0.072	131,841
8. Annual Risk of fatal bleed Cohen 2000[10] – upper bound	9547	0.171	55,778
9. Combining 2,3,4,6 & 7 (Worst Case Scenario)	10,161	0.044	231,195
10. Combining 5 & 8 (Best Case Scenario)	9455	0.282	33,561

Table 7.4 Watch and Rescue Model – Non-splenectomised patients.

Scenario	Cost (£)	QALY	ICER
1. Baseline Results	10,024	0.111	90,471
2. Typo Correction	10,024	0.111	90,471
3. Micro Cost	10,101	0.111	91,175
4. All Bleeding events	10,024	0.112	89,850
5. 0% Discount Rate	10,024	0.180	55,622
6. 6% Discount Rate	10,024	0.084	118,847
7. Annual Risk of fatal Bleed Cohen 2000[10] – lower bound	10,024	0.067	150,245
8. Annual Risk of fatal Bleed Cohen 2000[10] – upper bound	10,024	0.154	64,882
9. Combining 2,3,4,6 & 7	10,101	0.052	193,293
10. Combining 5 & 8	10,024	0.253	39,657

7.4.2 Discussion of the results of additional sensitivity analysis

The analysis (scenarios 1 – 4) presented in Tables 7.3 and 7.4 included sensitivity analyses from the manufacturer's submission document, Scenarios 5 to 10 involved additional analysis conducted by the ERG. In general, individual sensitivity analyses have less of an impact for the non-splenectomised group than for the splenectomised group.

The results for scenarios 5 to 8 show that the ICER is sensitive to the discount rate used and the annual risk of a fatal bleed. Given that there is much uncertainty around the true mortality rate from bleeding events, the analysis shows that there is a substantial impact on ICERs of varying the mortality risk between the upper and lower bounds of the confidence interval used in the Cohen study.

The impact of sensitivity analyses for scenarios 1 to 4 has been discussed previously in Section 5 of this report and requires no further elaboration here.

Of far greater importance is the effect on the ICER of a multivariate sensitivity analysis for each patient group. The large variation in QALY results presented in analyses 9 & 10 results in large changes in the ICER from £33,561 in a best case scenario to £231,195 in a worst case scenario for the splenectomised group and £39,657 in a best case scenario to £193,293 in a worst case scenario for the non-splenectomised patient population. It is only in these hypothetical best case analyses that the ICER begins to approach a value that society might be willing to pay for a QALY.

The large difference between analyses 9 and 10 suggests that there is potentially considerable uncertainty surrounding the results presented in the model. As correctly identified in the manufacturer's submission, the results are quite sensitive to the relative risk of mortality. Given that this figure is taken from one study,[10] one may argue that the result presents a bias in favour or against eltrombopag depending on what one assumes the relative risk of mortality to be.

The results as presented above beg the same argument for both patient groups surrounding the large levels of uncertainty. While the difference between best and worst case scenario is smaller for non-splenectomised patients than for the splenectomised patients, there is none the less a difference of over £150,000 in the ICERs presented. This combined with the failure to model any uncertainty around adverse events draws further questions as to the accuracy and applicability of the results. While some of the individual results presented do not have a

major impact on overall results, their impact is undoubtedly magnified when combined with other sensitivity analyses as is clearly illustrated in the tables above.

Further, from a cost perspective to the NHS, as discussed in Chapter 2 of the report, there is much debate and variation in evidence as to the incidence rates of ITP. Therefore given the price quoted for eltrombopag, it is likely that any discrepancies in a positive of negative direction would significantly impact on the projected budget impact figures for the NHS.

7.5 Additional sensitivity analysis: Long term model

The ERG conducted further research and analysis on the long-term models for both the splenectomised and non-splenectomised patient groups. Analysis focused on the treatment sequences presented on the cost-effectiveness frontier and the aspects which influenced this derivation.

7.5.1 Splenectomised patient group

As with the watch and rescue model, the analysis from the manufacturer's submission is included for completeness (Table 7.5). The results presented in Table 7.5 were previously discussed in Chapter 6 of this report.

Table 7.5 Long term model – Splenectomised patient group: manufacturer analysis

Scenario	Sequences	Cost	Life Years	QALY	Relative ICER
1. Base Case	RI-EP-RO-IV	18,527	1.986	1.428	
	RI-EP-IV-RO	21,133	1.986	1.429	11,235,680
	RI-IV-EP-RO	25,584	1.985	1.428	11,711,779
	IV-RI-EP-RO	60,626	1.986	1.429	150,959,104
2. Response Rate > $30x10^9$/L	RI-EP-RO-IV	16,400	1.986	1.428	
	RI-EP-IV-RO	18,285	1.986	1.429	6,798,229
	RI-IV-EP-RO	23,408	1.986	1.429	13,565,519
	IV-RI-EP-RO	54,337	1.986	1.429	106,979,580
3. Life Time Horizon	RI-EP-RO-IV	25,2519	42.308	15.692	
	RI-IV-EP-RO	32,3980	42.314	15.694	24,554,474
	IV-RI-EP-RO	469,238	42.314	15.694	297,159,117

RI = Rituximab; EP = Eltrombopag; RO = Romiplostim; IV = Intravenous Immunoglobulin; AD = Intravenous Anti D

In Table 7.6 the impact of varying assumptions that have the tendency to favour romiplostim are explored. Scenario 4 in Table 7.6 below allows romiplostim to work over a 12 week

period, the time period when it is most likely to have the highest response rate. While the lead sequence on the frontier remains the same, its relative effectiveness over the next sequence is much less than in the base case and hence the ICER falls to £6,520,304 from £11,235,680. This does not alter overall conclusion but the magnitude of the changes in the ICER of one sequence over another further serves to illustrate the point that there is a large amount of uncertainty evident from the model.

The analysis in scenario 5 should be taken with some caution and is presented as an illustration and it is unlikely that eltrombopag performed as poorly as this compared to romiplostim. However, the indirect meta-analysis reported by the manufacturer in Section 6.6 of their analysis does suggest that eltrombopag may be less effective than romiplostim. When eltrombopag is assumed to be 46% as effective as romiplostim, the lead sequences do not change but the margin between the first two sequences is much lower than in the base case. The actual figures do not really tell us that much in absolute terms, however the way in which they change between sequences in comparison to the base case illustrates the importance of this uncertainty in the relative effectiveness of eltrombopag.

Table 7.6 The impact of varying parameter values: Splenectomised patients

Scenario	Sequences	Cost	Life Years	QALY	Relative ICER
1. Base Case	RI-EP-RO-IV	18,527	1.986	1.428	
	RI-EP-IV-RO	21,133	1.986	1.429	11,235,680
	RI-IV-EP-RO	25,584	1.985	1.428	11,711,779
	IV-RI-EP-RO	60,626	1.986	1.429	150,959,104
4. Changing cycle length for RO & EP to 12 weeks	RI-EP-RO-IV	18,664	1.986	1.428	
	RI-IV-EP-RO	25,742	1.986	1.429	6,520,384
	IV-RI-EP-RO	50,802	1.986	1.429	150,959,106
5. Varying EP Response rate – 46% as effective as RO	RI-EP-RO-IV	18,910	1.985	1.425	
	RI-RO-EP-IV	19,008	1.985	1.426	96,008
	RI-IV-RO-EP	25,925	1.986	1.427	5,485,304
	IV-RI-RO-EP	50,984	1.986	1.427	150,959,109

RI = Rituximab; EP = Eltrombopag; RO = Romiplostim; IV = Intravenous Immunoglobulin; AD = Intravenous Anti D

Standard of care was not considered by GSK in their original submission as a comparator for the long term model. However, it was included as an option within their model. The ERG therefore undertook exploratory analysis to look at the impact of including standard of care in the model. The results show that while standard of care results in a lower cost of treatment, it

is substantially less effective (as anticipated) than any of the main treatment sequences presented by the manufacturer. The least costly option (RI-EP-RO-IV) in the base case analysis is associated with an incremental cost per QALY of over £240,000 when standard of care is introduced.

Table 7.7 The impact of varying structural assumptions: Splenectomised patients

Scenario	Sequences	Cost (£)	Life Years	QALY	Relative ICER
1. Base Case	RI-EP-RO-IV	18,527	1.986	1.428	
	RI-EP-IV-RO	21,133	1.986	1.429	11,235,680
	RI-IV-EP-RO	25,584	1.985	1.428	11,711,779
	IV-RI-EP-RO	60,626	1.986	1.429	150,959,104
6. Including Standard of Care in the Model	SC-SC-SC-SC-SC	1,179	1.972	1.354	
	RI-EP-RO-IV-SC	19,471	1.986	1.429	245,430
	RI-EP-IV-RO-SC	22,504	1.986	1.429	11,222,405
	IV-RI-EP-RO-SC	51,399	1.986	1.429	150,959,107
7. 0% of grade 4 bleeds are fatal	RI-EP-RO-IV	18,574	1.988	1.429	
	RI-EP-IV-RO	21,179	1.988	1.429	11,989,449
	RI-IV-EP-RO	25,628	1.988	1.429	12,562,922
	IV-RI-EP-RO	50,686	1.988	1.430	162,955,886
8. 100% of grade 4 bleeds are fatal	RI-EP-RO-IV	18,515	1.985	1.428	
	RI-EP-IV-RO	21,122	1.985	1.428	11,061,897
	RI-IV-EP-RO	25,574	1.986	1.429	11,516,854
	IV-RI-EP-RO	50,633	1.986	1.429	148,231,088
9.Discount Rate 0%	RI-EP-RO-IV	18,855	1.986	1.453	
	RI-EP-IV-RO	21,511	1.986	1.453	11,382,525
	RI-IV-EP-RO	26,034	1.986	1.453	11,835,733
	IV-RI-EP-RO	51,493	1.986	1.454	152,675,199
10. Discount Rate 6%	RI-EP-RO-IV	18,306	1.986	1.412	
	RI-EP-IV-RO	20,878	1.986	1.412	11,135,695
	RI-IV-EP-RO	25,281	1.986	1.412	11,627,509
	IV-RI-EP-RO	50,072	1.986	1.413	149,793,912

RI = Rituximab; EP = Eltrombopag; RO = Romiplostim; IV = Intravenous Immunoglobulin; AD = Intravenous Anti D; SC = standard of care

The standard of care option as presented in the model is reflective of patients receiving routine concomitant and rescue medication as per the RAISE trial and the manufacturer's watch and rescue economic evaluation. While standard of care is the least costly option it may not be considered effective enough in the treatment of long-term chronic ITP patients

who are considered as part of this model. Including standard of care also illustrates the importance of therapy on mortality. In scenario 6 adopting an active treatment results in at least a gain of 0.065 life years (approximately an extra 24 days) over the two year time horizon of the model compared to standard of care.

The model appears quite insensitive to changes in the percentage risk of WHO grade 4 bleeds being fatal, offering little or no difference in the relative ICERs (given their size in tens and hundreds of millions) between the extreme assumptions that 0% or 100% of grade 4 bleeds are fatal.

Over the two year time horizon, the model is not sensitive to changes in the discount rate used. However the results are likely to be magnified over a lifetime horizon. While the impact of various sensitivity analyses outlined above is minor when analyses are considered in isolation, it is likely that a much greater effect will be evident when certain combinations of analyses are presented together. Tables 7.8, 7.9 and 7.10 report the results of these additional analyses.

The following tables present various plausible combinations of analyses which may or may not impact on the results. The idea of this is to provide a sensitivity analysis looking at all possible scenarios and outcomes. For clarification, Tables 7.8, 7.9 and 7.10 describe 3 separate areas of uncertainty as follows:

A) Changes comparing romiplostim and eltrombopag over various time horizons and discount rates: Table 7.8.
B) Exploring the impact of a lower target value and low risk of a grade 4 bleed being fatal: Table 7.9.
C) Exploring the impact of a lower target value and high risk of a grade 4 bleed being fatal: Table 7.10.

Table 7.8 Exploring changes between the effectiveness of eltrombopag as compared to romiplostim from the meta analysis

Scenario	Sequences	Cost (£)	Life Years	QALY	Relative ICER
1. Base Case	RI-EP-RO-IV	18,527	1.986	1.428	
	RI-EP-IV-RO	21,133	1.986	1.429	11,235,680
	RI-IV-EP-RO	25,584	1.985	1.428	11,711,779
	IV-RI-EP-RO	60,626	1.986	1.429	150,959,104
Combine 4 & 5	RI-EP-RO-IV	19,116	1.985	1.424	
	RI -RO-EP-IV	19,638	1.985	1.426	330,372
	RI-IV-RO-EP	26,405	1.986	1.427	3,861,481
	IV-RI -RO-EP	51,465	1.986	1.428	150,959,109
Combine 3, 4 & 5	RI -RO-EP-IV	245,914	42.036	15.584	
	RI-IV-RO-EP	331,336	42.053	15.592	10,012,979
	IV-RI -RO-EP	476,594	42.054	15.593	297,159,118
Combine 3,4,5&6	SC-SC-SC-SC-SC	26,405	35.946	13.034	
	RI -RO-EP-IV	289,105	42.136	15.622	101,498
	RI-IV-RO-EP	385,442	42.152	15.631	11,292,240
	IV-RI -RO-EP	530,699	42.153	15.631	297,159,118
Combine 3,4,5,6&9	SC-SC-SC-SC-SC	62,202	35.946	24.204	
	EP -RI -RO-IV	574,409	42.094	30.515	81,165
	RI -RO-EP-IV	604,850	42.136	30.554	772,868
	RI-IV-RO-EP	803,191	42.152	30.570	12,337,218
	IV-RI -RO-EP	1,014,078	42.153	30.571	277,352,420
Combine 3,4,5,6&10	SC-SC-SC-SC-SC	16,598	35.946	9.489	
	RI -RO-EP-IV	196,477	42.136	11.060	114,518
	RI-IV-RO-EP	262,524	42.152	11.066	10,540,618
	IV-RI -RO-EP	381,007	42.153	11.066	297,671,551

RI = Rituximab; EP = Eltrombopag; RO = Romiplostim; IV = Intravenous Immunoglobulin; AD = Intravenous Anti D; SC = Standard of care

In general it is found that the model is quite robust to individual changes in the parameters, however, it is when analyses are combined, where the biggest changes from the base case occur. While some of changes made in the sensitivity analysis reflect methodological or structural uncertainty other changes represent more fundamental uncertainty in parameter values e.g. what is the relative difference between eltrombopag and romiplostim? There is a lack of direct evidence and the indirect treatment comparison while suggestive that eltrombopag is inferior to romiplostim is limited. The ERG is not suggesting that these figures are representative of states of the world that are most likely to exist. What these

analyses do illustrate, however, is the degree of uncertainty surrounding the results in the base case analysis with respect to judgements that can be made about what the model structure and input parameters.

Table 7.9 Exploring the impact of a lower target value and low risk of having a fatal grade 4 bleed: Splenectomised patients

Scenario	Sequences	Cost (£)	Life Years	QALY	Relative ICER
1. Base Case	RI-EP-RO-IV	18,527	1.986	1.428	
	RI-EP-IV-RO	21,133	1.986	1.429	11,235,680
	RI-IV-EP-RO	25,584	1.985	1.428	11,711,779
	IV-RI-EP-RO	60,626	1.986	1.429	150,959,104
Combine 2&7	RI-EP-RO-IV	16,455	1.988	1.429	
	RI-EP-IV-RO	28,338	1.988	1.429	7,267,616
	RI-IV-EP-RO	23,458	1.988	1.429	14,607,421
	IV-RI-EP-RO	54,384	1.988	1.430	116,121,979
Combine 2,7&5	RI -RO-EP-IV	17,041	1.988	1.426	
	RI-IV-RO-EP	23,596	1.988	1.427	4,146,528
	IV-RI -RO-EP	54,522	1.988	1.428	116,121,979
Combine 2,7,5&6	SC-SC-SC-SC-SC	1,658	1.988	1.357	
	RI -RO-EP-IV	18,042	1.988	1.427	236,218
	RI-IV-RO-EP	24,850	1.988	1.428	4,306,581
	IV-RI -RO-EP	55,776	1.988	1.428	116,121,981
Combine 2,3,7,5&6	SC-SC-SC-SC-SC	101,459	43.419	13.376	
	EP -RI -RO-IV	276,089	43.419	15.526	81,242
	RI-EP-RO-IV	282,607	43.419	15.532	1,091,223
	RI -RO-EP-IV	303,607	43.419	15.542	2,064,885
	RI-IV-EP-RO	375,316	43.419	15.547	14,130,163
	RI-IV-RO-EP	407,153	43.419	15.549	15,116,174
	IV-RI -RO-EP	536,528	43.419	15.550	216,100,175
Combine 2,7,5&9	RI -RO-EP-IV	17,341	1.988	1.450	
	RI-IV-RO-EP	24,014	1.988	1.452	4,198,475
	IV-RI -RO-EP	55,433	1.988	1.452	117,565,327
Combine 2,7,5&10	RI -RO-EP-IV	16,839	1.988	1.409	
	RI-IV-RO-EP	23,314	1.988	1.411	4,111,200
	IV-RI -RO-EP	53,908	1.988	1.411	115,143,703
Combine 2,7,5,3&9	EP -RI -RO-IV	495,398	43.419	30.003	
	RO-EP-RI-IV	502,862	43.419	30.011	891,370
	RI -RO-EP-IV	519,365	43.419	30.027	1,055,300
	RI-IV-RO-EP	695,496	43.419	30.040	13,558,183
	IV-RI -RO-EP	845,587	43.419	30.041	178,972,806
Combine 2,7,5,3&10	RI -RO-EP-IV	168,992	43.419	10.970	
	RI-IV-RO-EP	231,071	43.419	10.975	11,540,348
	IV-RI -RO-EP	345,761	43.419	10.976	223,440,050

RI = Rituximab; EP = Eltrombopag; RO = Romiplostim; IV = Intravenous Immunoglobulin; AD = Intravenous Anti D; SC = Standard of care

Romiplostim tends to perform better over a longer time horizon relative to eltrombopag. Again, the important point to note here is that there is considerable uncertainty surrounding the most cost-effective treatment sequences when various scenarios are combined. Various other combinations of analyses over alternative time horizons, changing discount rates and including standard of care in the model are explored and illustrated above.

Table 7.10 provides a similar analysis approach, the main difference being, it is assumed that patients with a grade 4 bleed are certain to die. i.e it is assumed here that 100% of grade 4 bleeds are fatal.

Table 7.10 Exploring the impact of a lower target value and high risk of having a fatal grade 4 bleed: Splenectomised patients

Scenario	Sequences	Cost (£)	Life Years	QALY	Relative ICER
Combine 2,8	RI-EP-RO-IV	16,387	1.985	1.428	
	RI -EP-IV-RO	18,272	1.985	1.428	6,690,335
	RI-IV-EP -RO	23,396	1.985	1.429	13,328,015
	IV-RI-EP-RO	54,325	1.985	1.429	104,914,764
Combine 2,8&3	RI -RO-EP-IV	251,851	41.325	15.473	
	RI-EP-RO-IV	251,942	41.331	15.476	32,641
	RI-IV-EP-RO	323,740	41.341	15.481	17,483,470
	IV-RI -EP -RO	453,136	41.342	15.481	161,436,920
Combine 2,8&5	RI -RO-EP-IV	16,954	1.984	1.425	
	RI-IV-RO-EP	23,523	1.985	1.427	3,799,045
	IV-RI -RO-EP	54,452	1.985	1.427	104,914,764
Combine 2,8,5&6	SC-SC-SC-SC-SC	1,181	1.967	1.352	
	RI -RO-EP-IV	17,957	1.984	1.426	228,828
	RI-IV-RO-EP	24,780	1.985	1.427	3,945,349
	IV-RI -RO-EP	55,709	1.985	1.428	104,914,765
Combine 2,8,5&9	RI -RO-EP-IV	17,251	1.984	1.449	
	RI-IV-RO-EP	23,940	1.985	1.451	3,842,043
	IV-RI -RO-EP	55,362	1.985	1.451	106,080,161
Combine 2,8,5,9&3	EP-RO- RI-IV	430,152	40.551	29.378	
	RO-EP- RI –IV	437,959	40.566	29.389	669,806
	RI -RO-EP-IV	455,092	40.594	29.411	790,908
	RI-IV-RO-EP	631,729	40.616	29.429	9,904,366
	IV-RI -RO-EP	781,855	40.617	29.430	128,602,590
Combine 2,8,5&10	RI -RO-EP-IV	16,753	1.984	1.408	
	RI-IV-RO-EP	23,243	1.985	1.410	3,769,743
	IV-RI -RO-EP	53839	1.985	1.410	104,123,143
Combine 2,8,5,10&3	RI -RO-EP-IV	157,865	40.594	10.863	
	RI-IV-RO-EP	220,113	40.616	10.870	8,879,922
	IV-RI -RO-EP	334,820	40.617	10.871	170,861,833

RI = Rituximab; EP = Eltrombopag; RO = Romiplostim; IV = Intravenous Immunoglobulin; AD = Intravenous Anti D; SC = Standard of care

The main conclusion from Tables 7.9 and 7.10 is that there is little or no effect on the treatment sequences in the model as a result of the percentage of grade 4 bleeds which are fatal.

In none of the various analyses presented above have any of the more costly sequences got an incremental cost per QALY that approaches a threshold value that society might be willing to pay. The introduction of the low cost 'standard of care' sequence means that no active treatment sequence is associated with an incremental cost per QALY that society might find acceptable.

These analyses illustrate the considerable structural and parameter uncertainty contained within the model. Some plausible changes and combinations of sequences favour eltrombopag and some do not. The main point however; is that the model results are surrounded by a considerable degree of uncertainty which make it difficult to draw concrete conclusions with regard to overall cost-effectiveness.

7.5.2 Non Splenectomised patient group

Due to the similarity between the two models, the results for non-splenectomised patients are similar in many respects to those for the splenectomised patient group. The only obvious difference is the fact that Anti D is included in the non-splenectomised model. It does not however occupy any prominent positions within the treatment sequences identified as being on cost-effectiveness frontier for any of the analyses conducted. Table 7.11 describes the results of the sensitivity analysis conducted by the manufacturer and again are only included for completeness.

Table 7.11 Long term model – Non Splenectomised patient group: manufacturer analysis

Scenario	Sequences	Cost	Life Years	QALY	Relative ICER
1. Base Case	RI-EP-RO-IV-AD	17,587	1.986	1.43	
	RI-EP-IV-AD-RO	19,992	1.986	1.43	10,749,060
	RI-IV-EP-AD-RO	23,986	1.986	1.43	15,402,007
	RI- IV-AD-EP-RO	26,932	1.986	1.43	164,623,320
2. Response Rate > 30 x 10^9/L	RI-EP-RO-IV-AD	15,870	1.986	1.43	
	RI-EP-IV-AD-RO	17,233	1.986	1.43	6,040,665
	RI-IV-EP-AD-RO	22,715	1.986	1.43	99,227,335
	IV-RI-EP-AD-RO	54,483	1.986	1.43	16,4090,975
	IV -EP-RI -AD-RO	59,574	1.986	1.43	219,607,583
3. Life Time Horizon	RI-EP-RO-IV-AD	260,199	42.643	15.819	
	RI-IV-EP-AD-RO	325,257	42.648	15.821	24,727,254
	RI-IV-AD-EP-RO	386,796	42.648	15.821	545,565,480

RI = Rituximab; EP = Eltrombopag; RO = Romiplostim; IV = Intravenous Immunoglobulin; AD = Intravenous Anti D

Table 7.12 The impact of varying parameter values:

Scenario	Sequences	Cost	Life Years	QALY	Relative ICER
1. Base Case	RI-EP-RO-IV-AD	17,587	1.986	1.43	
	RI-EP-IV-AD-RO	19,992	1.986	1.43	10,749,060
	RI-IV-EP-AD-RO	23,986	1.986	1.43	15,402,007
	RI- IV-AD-EP-RO	26,932	1.986	1.43	164,623,320
4. Changing cycle length for RO & EP to 12 weeks	RI-EP-RO-IV-AD	17,620	1.986	1.43	
	RI-EP-IV-AD-RO	19,963	1.986	1.43	7,036,474
	RI-IV-EP-AD-RO	24,053	1.986	1.43	7,313,726
	RI –IV-AD-EP-RO	27,040	1.986	1.431	25,818,933
5. Varying Eltrombopag Response rate – 33% as effective as Romiplostim	RI-RO-EP-IV-AD	18,395	1.986	1.428	
	RI-IV-RO-AD-EP	24,794	1.986	1.429	4,756,246
	RI- IV-AD-RO-EP	26,346	1.986	1.429	13,131,249

RI = Rituximab; EP = Eltrombopag; RO = Romiplostim; IV = Intravenous Immunoglobulin; AD = Intravenous Anti D

Table 7.13 The impact of varying the structural assumptions

Scenario	Sequences	Cost	Life Years	QALY	Relative ICER
1. Base Case	RI-EP-RO-IV-AD	17,587	1.986	1.43	
	RI-EP-IV-AD-RO	19,992	1.986	1.43	10,749,060
	RI-IV-EP-AD-RO	23,986	1.986	1.43	15,402,007
	RI- IV-AD-EP-RO	26,932	1.986	1.43	164,623,320
6. Inclusion of Standard of care in the model	SC-SC-SC-SC-SC-SC	1066	1.974	1.362	
	RI-EP-RO-IV-AD-SC	17930	1.986	1.43	247,995
	RI-EP-IV-AD-RO-SC	20490	1.986	1.43	11,441,574
	RI-IV-EP-AD-RO-SC	24259	1.986	1.431	14,539,385
	RI-IV-AD-EP-RO-SC	27365	1.986	1.431	173,529,204
7. 0% of grade 4 bleeds are fatal	RI-EP-RO-IV-AD	17,627	1.988	1.430	11,458,651
	RI-EP-IV-AD-RO	20,031	1.988	1.431	16,510,954
	RI-IV-EP-AD-RO	24,023	1.988	1.431	174,256,186
	RI- IV-AD-EP-RO	26,969	1.988	1.431	
8. 100% of grade 4 bleeds are fatal	RI-EP-RO-IV-AD	17,577	1.986	1.43	10,585,305
	RI-EP-IV-AD-RO	19,982	1.986	1.43	15,147,800
	RI-IV-EP-AD-RO	23,976	1.986	1.43	162,379,358
	RI- IV-AD-EP-RO	26,923	1.986	1.43	
9. Discount Rate 0%	RI-EP-RO-IV-AD	17,901	1.986	1.455	
	RI-EP-IV-AD-RO	20,353	1.986	1.455	10,889,079
	RI-IV-EP-AD-RO	24,409	1.986	1.455	15,559,291
	RI- IV-AD-EP-RO	27,411	1.986	1.455	166,633,199
10. Discount Rate 6%	RI-EP-RO-IV-AD	17,377	1.986	1.413	10,653,673
	RI-EP-IV-AD-RO	19,749	1.986	1.414	15,295,049
	RI-IV-EP-AD-RO	23,700	1.986	1.414	163,254,173
	RI- IV-AD-EP-RO	26,609	1.986	1.414	

RI = Rituximab; EP = Eltrombopag; RO = Romiplostim; IV = Intravenous Immunoglobulin; AD = Intravenous Anti D; SC = Standard of care

As Tables 7.12 and 7.13 illustrate single variant sensitivity analysis does not tend to change the lead sequence on the cost-effective frontier except when response rates are adjusted in line with the meta-analysis between eltrombopag and romiplostim. The manufacturer's submission correctly notes that these results should be taken with caution given the wide confidence intervals on the difference between the two drugs in the meta-analysis. More importantly, the results show that the model is open to a considerable amount of uncertainty.

This point is further illustrated in extra probabilistic sensitivity analysis which is reported in Section 7.6.

As with the splenectomised model above, when results are combined we see that the treatment sequences change. For example, based on the combination of the two sensitivity analyses conducted in the submission, the lead sequence on the cost-effectiveness frontier has romiplostim as the most cost effective treatment in a post rituximab treatment sequence. However, the magnitude of the ICERs reported are all still beyond those that might generally be considered acceptable. Of more importance is the fact that the model is suspect to many different combinations of sensitivity analyses. The multi–variant analyses conducted present quite similar conclusions to those already reported for the splenectomised model above. Therefore, they are reported in Appendix 3.

7.5.3 Further analysis conducted

Comparing the lead treatment sequence with a possible more clinically likely sequence

As an additional exploratory analysis request by NICE, the ERG has compared the lead treatment sequence presented by the manufacturer, with an alternative sequence identified as clinically plausible. The ERG feels that a likely clinically acceptable sequence would be to treat first with Rituximab and then IVIg. This is compared in Table 7.14 to the lead treatment sequence identified in the manufacturer's analysis.

Table 7.14 Comparing a selected clinically plausible sequence with the manufacturer's lead sequence from the base case analysis

Analysis	Sequence	Cost (£)	Life Years	QALY	ICER
Splenectomised	RI-EP-RO-IV	19,471	1.986	1.429	Dominant
2 year time horizon	RI-IV-SC	20,618	1.984	1.420	
Splenectomised	RI-EP-RO-IV	292,593	42.377	15.719	96,507
50 year time horizon	RI-IV-SC	234,715	40.850	15.119	
Non splenectomised	RI-EP-RO-IV-AD	17,930	1.986	1.430	Dominant
2 year time horizon	RI-IV-SC	19,039	1.985	1.422	
Non splenectomised	RI-EP-RO-IV-AD	281,261	42.703	15.842	92,053
50 year time horizon	RI-IV-SC	224,655	41.118	15.227	

RI = Rituximab; EP = Eltrombopag; RO = Romiplostim; IV = Intravenous Immunoglobulin; AD = Intravenous Anti D; SC =Standard of care

Over a 2 year time horizon, for both splenectomised and non splenectomised patient groups, the lead sequence identified by the manufacturer is less costly and more effective than the additional identified sequence. The manufacturer's lead sequence therefore dominates the sequence involving treatment with treat first with rituximab and then IVIg as presented in Table 7.14.

Over a longer life time horizon, for both patient groups, while the manufacturer's base case lead sequence remains more effective, the selected sequence for comparison is less costly. For both patient groups the incremental cost per QALY for the manufacturer's base case lead sequence is over £90,000 and this illustrates the importance of the choice of time horizon.

Exploring the impact of comparing the lead sequence with the same sequence without romiplostim

The manufacturer's submission correctly details that when the lead sequence with the inclusion of eltrombopag dominates the same sequence without eltrombopag. The ERG has undertaken further exploratory analysis to identify whether this is the case for romiplostim (one of eltrombopag's main comparator treatments).

Table 7.15 Exploring the impact of comparing the lead sequence with the same sequence without romiplostim

Analysis	Sequence	Cost (£)	Life Years	QALY	ICER
Splenectomised	RI-EP-RO-IV	18,527	1.986	1.428	Dominant
2 year time horizon	RI-EP-IV	22,449	1.985	1.427	
Splenectomised	RI-EP-RO-IV	252,519	42.303	15.691	Dominant
50 year time horizon	RI-EP-IV	354,772	41.889	15.535	
Non splenectomised	RI-EP-RO-IV-AD	17,930	1.986	1.430	Dominant
2 year time horizon	RI-EP-IV	20,471	1.986	1.430	
Non splenectomised	RI-EP-RO-IV-AD	281,261	42.703	15.842	Dominant
50 year time horizon	RI-EP-IV	342,411	42.456	15.750	

RI = Rituximab; EP = Eltrombopag; RO = Romiplostim; IV = Intravenous Immunoglobulin; AD = Intravenous Anti D

Table 7.15 shows that the lead sequence including romiplostim is less costly and more effective than the same sequence without romiplostim and is therefore dominant. A similar result was also reported for a similar analysis involving eltrombopag. The ERG therefore points out that the analysis presented by the manufacturer for eltrombopag should be interpreted cautiously.

Changes in cost of eltrombopag to reflect threshold cost identified for watch and rescue model

As correctly pointed out in the submission document, the models are very much cost-driven. Therefore the ERG has conducted some additional analysis assessing the impact on the treatment sequences of using the price of eltrombopag required to obtain a threshold of £20,000 per QALY in the watch and rescue model. The results are presented in Table 7.16.

Table 7.16 Treatment sequences at selected eltrombopag price level

Group	Sequence	Cost (£)	Life Years	QALY	ICER
Splenectomised	RI-EP-RO-IV	11,852	1.986	1.428	
P = £20.11	RI-EP-IV-RO	14,458	1.986	1.429	11,235,677
	RI-IV-EP-RO	22,356	1.986	1.429	20,779,355
	IV-RI-EP-RO	47,415	1.986	1.429	150,959,104
Non	RI-EP-RO-IV-AD	10,528	1.986	1.430	
Splenectomised	RI-EP-IV-AD-RO	12,933	1.986	1.430	10,749,063
P = £15.89	RI-IV-EP-AD-RO	20,393	1.986	1.430	28,769,959
	RI- IV-AD-EP-RO	26,932	1.986	1.430	365,373,761

P = price; RI = Rituximab; EP = Eltrombopag; RO = Romiplostim; IV = Intravenous Immunoglobulin; AD = Intravenous Anti D

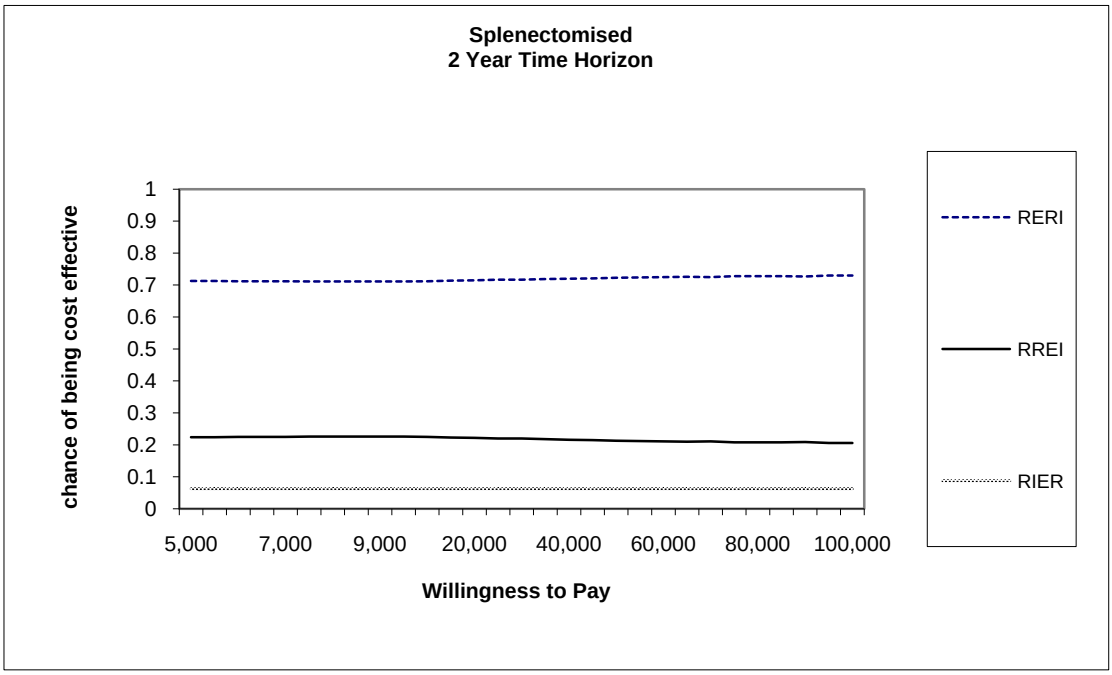
Surprisingly, changing the price of eltrombopag used in the model had little or no affect on the treatment sequences or indeed on the magnitude of one ICER relative to another. Even if eltrombopag is assumed to be free of charge (for argument sake), only one sequence on the frontier is eltrombopag lead. This is driven by the fact that rituximab lead sequences are marginally more effective than eltrombopag ones. However, what is more important is that the model seems to fail to pick up adequately on changes to many of the core values. Therefore, there may be an inability to deal with uncertainty in this model.

7.6 Probabilistic analysis: Long term model

In order to further explore the uncertainty between sequences, the ERG analysed a selection of rituximab lead sequences together for both the splenectomised and non-splenectomised patient groups. As deterministic analyses were difficult to interpret because of the degree of uncertainty present the ERG felt that any uncertainties in the model may be more clearly identified through further probabilistic sensitivity analysis. The manufacturer's submission was somewhat lacking in the in this respect although the model was well equipped to perform these tasks. This section aims to elaborate on the analyses presented and further address the issue of uncertainties between treatment sequences. The analysis presented in this section reports cost effectiveness acceptability curves for selected rituximab lead sequences over a two year and 50 year time horizon. All analyses are calculated using 1000 iterations from the Monte Carlo simulation provided within the manufacturer's model.

Figures 7.1 and 7.2 refer to splenectomised patient group and show the CEACs for three common plausible treatment sequences over a two year period and a 50 year period.

Figure 7.1 Cost-effectiveness acceptability curve; 2 year time horizon: splenectomised patients



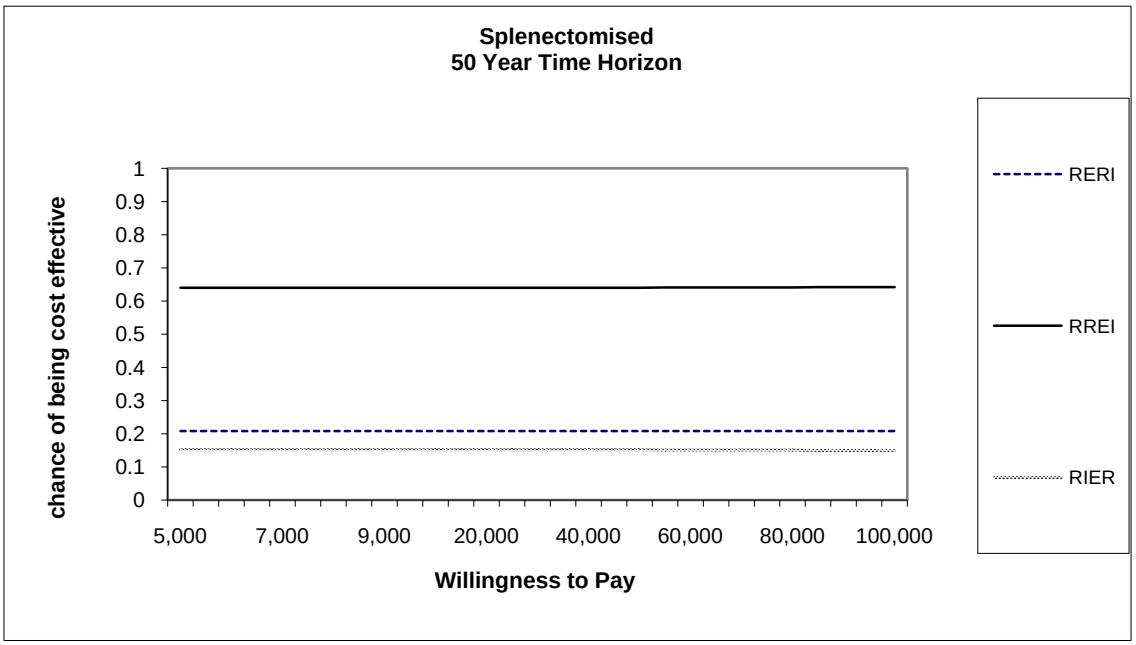
RERI= Rituximab, Eltrombopag, Romiplostim, IVIg

RREI= Rituximab, Romiplostim, Eltrombopag, IVIg

RIER= Rituximab, IVIg, Eltrombopag, Romiplostim

The results in Figure 7.1 show that over a two year time horizon, it is very likely that a treatment sequence with Eltrombopag administered after Rituximab is the most cost-effective approach. Figure 7.2 identifies the CEACs associated with the same treatment sequences over a 50 year time horizon.

Figure 7.2 Cost-effectiveness acceptability curve; 50 year time horizon: splenectomised patients

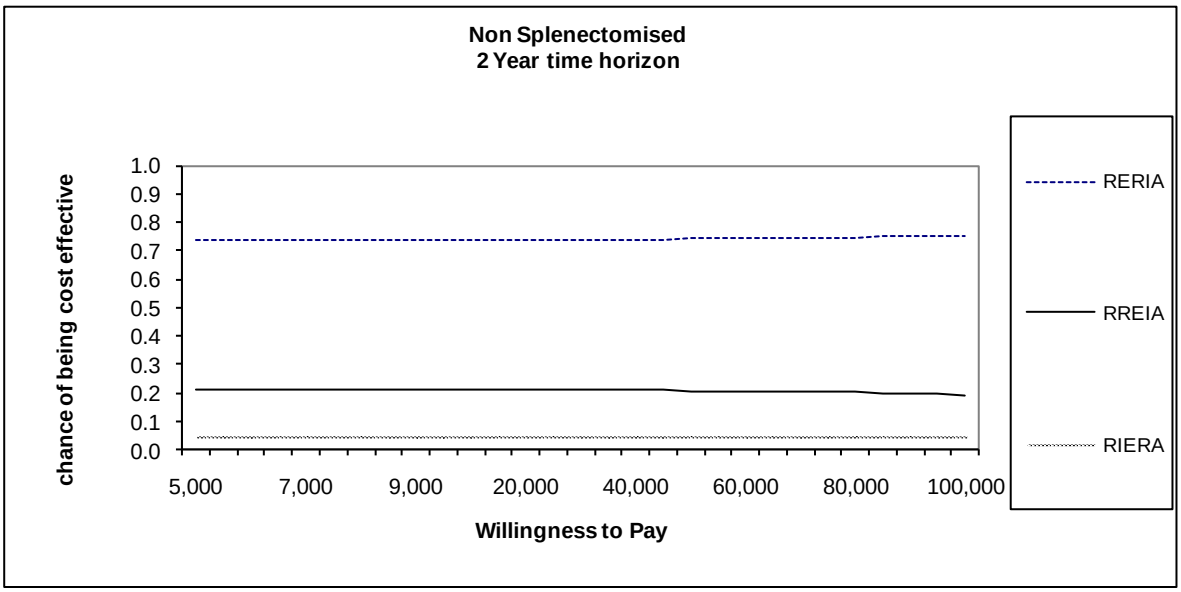


RERI= Rituximab, Eltrombopag, Romiplostim, IVIg
RREI= Rituximab, Romiplostim, Eltrombopag, IVIg
RIER= Rituximab, IVIg, Eltrombopag, Romiplostim

The evidence from Figure 7.2 suggests that a treatment sequence where romiplostim is administered post rituximab is the most likely to be cost-effective. This is in contrast with Figure 7.1 which favoured eltrombopag as a second treatment in a sequence. The main point to take from this analysis is that the model is very sensitive to the time horizon chosen for the analysis. The best data, which is admittedly limited relates to the shorter-term time horizon.

Figures 7.3 and 7.4 apply the same analysis to the non-splenectomised patient group:

Figure 7.3 Cost-effectiveness acceptability curve: 2 year time horizon; non-splenectomised patient group



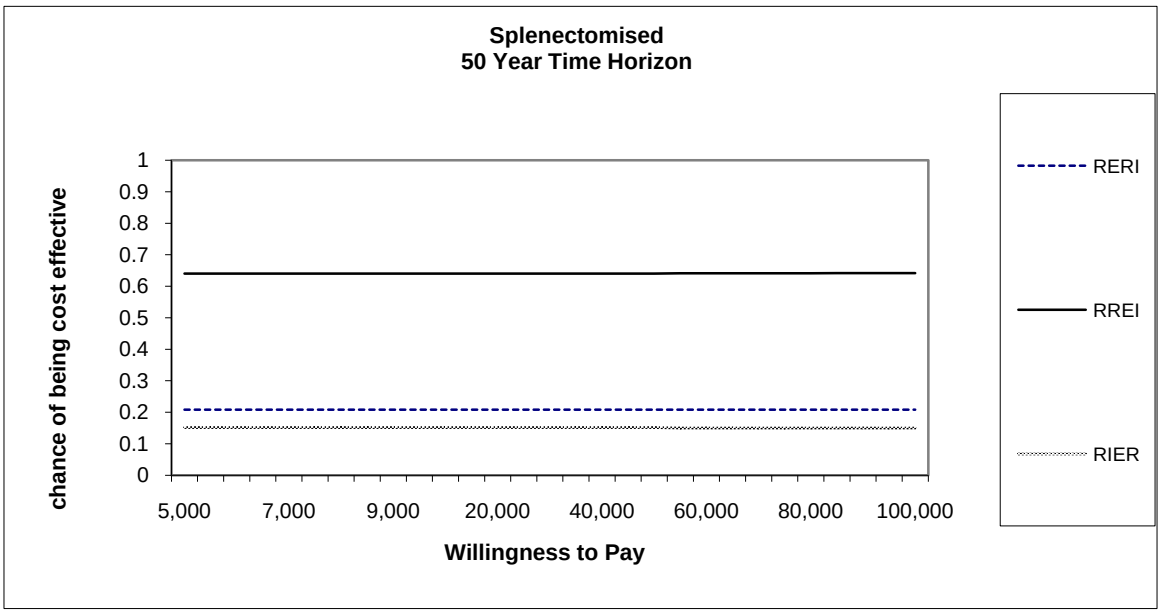
RERIA= Rituximab, Eltrombopag, Romiplostim, IVIg; Anti-D

RREIA = Rituximab, Romiplostim, Eltrombopag, IVIg; Anti-D

RIERA= Rituximab, IVIg, Eltrombopag, Romiplostim, Anti-D

As with the splenectomised patient group, Figure 7.4 clearly shows that a treatment sequence with eltrombopag prescribed post rituximab is the most likely to be cost-effective over a two year time horizon.

Figure 7.4 Cost-effectiveness acceptability curve: 50 year time horizon; non-splenectomised patient group



RERIA= Rituximab, Eltrombopag, Romiplostim, IVIg; Anti-D

RREIA = Rituximab, Romiplostim, Eltrombopag, IVIg; Anti-D

RIERA= Rituximab, IVIg, Eltrombopag, Romiplostim, Anti-D

As with the splenectomised group, over a longer time horizon (50 years) the treatment sequence using romiplostim post rituximab is more likely to be cost effective than using eltrombopag post rituximab (Figure 7.5).

What has not been shown is the effect of introducing a standard or care option into a probabilistic sensitivity analysis. Were this to be done then this treatments sequence would be associated with the highest cost-effectiveness over all values for society's willingness to pay that might be considered acceptable.

7.7 Summary of results

These additional analyses have demonstrated that the results of the cost-effectiveness analysis are not generally altered to any significant extent by univariant changes in the long term model. With regards to the Watch and Rescue model however, the analysis concludes that the model is sensitive to:

A) The costing approach adapted
B) The annual risk of a fatal bleed
C) Discount rate used in the analysis
D) The WHO grade of bleed applied in the model.

In addition to changes in these parameters, the results of the watch and rescue model are also sensitive to changes in the cost of eltrombopag, as reported in Chapter 5, although the reductions in the price of eltrombopag are substantially greater than those initially considered by the manufacturer.

However, the main limitation to the analysis as presented by the manufacturer was the lack of any multivariate sensitivity. The tables detailed above illustrate that combining a changes in various assumptions in both models have a substantial effect on the ICERs presented. Best and worst case scenarios illustrate the full scale of possible uncertainty in the model. This is much clearer from the Watch and Rescue model than the long-term model. However, in neither model are ICERs below typical thresholds considered worthwhile.

The long term model is quite robust to deterministic sensitivity analysis. However, introducing standard of care results in no active treatment sequence having a QALY below £30,000 and combining a life time horizon with a response rate of > $30x10^9$/L alters the treatment sequences and tends to favour romiplostim over eltrombopag. Of greater interest

however, is the probabilistic analysis which clearly favours eltrombopag over a two year time horizon and romiplostim over a 50 year time horizon when a standard of care option is not included in the analysis.

This chapter has concentrated on sensitivity analysis that makes eltrombopag less cost-effective. It is important to note that there are other plausible changes that may serve to make eltrombopag appear more cost-effective than is detailed in the industry submission; however these have not been modelled. The key issue from the analysis as a whole is that the direction and magnitude of these uncertainties are unknown. Much of the uncertainty arises as a result of a lack of comparable evidence between treatments in the literature. Further studies and trials may become available in the future and these would give a much clearer picture of the most appropriate and cost–effective treatment programme for chronic adult ITP patients. For this to happen, there is a requirement for more RCTs of eltrombopag compared with its competitor drugs conducted in a setting relevant to the treatment of ITP in the UK.

8 DISCUSSION

8.1 Summary of clinical effectiveness issues

8.1.1 The systematic review and use of evidence reporting on comparator treatment

The manufacturer identified 20 RCTs and 93 non-randomised comparative studies or case series in the systematic review reporting on eltrombopag or comparator treatments. However, 36 studies reporting comparator treatments included children or adolescents (< 18 years old).

The evidence on comparator treatments was not statistically described, e.g. using median and range, or statistically synthesised. Instead, evidence from one or two primary studies/ reviews was used for each comparator treatment in the economic model. The manufacturer stated that the evidence chosen for the economic model was the best available. However, by undertaking independent searches, the ERG identified the ASH guideline[7] and a high quality systematic review[62] where more reliable evidence on IVIg and anti-D was reported, although such data would be unlikely to affect the conclusions of the economic evaluation.

8.1.2 Methodological quality of the three eltrombopag trials

In terms of the representativeness of the study participants, only 3/109 (2.8%), 10/114 (8.8%), and 9/197 (4.7%) participants in the eltrombopag trials were from the UK. It is unclear whether the participants in the eltrombopag trials are representative of UK chronic ITP patients (see Table 4.19 for baseline characteristics of participants in the eltrombopag groups in the trials).

In addition, the decision problem specified that one group of patients considered should be non-splenectomised patients for whom splenectomy is contraindicated. However, patients who were suitable for splenectomy might also have been included in the eltrombopag trials.

ITT analysis was not used in TRA100773A and B as the manufacturer stated. A small number of randomised patients (8/109 [7.3%] in TRA100773A, 2/102 [2.0%] in TRA100773B) were excluded from the statistical analysis. Any degree of exclusion following randomisation may break the balance of the baseline patient characteristics achieved by randomisation.

There were relatively large proportions of participants who withdrew or were lost to follow-up in the trials, ranging from 7% to 21% across treatment groups. In TRA100773A and B there were more such participants in the placebo groups and in the RAISE trial there were

more such participants in the eltrombopag group. As such participants were counted as non-responders (platelet count), the results for platelet response might have favoured eltrombopag in studies TRA100773A and B, and placebo in the RAISE study.

8.1.3 Indirect comparison comparing platelet response rates between eltrombopag and romiplostim

More participants in the eltrombopag trial received concomitant ITP treatments than in the romiplostim trials. Concomitant treatment may have beneficial effects on disease progression, but on the other hand patients who received concomitant treatment might have more severe illness. The effect that this imbalance might have had on the indirect comparison results is therefore uncertain.

The manufacturer used an inappropriate method (Mantel-Haenszel fixed effect meta-analysis) to combine the two romiplostim trials. In addition, as there were more participants who did not complete the treatment (withdrew or were lost to follow-up) in the eltrombopag trial than in the romiplostim trials, assuming such participants were non-responders (worst scenario) might have biased the results in favour of romiplostim.

In the further analysis conducted by the ERG the odds ratios of romiplostim compared with placebo were estimated using a logistic regression model and the participants who did not complete the trials were all counted as responders (best scenario). Data were available for all participants but not by splenectomy status.

The results of further analysis indicate that the results for durable response appear to be sensitive to the method used for handling those who did not complete the trials but not the results for overall response rate, i.e. in the manufacturer's results eltrombopag had a lower durable response rate than romiplostim (OR 0.26, 95% CI 0.03 to 2.62) but in the 'best scenario' there were no differences in durable response rates between eltrombopag and romiplostim (OR 1.04, 95% CI 0.32 to 3.44); and for durable response the results from the manufacturer's submission (OR 0.17, 95% CI 0.03 to 0.82) and from the 'best scenario' (OR 0.26, 95% CI 0.07 to 0.97) were consistent, with both results indicating that eltrombopag is associated with a significantly lower overall response rate than romiplostim.

8.2 Summary of cost-effectiveness issues

The manufacturer submitted two economic models for the use of eltrombopag in the treatment of chronic adult ITP patients. The first was the use of eltrombopag as part of a watch and rescue management system and the second was the use of eltrombopag as part of a treatment

sequence in a longer term continuous care setting. Both models considered the cost-effectiveness of using eltrombopag for two patient groups: those who are splenectomised and those who are non-splenectomised (contra-indicated to having a splenectomy).

8.2.1 Watch and Rescue model

The watch and rescue model was informed mainly from the RAISE double blinded RCT and it compared for each patient group the cost-effectiveness of eltrombopag with a standard care package that did not including eltrombopag. Further assumptions were made based on both published data and clinical expert opinion. With respect to the expert opinion used it is not always clear how expert opinion was used to value parameters in the model and further which experts contributed to which issues. Furthermore, it is unclear whether or not the evidence information used is representative of a UK ITP population.

It is assumed that all patients in the non-splenectomised patient group are contra-indicated to having a splenectomy. However, it is unclear whether the data available to model this patient group are applicable as it is unclear whether the non-splenectomised trial participants that contributed data were actually contra-indicated to splenectomy.

The extent of uncertainty in parameter values may not be adequately described within the model as submitted by the manufacturer. In particular, the model is sensitive to substantial changes in the cost of eltrombopag. The price of the drug would need to be substantially below the anticipated market price for eltrombopag to be considered cost-effective at typical threshold values that society might be willing to pay. The model is also sensitive to the rate of mortality used, as was illustrated in Chapter 7. The additional analyses conducted by the ERG showed that the results are also quite sensitive to the discount rate applied in the model.

One failure of the industry submission was the failure to conduct multi-variant sensitivity analysis. Plausible changes to certain combinations of assumptions lead to substantial increases in the incremental cost per QALY for both patient groups. Further plausible combinations explored lead to substantial reductions in the ICERs reported. However, none result in eltrombopag have an incremental cost per QALY of £30,000 or less other than substantial reductions in price. The key point to gain from this is that there is substantial uncertainty in the model and the true ICER could lie anywhere between the best and worst case scenarios presented. Even in the best case scenario, it is unlikely that Eltrombopag is cost-effective at the regular threshold value used by NICE unless the price is reduced as well.

8.2.2 Long-term model

The long-term model assessed the use of eltrombopag as part of a treatment sequence for the treatment of ITP based on a cohort of 25 patients. Expert opinion was used throughout the model to inform the choice of model structure and parameter values. As these assumptions represent judgements made by the manufacturer and their advisors there basis can be questioned as alternative assumptions might have been made.

It is also difficult to unravel how the basis for the manufacturer's estimation of the population of patients who will require long term care. There is likely to be considerable uncertainty surrounding this estimate, which includes uncertainty around incidence rates, uptake rates and the proportion of patients requiring long-term care. Sensitivity analysis illustrates that changes in the assumptions used can lead to considerable variation in cost with little variation in QALYs gained in each treatment sequence.

Specifically, in relation to the model structure, the ERG notes that rituximab is the first line of treatment in the majority of treatment sequences on the cost-effectiveness frontier identified by the manufacturer. Rituximab is not licensed in the UK for the treatment of ITP patients and the relevance of these treatment strategies may be limited.

The evidence base used to estimate effectiveness of treatments in this model is limited. The data used is essentially observational and no directly comparative data were available. The limited indirect comparative data for eltrombopag vs. romiplostim was not used. It is worth noting that, although not strong, these data were the best available and they favoured a comparator treatment (romiplostim) over eltrombopag. Furthermore, apart from the use of Anti D, assumptions incorporated in both the splenectomised and non splenectomised models were essentially the same.

With respect to health state utilities two different measures of utility were used to inform the model. It is unclear how comparable these methods are for ITP patients. More importantly, however, is the issue that the manufacturer did not incorporated and utility decrement due to adverse events associated with eltrombopag or any of the comparator treatments in the model. The only utility decrement measured is in relation to bleeding events. The direction of the bias this introduces is unclear but it is quite plausible that it against eltrombopag.

The sensitivity analysis conducted by the ERG in Chapter 7 highlights a number of issues of uncertainty. In general the results for both patient groups appear robust in the deterministic analysis. Various combinations of plausible variation are explored in further deterministic

analyses and multi-variant analyses. It is found that the results are influenced and are most sensitive to changes in:

- Time horizon
- Response rate
- Response target value

In the long-term model individual changes do not appear to affect the treatment sequences of the model, however, when combined it is found that using a platelet response rate of $>30x10^9$/L and increasing the time horizon to a 50 years romiplostim replaces eltrombopag as the most cost–effective treatment option post rituximab. Further combinations of analysis for both patient groups are discussed in Chapter 7.

A further treatment sequence considered in the additional sensitivity analysis was the inclusion of a "standard of care" sequence, which essentially only allowed patients to use rescue medications. The inclusion of this option may be debatable but it is worth noting that no treatment sequence including an active treatment was associated with an ICER below £30,000.

The probabilistic analysis as presented by the manufacturer was limited and no CEACs were reported. The ERG, as shown in Chapter 7, presented further sensitivity analyses to more fully explore issues of uncertainty in the model. The results show that over a two year time horizon (where standard of care was not included in the treatment sequence), eltrombopag was, when used after rituximab in a sequence for both patient groups most likely to be cost-effective. However, over a 50 year time horizon, the results favoured romiplostim. These results were applicable to both the splenectomised and non – splenectomised patient groups.

The ERG recognises that there is a very limited evidence base for assessing the cost–effectiveness of ITP treatments and that the evidence base for eltrombopag provided by the manufacturer was the best available source of evidence to inform the models. These data were also of superior quality than the data available for any of the comparator treatments (romiplostim excepted). To overcome the limitations of the overall evidence base, well designed and adequately powered RCTS of eltrombopag against its comparator drugs relevant to the UK are required.

8.3 Overall summary

Based on the evidence submitted and the additional work conducted by the ERG, the following are the main issues that a decision maker needs to note.

Effectiveness

- Eltrombopag appears to be a safe treatment for ITP.
- Eltrombopag has short term efficacy for the treatment of ITP.
- There is no robust evidence on long-term efficacy of eltrombopag.
- Eltrombopag appears to be less effective in achieving an overall response rate (four or more weeks platelet count $\geq 50 \times 10^{9}$/L) than romiplostim in a 6-month intervention period.
- There is no robust evidence on long-term effectiveness of eltrombopag compared to other relevant comparators.

Watch and Rescue model

- Is clinical evidence used to support the model reflective of the UK population?
- Substantial reductions in cost of eltrombopag are needed before the incremental cost per QALY is less than £30,000.
- Increases in the chance of dying from a bleeding event will improve the cost-effectiveness of eltrombopag. If they tend towards the upper boundary considered by the manufacturer, and the price of eltrombopag is reduced then it is plausible that the cost per QALY could be reduced to less than £30,000.
- Are adverse events likely to have a significant impact on patients using the drug? Other than bleeding there is no evidence of adverse events in the economic model. The effect of this exclusion is unclear but might represent a bias against eltrombopag.

Long-term model

- Is clinical evidence used to support the model reflective of the UK population?
- The use of non-randomised non comparative data is likely to result in biased estimates. The magnitude and direction of these biases is uncertain.
- The manufacturer chose to ignore the indirect treatment comparison data available for the comparison of eltrombopag with romiplostim. Inclusion of such data along with other plausible changes in the effectiveness of romiplostim substantially alters the order of treatments in terms of cost-effectiveness. A decision is needed as to whether such data are sufficiently robust.

- Inclusion of the standard of care sequence results in no active treatment sequence having an ICER below £30,000. It is unclear whether such a sequence is plausible.
- When excluding a standard of care sequence, a sequence where eltrombopag is used after rituximab is the least costly but least effective of the non-dominated sequences. None of the other sequences have an ICER below £30,000.
- The model is sensitive to the time horizon of the model. If the time horizon is restricted to 2 years (the strongest data only pertain to this time horizon) then a treatment sequence where eltrombopag is given after failure to respond with rituximab would be most likely to be cost-effective. A 50 year time horizon favours a sequence involving romiplostim. If a standard of care option were included it is less likely that an active treatment sequence would be considered worthwhile.
- Has the manufacturer correctly estimated their target patient population and the numbers of patients who will require long-term treatments? Many assumptions are used and a judgement is needed as to how applicable these are.

8.4 Implications for research

It is clear from the manufacturer's submission that there is a paucity of good quality evidence for the burden of disease and the treatment of ITP. What can be concluded is that ITP patients are being exposed to drugs with considerable side-effect profiles but with little evidence for efficacy, safety, effectiveness or cost-effectiveness. As a consequence of this dearth of evidence the following research recommendations are made:

- Epidemiological research is required to determine the true prevalence of ITP in the UK, and the proportion of patients requiring treatment and developing complications of the disease and treatments.
- Large good quality RCTs are needed to determine the best second/third line therapies comparing romiplostim, eltrombopag and possibly rituximab with each other. Such trials should include a full economic evaluation and hence have a long enough follow-up to capture the most important economic differences. Consideration may be needed as to how such trials might be funded because such head to head studies may not be in the best commercial interest of individual manufacturers.
- As so few medical treatments are actually licenced for use as treatments the use of romiplostim, eltrombopag and possibly rituximab should also be considered, and investigated, as first line therapy. Such investigation should involve the design and conduct of large good quality RCTs comparing the use of these therapies against each other. These trials should include economic evaluations.

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10 APPENDICES

Appendix 1 Independent searches undertaken by ERG

Medline/Embase search for Eltrombopag

Database: Ovid MEDLINE(R) (1996- Oct wk 2 2009), Ovid MEDLINE(R) In-Process (14th Oct 2009), EMBASE (1996-wk 41 2009)

Search Strategy:

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1 purpura, thrombocytopenic, idiopathic/ use medf
2 idiopathic thrombocytopenic purpura/ use emef
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 remove duplicates from 17
19 from 18 keep 1-81

Medline/Embase search for clinical effectiveness of comparators

Database: Ovid MEDLINE(R) (1966- Oct wk 2 2009), Ovid MEDLINE(R) In-Process (14th Oct 2009), EMBASE (1966-wk 41 2009)

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 eme
81. meta-analysis.pt.
82. review.pt.
83 meta-analysis/
84 systematic review/
85. randomized controlled trials/
86. (controlled or design or evidence or extraction).ab.
87. (sources or studies).ab.
88. or/60-87
89. 59 and 88
90. case report/ use emez
91. case reports.pt.
92. 89 not (90 or 91)
93. exp child/ or exp infant/
94. exp adult/
95. 93 not 94
96 92 not 95
97. limit 96 to english language

DARE and HTA Databases (October 2009)

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1 MeSH Purpura, Thrombocytopenic, Idiopathic EXPLODE 1 2 3 4 5
2 itp OR aitp
3 "idiopathic thrombocytop*
4 "immune thrombocytop*
5 "autoimmune thrombocytop*
6 #1 or #2 or #3 or #4

Appendix: 2 Description of calculations conducted in chapter 7: additional sensitivity analysis

Appendix 2 details all of the changes to the economic models conducted by the ERG while completing the additional analyses in Chapter 7. Any changes not directly referenced can be achieved by combining a number of the changes outlined in this Appendix.

Watch and Rescue model:

Table A1: Using Cell H38, settings tab to select the splenectomised patient group:

Reference	Details	Tab	CELL	Original calculation	ERG edit
Table 7.3					
Line 2	Typing corrections made to the model	ITP meds	AH40 AI40 AG50	12,000 14,100 14,100	120,000 140,000 140,000
Line 3	Sensitivity analysis using a micro costing approach	Settings Tab	H23	Macro	Micro
Line 4	Sensitivity analysis using all bleeding events	Settings Tab	H30	Clinically significant bleeding	All Bleeding
Line 5	Varying the discount rate for costs and benefits to 0%	Death	H26	3.5%	0%
Line 6	Varying the discount rate for costs and benefits to 6%	Death	H26	3.5%	6%
Line 7	Varying the annual risk of a fatal bleed to the lower bound reported in the Cohen 2000 study[10]	Death	H32	2.76	1.6
Line 8	Varying the annual risk of a fatal bleed to the upper bound of the Cohen 2000 study[10]	Death	H32	2.76	3.9
Line 9	Combining analyses 2,3,4,6 & 7 above to detail a worst case scenario	Combine changes in lines 2,3,4,6 and 7 above			
Line 10	Varying analyses 1,5 & 8 above to detail a best case scenario	Combine changes in lines 5 and 8 above			

Table A2: Using cell H38, settings tab to select the non-splenectomised patient group

Reference	Detail	Tab	CELL	Original calculation	ERG edit
Table 7.4					
Line 2	Typing corrections made to the model	ITP meds	AH40 AI40 AG50	12,000 14,100 14,100	120,000 140,000 140,000
Line 3	Sensitivity analysis using a micro costing approach	Settings Tab	H23	Macro	Micro
Line 4	Sensitivity analysis using all bleeding events	Settings Tab	H30	Clinically significant bleeding	All Bleeding
Line 5	Varying the discount rate for costs and benefits to 0%	Death	H26	3.5%	0%
Line 6	Varying the discount rate for costs and benefits to 6%	Death	H26	3.5%	6%
Line 7	Varying the annual risk of a fatal bleed to the lower bound reported in the Cohen 2000 study[10]	Death	H32	2.76	1.6
Line 8	Varying the annual risk of a fatal bleed to the upper bound of the Cohen 2000 study[10]	Death	H32	2.76	3.9
Line 9	Combining analyses 2,3,4,6 & 7 above to detail a worst case scenario	Combine changes in lines 2,3,4,6 and 7 above			
Line 10	Varying analyses 1,5 & 8 above to detail a best case scenario	Combine changes in lines 5 and 8 above			

Long term continuous care model: Splenectomised

Table A3: Splenectomised patient group

Reference	Detail	Tab	CELL	Original calculation	ERG edit
Table 7.5					
line 2	Varying the response rate for the model to a platelet count of > $30*10^9$/L	Main Control		Select C174	Select C176
Line 3	Running the model over a life time horizon	Results Batch	E18	2	50
Table 7.6					
Line 4	Adjusting the cycle lengths for Romiplostim and Eltrombopag from 8 to 12 weeks	Data Response	I69 I70	8 8	12 12
Line 5	Varying the response rate for Eltrombopag in line with the Meta analysis carried out by the manufacturer	Data Response	J23 K23 L23	J23 K23 L23	J23 = F24*.46 K23 = G24*.46 L23 = H24*.46
Table 7.7					
Line 6	Allowing the model to include standard of care as a treatment option	Main Control	G129	Deselect Standard of Care	Select Standard of Care
Line 7	Assuming 0% of WHO grade 4 bleeds are fatal	Default Data Data – Bleed Risk	H248 I38 I39	80% I38 I39	0% I38 = F38 I39 = F39
Line 8	Assuming 100% of WHO grade 4	Default Data	H248	80%	100%

	bleeds are fatal	Data – Bleed Risk	I38 I39	I38 I39	I38 = F38 I39 = F39
Line 9	Assuming a discount rate for costs and benefits of 0%	Main Control	F71 F75	3.5 3.5	0 0
Line 10	Assuming a discount rate for costs and benefits of 6%	Main Control	F71 F75	3.5 3.5	6 6

Long term continuous care model: Non-splenectomised

Table A4: Non-splenectomised patient group

Reference	Detail	Tab	CELL	Original calculation	ERG edit
Table 7.11					
line 2	Varying the response rate for the model to a platelet count of > $30*10^9$/L	Main Control		Select C174	Select C176
Line 3	Running the model over a life time horizon	Results Batch	E18	2	50
Table 7.12					
Line 4	Adjusting the cycle lengths for Romiplostim and Eltrombopag from 8 to 12 weeks	Data Response	I69 I70	8 8	12 12
Line 5	Varying the response rate for Eltrombopag in line with the Meta analysis carried out by the manufacturer	Data Response	J23 K23 L23	J23 K23 L23	J23 = F24*.33 K23 = G24*.33 L23 = H24*.33
Table 7.13					
Line 6	Allowing the model to include standard of care as a treatment option	Main Control	G129	Deselect Standard of Care	Select Standard of Care
Line 7	Assuming 0% of WHO grade 4	Default Data	H248	80%	0%

	bleeds are fatal	Data – Bleed Risk	I38 I39	I38 I39	I38 = F38 I39 = F39
Line 8	Assuming 100% of WHO grade 4 bleeds are fatal	Default Data Data – Bleed Risk	H248 I38 I39	80% I38 I39	100% I38 = F38 I39 = F39
Line 9	Assuming a discount rate for costs and benefits of 0%	Main Control	F71 F75	3.5 3.5	0 0
Line 10	Assuming a discount rate for costs and benefits of 6%	Main Control	F71 F75	3.5 3.5	6 6

Appendix 3: Additional multi-variant sensitivity analysis for non – splenectomised patients

Scenario	Sequences	Cost (£)	Life Years	QALY	Relative ICER
1.Base Case	RI-EP-RO-IV-AD	17,587.07	1.986	1.43	
	RI-EP-IV-AD-RO	19,992.16	1.986	1.43	10,749,060
	RI-IV-EP-AD-RO	23,985.54	1.986	1.43	15,402,007
	RI- IV-AD-EP-RO	26,931.85	1.986	1.43	164,623,320
Combine 4&5	RI-EP-RO-IV-AD	18,594	1.985	1.43	
	RI -RO-EP-IV-AD	18,843	1.986	1.43	131,277
	RI -RO -IV-AD-EP	22,109	1.986	1.43	3,409,416
	RI-IV-RO-AD-EP	25,026	1.986	1.43	3,649,945
	IV-RI –AD-RO-EP	26,643	1.986	1.43	8,272,760
Combine 3,4&5	RI -RO-EP-IV-AD	255.789	42.446	15.742	
	RI-IV-RO-AD-EP	340.418	42.467	15.752	8,376,638
	RI –IV-AD-RO-EP	372.302	42.469	15.753	27,099,473
Combine 3,4,5&6	SC-SC-SC-SC-SC	24,557	36.451	13.253	
	RI -RO-EP-IV-AD	280,588	42.538	15.777	101,450
	RI-IV-RO-AD-EP	371,512	42.559	15.787	8,999,707
	RI -IV-AD-RO-EP	411,704	42.561	15.788	34,161,055
Combine 3,4,5,6&9	SC-SC-SC-SC-SC	58,227	36.451	24.712	
	EP -RO -RI-AD-IV	575,080	42.487	30.942	82,964
	RI -RO-EP-IV-AD	594,124	42.538	30.989	399,187
	RI-IV-RO-AD-EP	784,342	42.559	31.009	9,473,536
	RI - IV-AD-RO-EP	877,936	42.561	31.012	39,712,006
Combine 3,4,5,6&10	SC-SC-SC-SC-SC	15,367	36.451	9.627	
	RI -RO-EP-IV-AD	189,275	42.538	11.144	114,622
	RI-IV-RO-AD-EP	251,004	42.559	11.152	8,587,977
	RI –IV-AD-RO-EP	276,444	42.561	11.152	30,571,396

Scenario	Sequences	Cost (£)	Life Years	QALY	Relative ICER
Combine 2&7	RI-EP-RO-IV-AD	15,916	1.988	1.430	
	RI-EP-IV-AD-RO	17,278	1.988	1.431	6,439,218
	RI-IV-EP-AD-RO	22,759	1.988	1.431	106,122,394
	IV-RI-EP-AD-RO	54,526	1.988	1.431	178,118,731
	IV -EP-RI-AD-RO	59,617	1.988	1.431	241,279,108
Combine 2,7&5	RI -RO-EP-IV-AD	17,048	1.988	1.428	
	RI-IV-RO-AD-EP	23,371	1.988	1.430	3,667,494
	RI - IV-AD-RO-EP	24,501	1.988	1.430	5,769,531
	IV-RI-AD-RO-EP	56,267	1.988	1.430	178,118,729
Combine 2,7,5&6	SC-SC-SC-SC-SC	1,258	1.988	1.377	
	RI -RO-EP-IV-AD	17,380	1.988	1.428	313,235
	RI-IV-RO-AD-EP	23,788	1.988	1.430	3,716,588
	RI - IV-AD-RO-EP	25,029	1.988	1.430	6,340,285
	IV-RI-AD-RO-EP	56,795	1.988	1.430	178,118,729
Combine 2,3,7,5&6	SC-SC-SC-SC-SC	86,812	43.419	13.767	
	EP-RO-RI-IV-AD	266,693	43.419	15.723	91,993
	RO-EP-RI-IV-AD	271,968	43.419	15.730	682,952
	RI -RO-EP-IV-AD	298,997	43.419	15.741	2,442,697
	RI-IV-RO-AD-EP	401,328	43.419	15.751	10,814,632
	RI - IV-AD-RO-EP	444,676	43.419	15.752	31,827,023
	IV-AD-RI-RO-EP	533,200	43.419	15.753	318,744,337
	IV-RI-AD-RO-EP	577,734	43.419	15.753	361,557,605
Combine 2,7,5&9	RI -RO-EP-IV-AD	17,351	1.988	1.452	
	RI-IV-RO-AD-EP	23,790	1.988	1.454	3,712,281
	RI –IV-AD-RO-EP	24,941	1.988	1.454	5,840,173
	IV-RI-AD-RO-EP	57,215	1.988	1.454	180,337,224
Combine 2,7,5&10	RI -RO-EP-IV-AD	16,843	1.988	1.411	
	RI-IV-RO-AD-EP	23,084	1.988	1.413	3,637,013
	RI –IV-AD-RO-EP	24,204	1.988	1.413	5,721,380
	IV-RI-AD-RO-EP	55,628	1.988	1.413	176,615,069

Scenario	Sequences	Cost (£)	Life Years	QALY	Relative ICER
Combine 2,7,5,3&9	EP -RO -RI-IV-AD	472,892	43.419	30.586	
	RO-EP-RI-IV-AD	478,908	43.419	30.597	555,541
	RI -RO-EP-IV-AD	566,829	43.419	30.614	5,119,389
	RI-IV-RO-AD-EP	757,335	43.419	30.631	10,475,705
	RI –IV-ADRO-EP	831,972	43.419	60.635	27,312,189
	IV-RI-AD-RO-EP	986,353	43.419	60.636	274,905,479
Combine 2,7,5,3&10	RI -RO-EP-IV-AD	180,345	43.419	11.083	
	RI-IV-RO-AD-EP	244,825	43.419	11.090	9,423,690
	RI –IV-AD-RO-EP	264,997	43.419	11.091	21,108,797
	IV-RI-AD-RO-EP	382,945	43.419	11.092	343,148,662
Combine 2&8	RI-EP-RO-IV-AD	15,858	1.985	1.43	
	RI -EP-IV-AD-RO	17,222	1.986	1.43	5,948,737
	RI-IV-EP –AD-RO	22,704	1.986	1.43	97,641,449
	IV-RI-EP-AD-RO	54,472	1.986	1.43	160,922,799
	IV-EP-RI-AD-RO	59,564	1.986	1.43	214,784,911
Combine 2,8&3	RI -RO-EP-IV-AD	381,655	42.013	15.683	
	RI-EP-RO-IV-AD	272,798	42.003	15.688	328,815
	RI-IV-EP-AD-RO	329,498	42.030	15.691	19,694,533
	RI-IV-EP –AD-RO	341,137	42.031	15.691	42,588,318
	IV -EP-RI-AD -RO	482,714	42.032	15.691	220,278,733
Combine 2,8&5	RI -RO-EP-IV-AD	16,970	1.985	1.427	
	RI-IV-RO-AD-EP	23,310	1.985	1.429	3,366,725
	RI - IV-AD-RO-EP	24,441	1.985	1.429	5,301,319
	IV-RI-AD-RO-EP	56,209	1.985	1.429	160,922,797
Combine 2,8,5&6	SC-SC-SC-SC-SC	897	1.972	1.373	
	RI -RO-EP-IV-AD	17,303	1.985	1.427	301,907
	RI-IV-RO-AD-EP	23,728	1.985	1.429	3,411,677
	RI -IV-AD-RO-EP	24,971	1.985	1.430	5,824,927
	IV-RI-AD-RO-EP	56,739	1.986	1.430	160,922,797
Combine 2,8,5&9	RI -RO-EP-IV-AD	17,271	1.985	1.452	
	RI-IV-RO-AD-EP	23,727	1.985	1.453	3,403,877
	RI -IV-AD-RO-EP	24,880	1.985	1.454	5,360,398
	IV-RI-AD-RO-EP	57,156	1.985	1.454	162,714,435

Scenario	Sequences	Cost (£)	Life Years	QALY	Relative ICER
Combine 2,8,5,9&3	EP-RO- RI-IV-AD	427,185	41.410	30.148	
	RO-EP- RI–IV-AD	433,645	41.429	30.163	428,543
	RI -RO-EP-IV-AD	522,257	41.459	30.187	3,726,567
	RI-IV-RO-AD-EP	713,460	41.490	30.212	7,690,522
	RI -IV-AD-RO-EP	788,201	41.495	30.216	20,045,930
	IV-RI-AD-RO-EP	942,606	41.496	20.216	197,520,133
Combine 2,8,5&10	RI-EP-RO-IV-AD	16,767	1.985	1.411	
	RI-IV-RO-AD-EP	23,029	1.985	1.412	3,341,389
	RI -IV-AD-RO-EP	24,145	1.985	1.413	5,260,977
	IV-RI-AD-RO-EP	55,571	1.985	1.413	159,705,787
Combine 2,8,5,10&3	RI-EP-RO-IV-AD	172,566	41.459	11.009	
	RI-IV-RO-AD-EP	.237,261	41.490	11.018	7,262,297
	RI -IV-AD-RO-EP	257,463	41.495	11.019	16,247,797
	IV-RI-AD-RO-EP	375,422	41.496	11.019	262,388,370