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

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Graham Mowatt led the Evidence Review Team and summarised and critiqued the manufacturer's submission of the effectiveness evidence. Charles Boachie critiqued the statistical methods used and provided statistical expertise required for other sections of the report. Mark Crowther provided clinical advice and drafted the background and critique of the manufacturer's decision problem. Cynthia Fraser conducted the literature searches and critiqued the methods used for identifying relevant literature. Rodolfo Hernandez conducted the critique of the manufacturer's economic evaluation. Xueli Jia assisted in the critique of the manufacturer's submission of effectiveness evidence. Laura Ternent summarised the manufacturer's economic model and assisted in critiquing the economic model. She also conducted the additional economic analyses.

Conflicts of interest

None

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the Chief Scientist Office of the Scottish Government Health Directorates or of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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SUMMARY

Scope of the submission

The submitted evidence related to the use of romiplostim for the treatment of chronic immune or idiopathic thrombocytopenic purpura (ITP) in adults with a platelet count which is <30 x10^9/l and are:

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

The analysis however primarily considers evidence where the cut-off for treatment is <50 x10^9/l; higher than would typically be used in practice in the UK.

Summary of submitted clinical effectiveness evidence

Evidence on the efficacy of romiplostim came from two RCTs. In non-splenectomised patients, initial response rate, mean time to response, and durable response rate were 88% (36/41), 2.0 weeks, and 25/41 (61%) respectively. Amongst splenectomised patients, the results were 79% (33/42), 3.0 weeks, and 38% (16/42) respectively [redacted] The efficacy of 24-week administration of romiplostim was significantly better than placebo in the above outcomes and also in [redacted] and in reduction of concurrent ITP therapy.

Evidence from the manufacturer-conducted RCT and evidence from seven manufacturer-conducted case series was used for reporting safety of romiplostim. Amongst non-splenectomised patients, overall bleeding events, severe/life-threatening/fatal bleeding events, any types of adverse events, severe adverse events, and mortality were [redacted] respectively and amongst splenectomised patients, [redacted] Adverse events with a > 10% incidence in the romiplostim arm compared with the placebo arm included, in non-splenectomised patients, [redacted] in splenectomised patients,

[redacted]

When evidence from the seven manufacturer-conducted case series was taken into account, any types of adverse events, severe adverse events, and mortality using romiplostim for both patient groups were [redacted](rates higher than used in the economic model) and [redacted] respectively.

The ITP-Patient Assessment Questionnaire (ITP-PAQ) results change from baseline provided by the RCTs indicated that splenectomised patients in the romiplostim group had a statistically significant ($p < 0.05$) improvement in the Symptoms, Bother, Social Activity, and Women's Reproductive Health scales compared with placebo, while in non-splenectomised patients the romiplostim group had a statistically significant improvement in the Activity scale. The differences in mean change scores in EQ-5D between the romiplostim and placebo patients were not statistically significant.

Evidence from existing reviews and primary studies from complementary searches were used for reporting efficacy and safety of comparator drugs. As no data synthesis of reviews and primary studies was conducted in the submission, values used in the economic models were based on the literature identified by the manufacturer. The values were assumed to be the same between non-splenectomised and splenectomised unless otherwise specified.

For efficacy of intravenous steroids, initial response rate, maximum time to respond, and mean response duration were 46%, 0 cycle (1 cycle = 4 weeks), and 1 cycle respectively; for IVIg, 81% (79% in splenectomised patients), 0 cycle, and 1 cycle; for anti-D, 46% (not indicated for use in splenectomised patients), 0 cycle, and 1 cycle; for rituximab, 58%, 2 cycles, and 19 cycles; for danazol, 45% (60% in splenectomised patients), 4 cycles, and 147 cycles; for dapsone, 50% (47% in splenectomised patients), 1 cycle, and 20 cycles; for azathioprine, 50% (63% in splenectomised patients), 4 cycles, and 20 cycles; for mycophenolate mofetil, 57% (44% in splenectomised patients), 4 cycles, and 6 cycles; for ciclosporin, 50% (63% in splenectomised patients), 2 cycles, and 16 cycles (13 cycles in splenectomised patients); for cyclophosphamide, 70% (61% in splenectomised patients), 2 cycles, and 27 cycles; and for vinca alkaloids, 67% (53% in splenectomised patients), 1 cycle, and 1 cycle.

For safety of corticosteroids, rates of severe adverse events and any other adverse events were 3% and 70%; for IVIg 2% (range 1% to 4%) and 0%; for anti-D 3% and 0%; for rituximab 3% and 0%; for danazol 16% and 35%; for dapsone 11% (range 3% to 27%) and 24%; for immunosuppressants (azathioprine, mycophenolate mofetil, ciclosporin) 15% (range 11% to 30%) and 12% to 36%; and for cytotoxics (cyclophosphamide, vinca alkaloids) 21% and 30%.

Summary of submitted cost-effectiveness evidence

The manufacturer submitted their economic evaluation. The economic model was a cohort type model constructed in Microsoft Excel in which the two patient populations were modelled. The model evaluated the cost-effectiveness of romiplostim compared to standard care, defined by reference to international guidelines in the treatment of ITP and their own commissioned survey. In the model, patients initially enter a watch and rescue state or are treated firstly with romiplostim.

The results from the revised base case analysis show that in non-splenectomised patients using romiplostim as a first option treatment results in an ICER of £14,840. In splenectomised patients the ICER was £14,655. The ERG requested that a number of additional analyses were conducted. Including using the EQ-5D data available from the RCTs; sensitivity analysis around the decrements to utility for serious adverse effects (AE); inclusion of the cost of a bone marrow assessment required when response to the drug is lost; inclusion of the full costs for a blood film test (required before treatment); the impact of a reduced number of blood counts and clinic visits; whether the drug cost calculations double counted physician visits. The impact of these changes in uni-variant sensitivity analysis was negligible for both patient groups. Additional sensitivity analyses were performed by the ERG on: the number of romiplostim vials used; whether patients enter the comparator arm on watch and rescue or on an active treatment; combining all uni-variant sensitivity analyses into a multi-variant analysis. The combined sensitivity analysis provides far larger changes in the ICER than are reflected in the one-way sensitivity analysis. Of far greater importance was whether individuals enter the model on watch and rescue or an active therapy in the comparator arm (ICER equals £21,674 for non-splenectomised patients and £29771 for splenectomised patients). Combining all the separate sensitivity analyses, with the additional assumption that watch and rescue is not the first line treatment increases the ICERs further (non-splenectomised = £37,290; splenectomised = £131,017).

Commentary on the robustness of submitted evidence

Overall the quality of the RCTs reporting romiplostim are relatively high and the ERG found no evidence that any data of consequence were missed in the reviews or that data extraction was inaccurate. The inclusion/exclusion criteria relating to the included studies did not fully accord with the final scope issued by NICE. Furthermore, no criteria were set for defining patients who were medically contraindicated to splenectomy. The evidence base for both romiplostim and the comparator treatments was limited. Furthermore, the methods used to combine data from individual studies for the same comparator treatment were methodologically questionable and it is possible that the estimates were biased. These potential biases were of unknown direction and magnitude.

Whilst the decision problem, description of alternatives and perspective were all well outlined in the submission, there were some concerns about the way the decision problem was addressed in the economic model which relate to the structure of the economic model and whether patients enter the model on watch and rescue or an active treatment.

The methods used to synthesise treatment effectiveness of both romiplostim and the comparators were a central component of the economic model (although they were not fully described in the actual submission document). Data on the effectiveness of romiplostim which primarily came from the romiplostim arms of two RCTs were used solely as observational data. In addition, data for the comparators came from reviews and additional searches, which were obtained by the simple aggregation of data from identified studies. There were a number of concerns raised by the ERG about the pre-model data analyses and the statistical and epidemiological techniques employed. These concerns related to the manufacturer not adjusting the findings for confounding factors (e.g. severity of ITP, age, number of previous treatments, concurrent treatments, and withdrawal rates) which may affect the reliability and size of the treatment effect.

The type of utilities data used did provide some concern to the ERG given that the manufacturer did not use the preferred method of obtaining utilities data in their base case analyses, even though this method was available to them. This concern was explored in a uni-variant sensitivity analysis provided in response to points raised for clarification.

Key issues

- Evidence on use of ITP treatment options came from a survey which had only a [redacted]% response rate from UK haematologists. It is unclear how representative this is of UK practice.

- The effectiveness evidence for the comparator treatments were not identified and summarised systematically and some relevant data may have been missed. The ERG did not identify any additional evidence that would have made a material difference to the results.
- The effectiveness data for both romiplostim and the comparator treatments were limited. Particularly with respect to longer term outcomes.
- The differences in clinical effectiveness between romiplostim and comparator drugs are uncertain and may be biased (due to the simple methods used to compare the non-randomised, non-comparative observational data available for the treatments).
- Data for the subgroups (non-splenectomised and splenectomised) are limited and estimates were frequently assumed to be the same for both patient groups.
- Assumptions about the wastage of romiplostim have an effect on cost-effectiveness. The base case industry submission assumed that there will be no wastage, but if there was, then the cost-effectiveness of romiplostim will be reduced.
- If the appropriate comparator for romiplostim is an active treatment rather than watch and rescue then the use of romiplostim is far less likely to be considered cost-effective.
- In the romiplostim trials a conventional assumption that censored patients behave in the same way as non-censored patients was made. If an alternative assumption was made that censored patients ceased to respond then the use of romiplostim was far less likely to be considered cost-effective.
- The extent and direction of bias caused by the use of indirect comparisons of non-comparative observational data are unclear. If the manufacturer's base case overestimated the relative effectiveness of romiplostim then romiplostim was far less likely to be considered cost-effective.

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ABBREVIATIONS LIST

ADRs	Adverse drug reactions
AE	Adverse events
ASH	American Society for Hematology
BCSH	British Committee for Standards in Haematology
BNF	British National Formulary
CADTH	Canadian Agency for Drugs and Technologies in Health
CEACs	Cost-effectiveness acceptability curves
CI	Confidence interval
CMH	Cochran Mantel-Haenszel test
CRD	Centre for Reviews and Dissemination
EMEA	European Medicines Agency
EQINDEX	EQ-5D index score
EQVAS	EQ-5D visual analogue score
ERG	Evidence Review Group
FDA	Federal Drug Administration
HIV	Human immunodeficiency virus
HRQoL	Health related quality of life
HTA	Health Technology Assessment
IC	Incremental cost
ICER	Incremental cost effectiveness ratio
IQ	Incremental QALYs
ITP	Idiopathic Thrombocytopenic Purpura
ITP-PAQ	ITP-Patient Assessment Questionnaire
IVIg	Intravenous immunoglobulin
MeSH	Medical subject headings
MMF	Mycophenolate mofetil
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
OR	Odds ratio
PRO	Patient reported outcome
PSA	Probabilistic sensitivity analysis
QALY	Quality adjusted life year
RCT	Randomised controlled trial
STA	Single Technology Assessment
TPO	Thrombopoietin
TTO	Time Trade Off
WAC	Wholesale Acquisition price

1 INTRODUCTION TO THE ERG REPORT

The remit of the evidence review group (ERG) is to comment on the clinical and cost-effectiveness evidence submitted to NICE as part of the single technology review process. Evidence has been submitted to NICE by Amgen Inc. The information considered by the ERG related to an interim submission report (supported by an economic model) and a detailed response to points for clarification provided by Amgen as well as a revised economic model. The ERG also conducted additional systematic reviewing and further modelling (using the manufacturer's revised model).

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

1. Patients who are refractory to splenectomy; or
2. Patients who are inadequate responders to corticosteroids and have medical contraindications to splenectomy.

2 BACKGROUND

Platelets are bloods cells whose role is to stop bleeding by plugging any breaches in the vascular system and to initiate and propagate blood coagulation. Immune thrombocytopenic purpura (ITP) is an immune condition where auto-antibodies are formed against the body's own platelets. Antibody binding leads to increased clearance of platelets by the reticuloendothelial system, predominantly in the spleen. 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. Many patients with ITP have a platelet count above 30 x 10^9/l and hence do not require treatment. Higher platelet counts, however, are required for certain operative procedures to be performed safely.

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, human immunodeficiency virus (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.

No large registry data exist in 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. This is a lower rate than that reported in 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 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, therefore treatment is recommended by the BCSH[3] and the American Society for Hematology (ASH)[7] 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. In the UK there are only three licensed medical therapies for ITP (corticosteroids, intravenous immunoglobulin and anti-D) and evidence for these and other therapies for ITP is limited and often confined to case series. 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.

Splenectomy, a surgical treatment, has been reported as being a curative procedure in 66% of patients[8] but is associated with mortality from the operation itself and the long term complications of asplenia. It is recommended for those patients who are fit enough when first line treatment fails.

Failure to respond to first and second line treatments or require unacceptably high doses of steroids was reported in 11% to 35% of patients.[3] Data for other treatments, which are all immune-suppressants, carry considerable side-effects, and 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. More recent novel treatments include the thrombopoietin analogues (romiplostim and eltrombopag) which appear to increase platelet production.

Retrospective cohorts have demonstrated variable mortality from refractory ITP while the largest pooled case series[9] 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 of whether these data can be applied to modern practice. More recent case series have demonstrated lower mortality but considerable treatment-related mortality and morbidity.[10]

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 discuss that the best clinical guidance available are guidelines from the American Society of Hematology and the British Committee for Standards in Haematology. Both the BCSH and ASH guidelines were developed by 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. In addition much of the evidence is level IV (expert opinion, formal consensus). As there are only three licensed drug treatments in this area, the manufacturer conducted a survey of haematologists in the UK to determine current practice (haematologists are the clinicians who tend to treat the majority of ITP patients). The survey was sent to [redacted] haematologists in the UK and the response rate was [redacted]%. It was sent to both consultants and trainees therefore the validity of the trainees' responses is questionable. Furthermore, no consideration was given to

clustering of responses by centre. Also the large number of non-responders may have produced a biased result. Apart from the one question there is no differentiation between adults and children, who have marked differences in treatment. However the results of the survey presented in Table 4.1.1 of the manufacturer's submission are broadly similar to the BCSH guidelines. The views of patients are represented by a submission from the ITP support association who feel there is a need for new safer treatments for ITP.

In conclusion the manufacturer does appear to understand the current state of service provision in the UK for chronic ITP and the submission is based on this**.**

3 CRITIQUE OF MANUFACTURER'S DEFINITION OF DECISION PROBLEM

3.1 Population

The STA submission is that romiplostim is to be used for adult patients who have a platelet count which is <30 x 10^9/l and are:-

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

This is different to the European Medicines Agency (EMEA) submission which is:

- Romiplostim is indicated for adult chronic ITP patients who are refractory to splenectomy.
- Romiplostim may be considered for adult non-splenectomised chronic ITP patients who have had an inadequate response to or are intolerant of corticosteroids and immunoglobulins and in whom splenectomy is medically contraindicated.

There may be patients, however, with a platelet count >30 x 10^9/l who require treatment who would be missed by this submission (e.g. if they are bleeding or are required to undergo an operative procedure).

Due to the lack of good registry data the prevalence of the patients in the UK can only be estimated. In the executive summary of the manufacturer's submission an incidence of 2,220 patients per year was quoted but this was an error and was modified in the response document. The response quotes a prevalence of between [redacted][11,12] based on the manufacturer's study using the GP database. GP databases may be unreliable as diseases are often classified incorrectly and this is suggested by the wide variation between years in both prevalence (2.1 to 8.1 per 100,000 per year) and incidence (1.0 to 3.7 per 100,000 per year) as this disease should have a stable prevalence and incidence year to year.

Using the incidence rates quoted in the BCSH guidelines (5.8-6.6 per 100,000 per year) this would give a UK incidence of between 3538 and 4026 cases. However, the Newcastle cohort, which is the most recent UK cohort gives an incidence of 1.13 per 100,000 giving a UK incidence of 603 cases per year. Assuming from the Newcastle and Portielje cohorts that 13-15% of these

patients either are refractory or require ongoing treatment (hence eligible for romiplostim), which is a lower proportion than is quoted in Table 8.1 of the manufacturer's submission, then between 103 and 603 new patients each year would be eligible for romiplostim in the UK.

The main studies [redacted] the manufacturer uses as the data for clinical effectiveness enrolled [redacted] patients from the UK [redacted] from the European Union [redacted] from the USA. Also the trial patients as a whole were unrepresentative of the UK ITP population based on [redacted] The patients enrolled in the non-splenectomy study were also a different patient group from [redacted] (see page 51 of the manufacturer's submission).

In conclusion the manufacturer's submission discusses the problem of accurately determining the true patient base in the UK but may underestimate the numbers that will be treated. Also, the main effectiveness studies may not be applicable to UK patients.

3.2 Intervention

The technology submitted is a thrombopoetin agonist (romiplostim), which is given as a weekly subcutaneous injection at a hospital with the aim of increasing the platelet count in ITP. The drug is titrated dependent on the platelet count starting, at a dose of 1µg/kg increasing to a maximum of 10µg/kg. Romiplostim is licensed by the US Federal Drug Administration (FDA) and has been given a positive opinion by the EMEA**.**[13]

3.3 Comparators

Comparators that are chosen are corticosteroids, watch and rescue with IVIg, watch and rescue with anti-D, rituximab, immunosuppressives (azathioprine, mycophenolate mofetil, ciclosporin), danazol, dapsone and cytotoxic agents (cyclophosphamide and the vinca alkaloids) and these are the major comparators from the BCSH and ASH guidelines and the manufacturer's survey of clinicians. As discussed above only steroids, IVIg and anti-D are licensed for treatment for ITP.

Two possible comparators are not discussed Campath, (as discussed in the BCSH guidelines) and Eltrombopag. Eltrobompag is an oral thrombopoietin agonist which has undergone clinical trials[14]

and achieved FDA approval on the 20th November 2008 for the treatment of ITP.[15] The submission should therefore be re-examined in the future in the light of these two comparators. Within the economic model the manufacturer outlined a comparison of two alternative sequences of treatments, one including initial treatment with romiplostim and the other not including romiplostim. This model allowed for the initial treatment with romiplostim compared with initial management of watch and rescue. It is perhaps arguable that a more appropriate comparison would be between initial treatment with romiplostim and an initial active therapy. The implications of this comparison are discussed in Chapters 5 and 6.

3.4 Outcomes

The submission attempted to assess all relevant and valid outcomes: proportion of patients with any platelet response (overall response); proportion of patients with durable long term response and/or duration of response; time to platelet response; reduction in the need for rescue medications or chronic therapies; bleeding episodes; adverse effects of treatments; mortality; and health related quality of life. The submission concentrated on platelet response, an outcome important to clinicians but likely to be of less importance to patients than the number of bleeding episodes, adverse events and mortality, all of which would affect overall quality of life.

3.5 Time frame

As ITP is a chronic condition where individuals experience a sequence of therapies, studies reporting long term response to therapy are required to assess the effectiveness and cost-effectiveness of therapy. Stasi and colleagues provide an illustration of this.[16] In their study, 121 patients were treated with prednisolone (1 mg/kg for 1 month). Refractory or relapsed cases underwent splenectomy and/or other therapy modalities. An initial complete response was observed in 38.8% cases and a sustained complete remission (> 6 months) was attained in 18.7%. At the time of last follow-up only 11 patients remained in complete remission. Long-lasting recoveries were observed in 7 other cases following alternative treatments. Spontaneous remissions occurred in 8 of 87 untreated cases after observation periods of ≥ 6 months. At last control, 43 patients were in complete remission and free from therapy, and 52 were still on therapy.

As described earlier there is considerable variation in practice with respect to the management of ITP, reflecting the paucity of high quality evidence. As described in the next chapter, much of

the evidence comes from small non-randomised, non-comparative studies with typically only short follow-up periods.

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 at 19th May 2008 are reported in Appendix 1 of the submission report. The major biomedical databases were searched (MEDLINE, MEDLINE In Process, EMBASE, CINAHL, Science Citation Index, Biosis and the Cochrane Library which included CENTRAL, DARE and NHSEED). Other potentially relevant sources that could have been searched were the HTA Database and appropriate conference abstracts.

The free text search terms and subject heading terms (MeSH) for MEDLINE, that were included in the search strategies, are listed along with the boolean operators that were used to combine the terms. Appropriate MeSH and text terms were used but proprietary names were not consistently included in the searches. The subject heading terms, applicable to the other databases (e.g. EMTREE terms), were not reported so it is unclear if these strategies were correctly undertaken. Two in-house databases of clinical trials and adverse reactions were also searched.

Intervention

The manufacturer's search strategy for MEDLINE was replicated by the ERG with the inclusion of the term *nplate.tw,rn.* The searches were adapted for the other databases using the appropriate subject heading terms. In addition, recent proceedings (2005-7) of the American Society of Hematology (ASH) were searched using the terms romiplostim, AMG 531, AMG531 and nplate. Two papers and 9 abstracts were identified which had not been included in the submission. Clarification was sought from the manufacturer who confirmed the reasons for exclusion: 6 were secondary references to studies already included or reported data that had been incorporated in other papers while five were deemed by the manufacturer as not relevant to the decision problem.

Comparators - Effectiveness

The submission report states that, due to the large number of comparators and diversity in the clinical evidence, it was not possible to conduct an extensive and full systematic search. Instead a pragmatic approach was adopted. Two clinical guidelines and nine reviews were identified, and primary studies cited in these evidence summaries were assessed for inclusion in the submission. Complementary searches for additional evidence on each comparator, using the searches described in Appendix 2 of the submission report, were undertaken for studies published after

these reviews had been completed. For most comparators this meant that searches were undertaken from 2006-8, but from 1994 onwards for IVIg and anti-D, while no date restriction was used for danazol and azathioprine. The reported MEDLINE search strategies were appropriate.

No details of how these reviews and guidelines were identified were given, so clarification was sought from the manufacturer who replied that the searches, as detailed in Appendix 1, were used. However, the searches documented in Appendix 1 relate to the identification of primary studies and the majority had date restrictions imposed so would not have been able to identify the reviews. It would have been more appropriate to have combined the search terms, as listed, with a search filter to identify systematic reviews,[17] and without imposing any date restriction: but this does not appear to have been undertaken. Most of the identified reviews and guidelines did not undertake comprehensive literature searches or gave insufficient information to permit assessment. For example, the review by Godeau and colleagues[10] only searched Pubmed and gave no details of the search terms used or explicitly stated the time period covered. The exception was the systematic review by Arnold and colleagues.[18]

Since the majority of the selected reviews did not appear to have undertaken adequate literature searching - and so may have missed important studies - the ERG undertook independent searches for the comparator studies. Details are provided in Chapter 6 and in Appendix 1 of the ERG report.

Comparators - Safety

No details of how the studies on safety were identified was given so clarification was sought from the manufacturer who provided a detailed response. The search terms that were used to try to identify adverse events for IVIg, Anti-D and rituximab did not include the key ones and appear to relate more to quality of life studies. For example for MEDLINE, the most relevant MeSH term Drug toxicity/ was not used and while subheadings were used, they did not include the most relevant ones: adverse events (ae), complications (co), toxicity (to) or drug effects (de).[19] However, the literature searches for the effectiveness studies were sufficiently broad that they would probably have captured the majority of the studies, although date restrictions used would have limited the time period covered.

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

Details of the inclusion criteria, which are generally considered to be appropriate to the decision problem, are given in Table 1.

Table 1 Details of the inclusion criteria for the decision problem considered

	Clinical effectiveness
Population	Adults with ITP with platelet counts less than 30,000 per microlitre in whom at least one prior treatment regimen has failed. The following subgroups were assessed: 1. Second line treatment for non-splenectomised patients with inadequate response to initial corticosteroid treatment, where splenectomy is medically contraindicated. 2. ITP patients refractory to splenectomy.
Intervention	Romiplostim administered as a weekly subcutaneous injection at an initial dose of 1 μg/kg with subsequent dose titration to maintain a platelet count $\geq 50 \times 10^9$/l (not exceeding a dose of 10 μg/kg).
Comparators	Corticosteroids Watch and rescue with intravenous immunoglobulin (IVIg) as needed Watch and rescue with anti-D immunoglobulin as needed (non-splenectomised patients only) Rituximab Immunosuppressives (azathioprine, mycophenolate mofetil, ciclosporin) Danazol Dapsone Cytotoxic agents (e.g. cyclophosphamide, vinca alkaloids)
Outcomes	Proportion of patients with any platelet response (overall response) Proportion of patients with durable or long-term response, and/or duration of response Time to platelet response Reduction in need for rescue medications or chronic therapies Bleeding episodes Adverse effects of treatment

	Mortality Health-related quality of life
Study design	Systematic reviews, review articles, RCTs, non-randomised comparative studies, case series.
Inclusion criteria	For romiplostim for efficacy outcomes, only RCTs in which the dosing paradigm described in the decision problem and in the anticipated label for the product (i.e. 1 μg/kg starting dose followed by dose titration based on platelet count)
Exclusion criteria	Studies relating to secondary thrombocytopenia associated with other conditions, ITP in childhood or pregnancy or including less than 5 patients. Dose finding studies of romiplostim were excluded from the analysis of efficacy.

Source: manufacturer's submission.

The manufacturer stated that it recognised splenectomy as a treatment option but would not be including it as a comparator in the non-splenectomised patient population because the proposed indication for romiplostim was for patients where splenectomy was medically contraindicated. Two possible comparators were not included in the list of comparators – Campath and Eltrombopag.

4.1.3 Table of identified studies

Table 2 lists studies reporting romiplostim. Al studies were sponsored and conducted by Amgen Inc.

Table 2 Studies reporting romiplostim

Study, design, links with other studies	Population, N, baseline platelet count, spleen status	Intervention	Publication status
Efficacy & safety			
(1) Study 20030212, RCT (2) Study 20030105, RCT	(1) 62, $\leq 35 \times 10^9$/l, non-splenectomised (2) 63, $\leq 35 \times 10^9$/l, splenectomised	In both (1) & (2): A, romiplostim plus standard of care, 24wk B, placebo plus standard of care, 24wk	Peer-reviewed journal[11] and abstracts[11,20,21]
Study 20030213 ('open label study'), case series. Patients completing the Kuter 2008 study, whose platelet counts subsequently fell to $\leq 50 \times 10^9$/l after discontinuation of romiplostim or placebo were eligible to enrol. Patients completing other romiplostim studies (20000137A, 20000137B, 20010218, 20040209, 20060131) were also eligible to enrol.	142 were analysed in the submission, $\leq 50 \times 10^9$/l, a mixture of non-splenectomised and splenectomised patients.	Romiplostim, up to 96wk or longer	On-going, to be completed in Dec. 2009. Published as abstracts.[22-26]

Study, design, links with other studies	Population, N, baseline platelet count, spleen status	Intervention	Publication status
Safety			
(1) Study 20000137A, dose-finding case series (2) Study 20000137B, dose-finding RCT	(1) 24, (2) 21 In both (1) & (2): $\leq 35 \times 10^9$/l ($\leq 55 \times 10^9$/l if receiving corticosteroid), a mixture of non-splenectomised and splenectomised patients.	In (1), romiplostim once a week at various doses x 1-2wk; In (2), A, romiplostim once a week at various doses x 6wk; B, placebo x 6wk	Peer-reviewed journal [27]
Study 20010218, dose-finding case series	16, $\leq 30 \times 10^9$/l ($\leq 50 \times 10^9$/l if receiving corticosteroid), a mixture of non-splenectomised and splenectomised patients, NR failed prior treatment(s) or not.	Romiplostim once a week at various doses x 2wk	Peer-reviewed journal[28] and abstract[29]
Study 20040209, case series	$\leq 20 \times 10^9$/l or experiencing bleeding, a mixture of non-splenectomised and splenectomised patients, NR number of patients analysed in the submission.	Romiplostim, NR duration	On-going, to be completed in Dec. 2010.
Study 20050123, case series Sub-study of Kuter 2003 study and study 20030213.	NR	Romiplostim	*No material for this study available.*

Study, design, links with other studies	Population, N, baseline platelet count, spleen status	Intervention	Publication status
Study 20060131, RCT	210, < 50 x 10^9/l, non-splenectomised	(A) romiplostim x 52wk; (B) standard of care x 52wk	On-going, to be completed Jan. 2010.
Study 20050162, dose-finding case series, Japan	16, NR baseline platelet counts, spleen status, or failed prior treatment(s) or not.	Romiplostim, NR duration	Abstract [30]
On-going studies (data not used in the submission)			
Study 20060113, case series, Japan. Participants were those who previously took part in romiplostim studies.	40, ≤ 50 x 10^9/l, NR spleen status, failed prior treatment(s) or not.	Romiplostim, once a week, NR duration	On-going, to be completed by Jul. 2011.
Study 20060216, RCT, Japan	30, ≤ 35 x 10^9/l, NR spleen status.	(A), romiplostim once a week x 12wk (B), placebo x 12wk	On-going, to be completed June 2009.

Notes:

1. NR, not reported; wk, weeks.

4.1.4 Relevant studies not included in the submission

Details of relevant studies not included in this submission are given in Section 6.1.

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

The manufacturer's submission included a description of the methodological quality of the two romiplostim RCTs (Studies 20030105 and 20030212) in the text but it was unclear whether they had been assessed using a quality assessment instrument. The ERG queried whether an established checklist had been used and in the response to clarification queries document the two RCTs were assessed using the Centre for Reviews and Dissemination (CRD) checklist (Amgen response to points for clarification, B4). The results of the quality assessment are shown in Table 3.

Both studies were good quality RCTs based on the CRD checklist assessment. Patients were enrolled in a 2:1 ratio to receive romiplostim or matching placebo. Randomisation was stratified by baseline concurrent ITP therapy (yes or no) within each study. Although the studies were described as double blind in the manufacturer's submission, according to the checklist the participants, individuals who administered the intervention and outcome assessors were all blinded. To maintain the blind, romiplostim and placebo were supplied in identical vials.

However the manufacturer's submission also stated that blinding in the two studies may have been compromised by the investigator and patients' knowledge of platelet counts. Investigators required rapid results from their local laboratory, generally during the same visit, for dosing decisions and patient care, making it impractical to use a central laboratory to blind investigators or patients to platelet results (this is described further in Section 4.1.7 under the description and critique of the statistical approach used in the romiplostim studies).

As described in Section 3.1 few data from the romiplostim studies related to patients from the UK so the extent to which the RCTs participants were representative of adult chronic ITP patients in the UK is unclear.

Table 3 Assessment of the two romiplostim RCTs using CRD criteria

	Study 20030105 Splenectomised	Study 20030212 Non-splenectomised
Was the method used to assign participants to the treatment groups really random?	Y	Y
What method of assignment was used?	blocked randomisation with stratification according to concurrent use of ITP treatments, allocated centrally via IVRS	blocked randomisation with stratification according to concurrent use of ITP treatments, allocated centrally via IVRS
Was the allocation of treatment concealed?	Y	Y
What method was used to conceal treatment allocation?	central randomisation by IVRS, and identical appearance of vials of placebo and romiplostim	central randomisation by IVRS, and identical appearance of vials of placebo and romiplostim
Was the number of participants who were randomised stated?	Y	Y
Were the eligibility criteria for study entry specified?	Y	Y
Were details of baseline comparability presented?	Y	Y
Was baseline comparability achieved?	Y	Y
Were the participants who received the intervention blinded to the treatment allocation?	Y	Y
Were the individuals who administered the intervention blinded to the treatment allocation?	Y	Y
Were the outcome assessors blinded to the treatment allocations?	Y	Y
Was the success of the blinding procedure assessed?	N	N
Were any co-interventions identified that may influence the outcomes for each group?	Y randomisation was stratified according to concurrent use of ITP treatments	Y randomisation was stratified according to concurrent use of ITP treatments
Was an intention-to-treat analysis included?	Y	Y
Were at least 80% of the participants originally included in the randomisation process followed up in the final analysis?	Y	Y

Source: response to clarification queries document.

Notes:
1. Y, Yes; N, No; IVRS, interactive voice response system.

The submission stated that all randomised patients were included in an intention-to-treat analysis according to their randomised treatment group, while the report of the studies by Kuter and colleagues[11] stated (p 397) that analysis was per protocol. However efficacy analysis was by intention-to-treat. One non-splenectomised patient randomly assigned to placebo received three doses of romiplostim in error and was included in the safety analysis as a patient given romiplostim and in the efficacy analysis as a patient given placebo. Kuter and colleagues[11] also stated that the use of any rescue drugs, irrespective of effect, required that the patient be excluded from the primary endpoint analysis and that all platelet counts for the next eight weeks be excluded from the analysis of other endpoints of platelet response.

The additional romiplostim studies included in the integrated safety analysis of all ITP studies were not critically appraised ([redacted]).

The manufacturer's submission did not critically appraise the included studies that reported comparator treatments, nearly all of which were case series. The ERG queried this and the manufacturer stated that they felt that attempting to undertake a formal quality assessment of the large number of uncontrolled studies would not add significant value to their analysis. Instead they attempted to take account of the poor quality of comparator data in their analysis and interpretation of results (Amgen response to points for clarification, B4b). However aspects of the methodological quality of the case series that it would have been useful to appraise include whether they were prospective, whether there was consecutive recruitment, whether length of follow-up was sufficient, and loss to follow-up.

4.1.6 Description and critique of manufacturer's outcome selection

The primary outcome measure in the manufacturer's submission was the incidence of durable response, prospectively defined as achieving at least six weekly platelet responses (platelets $\geq$ 50 x 10^9/l) during the last eight weeks of treatment with no rescue medications administered at any time during the 24 week treatment period.

Secondary efficacy outcome measures included:

- Incidence of transient platelet response, defined as four or more weekly platelet responses (platelets $\geq$ 50 x 10^9/l) without a durable response (excluding platelet responses within eight weeks after rescue medications);
- Incidence of overall platelet response (either a durable response or a transient response);

- Time to first weekly platelet response (platelets $\geq 50 \times 10^9$/l);
- Number of weekly platelet responses (platelets $\geq 50 \times 10^9$/l);
- Proportion of patients requiring rescue medications;
- Incidence of > 25% reduction from baseline or discontinuation of concurrent ITP therapy;
- Frequency of durable response with stable dose (dose maintained within 1 µg/kg during the last eight weeks of treatment).

Patient reported outcome (PRO) measures in the manufacturer's submission included:

- Change from baseline for the EQ-5D;
- Change from baseline for the ITP-Patient Assessment Questionnaire (ITP-PAQ).

Safety outcomes included the incidence and severity of adverse events, and mortality.

Outcomes defined retrospectively included bleeding (assessed as an analysis of bleeding events reported as safety adverse events) and [redacted].

[redacted]

These outcome measures were considered to be appropriate. The tools used to measure health-related quality of life, the [redacted] and the ITP-specific ITP-PAQ, were considered appropriate for this purpose.

A target platelet count of$\geq 50 \times 10^9$/l was defined, although treatment is only recommended for patients with a platelet count $\leq 30 \times 10^9$/l. The submission stated that the target count of $\geq 50 \times 10^9$/l was developed in conjunction with registry authorities and is generally recognised as a conservative effective therapeutic level, at which the risk of spontaneous bleeding is minimal. The ERG queried why a target level of $\geq 50 \times 10^9$/l was selected and in the response to clarification queries document (Amgen response to points for clarification, A2) the manufacturer reiterated their rationale for this and added that, in addition, the literature review

of efficacy data for ITP comparator treatments identified a platelet count > 50 x 10^9/l as the most commonly reported efficacy endpoint.

4.1.7 Description and critique of the statistical approach used

Romiplostim studies

There were two RCTs used by the manufacturer to evaluate the efficacy of romiplostim. Both studies were identical in design with the exception that patients enrolled into study 20030212 were non-splenectomised and patients enrolled into study 20030105 were splenectomised. An open label extension study, study 20030213, was used to derive the time to failure outcome of patients.

The manufacturer provided a table of patient demographics and baseline characteristics (Table 6.3.2 in the manufacturer's submission). Age, sex nor weight were not balanced between groups and should have been adjusted for in the sensitivity analysis of the primary outcome. Data in the table were reported as median (maximum-minimum) or number (%). In this case reporting median (interquartile range) together with the range would have been more helpful.

The statistical approach used in these studies was computationally sound and robust. The study was powered to demonstrate the efficacy or otherwise of the technology. However, there was no explanation of how the manufacturer came to anticipate that the true difference of response rate between the romiplostim and placebo group would be 40%. The sample size of 60 subjects for each study enrolled in a 2:1 ratio to receive romiplostim or matching placebo had approximately 87% power to detect the anticipated difference of 40% in incidence of durable platelet response between romiplostim and placebo using two-sided Fisher's exact test at a significance level of 0.05.

It is stated in the published report of the studies that statistical analysis was by per-protocol, while the manufacturer's submission states intention to treat analysis. However, it is clear from the submission that intention to treat analysis was undertaken.

The Cochran Mantel-Haenszel test compares two groups on a binary response adjusting for control variable. It is normally used where data are presented in N 2x2 contingency tables, where N is the number of strata. The null hypothesis is the response is conditionally independent of any given strata. The use of the Cochran Mantel-Haenszel test as the method for comparing the response between romiplostim and placebo stratified by baseline concurrent ITP was appropriate.

Kuter and colleagues[11] reported that multivariate analysis showed baseline weight less than 70 kg was significantly associated with increased rates of durable response (p=0.0106), greater number of weeks with platelet response (p=0.008) and lower use of rescue drugs (p=0.0285). However, there was a slight imbalance in median weights between romiplostim and placebo in the non-splenectomised group as reported in Table 6.3.2 of the manufacturer's submission. We were unable to assess the effect this baseline weight imbalance would have on the effect of the primary outcome in the splenectomised group.

The manufacturer reported using a sequential statistical testing [redacted] This does not protect against an overall Type I error.

To minimise potential bias in study conduct or analysis, the manufacturer reported that access to blinded data was restricted to only the individuals who required access for essential data capture, validation, and preparation for the reporting of results. In addition, the report contains several other measures that were put in place by the manufacturer to ensure total treatment allocation concealment until a patient had completed or withdrawn from the study. Also, it is stated in the report that all the statistical methods to be used in the analysis of the trial data were prospectively defined while the data remained blinded. Thus, the manufacturer put in place appropriate measures to ensure allocation concealment from individuals undertaking the outcomes assessment.

The manufacturer reports in their submission that blinding in the phase 3 studies may have been compromised by the investigator and the patients' knowledge of platelet counts. The manufacturer claims that it was impractical to use a central laboratory to blind investigators or patients due to the fact that laboratory results were generally needed during the same visits by investigators for dosing decisions and patient care. Also, due to the fact that platelet counts were generally unresponsive after treatment with placebo and increased rapidly following treatment with romiplostim, for some patients treatment assignment may have become apparent after several weeks of dosing. The manufacturer attributes this potential unblinding of individual subjects as the cause of the large number of withdrawals of placebo subjects (8 [38%] subjects from the non-splenectomised group and 12 [57%] subjects from the

splenectomised group). The manufacturer claims in the submission that these withdrawals would have limited effect on efficacy since outcomes were based on objective measurement of platelet counts. That is true, but missing values for 57% of subjects, as is the case of placebo subjects in the non-splenectomised group may potentially give biased estimates in favour of romiplostim. For example, we may not know if platelet counts naturally improve after falling for some time and therefore the increases in the subjects receiving romiplostim completing the study follow-up.

The manufacturer also stated that the large number of withdrawals in the placebo arm due to the unblinding of individual subjects may have had an effect on subjective endpoints such as patient reported outcomes (PRO) assessments, the use of concurrent and rescue ITP medication and adverse events reporting. This is important since some of these subjective endpoints might have been fed into the economic model. In the event, patient reported quality of life and complications data (other than bleeding) were not incorporated into the model although arguably they should have been. The manufacturer, therefore, should have used a more robust method of imputation such as multiple imputations instead of the last value carry forward used.

The manufacturer provided evidence of the [redacted] outcome (Table [redacted] of the manufacturer's submission) data. These data consisted of the [redacted] These calculations have been rechecked using the data provided and the results are reproducible.

The manufacturer provided results of analysis from the PRO measures. These included the change from baseline EQ-5D, EQ-5D VAS scores and the ITP-PAQ scores. General Linear Models repeated measure mixed models were used to analyse the pooled change baseline score to week 24 from the two studies. The analyses were controlled for age, gender, splenectomy status, and the use of baseline ITP medications. The EQ-5D index score and the EQ-5D VAS scores were analysed using linear regression stratified by responders (platelet counts > 50 x 10^9/l or > 30 x 10^9/l) and non-responders (platelet counts < 50 x 10^9/l or <30 x 10^9/l) and controlling for age (<40, 40-65, >65 years) and gender.

The manufacturer provided tables for the results of all the analyses in the phase 3 studies, the PRO analyses and rates of bleeding. In all cases romiplostim proved to be more efficacious than placebo with p-values <0.05 at the 0.05 significance level. Where possible, the ERG

recalculated these values and our values agreed with those in the submission. Overall, the quality of the statistical evaluation of the clinical studies appeared to be high and enabled a robust assessment of the efficacy of romiplostim. The same, however, cannot be said about the quality of the analyses of safety and PRO. The inability to totally blind patients and investigators may have had an impact on the safety and PRO outcomes.

Meta-analysis

There has been no formal meta-analysis performed either on romiplostim or the comparators. Neither were there any indirect or mixed treatment comparisons. The reason given by the manufacturer was that there is only one phase 3 RCT for romiplostim-plus-standard-of-care versus placebo-plus-standard-of-care in each of the key ITP populations. Data on romiplostim used in the economic model were derived from the romiplostim arms of the trials and effectively this treated these data as observational.

The manufacturer also explained that data on the comparators were derived from single-arm studies and so no formal meta-analysis could be done. However, where there was more than one relevant comparator treatment, estimates of efficacy were combined by taking a weighted average, weighting by sample size. Also, reasons such as lack of placebo controlled trials involving the comparator and the complexity of ITP treatment were given for not conducting indirect/mixed treatment comparisons.

Further clarification was sought from the manufacturer as to why the weighted average was preferred over other alternatives such as median and range. The manufacturer responded "Using a weighted average to derive a pooled estimate of efficacy provides the best estimate of efficacy as it appropriately takes into account the variability in efficacy observed in the individual studies. Alternative methods, such as using the median (which ignores study variability), were considered; however, an approach using the average rather than the median was considered more appropriate."

Simply pooling of effect sizes as has been done by the manufacturer has the potential of producing biased and unreliable estimates. Weighting by sample size also has the potential for large studies of low quality to dominate the pooled estimates. In effect the manufacturer conducted an analysis similar to a fixed effect meta-analysis, the implicit assumption of which is that the true effect does not differ between studies. No attempt was made to assess evidence of heterogeneity in the analysis although the heterogeneous nature of the included studies is apparent. An estimate of the between study variance could have been used to modify the weights used to calculate the summary estimates. Previous research has compared the results

obtained from pooling observational data and RCT data.[31,32] This research suggested that, compared with the pooled RCT data, pooling observational data may lead to biased estimates (of perhaps as much as 30% to 100% of the relative effect size) either for or against the experimental treatment (in this case romiplostim).

With the exception of IVIg which had a relatively high number of studies included in the pooled results, the other comparators had very few studies and an alternative method of analysis might perhaps have yielded no significant difference from that contained in the submission. In the case of IVIg, if there was any bias in the pooled estimate it, was likely to favour IVIg over romiplostim and therefore should not affect the conclusions on the effectiveness of romiplostim compared with IVIg based on these results alone.

In conclusion, it is well known that evidence from non-randomised sources can bias estimates of effect sizes for an intervention to either over or underestimate its effectiveness.[33] The results from pooling of studies for treatments and from comparisons drawn between treatments should be treated with caution.

4.2 Summary statement of manufacturer's approach

The manufacturer's submission is complete on its own terms in its identification of studies reporting romiplostim. However, the pragmatic approach adopted by the manufacturer to identify comparator studies relied on non-systematic reviews with sub-optimal literature searches to identify all the key studies published up to the date of publication of the reviews.

The methodological quality of the two romiplostim RCTs (Studies 20030105 and 20030212) by Kuter and colleagues[11] has been discussed earlier in the text and assessed using the CRD checklist. However the methodological quality of the additional romiplostim studies included in the integrated safety analysis of all ITP studies, the included studies reporting comparator treatments, and the included reviews, were not formally assessed.

The statement of the decision problem was similar to the final scope issued by NICE, with some discrepancies. In the scope splenectomy was listed as a comparator. However the decision problem stated that splenectomy would not be included as a comparator in the non-splenectomy patient population because the proposed indication for romiplostim was for patients in whom splenectomy was medically contraindicated. Corticosteroids were also listed in the scope as a comparator and the decision problem. However the submission stated that in the assessment all patients were assumed to have received a course of corticosteroids prior to all treatment pathways modeled and that therefore papers on corticosteroid use had

not been reviewed in detail (although high dose intravenous steroids may be seen as a different therapy to standard first dose steroids). Although the manufacturer's population inclusion criteria were adults with platelet counts < 30 x 10^9l, the ITP safety set included [redacted]

Data on all specified outcomes were reported for the romiplostim studies but data for the comparator treatments were only available for a more limited range of outcomes (and this is a limitation of the underlying evidence base), including overall platelet response, time to platelet response, and proportion of patients with durable or long-term response and/or duration of response, with very few studies reporting bleeding events.

Due to the lack of placebo-controlled trials involving comparator treatments, the complexity of the treatment paradigm for ITP and the heterogeneity of the data, a formal indirect mixed treatment comparison was not undertaken.

4.3 Summary of submitted evidence

4.3.1 Summary of results

Romiplostim - efficacy

Durable platelet response

In the two RCTs by Kuter and colleagues[11] comparing romiplostim with placebo in splenectomised patients (Study 20030105) and non-splenectomised patients (Study 20030212) the primary efficacy outcome of durable platelet response was defined as achieving at least six weekly platelet responses (platelets ≥ 50 x 10^9/l) during the last eight weeks of treatment with no rescue medications administered at any time during the 24 week treatment period.

Splenectomised patients

In the RCT of splenectomised patients (Study 20030105), 16/42 (38%) patients in the romiplostim group and 0/21 (0%) patients in the placebo group achieved a durable platelet response. The odds ratio estimated by the ERG using an assumption of 1 event in the placebo (and hence biased against romiplostim) was OR 8.5 95% CI 1.15 to 372).

Non-splenectomised patients

In the RCT of non-splenectomised patients (Study 20030212) 25/41 (61%) patients in the romiplostim group and 1/21 (5%) patients in the placebo group achieved this outcome (OR 24.4, 95% CI 3.3 to 179.2).

Transient platelet response

A transient platelet response was defined as four or more weekly platelet responses (platelets $\geq 50 \times 10^9$/l) without a durable response (excluding platelet responses within eight weeks after rescue medication). Although listed as a secondary efficacy outcome measure on p 46 of the manufacturer's submission, the submission did not report any results for this outcome for either splenectomised (Study 20030105) or non-splenectomised patients (Study 20030212).

Overall platelet response

Overall platelet response was defined as either a durable platelet response or a transient platelet response.

Splenectomised patients

In the RCT of splenectomised patients (Study 20030105), 33/42 (79%) patients in the romiplostim group and 0/21 (0%) patients in the placebo group achieved an overall platelet response (estimated using the same assumption used for durable platelet response the odds ratio was 16.6 95% CI 2.37 to 706).

Non-splenectomised patients

In the RCT of non-splenectomised patients (Study 20030212) 36/41 (88%) patients in the romiplostim group and 3/21 (14%) patients in the placebo group achieved this outcome (OR 34, 95% CI 7.8 to 155.4).

Time to first weekly platelet response (platelets $\geq 50 \times 10^9$/l)

Splenectomised patients

The Kaplan-Meier estimated median time to the first platelet response was 3.0 weeks (95% CI 2 to 5 weeks) in the RCT of splenectomised patients (Study 20030105)

Non-splenectomised patients

In the RCT of non-splenectomised patients (Study 20030212) the estimated median time to the first platelet response was 2.0 weeks (95% CI 1 to 3 weeks).

Number of weeks with a platelet response (platelets $\geq 50 \times 10^9$/l)

Splenectomised patients

In the RCT of splenectomised patients (Study 20030105), the mean number of weeks with a platelet response was 12.3 (SD 7.9) for patients in the romiplostim group compared with 0.2 (SD 0.5) for patients in the placebo group (difference 12.1, 95% CI 8.7 to 15.6 weeks).

Non-splenectomised patients

In the RCT of non-splenectomised patients (Study 20030212), the mean number of weeks with a platelet response was 15.2 (SD 7.5) for patients in the romiplostim group compared with 1.3 (SD 3.5) for patients in the placebo group (difference 13.9, 95% CI 10.5 to 17.4 weeks).

Need for rescue medications

Splenectomised patients

In the RCT of splenectomised patient[redacted] patients in the*romiplostim group and[redacted] patients in the placebo group required rescue medication*during the treatment period[redacted].

Non-splenectomised patients

In the RCT of non-splenectomised patients[redacted] patients in the*romiplostim group and[redacted] patients in the placebo group received rescue medication[redacted].

Incidence of > 25% reduction from baseline or discontinuation of concurrent ITP therapy

Splenectomised patients

In the RCT of splenectomised patients (Study 20030105), 12/42 (29%) patients in the romiplostim group and 6/21 (29%) patients in the placebo group were receiving concurrent ITP therapies at baseline. At week 25 of the study, 4 (33%) of the 12 patients in the romiplostim group had a > 25% reduction in concurrent ITP treatment (the remaining eight (67%) patients had discontinued all concurrent ITP therapies) compared with 1 (17%) of the 6 patients in the placebo group.

Non-splenectomised patients

In the RCT of non-splenectomised patients (Study 20030212), 11/41 (27%) patients in the romiplostim group and 10/21 (48%) patients in the placebo group were receiving concurrent ITP therapies at baseline. At week 25 of the study, four (36%) of the 11 patients in the romiplostim group had a > 25% reduction in concurrent ITP treatment compared with two (20%) of the ten patients in the placebo group. An additional 4 (36%) of the 11 patients in the romiplostim group had discontinued all concurrent ITP therapies compared with an additional three (30%) of the ten patients in the placebo group.

Frequency of durable response with stable dose

A stable dose was defined as a dose maintained within ± 1 µg/kg during the last eight weeks of treatment.

Splenectomised patients

In the RCT of splenectomised patients (Study 20030105), 13/42 (31%) patients in the romiplostim group were able to achieve a durable platelet response at a stable dose compared with none of the placebo group. An ERG estimation of odds ratio, assuming minimal events in placebo group so slightly biased against romiplostim, gave an OR 8.5 95% CI 1.15 to 371.79. The width of the confidence interval includes differences in clinical effectiveness that are clinically implausible but serves to show that the small quantity of data gives a statistically significant but imprecise benefit for romiplostim.

Non-splenectomised patients

In the RCT of non-splenectomised patients (Study 20030212) 21/41 (51%) patients were able to achieve a durable platelet response at a stable dose, compared with none of the placebo group. An ERG estimation of odds ratio, assuming minimal events in placebo group so slightly biased against romiplostim, gave an OR 16.60 95% CI 2.37 to 706.35. Again the width of the confidence interval highlights that these data are based on a small study.

Time to failure on romiplostim

This was a retrospectively defined outcome [redacted]

The manufacturer'susubmission stated (p54) [redacted] Failure of response was defined as [redacted] Time to failure was calculated as [redacted] The mean_response time was estimated to be [redacted] In the manufacturer's response to points for*clarification (Amgen response to points for clarification, B6) best case and worst case scenarios were estimated [redacted]

Assuming that censored patients did not fail (a best case scenario) the mean time to failure was estimated by the ERG as 1217 weeks. Assuming that all censored patients did fail (a worst case scenario) gave a mean time to failure as estimated by the ERG of 70 weeks.

Romiplostim – safety

Bleeding episodes

This was a retrospectively defined outcome, assessed by an analysis of bleeding events reported as adverse events. Table 4 shows a post-hoc analysis of reported safety adverse events of bleeding for the two RCTs of splenectomised (Study 20030105) and non-splenectomised patients (Study 20030212). Further data were obtained the manufacturer's response to the ERG's clarification queries which provided data for the two RCTS separately rather than pooled as in the manufacturer's submission. For the categories of 'Overall bleeding events' and 'Grade 2 or higher bleeding events' the numbers subsequently given for the romiplostim patients in the individual studies do not sum to the totals reported in the manufacturer's submission [redacted] on the information from the individual studies the pooled results for 'Overall bleeding events' for the romiplostim groups would be 48/84 (57%) rather than 45/84 (54%) and the pooled results for 'Grade 2 or higher bleeding events' should be 13/84 (15%) and not 12/84 (15%) (also 12/84 is 14% rather than 15%). [redacted] reported in Table 5 [redacted]

Table 5 shows the rates of all bleeding events [redacted]

Splenectomised patients

Across [redacted] bleeding events [redacted] (Table 5).

Non-splenectomised patients

Across [redacted] bleeding events the percentage of patients experiencing a bleed [redacted] Table 4). [redacted] Table 6 shows the rates of [redacted]

[redacted]

Table 4 Post-hoc analysis of reported safety adverse events of bleeding from the two romiplostim RCTs

	RCT of splenectomised patients (study 20030105)		RCT of non-splenectomised patients (study 20030212*)		Both studies	
	Romiplostim	**Placebo**	**Romiplostim**	**Placebo**	**Romiplostim**	**Placebo**
Overall bleeding events	28/42 (67%)	15/21 (71%)	20/42 (48%)	10/20 (50%)	45/84 (54%)	25/41 (61%)
Serious bleeding events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2 or higher bleeding events (moderate, severe, life-threatening or fatal	9/42 (21%)	8/21 (38%)	4/42 (10%)	6/20(30%)	12/84 (15%)	14/41 (34%)
Grade 3 or higher bleeding events (severe, life threatening or fatal	4/42 (10%)	4/21 (19%)	2/42 (5%)	1/20 (5%)	6/84 (7%)	5/41 (12%)

*Source: manufacturer's submission and response to clarification queries document.

Notes (from manufacturer's submission):

[redacted]

Table 5 Rates of all bleeding events in the two romiplostim RCTs

	Number of events		Person-weeks of follow-up		Rate per person-month		Rate per 100 person-months		Monthly probability	
	Romiplostim	Placebo	Romiplostim	Placebo	Romiplostim	Placebo	Romiplostim	Placebo	Romiplostim	Placebo
RCT of splenectomised patients (study 20030105)										
Platelet count < 50,000	[redacted]									
Platelet count > 50,000	[redacted]									
Missing	[redacted]									
Total	[redacted]									
RCT of non-splenectomised patients (study 20030212)										
Platelet count < 50,000	[redacted]									
Platelet count > 50,000	[redacted]									
Missing	[redacted]									
Total	[redacted]									
Both studies										
Platelet count < 50,000	[redacted]									
Platelet count > 50,000	[redacted]									
Missing	[redacted]									
Total	[redacted]									

Source: manufacturer's submission and response to clarification queries document.

Table 6 Rates of bleeding-related hospitalisation in the two romiplostim RCTs

	Number of events		Person-weeks of follow-up		Rate per person-month		Rate per 100 person-months		Monthly probability	
	Romiplostim	Placebo	Romiplostim	Placebo	Romiplostim	Placebo	Romiplostim	Placebo	Romiplostim	Placebo
RCT of splenectomised patients (study 20030105)										
Platelet count < 50,000	[redacted]									
Platelet count > 50,000	[redacted]									
Missing	[redacted]									
Total	[redacted]									
RCT of non-splenectomised patients (study 20030212)										
Platelet count < 50,000	[redacted]									
Platelet count > 50,000	[redacted]									
Missing	[redacted]									
Total	[redacted]									
Both studies										
Platelet count < 50,000	[redacted]									
Platelet count > 50,000	[redacted]									
Missing	[redacted]									
Total	[redacted]									

Source: manufacturer's submission and response to clarification queries document.

Other adverse effects

Rates for the different categories of adverse effects for the two romiplostim RCTs (Studies 20030105 and 20030212) are shown in Table 7. In the evidence provided by the manufacturer no assessment was made as to whether any differences were statistically significant.

All patients

Across both studies all 84 of the romiplostim patients and 39/41 (95%) of the placebo patients experienced an adverse event (Table 7). [redacted] most common adverse event*overall [redacted] When data were pooled across both patient groups adverse events with a > 10% incidence in the romiplostim arms compared with the placebo arms were [redacted]

Across both studies 34/84 (40%) of patients in the romiplostim groups experienced a treatment-related adverse event compared with 11/41 (27%) in the placebo groups.

Splenectomised patients

As Table 7 shows in the RCT of splenectomised patients (Study 20030105) a similar percentage of patients in each group experienced a severe adverse event, while slightly more patients in the romiplostim group and none in the placebo group experienced a life-threatening event although three patients (14%) in the placebo group died.

The most common adverse event in the RCT of splenectomised patients was [redacted] Adverse events with a > 10% incidence in the romiplostim arm compared with the placebo arm for splenectomised patients*were: [redacted]

In the RCT of splenectomised patients [redacted] in the placebo group. In this study [redacted] in the romiplostim group experienced a severe treatment-related adverse event.

Non-splenectomised patients

In the RCT of non-splenectomised patients (Study 20030212) a higher percentage of patients in the placebo group compared with the romiplostim group experienced a severe

adverse*event, while a similar percentage in each group experienced a life-threatening adverse event. One patient (2%) in the romiplostim group [redacted]

The most common adverse event in the RCT of non-splenectomised patients was [redacted] The adverse events with a > 10% incidence in the romiplostim arm compared with the placebo arm were [redacted]

In the RCT of non-splenectomised patients [redacted] experienced a treatment-related adverse event compared with [redacted] placebo group.

Table 7 Adverse events in the two romiplostim RCTs

	RCT of splenectomised patients (Study 20030105)		RCT of non-splenectomised patients (Study 20030212)		Both studies	
Type of adverse event	**Romiplostim (n=42)**	**Placebo (n=21)**	**Romiplostim (n=42)**	**Placebo (n=20)**	**Romiplostim (n=84)**	**Placebo (n=41)**
Any	42 (100%)	20 (95%)	42 (100%)	19 (95%)	84 (100%)	39 (95%)
Severe	15 (36%)	7 (33%)	8 (19%)	5 (25%)	23 (27%)	12 (29%)
Life-threatening	2 (5%)	0 (0%)	2 (5%)	1 (5%)	4 (5%)	1 (2%)
Fatal	0 (0%)	3 (14%)	1 (2%)	0 (0%)	1 (1%)	3 (7%)

Source: manufacturer's submission and response to clarification queries document.

Notes:

[redacted]

Table 8 The five most common adverse events in the two romiplostim RCTs

	RCT of splenectomised patients (Study 20030105)		RCT of non-splenectomised patients (Study 20030212)			Both studies	
Event	**Romiplostim**	**Placebo**	**Event**	**Romiplostim**	**Placebo**	**Event**	**Romiplostim**	**Placebo**
Five most common adverse events								
Headache							29 (35%)	13 (32%)
Epistaxis							28 (33%)	12 (29%)
Fatigue							27 (32%)	10 (24%)
Arthralgia								
Diarrhoea								
Adverse events with a > 10% higher incidence in the romiplostim arm								
Myalgia								
Dizziness								
Pharyngolaryngeal pain								
Pyrexia								
Arthralgia								
Insomnia								
Diarrhoea								

Source: manufacturer’s submission and response to clarification queries document.

Adverse drug reactions (ADRs) were defined as undesirable effects reasonably associated with the use of a drug, which may occur as part of the pharmacological action of the drug or be unpredictable in occurrence. Adverse events with a≥ 5% difference between romiplostim and placebo groups were considered ADRs. Table 9 shows the ADRs for the two patient groups.

All patients

Across both studies, headache (29/84, 35%) was the most common adverse drug reaction amongst romiplostim patients, followed by arthralgia (22/84, 26%), dizziness (14/84, 17%) and insomnia (13/84, 15%).

Splenectomised patients

Three patients in the placebo group died, with causes of death pneumonia, pulmonary embolism and cerebral haemorrhage.

Non-splenectomised patients

In the RCT of non-splenectomised patients (Study 20030212) one patient in the romiplostim group died, the cause of death being an intracranial haemorrhage.

The manufacturer also conducted an integrated analysis of safety for the regulatory submission of the romiplostim marketing application [redacted] The ITP safety set included data from [redacted] Table 10 shows a summary of the adverse events for the ITP safety set [redacted]

[redacted]

In the ITP safety set [redacted]

Eight patients died during the romiplostim clinical study program, five (2%) romiplostim patients and three (7%) placebo patients, with none of the deaths considered to be treatment-related. Of the romiplostim-treated patients, causes of death were intracranial haemorrhage, pneumococcal pneumonia, cardiac arrest, hepatic and renal failure, and acute respiratory distress syndrome. Among the placebo-treated patients causes of death were primary atypical pneumonia, pulmonary embolism, and cerebral haemorrhage.

In the ITP safety set [redacted] romiplostim-treated patients reported [redacted]

The manufacturer stated that the following were topics covered in the draft Summary of Product Characteristics and were either observed or potential class effects based on the pharmacological mechanism of action of thrombopoietin (TPO) receptor stimulators.

- Identified risks
    - Recurrence of thrombocytopenia and bleeding after cessation of treatment; and
    - Increased reticulin in the bone marrow.

- Potential risks
    - Thrombotic/thromboembolic complications;
    - Progression of existing myeloid malignancies or myelodysplastic syndromes (MDS); and

Cross reacting antibodies to endogenous thrombopoietin **

Table 9 Adverse drug reactions in the two romiplostim RCTs

	RCT of splenectomised patients (Study 200301050		RCT of non-splenectomised patients (Study 20030212)		Both studies	
Adverse drug reaction	**Romiplostim** [redacted]	**Placebo** [redacted]	**Romiplostim** [redacted]	**Placebo** [redacted]	**Romiplostim (n=84)**	**Placebo (n=41)**
Headache	[redacted]	[redacted]	[redacted]	[redacted]	29 (35%)	13 (32%)
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	22 (26%)	8 (20%)
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	14 (17%)	0 (0%)
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]	13 (15%)	3 (7%)
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]	12 (14%)	1 (2%)
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]	11 (13%)	2 (5%)
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	9 (11%)	0 (0%)
Shoulder pain	[redacted]	[redacted]	[redacted]	[redacted]	7 (8%)	0 (0%)
Dyspepsia	[redacted]	[redacted]	[redacted]	[redacted]	6 (7%)	0 (0%)
Paraesthesia	[redacted]	[redacted]	[redacted]	[redacted]	5 (6%)	0 (0%)

Source: manufacturer's submission and response to clarification queries document.

Table 10 Overall summary of adverse events (ITP safety set)

Type of adverse event	Placebo [redacted]	Romiplostim [redacted]
Any	[redacted]	[redacted]
Severe	[redacted]	[redacted]
Life-threatening	[redacted]	[redacted]
Fatal	[redacted]	[redacted]
Serious adverse events	[redacted]	[redacted]
Treatment-related adverse events:		
Any	[redacted]	[redacted]
Severe	[redacted]	[redacted]
Life-threatening	[redacted]	[redacted]
Fatal	[redacted]	[redacted]
Treatment-related serious adverse events	[redacted]	[redacted]
Patients who withdrew from study due to adverse events	[redacted]	[redacted]

Source: manufacturer's submission and response to clarification queries document.

Notes:

[redacted]

Romiplostim - health-related quality of life

ITP-PAQ

The ITP-Patient Assessment Questionnaire (ITP-PAQ) is a disease-specific instrument to assess HRQoL in ITP patients.

Splenectomised patients

ITP-PAQ change from baseline results indicated that the romiplostim group had a statistically significant ($p < 0.05$) improvement in the Symptoms, Bother, Social Activity, and Women's Reproductive Health scales compared with placebo.

Non-splenectomised patients

The romiplostim group had a statistically significant improvement in the Activity scale. When the ITP-PAQ information for the two studies was combined the romiplostim patients experienced statistically significant improvements on three of four physical health scales (Symptoms, Bother and Activity), both of the emotional health scales (Fear and Psychological) and on Social Activity, and Women's Reproductive Health scales (Menstrual Symptoms subscale). No statistically significant differences in improvement between the romiplostim and placebo groups were found for Fatigue, Overall QoL, Work, and Fertility.

EQ-5D

Table 11 summarises the EQ-5D change scores from baseline to week 24 for the two romiplostim RCTs (Studies 20030105 and 20030212). In both studies, EQ-5D scores (EQINDEX and EQVAS) for the romiplostim patients improved during this period, while for the placebo patients only the EQVAS score improved in the RCT of non-splenectomised patients. The differences in mean change scores in the individual studies between the romiplostim and placebo patients were not statistically significant, although when taken together there was a statistically significant difference in favour of romiplostim in the analysis using the final score as dependent variable adjusted for baseline score.

Splenectomised patients

Adjusted mean change scores from baseline for patients with platelet counts > 50 x 10^9/l or > 30 x 10^9/l (responders) during the last four weeks of the study were higher than those with platelet counts < 50 x 10^9/l or < 30 x 10^9/l (non-responders), although the difference was statistically significantly different only between responders with platelet count > 30 x 10^9/l and non-responders with platelet count < 30 x 10^9/l.

Non-splenectomised patients

Adjusted mean change scores from baseline for those with platelet counts > 50 x 10^9/l or > 30 x 10^9/l (responders) were also higher than those with platelet counts < 50 x 10^9/l or < 30 x 10^9/l (non-responders), but the difference was not statistically significant. When both studies were taken together, there was a statistically significant difference in EQVAS in favour of those with platelet counts > 50 x 10^9/l (responders) compared with platelet counts < 50 x 10^9/l

(non-responders), in analysis using the final score as dependent variable adjusted for baseline score and covariates. There was also a statistically significant difference in EQVAS in favour of those with platelet counts > 30 x 10^9/l (responders) compared with platelet counts < 30 x 10^9/l (non-responders), in analysis using the change score as dependent variable and also in analysis using the final score as dependent variable adjusted for baseline score and covariates.

Table 11 EQ-5D change scores, baseline to week 24

	Mean change	SD	95% CI	Mean change	SD	95% CI	p[1]	p[2]
RCT of splenectomised patients (study 20030105)								
	Romiplostim (n=42)			**Placebo (n=21)**				
EQINDEX	0.03	0.17	-0.02 to 0.09	-0.05	0.21	-0.15 to 0.04	0.092	0.071
EQVAS	2.79	21.41	-4.80 to 10.38	-1.81	14.83	-8.56 to 4.94	0.394	0.266
RCT of non-splenectomised patients (study 20030212)								
	Romiplostim (n=41)			**Placebo (n=21)**				
EQINDEX	0.02	0.16	-0.03 to 0.07	-0.01	0.10	-0.05 to 0.04	0.468	0.080
EQVAS	8.68	14.67	3.98 to 13.37	4.15	17.28	-3.94 to 12.24	0.293	0.077
Both studies								
	Romiplostim (n=83)			**Placebo (n=42)**				
EQINDEX	0.03	0.16	-0.01 to 0.06	-0.03	0.17	-0.08 to 0.02	0.071	0.017
EQVAS	6.01	18.14	1.78 to 10.25	1.10	16.15	-4.00 to 6.20	0.152	0.041

Source: manufacturer's submission and response to clarification queries document.
Notes:

1. RCT of splenectomised patients (study 20030105). Sample size: EQINDEX, romiplostim=37; EQVAS, romiplostim = 33.
2. RCT of non-splenectomised patients (study 20030212). Sample size: EQINDEX, romiplostim=39, placebo=20; EQVAS, romiplostim = 40, placebo=20.
3. Both studies. Sample size: EQINDEX, romiplostim=76, placebo=41; EQVAS, romiplostim = 73, placebo=41.
4. p^1, linear regression using change scores as dependent variables
5. p^2, linear regression using final score as dependent variable adjusted for baseline score

Comparator treatments - efficacy

The data for each treatment is summarised in Table 12 and briefly described in the text below.

Corticosteroids

The manufacturer stated that, as in their submission all patients were assumed (in practice this is unlikely to be always true as there are some situations where steroids would not be used e.g. uncontrolled diabetes, HIV) to have received a course of corticosteroids prior to the treatment pathways modeled, papers on corticosteroid use were not reviewed in detail. Corticosteroids were not listed in the table summarising the efficacy of ITP comparator treatments that was included in the manufacturer's submission (Table 6.8.3). However, results were reported in the text for two reports by Stasi and colleagues[16] and Ben-Yehuda and colleagues,[34] with corticosteroid treatment producing an initial platelet response in approximately two-thirds of patients, but remission only sustained in approximately 10-20% once steroids were reduced or stopped.

IVIg

Results were based on the ASH guidelines[7] that included 14 case series,[35-48] and 17[49-65] of 26 additional reports identified from the manufacturer's literature search (the remaining nine studies could not be sourced in time for the review).

In the review of 14 case series in the ASH guidelines,[7] approximately 75% of patients had a platelet response. The manufacturer stated that pooling data across the studies that they reviewed, 80.5% of patients had a platelet response ($\geq$50 x 10^9/l.[49,50,52-55,57,58,60-62,65] The response generally occurred within a few days but was generally transient, lasting between three to four weeks on average.[3,10]

Anti-D

Results were based on the ASH guidelines[7] that included five case series,[45,66-69] and an additional seven reports identified from the manufacturer's literature search.[60,70-75] The review of case series in the ASH guidelines[7] and the studies by Scaradavou and colleagues,[75] Aledort and colleagues[70] and Unsal and colleagues[60] suggested that approximately 46% of non-splenectomised patients reach a platelet count of $\geq$50 x 10^9/l, with higher numbers of patients reaching a platelet threshold of 20 or 30 x 10^9/l. The response is generally transient, lasting approximately 2-3 weeks, or slightly longer with the 75 ug/kg dose.[7,73] In a study by Cooper and colleagues[71] involving 28 non-splenectomised patients, intermittent treatment with anti-D as required repeatedly increased counts in 68% of patients, with 25-30% showing responses lasting longer than one year.

Rituximab

Results were based on the systematic review by Arnold and colleagues[18] that included 18 case series[76-93] and a dose-finding phase II study,[94] the review by Zhou and colleagues[95] that included 12 reports,[77,79,81,87,89,90,92,94,96-100] the systematic review by Vesely and colleagues[101] that reported data on splenectomised patients from eight case series[81,82,87,94,98,99,102,103] and three additional reports identified from the manufacturer's literature search.[104-106] The manufacturer reported that the overall platelet response was estimated as 62.5% in the systematic review by Arnold and colleagues,[18] 52.9% in the review by Zhou and colleagues,[95] 58.5% in the systematic review of splenectomised patients by Vesely and colleagues[101] and 60% and 75% in the studies by Godeau and colleagues[104] and Zaja and colleagues[106] respectively. Arnold and colleagues[18] reported a median time to response of 5.5 weeks and a median response duration of 10.5 months.

In their economic model the manufacturer averaged the response rate from the review by Arnold and colleagues,[18] and the review by Zhou and colleagues,[95] to get a response rate of 58%. Also within the model the summary data from Godeau and colleagues,[104] Zaja and colleagues[106] and Cooper and colleagues[79] were used to estimate a duration of response of 17.4 months.

Danazol

Results were based on the systematic review by Vesely and colleagues[101] that reported data on splenectomised patients from 11 case series[102,107-116] a case series by Maloisel and colleagues,[117] as well as 13 studies listed in their paper as major reports,[107,110-112,115,118-124] and an additional ten reports identified from the manufacturer's literature search.[116,125-133]

Splenectomised patients

The manufacturer reported a rate of 60% post-splenectomy in the review by Vesely and colleagues.[101] The same crude aggregation of data across studies were used in the manufacturer's economic model. Data from seven case series[111,112,117,124,126-128] were used to estimate a mean duration of response of 136 months.

Non-splenectomised patients

Maloisel and colleagues[117] reported an overall platelet response of 67% in their study of 57 patients. Maloisel and colleagues[117] also looked at 13 previous reports, across which the average overall response was 40%. The study by Maloisel and colleagues[117] reported a median time to response of three months and that 47% of patients were still responding after 119 months.

In the manufacturer's economic model a crude aggregation across these two studies[117] gave an overall response of 45%. The duration of response was taken to be the same as that reported above for splenectomised patients.

Dapsone

Splenectomised patients

Results were based on the systematic review by Vesely and colleagues[101] that reported data on splenectomised patients from five case series.[134-138] The overall response rate was 47% in the splenectomised patients reported in this review. This related to data from a total of 15 patients and was the same data used in the economic model. It was assumed that the duration of response for splenectomised patients was the same as non-splenectomised patients (described below). In the study by Hernandez and colleagues[136] 27% of 15 patients discontinued dapsone..

Non-splenectomised patients

Results were based on the systematic review for non-splenectomised patients by Godeau and colleagues[10] that included three case series[136,139,140] In the three studies included in the review by Godeau and colleagues[10] most patients were non-splenectomised and these data have been taken within the economic model to represent non-splenectomised patients. Overall response rates were 40%,[136] 50%[140] and 62%,[139] while the 1997 study by Godeau and colleagues[140] reported a median time to response of three weeks, with 30% of patients still responding at one year all but one on continuous treatment. Within the economic model these data were crudely aggregated to give an overall response rate of 54%. From the data reported in Godeau and colleagues[140] and assuming an exponential extrapolation, the mean duration of response was estimated at 17.9 months.

Eleven per cent of 66 patients discontinued dapsone due to adverse events in the study by Godeau and colleagues,[140] and 3% of 90 discontinued in the study by Damodar and colleagues.[139]

Azathioprine

Splenectomised patients

Results were based on the systematic review by Vesely and colleagues[101] that reported data on splenectomised patients from ten case series[102,141-149] and one additional report of six studies identified from other reviews and the manufacturer's literature search.[129] The remaining five studies could not be sourced in time for the review. Studies in splenectomised patients suggested an overall response rate of approximately 60%.[129,141,148] Within the economic model

the response rate was estimated as 63% based on data from one review[101] and two case series[129,141] (one of which also appeared to be included in the review [Bouroncle 1969]). The mean response time was extrapolated from the results of one case series[148] as 18.8 months.

Non-splenectomised patients

The response rate in non-splenectomised patients was reported as 50%.[10] Within the economic model the response rate was assumed to be 50% based on the results of 1 case series.[129] Quiquandon and colleagues[148] reported a time to response of approximately four months. The ASH guidelines reported that, across a number of case series, approximately 20% of patients sustained a normal platelet count lasting from months to years off-treatment.[7] Within the economic model it was assumed that the mean duration of response for non-splenectomised patients was the same as that described above for splenectomised patients.

Mycophenolate mofetil (MMF)

Splenectomised patients

Results were based on the systematic review by Godeau and colleagues[10] that included four case series[150-153] only two of which related to splenectomised patients[150,153] and the systematic review by Vesely and colleagues[101] that reported data on splenectomised patients from one case series.[150] The response rates were 39%[153] and 57%.[150] The data from these two studies were crudely aggregated together to give a response rate of 44%. The mean duration of response within the economic model was assumed to be the same as that for non-splenectomised patients described below. Eleven per cent (2/18) of patients discontinued MMF due to adverse effects.[153]

Non Splenectomised patients

Results were based on the systematic review by Godeau and colleagues[10] that included four case series[150-153] only three of which reported response rate data for splenectomised patients.[150-152] Overall response rates of 50%[150] and 67%[152] were reported for non-splenectomised patients. In the economic model the response rate was calculated as 57% based on a crude aggregation of data from two case series.[150,152] The time taken to reach the maximum platelet count was four-to-five months in two reports.[150,152] Kotb and colleagues reported that 6/9 (67%) patients were still responding at a median follow-up of 35 months while still on treatment, while Hou and colleagues reported that 38% of 21 patients were still responding at a median follow-up of six months, with half still on treatment. Within the economic model the mean duration of response was extrapolated from these data and the mean duration of response was estimated as 5.24 months

Ciclosporin

Splenectomised patients

Results were based on the systematic review by Vesely and colleagues[101] that reported data on splenectomised patients as well as four case series[154-157] and an RCT.[158] In the three studies included in the review by Vesely and colleagues[101] the response rates were 45% (5/11), 50% (3/6) and 76% (16/21). In the economic model submitted by the manufacturer summary estimates for initial platelet response were derived for splenectomised patients. For splenectomised patients data were taken from the review by Vesely and colleagues[101] and 2 case series.[156,157] From a crude aggregation of data from 38 patients a rate of 63% was estimated.

In the three studies included in the review by Vesely and colleagues[101] with data on splenectomised patients, the longer-term response rates off-treatment were 17% (1/6) at 18 months, 27% (3/11) at one year, 18% (2/11) and 20% (2/10) at two years, and 42% (5/12) at three years. Within the manufacturer's economic model similar but not identical information for up to two years follow-up was used to estimate longer term response rates. Data came from two studies referred to as Peng 2003[156]and Zver 2006.[157] The mean duration of response was estimated from these data as 11.9 months.

Non-splenectomised patients

Results were based on the systematic review by Godeau and colleagues[10] that included three case series[155-157] and an RCT.[158] Initial platelet response > 50 x 10^9/l was reported by one study[158] in the review by Godeau and colleagues[10] and achieved by 5/10 (50%) of non-splenectomised patients. These same data were used in the economic model to estimate the initial platelet response for non-splenectomised patients. Long-term response was reported for one study[158] included in the review by Godeau and colleagues,[10] with 2/10 (20%) pre-splenectomy patients still responding off-treatment at two years. Within the manufacturer's economic model the mean duration of response was estimated from these data as 14.9 months.

Cyclophosphamide

Splenectomised patients

Results were based on the review by Vesely and colleagues[101] that reported data on splenectomised patients from five case series.[102,145,146,159,160] In the systematic review by Vesely and colleagues,[101] 51/83 (61%) of splenectomised patients achieved an initial platelet response. These same data were used within the economic model submitted by the

manufacturer. Within this model the mean duration of response was assumed to be the same as amongst non-splenectomised patients described below.

Non-splenectomised patients

Results were based on the ASH guidelines[7] that included reports of five case series.[146,159-162] The ASH guidelines reported an overall response in 60-80% of non-splenectomised patients, within the economic model submitted by the manufacturer the same data were used to assume a 70% initial platelet response. Twenty to 40% of these patients sustained a normal platelet count for two-to-three years after discontinuing treatment. Mean duration of response was estimated in the economic model as 24.9 months. These data were based upon the two to three year follow-up data abstracted from one study.

Vinca alkaloids

Splenectomised patients

Results were based on the ASH guidelines[7] that included 12 case series[146,163-173] and an RCT[174] comparing two vinblastine regimens, and a review by Vesely and colleagues[101] that reported data on splenectomised patients from 11 case series[102,146,163-166,169,171,173,175,176] and the RCT[174] comparing two vinblastine regimens. The ASH guidelines[7] and Vesely and colleagues[101] reported a lower initial response rate for splenectomised patients of 50% and 53% (55/103) respectively. Within the economic model submitted by the manufacturer the data from Vesely and colleagues[101] were used as the initial response rate. Within the economic model submitted by the manufacturer the mean duration of response was assumed to be the same as that assumed for the non-splenectomised patients.

Non-splenectomised patients

The ASH guidelines also provide data on non splenectomised patients. In the studies included in the ASH guidelines the initial response rate > 50 x 10^9/l was approximately 67%, with a response generally seen within 1-3 weeks.[7] These same data were used in the economic model submitted by the manufacturer as the initial platelet response rate.

In the studies included in the ASH guidelines[7] and BCSH guidelines,[3] < 10% of patients had sustained normal platelet counts requiring no further treatment for at least three months. The data from the ASH guidelines were used within the economic model submitted by the manufacturer to estimate the mean duration of response of 1.3 months.

Table 12 Summary of evidence of efficacy for comparator interventions

Comparator	Initial response	Number of patients / type of studies	Duration of response*	Number of patients / type of studies
IViG	EM: 80.5%	EM: 12 case series [49,50,52-55,57,58,60-62,65] (303 patients)	EM: not stated. 4 weeks	Not stated
	75%	ASH guidelines[7]	3 to 4 weeks	BCSH guideline and 1 study[3,63]
Anti D (non-splenectomised patients only)	Approx 46%	ASH guidelines,[7] & 3 case studies[60,70,75]		
	EM: 46%	EM: 2 case series[60,75] (272 patients)		
	intermittent treatment with anti-D as required repeatedly 68%	1 case study[71] (28 patients)	25-30% showing responses lasting longer than one year	1 case study[71] (28 patients)
Rituximab	EM: 58%	Av of 2 reviews[18,95]	EM: Mean duration of response 17.4 mths	3 case series[79,104,106]
	62.5%	1 review[18]	10.5 months	1 review[18]
	52.9%	1 review [95]	Not reported	
	58.5% splenectomised patient	1 review[101]	Not reported	
	75%	1 case series[64]		
	60%	1 case series[106]		
Danazol (splenectomised)	60%	1 review[101]		
	EM: 0.6	1 review[101] (90 patients)	Mean duration of response 136 months	7 case series[111,112,117,124,126-128]
Danazol (non-splenectomised)	EM: 0.45	2 studies (1study and 1 review?)[117] (276 patients)	Mean duration of response 136 months	7 case series[111,112,117,124,126-128]
	67%	1 case series[117] (57 partients)	47% of patients were still responding after 119 months	1 case study[117] (57 patients)
	40%. Average response across 14 case studies	1 review[117]		
Dapsone mostly non-splenectomised	40%,[136]50%[140] 62%,[139]	Review of 3 cases series[10]	30% of patients still responding at one year, all but one on continuous treatment	1 study[140]
non-splenectomised	EM: 54%	3 case series[136,139,140] (136patients)	Mean response duration 17.9 months	Extrapolated from one of the Godeau studies, which one is unclear
splenectomised patients	47%	Review[101] (7patients)		
Azathioprine	Approximately 60%	1 review[101] and 3 case studies[129,141,148]		
Splenectomised				
	EM: 63%	1 review[101] and 2 case series[129,141] (148 patients)	Mean duration of response 18.8 months	1 case study[148]

Comparator	Initial response	Number of patients / type of studies	Duration of response*	Number of patients / type of studies
Non-splenectomised	50%	1 case series[10]	Approx 20% sustained response lasting from months to years off-treatment.	ASH guidelines[7]
	EM 50%	1 case series[129] (60 patients)	Mean duration of response 18.8 months	1 case study [148]
Mycophenolate mofetil (MMF) Splenectomised	39%[153] 57%[150]	2 reviews[10,101] reporting 2 case series[150,153]		
	EM 44%	2 case studies[150,153] (25 patients)	Assumed to be the same as non-splenectomised patients	
Non-splenectomised	50%[150] 67%[152]	1 review[10] of 2 case series[150,152]	38% patients still responding at median of 6 months	1 case study[150](21 patients)
	EM 57%	2 case series[150,152] (23 patients)	Mean duration of response 5.4 months	1 case study[150] (21 patients)
Ciclosporin Splenectomised	45% (5/11)[154] 50% (3/6)[155] 76% (16/21)[158]	1 review[101] of 1 RCT[158] and 2 case series[154,155]	17% (1/6) at 18 months, 27% (3/11) at one year, 18% (2/11) at two years 20% (2/10) at two years 42% (5/12) at 3 years	3 studies[154,155,158]included in 1 review[101]
	EM 63%	1 review[101] and 2 case series[156,157] (38 patients)		2 case series[156,157] The mean duration of response was estimated from these data as 11.9 months
Non-splenectomised	50%	1 review[10] (1 RCT[158] (10 patients)	2 of 10 (20%) responding off-treatment at 2 years	1 RCT (10 patients)[158]
	EM 50%	1 RCT[158] (10 patients)	Mean duration of response 14.9 months.	1 RCT (10 patients)[158]
Cyclophosphamide Splenectomised	61% (used also in EM)	1 review[101] and 5 case series[102,145,146,159,160](83 patients)	Mean duration of response 24.9 months	1 RCT[158]
Non-splenectomised	60-80%	ASH guidelines[7] of 5 case series[146,159-162]	20-40% sustaining a normal platelet count 2 to 3 years	ASH guidelines[7]
	EM 70%	ASH guidelines[7]	Mean duration of response 24.9 months	1 RCT [158]
Vinca alkaloids Splenectomised	50%	ASH guidelines[7]	Mean duration of response 1.3 months	ASH guidelines[7]
	53% (used in EM as well)	1 Review[101]103 patients		
Non-splenectomised	67% (used in EM as well)	ASH guideline[7]	Mean duration of response 1.3 months	ASH guidelines[7]

Source: manufacturer's submission
EM = economic model; * where the result of the economic model are reported the mean response time is reported as calendar months rather than number of 4 weekly cycle periods

Comparator treatments – safety

Corticosteroids

Results were based on 15 reports, including full papers, guidelines, published abstracts and unpublished reports.[7,16,64,130,177-187] Adverse events or long-term complications affect nearly three-quarters of ITP patients receiving corticosteroids,[130,184] and include diabetes, hypertension, osteoporosis, anxiety, insomnia, gastritis, infections, fractures, obesity and excessive weight gain, psychosis, depression, headache, cramps, and alopecia.[7,16,64,130,177-179,182,183,185,187] Long-term use of systemic, high-dose corticosteroids may result in corticosteroid-induced lipodystrophy (CIL), categorised by adipose-tissue accumulation in the face ("moon face"), dorsocervical region ('buffalo hump'), and abdomen, and/or reduced subcutaneous fat thickness in the limbs.[180]

IVIg

Results were based on three reports.[7,188,189] The ASH guidelines[7] and Talecris-Biotherapeutics[188] indicated that up to 75% of ITP patients experience adverse events, including mild headache, backache, nausea, cough, injection site reaction and fever. FDA prescribing information for IVIg includes a black box warning addressing the risk of severe reactions, such as renal dysfunction, acute renal failure, osmotic nephrosis, and death. On rare occasions, IVIg may cause a precipitous decrease in blood pressure and induce anaphylaxis, even when the patient is not known to be sensitive to immune globulin preparations. The Sandoglobulin SPC stated that IVIg may precipitate thromboembolic events such as myocardial infarction, pulmonary embolism, stroke and deep vein thrombosis due to increased blood viscosity caused by immunoglobulin infusion.[189]

Anti-D

Results were based on four reports.[70,71,75,190] In a report by Aledort and colleagues[70] involving 98 ITP patients, approximately 70% of patients experienced adverse events, mostly mild to moderate in intensity, the most common of which were chills (34.7% of patients), pyrexia (26.5%), increased blood bilirubin (21.4%) and headache (14.3%). Discontinuation rates of up to 4% have been reported.[71,75] FDA prescribing information for anti-D includes a black box warning for potentially fatal (though uncommon) intravascular haemolysis associated with disseminated intravascular coagulation (DIC) and complications including clinically compromising anaemia and acute renal insufficiency. Other serious but less common reactions include death, rapid or worsening of anaemia, and end-organ failure.

Rituximab

Results were based on the systematic review by Arnold and colleagues[18] that included 19 studies involving 306 ITP patients, in which approximately 22% of patients receiving rituximab experienced mild to moderate adverse events. Ten patients (3%) experienced severe or life-threatening adverse events. Nine deaths were temporally associated with rituximab use, including three cases of fatal bleeding and one case of postoperative fatal pulmonary embolism, although causality was not determined.[18]Adverse events occurred at the following rates (0.3% unless otherwise stated): Grade 1 or 2 - rash or allergic reaction (2%), infusion-related (18%), serum sickness, thrombocytosis, panniculitis, leg cramp/diarrhoea; Grade 3 or 4 – pneumonia (1.3%), bronchospasm, anaphylactic reaction, muscle pain, meningitis, retinal artery thrombosis, pulmonary embolism; Grade 5 - respiratory failure, pneumonia, haemorrhage (0.7%), hepatic failure, infection (0.7%) and pulmonary embolism.

Danazol

Results were based on three reports.[117,191,192] In a report by Maloisel and colleagues[117] involving 57 ITP patients, nine patients (16%) discontinued danazol due to severe adverse events, including increased levels of aspartate or alanine aminotransferase (9%), intracranial hypertension (3%), skin rash (2%) and rhabdomyolysis (2%). Mild or moderate adverse events were observed in 20 patients (36%), including weight gain and oedema (9%), liver test abnormalities (9%), amenorrhea (5%), nausea (3%), hypertension (3%), diabetes mellitus (2%), headache (2%), phlebitis (2%), skin rashes (2%) and hair loss (2%). George and colleagues[191] reported that danazol may cause cytopenias, gastrointestinal symptoms, and acute thrombocytopenia. The SPC stated the following adverse events: androgenic effects; hirsutism and hair loss; menstrual disturbances; backache and muscle cramps; hypertension and tachycardia, and; benign intracranial hypertension.

Dapsone

Results were based on three reports.[139,140,192] In a report by Damodar and colleagues[139] involving 55 ITP patients, side effects requiring discontinuation of therapy were observed in three (5%) patients. In a report by Godeau and colleagues[140] involving 66 patients, seven (11%) had to stop treatment due to methaemoglobinaemia (1), rash (1), nausea and vomiting (2), haemolysis (1), headache and vomiting (1), and mild hepatitis (1),while other adverse events that did not require treatment to be stopped were nausea (7) and rash (4). The SPC stated the following adverse events: haemolysis and methaemoglobinaemia; agranulocyctosis (rare); Stevens-Johnson syndrome (rare); ‘dapsone syndrome’, and; peripheral neuropathy.

Azathioprine

Results were based on three reports.[193-195] Huber and colleagues[195] and Cines and colleagues[193] reported that use of azathioprine in ITP patients may cause weight gain, fluid retention, GI symptoms, leucopenia, thrombocytopenia, and lymphomas. The SPC [194] stated that very common (occurring in > 10% of patients) adverse events included viral, fungal and bacterial infections, and myelosuppression.

Ciclosporin

Results were based on three reports.[155,158,196] In a report by Emilia and colleagues[155] involving 12 ITP patients, side effects included moderate hypertension (3, 25%), gingival hyperplasia (3), fatigue (2, 17%), paraesthesia (2), myalgia (2), dyspepsia (2), hypertrichosis (1, 8%) and tremor (1). One patient had to discontinue ciclosporin treatment due to candidiasis of the oropharynx.[155] In the report by Kappers-Klunne and colleagues[158] involving 20 patients, six patients (30%) discontinued ciclosporin due to the following side effects: hypertension, severe headache, muscle ache, raised creatinine, fatigue and nausea. Of the remaining 14 patients, three did not report any toxicity, while the remaining 11 patients experienced the following adverse events: hypertension (5, 25%), muscle ache (5), headache (2, 10%), raised serum creatinine (2), gum hyperplasia (1, 5%) nausea (1) and paraesthesia (1). [158] The SPC stated that ciclosporin was associated with the following adverse effects: renal impairment; predisposing patients to infection, and; increased risk of malignancies. Very common side effects (> 10%) include hyperlipidaemia, hypercholesterolaemia, tremor, hypertension and renal dysfunction, while common (1-10%) side effects include nausea, vomiting, diarrhoea, hepatic dysfunction, hyperkalaemia, hypomagnesaemia, myalgia and paraesthesia.[196]

Mycophenolate mofetil (MMF)

Results were based on three reports.[150,153,197] In the study by Provan and colleagues[153] involving 18 patients (17 of whom had undergone splenectomy) no severe toxicity was seen, although two (11%) patients discontinued MMF within the first month due to side effects (headache) and another patient could not tolerate the 1g bd dose due to headaches. In the study by Hou and colleagues[150] MMF was well tolerated with only slight nausea and diarrhoea recorded in 3/21 (14%) patients and there was no premature withdrawal from the study. The SPC[197] stated that MMF therapy was associated with the following adverse events: increased risk of malignancy; bone marrow suppression; predisposition patients to infection, and; cases of progressive multifocal leukoencephaly.

Cyclophosphamide

Results were based on three reports.[159,198,199] In the study by Reiner and colleagues[159] involving 20 patients, adverse events included neutropenia (three patients), acute deep vein thrombosis (two patients) and psoas abscess (one patient). Hershman and colleagues[199] reported secondary malignancies in breast cancer patients. The SPC[198] stated Cyclophosphamide was associated with the following adverse events: myelosuppression; amenorrhoea and azoospermia; haemorrhagic cystitis; alopecia; mucositis, and; nausea and vomiting.

Vinristine

Results were based on three reports.[146,170,200] In a letter by Linares and colleagues[170] involving eight non-splenectomised patients all patients tolerated the treatment without side effects. In the report by Pizzuto and colleagues[146] involving 19 patients, six (32%) developed neuropathy. The SPC[200]stated that when used as a single weekly agent vincristine was associated with the following adverse events: leucopenia; neuritic pain; alopecia; paraesthesia, and; muscle wasting.

4.3.2 Critique of submitted synthesis

The ERG assessed the clinical effectiveness part of the manufacturer's submission for its quality as a systematic review using the questions in CRD report 4 (Table 13).

Table 13 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?	Partially. The criteria do not fully accord with the decision problem. These include: • No criteria set for patients' baseline platelet counts (should be ≤ 30 x 10^9/l unless the patient experienced bleeding or was being prepared for surgery); • No criteria set for defining patients who are medically contraindicated to splenectomy; • No criteria set for duration of ITP (should be ≥ 6m for chronic ITP).
2. Is there evidence of a substantial effort to search for all relevant research?	Uncertain. • Existing reviews of comparator drugs were used as main evidence supplemented by searching for primary studies published after the reviews. However, the quality of the existing reviews is generally poor, and a total of 17 studies were missed in the supplementary searches. • Evidence from a survey conducted by the manufacturer was also used, but the response rate of the survey [redacted] was low.
3. Is the validity of included studies adequately assessed?	Partially. The validity of the two romiplostim RCTs included for efficacy was assessed (using the CRD checklist), but none of the other included studies/reviews.
4. Is sufficient details of the individual studies presented?	Yes. Characteristics and results of all primary studies/reviews were reported in detail.
5. Are the primary studies summarised appropriately?	Uncertain. • Very little synthesis of the reviews and primary studies; Evidence was not synthesised by patient subgroups (non-splenectomised and splenectomised).

In the manufacturer's submission the presentation of information was variable. In parts of the submission percentages were presented in the text without providing the numbers used to calculate them. The ERG queried this and fuller information was subsequently provided in the response to clarification queries document (Amgen response to points for clarification,

B1). Parts of the submission discussing the results of the comparator treatments were imprecise (e.g. p91 '…the majority of comparator treatments…', '…a few RCTs…') when it would have been more informative to be more specific. The ERG queried the fact that in the submission there were no flow diagrams showing the flow of studies from those identified by the search strategies through to those included in the review of clinical effectiveness, and this was subsequently provided in the response to clarification queries document (Amgen response to points for clarification, B3b). Nevertheless comparison of the flow diagrams, spreadsheets and tables highlighted inconsistencies so it was not always clear which studies were included.

For some outcomes (e.g. bleeding events) relating to the romiplostim RCTs only pooled data for splenectomised and non-splenectomised patients were presented. The ERG queried this and separate data for this and other outcomes for splenectomised and non-splenectomised patients were subsequently provided in the response to clarification queries document (Amgen response to points for clarification, B2). However, when the data from the individual studies were compared with the data for the pooled studies there were occasional discrepancies. For example, the submission stated that overall bleeding events were experienced by 45/84 (54%) romiplostim patients across both studies while the response to clarification queries document stated that this outcome was experienced by [redacted] splenectomised and [redacted] non-splenectomised patients (Amgen response to points for clarification, B2, Tables 19 and 20), which would give an overall rate of 57% rather than the 54% quoted in Table 6.4.3 of the manufacturer's submission. For grade 2 or higher bleeding events, the submission stated that this outcome was experienced by 12 romiplostim patients across both studies while the response to clarification queries document stated that it was experienced by nine splenectomised and [redacted] non-splenectomised patients (Amgen response to points for clarification, B2, Tables 19 and 20). For the outcome of [redacted], the submission stated that across both studies there were [redacted] bleeding events in patients with a platelet count < 50 x 10^9/l [redacted] bleeding events in patients with a platelet count > 50 x 10^9/l (Table 6.4.4). However the response to clarification queries document stated that there were [redacted] bleeding events in splenectomised patients [redacted] bleeding events in non-splenectomised patients with a platelet count < 50 x 10^9/l [redacted] events in splenectomised [redacted] events in non-splenectomised*patients with a platelet count > 50 x 10^9/l [redacted] (Amgen response to points for clarification B2, Tables 17 and 18). In the placebo group the submission stated that across both studies there were [redacted] weeks of follow-up in patients with a platelet count < 50 x 10^9/l (Table 6.4.4), while the response to clarification queries document stated that there were

[redacted] weeks of follow-up in splenectomised patients [redacted] weeks of follow-up in non-splenectomised patients with a platelet count < 50 x 10^9/l [redacted] (Amgen response to points for clarification, B2, Tables 17 and 18). For the outcome of bleeding-related hospitalisations [redacted] the submission stated that across both studies there were [redacted] weeks of follow-up in patients with a platelet count < 50 x 10^9/l (Table 6.4.5), while the response to clarification queries document stated that there were [redacted] weeks of follow-up in splenectomised patients [redacted] weeks of follow-up in non-splenectomised patients with a platelet count < 50 x 10^9/l [redacted] (Amgen response to points for clarification, B2, Tables 21 and 22).

The methodological quality of the two romiplostim RCTs was described in the text of the submission but it was unclear whether the studies had been assessed using an established checklist. The ERG queried this and in the response to clarification queries document the two RCTs were assessed using the Centre for Reviews and Dissemination criteria (Amgen response to points for clarification, B4). Although the manufacturer stated that for both studies an intention-to-treat analysis was undertaken, the report of the studies by Kuter and colleagues states (p 397) that analysis was per protocol. Details of the implications of this were reported in 4.1.5.

The manufacturer's submission stated that a lack of placebo-controlled trials for comparator treatments, in addition to the complexity of the treatment paradigm for ITP and the heterogeneity of the data, meant that it was not possible to undertake a formal indirect mixed treatment comparison. Our critique of whether this was or was not appropriate was provided in Section 4.1.7.

Only romiplostim RCTs in which the dosing paradigm described in the decision problem and in the anticipated label for the product (i.e. weekly subcutaneous injection at an initial dose of 1 µg/kg with subsequent dose titration to maintain a platelet count ≥ 50 x 10^9/l and not exceeding a dose of 10 µg/kg) were used as the basis for the clinical evidence of efficacy. This consisted of the two romiplostim RCTs by Kuter and colleagues[11] (studies 20030105 and 20030212) and resulted in a number of studies of romiplostim with a different dosing paradigm not being included in the analysis of efficacy.

Although the manufacturer's patient inclusion criteria were adult patients with platelet counts < 30 x 10^9/l, the ITP safety set included at least three studies (study numbers 20060131,

20010218, 20050162) where subjects with a platelet count < 50 x 10^9/l were enrolled. This may have resulted in a better adverse event profile for the romiplostim ITP safety set than would have been the case had only studies been included with patients whose platelet counts were < 30 x 10^9/l.

The inclusion criteria in the two romiplostim RCTs by Kuter and colleagues[11] stated that 'eligibility for both studies was identical and included…no active malignancy…'. However the manufacturer's submission stated (p70) that [redacted] treated patient withdrew from the study because of [redacted].

Of the eight patients who died during the romiplostim clinical study program. All three of the placebo group deaths occurred in the RCT of splenectomised patients (Study 20030105). Of the five romiplostim-treated patients who died, one death occurred in the RCT of non-splenectomised patients (Study 20030212), three deaths occurred in the open label study (Study 20030213) and one death occurred in an open label individual patient protocol (Study 20040209). Two of these patients would have been ineligible for the RCTs included for efficacy as one patient had pre-existing malignant hepatic neoplasm and the other was only one year old. It is unclear if there were other patients included in the integrated safety analysis of all ITP studies who would have been ineligible for inclusion in the two RCTs included for efficacy.

Although the manufacturer's submission stated, in relation to the two romiplostim RCTs,[11] that the primary analysis compared the incidence of durable response in the treatment groups using the Cochran-Mantel-Haenszel test for the odds ratio of the two groups and Kuter and colleagues[11] also stated that 'the common odds ratio was estimated together with the 95% CI', no OR data was presented in the manufacturer's assessment of clinical evidence. The ERG requested clarification on this and OR data were subsequently provided in the response to clarification queries document (items B1 and D7).

For comparative treatments, studies were identified from existing guidelines and reviews, and searches of the literature from the date of the reviews onwards. However, of the nine reviews included, only three could be classed as systematic reviews (those by Godeau and colleagues, Vesely and colleagues and Arnold and colleagues) and of these only one (Arnold and colleagues) contained a comprehensive search strategy to identify potentially relevant studies. The other were review articles with no methods sections, therefore it was unclear how comprehensive their search strategies were, while the paper by Maloisel and colleagues was a

case series which also included in its discussion section a table detailing some additional reports along with their main results.

The manufacturer's submission stated that there were few reliable methods for critically appraising studies such as case series and that, rather than attempting to undertake a formal critical appraisal on all studies, their approach was to try to take account of the fact that efficacy data on comparator treatments was only available from unblinded, uncontrolled studies, which were frequently of poor quality, and that this type of data was likely to overestimate treatment effects while under-reporting safety data. The ERG queried this and in the response to clarification queries document the manufacturer stated that they felt that attempting to undertake a formal quality assessment of the large number of uncontrolled trials would not add significant value to their analysis and that instead they attempted to take account of the poor quality of comparative data in their analysis and interpretation of results (Amgen response to points for clarification, B4b). However the sections of the submission reporting the efficacy and safety of the comparator treatments make no mention of the methodological quality of the studies whose results are reported. Aspects of methodological quality that it would have been useful to appraise in relation to case series include whether they were prospective, whether there was consecutive recruitment, whether length of follow-up was adequate and loss to follow-up.

Some of the included reports included types of patients who in the manufacturer's statement of the decision problem were excluded. For example the manufacturer's submission quotes an overall platelet response rate of 52.9% for rituximab from the review paper by Zhou and colleagues.[95] However in this review three studies (n=82, 23%) out of the 12 studies included (n=361) were of children, although the population considered in the manufacturer's submission was adults with ITP. In this instance removing the three studies involving children did not affect the value reported for this outcome. In other reports, for example the systematic review by Vesely and colleagues, the inclusion criteria in terms of platelet counts were $< 50 \times 10^9$/l (as opposed to $< 30 \times 10^9$/l as stated in the final scope issued by NICE and the manufacturer's statement of the decision problem (page 13). Also it was unclear how many of the non-splenectomised patients in the comparative studies were actually medically contra-indicated for splenectomy, which was the definition stated in the manufacturer's decision problem for this subgroup of patients (page 13) 'Second line treatment for non-splenectomised patients with inadequate response to initial corticosteroid treatment, where splenectomy is medically contra-indicated.'

Corticosteroids were listed in the manufacturer's decision problem as a comparator, although in the submission no efficacy data were provided for corticosteroids. The reason given for this was that in the submission all patients were assumed to have received a course of corticosteroids prior to all treatment pathways modeled and that therefore papers on corticosteroid use had not been reviewed in detail. However adverse effects associated with corticosteroids were reported in more detail.

The manufacturer's submission stated that data used in the base case cost-effectiveness analysis were taken from the study types that were available for each comparator, mainly single-arm studies such as cohort studies and case series. Most studies assessed overall platelet response, generally defined as using a platelet threshold of 50 x 10^9/l, although the outcomes used and the exact definitions of these outcomes varied between studies. According to the submission most studies presented data on the following outcomes, and these were used in the economic modelling:

- Percentage of patients with overall platelet response, where platelet response is generally defined as reaching a threshold, generally 50 x 10^9/l;
- Time from treatment initiation to treatment response; and
- Proportion of patients with durable or long-term response, and/or duration of response (only available from studies with long-term follow-up).

Data on the efficacy of comparator treatments were reported in the text of the submission (Section 6.8.4), Table 6.8.3 of the submission, an Excel file containing efficacy data on ITP comparator treatments included as part of the submission and an Excel file containing the cost-effectiveness model that was included as part of the submission. However the summary efficacy data given for the comparator treatments in the economics section was not clearly or consistently reported as such in the effectiveness section and it was necessary to cross-refer between these various data sources in order to ascertain how the summary values were calculated and the number of reports from which this information was derived.

The manufacturer reported an initial response rate for dapsone of 50% for pre-splenectomised patients in Table 7.1 of the submission, based on pooling results from three studies (34/55; 33/66; 6/15). However pooling these data gives a rate of 54%, not 50%.

4.4 Summary

4.4.1 Efficacy and safety of romiplostim

The efficacy of romiplostim was derived from two RCTs reporting romiplostim versus placebo in splenectomised and non-splenectomised patients, with a 24 week follow-up. Based upon the trial data patients receiving romiplostim had a higher durable platelet response in both the splenectomised and non-splenectomised studies. Patients receiving romiplostim had a better overall platelet response and less need for rescue medications. Amongst both patient groups the duration of platelet response was statistically significantly higher for those receiving romiplostim compared with those receiving placebo. For both patient groups a higher proportion of the romiplostim patients who were receiving concurrent ITP therapies at baseline had a > 25% reduction in concurrent ITP treatment at week 25 of the studies. More patients who were receiving romiplostim (31% and 51%) within the splenectomised and non-splenectomised groups were able to achieve a durable platelet response at a stable dose compared with none who received placebo. The mean response time on romiplostim was estimated by the manufacturer to be [redacted] weeks, calculated using data from the [redacted]. Although listed as a secondary efficacy outcome in the manufacturer's submission, transient platelet response was not reported.

For the splenectomised patient group, those receiving romiplostim [redacted] chance of [redacted] of bleeding events [redacted] The monthly probability of a bleeding event was [redacted] Amongst non-splenectomised patients, across most categories of bleeding events the percentage experiencing a bleed was similar other than for grade 2 or higher bleeding events in which a higher percentage of patients who had receive a placebo experienced an event. The monthly probability of a bleeding event was [redacted] Across both patient groups the monthly probability of bleeding-related hospitalisation was [redacted]

In terms of other adverse events splenectomised patients had [redacted] an adverse event or a severe adverse [redacted] those receiving romiplostim [redacted] to have a life-threatening event. Three patients receiving placebo died compared with none in the romiplostim group.

For non-splenectomised patients [redacted] experienced an adverse event or a life-threatening adverse event, while the likelihood of experiencing a severe adverse event was higher

amongst those [redacted] One patient (1/42, 2%) died in the romiplostim group compared with none in the placebo group.

In the integrated safety analysis of all ITP studies (ITP safety set), the study duration-adjusted*event rates were [redacted] those receiving romiplostim for [redacted] the ITP safety set, [redacted] romiplostim-treated patients reported [redacted] compared with [redacted] placebo-treated patients.

For health-related quality of life amongst splenectomised patients the ITP-PAQ change from baseline results showed that romiplostim treated patients had a statistically significant improvement in the Symptoms, Bother, Social Activity, and Women's Reproductive Health scales compared with placebo. For EQ-5D, there was no evidence of a statistically significant difference between randomized groups but adjusted mean change scores from baseline for patients with platelet counts > 30 x 10^9/l (responders) during the last four weeks of the study were statistically significantly higher than those with platelet counts < 30 x 10^9/l (non-responders). Amongst non-splenectomised patients those receiving romiplostim had a statistically significant improvement in the activity scale. The difference in EQ-5D change scores between responders and non-responders was not statistically significant.

The manufacturer's submission identified all relevant romiplostim studies and, overall, provided an unbiased estimate of short term treatment efficacy. Relevant outcomes were clearly presented. However, data relating to romiplostim were used in the economic model as if they came from a non-randomised, non comparative study. The quality of the studies was high based on the CRD checklist assessment, although blinding may have been compromised by the investigator and patients' knowledge of platelet counts. Only romiplostim RCTs in which the dosing paradigm described in the decision problem were used as the basis for the clinical evidence on efficacy, resulting in a few other romiplostim studies being excluded. Although the manufacturer's patient inclusion criteria were adult patients with platelet counts < 30 x 10^9/l, the ITP safety set included at least three studies where subjects with a platelet count < 50 x 10^9/l were enrolled.

4.4.2 Efficacy and safety of comparator treatments

Evidence on comparator treatments was provided in the text and tables of the manufacturer's submission and also in two Excel files on efficacy and safety that were included with the

submission, with summary values in an Excel file containing the cost-effectiveness model. The adverse events information reported below is for both splenectomised and non-splenectomised patients. The manufacturer stated that [redacted] As agreed criteria for the classification of bleeding episodes have only been introduced relatively recently it is likely that heterogeneous criteria may have been used across comparator studies reporting this outcome. As the manufacturer's submission assumed that all patients had received a course of corticosteroids prior to the treatment pathways modelled, papers on corticosteroid use were not reviewed in detail and efficacy data were not reported. In terms of safety, the manufacturer reported that adverse events or long-term complications affected nearly 75% of patients receiving corticosteroids.

Summary results for the effectiveness of comparator treatments are reported in Table 12. The data summarised in Table 12 came from studies reporting comparator treatments by using the ASH and BCSH guidelines, recent reviews and undertaking a literature search to identify key studies published since the reviews. However, of the nine reviews included by the manufacturer, only three could be classed as systematic reviews and only one of these contained a comprehensive search strategy. The ERG identified an additional systematic review and 17 additional case series that potentially could also have been included.

In the manufacturer's submission neither the reviews nor the individual comparator studies were formally assessed in terms of their methodological quality. Some reports contained types of participants (e.g. children) who were excluded in the manufacturer's statement of the decision problem. In other reports the inclusion criteria in terms of platelet count was < 50 x 10^9/l as opposed to < 30 X 10^9/l as stated in the final scope issued by NICE and the manufacturer's statement of the decision problem. The manufacturer calculated pooled estimates for the efficacy of individual comparator treatments by taking a weighted average weighted by sample size, in effect simply pooling the data from each study and treating the combined data set as though it was one study. This is an unreliable approach to combining results from separate studies and other approaches, e.g. taking the median across studies, could have been explored.

Data on efficacy was reported in the text, tables and Excel files included as part of the submission and summary efficacy data was not clearly or consistently reported as such in the effectiveness section. In order to ascertain how summary values were calculated and the

number of reports used to derive this information it was necessary to cross-refer between these various sources of data.

5 ECONOMIC EVALUATION

5.1 Introduction and overview of manufacturer's economic evaluation

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

- A description of the literature search used to retrieve any relevant cost-effectiveness studies from the published literature relating to Romiplostim (Appendix 2 of manufacturer's submission pp190)
- A report on the de novo economic evaluation conducted by Amgen including (p108-159). The assumptions of the model are outlined on pages 114-116. The patient pathway for ITP is outlined in Figure 7.1 p 117 and a schematic of the model structure is provided in Figure 7.2, pp119.
- A summary of costs included in the model is provided in Table 7.4 of the manufacturer's submission.
- The results of the base case analysis are presented on pages 147 to 192.
- An Excel based electronic copy of the model was also provided.

Following receipt of the submission, the ERG responded with a number of points for clarification from Amgen. The points for clarification specifically relating to the economic evaluation included:

- Whether the estimated likely usage of treatments reflected UK practice
- Durability of treatment response for romiplostim. More specifically, how the duration of response was estimated.
- Clarification of where estimates of bleeding came from and whether they matched those quoted elsewhere in the manufacturer's submission (Table 6.4.4 to 6.4.6).
- Why the EQ-5D data from the RCTs was not used in the analysis and how they compare to the TTO values used within the economic model.
- The need to run sensitivity analysis around the decrements to utility for serious adverse effects (AE).
- Whether the cost of a bone marrow assessment required when response to the drug is lost was accounted for in the economic evaluation.
- Whether the full costs for a blood film test (required before treatment) were included. This test requires the patient to attend a few hours/day before the appointment as the film takes time to process and examine.

- What the impact would be of a reduced number of blood counts and clinic visits as doctors would not check their patient's blood count or see them in clinic as much as suggested in the model.
- Whether unit cost of romiplostim used in the original submission was reasonable for the UK and what the impact would be of varying the cost.
- Whether the Drug cost calculations double counted physician visits.
- What the rationale was for using a beta distribution based on a +/-30% variation in the proportion of patients on romiplostim responding to treatment as opposed to data from the RCT.
- Specifically relating to the probabilistic sensitivity analysis
    - It was not clear why different distributions have been used for romiplostim for some parameters. Can this be clarified?
    - Why no distributions were assigned to unit costs given data from reference costs and other sources could have been used.

Amgen responded to these points for clarification. These points will be outlined in the critique of the economic evaluation section. In addition to these points, the manufacturer submitted a revised cost effectiveness model.

This section will focus on the manufacturer's original submission, using the updated information from the clarification document, where appropriate.

5.2 Cost-effectiveness analysis methods

As part of the manufacturer's submission a systematic search was undertaken to identify any relevant cost-effectiveness studies from the published literature relating to romiplostim. A search strategy was identified with appropriate key terms identified and a range of databases searched. The HTA database was again omitted from their searched. The search was undertaken in May 2008 without date restriction. This search strategy did not identify any studies which have previously assessed the cost-effectiveness of romiplostim. The search strategies conducted by the ERG also did not identify any studies which have previously assessed the cost-effectiveness of romiplostim.

As no published economic evaluations were found during the literature searches, the manufacturer's submission is based on a de novo economic evaluation to examine the cost-effectiveness of romiplostim in adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP). The following section provides an overview of the cost-

effectiveness analysis methods used by the Amgen, 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 economic evaluation and its assumptions will follow this overview (Section 5.3).

5.2.1 Natural History

Two populations were modelled: (1) Adult non-splenectomised chronic ITP patients where splenectomy is medically contraindicated and (2) patients refractory to splenectomy. Within the model patients were assumed to have an initial platelet count of $<50 \times 10^9$/l. In the economic evaluation two different care pathways were modelled: (i), a 'standard-of-care' pathway (ii) the same pathway with the addition of Romiplostim. The treatments modelled in the care pathways were:

- Watch and rescue with IVIg, anti-D immunoglobulin (non-splenectomised patients only) and IV corticosteroids as needed
- Rituximab
- Immunosuppressives (azathioprine, mycophenolate mofetil, ciclosporin)
- Danazol
- Dapsone
- Cytotoxic agents (e.g. cyclophosphamide, vinca alkaloids)

The care pathway used as the basis for the economic model is shown in Figure 7.1 of the manufacturer's submission (pg 192). Amgen developed this care pathway to reflect UK practice and based it on current guidelines and their own commissioned survey.

In the model, patients with a platelet count of $<50 \times 10^9$/l enter the model either in the comparator arm where they firstly enter the model at the watch and rescue stage with treatment with either IVIg, anti-D or IV corticosteroids. Alternatively patients with a platelet count of $<50 \times 10^9$/l enter the model where they are treated firstly with romiplostim, followed by watch and rescue. In the model patients move through the care pathway, consisting of active therapies and watch and rescue. When a patient becomes refractory to an active treatment they move back to watch and rescue.

5.2.2 Treatment effectiveness

The methods used to synthesise treatment effectiveness of both romiplostim and the comparators were a central component of the manufacturer's submission. As outlined in Section 4.3.1 the data on the effectiveness of romiplostim primarily came from the romiplostim arms of two RCTs (Study numbers 20030212 and 20030105) but which were used solely as observational data. Data for the comparators came from reviews and additional searches. The data for each comparator were obtained by the simple aggregation of data from identified studies. Effectively, indirect comparisons were made between absolute treatment effectiveness data without any explicit consideration of potential effect modifiers. The method used can not be characterised as being robust, it is therefore difficult to state with any degree of certainty how effective the treatments are.

5.2.3 Health related quality of life

Quality adjusted life years (QALYS) were used to measure the impact of ITP on health related quality of life. The authors commissioned their own research to provide information on health related quality of life. Amgen identified seven health states to be used in the cost-effectiveness model based on data form the romiplostim clinical trials, supported by information from clinical experts. The seven health states identified were:

1. Sufficient platelets, no outpatient bleed
2. Sufficient platelets, outpatient bleed
3. Low platelets, no outpatient bleed
4. Low platelets, outpatient bleed
5. Intracranial haemorrhage (2-6 months)
6. gastrointestinal bleed
7. Other bleeding events

A pilot survey of 135 random members of the general public to provide health utility values for the ITP states above was commissioned by the manufacturer. Members of the general public were selected from a sample of 300,000 individuals. In the pilot, two methods of completing the questionnaire were tested: a web based method and a face-to-face completion of the survey. Amgen stated that this was to compare the values obtained in the web based survey with that of the face-to-face, although the results of this pilot phase were not presented. Furthermore, no details were provided of the scenarios for which valuations were obtained. For the main survey, 359 respondents from the same general population sample completed a web based version of the survey, with all respondents completing the evaluation of the five health states using the time trade off (TTO) method. The values obtained from this

survey were reported in Table 7.3 of the manufacturer's submission which is reproduced as Table 14 below.

Table 14 Health effects used in the model

Health state	**Web based values (base case)**		**Face to Face**	
	Mean	SD	Mean	SD
Platelets >50 and no bleed	[redacted]	[redacted]	[redacted]	[redacted]
Platelets >50 and outpatient bleed	[redacted]	[redacted]	[redacted]	[redacted]
Platelets <50 and no bleed	[redacted]	[redacted]	[redacted]	[redacted]
Platelets <50 and outpatient bleed	[redacted]	[redacted]	[redacted]	[redacted]
Platelets <50 and intracranial haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]

Other utility values

Health state	**Utility value**	**Source**
Platelets <50 and gastrointestinal bleed	0.54	Regier DA, 2006
Platelets <50 and other bleed requiring hospitalisation	0.54	Assumed the same as a GI bleed.

As stated in section 7.2.8 of the manufacturer's submission (P133) NICE's preferred method of measuring HRQoL in adults is to use the EQ-5D and given that EQ-5D data was available from the romiplostim RCTs, the ERG requested clarification from Amgen as to why these values were not used. In addition the ERG requested information about how the TTO values used in the submission differed from those of the RCT. Further details of the EQ-5D data were provided by Amgen in the clarification document (pg 66-67) but this was not used in the economic model except as a sensitivity analysis.

5.2.4 Resources and costs

The summary of costs included in the economic model are presented in Table 7.4 of the manufacturer's submission. The resources included in the economic evaluation are divided into two components: treatment costs and costs of managing bleeds. Treatments costs included the cost of the romiplostim vial, romiplostim costs per patient per four week cycle for splenectomised and non-splenectomised patients and the costs of other drugs. The costs of managing bleeds was broken down into four components: the costs of managing an

outpatient bleed, the cost of another bleed requiring hospitalisation, the cost of a gastrointestinal bleed and the cost of intracranial haemorrhage.

[redacted]. Using an exchange rate of [redacted]. The exchange rate used was appropriate for the time at which the report was submitted. However, the ERG requested new analysis given that recent exchange rate fluctuations put the cost of romiplostim outside the range of prices tested in the economic evaluation.

[redacted] used to cost Romiplostim in the economic model was the only price information available to Amgen at the time of submission, it was argued that it was appropriate to use this price. However, Amgen has subsequently provided updated pricing information for Nplate for the UK market. The anticipated prices for Nplate are £[redacted] for [redacted] and £482 for 250mcg. The consequences for the cost-effectiveness of romiplostim given this change in price will be reported below and discussed in the critique of the economic evaluation.

The economic evaluation assumes the availability of both 250mg vial and [redacted], although the [redacted] is unlikely to be available immediately.

Romiplosim cost per four week cycle for both splenectomised and non splenectomised patients is a function of the mean dose of Romiplostim and the number of weeks in the cycle. In addition, four laboratory tests (£12 each) and two physician visits (£112 per visit) are included in this four week cycle. The number of laboratory treats and physician visits associated with Romiplostim treatment was based on the romiplostim trial protocol. The calculations for this presented the manufacturer's original submission (Table 7.4) for non-splenectomised and splenectomised patients appear to be incorrect.

A revised cost of £1.93/mcg (at the revised cost of romiplostim) was presented in the manufacturer's response to points for clarification. The revised costs for non-splenectomised patients based on an average weight of 83.7 in the revised manufacturer's model are broken down into the new per mg price of £1.93 which is based [redacted] of [redacted]. The price of a 250mg vial is simply the price per mg multiplied by the vial size (250). The cost of romiplostim is a function of the number of vials needed, weight and number of doses. Overall a 4 week cycle dose of

romiplostim is £1,793.04. Including the costs of laboratory tests (x4) and physician visits (x2), the total cost for non-splenectomised patients is £2,055.04.

The revised costs for splenectomised patents is £2922.64 based on an average weight of 83.7kg but a larger mean number of vials (1.38 as opposed to 0.93 for non-splenectomised patients.

One of the points for clarification was that the cost would need to be incurred for whole vials as it is likely that any remaining drug would be wasted. Under this scenario the average cost of romiplostim for a 4 weekly period was £2190 and £4118 for a non-splenectomised (assuming 1 vial per dose) and splenectomised patient (assuming 2 vials per dose) respectively.

The costs of drugs used in treatment and the costs of managing bleeds were taken from the BNF and NHS reference costs.

The ERG raised additional questions with regard to the costs used in the economic evaluation of Romiplostim. This included whether the costs of antibody test and bone marrow assessments had been included in the costing analysis. In addition to this the ERG also questioned whether the full costs of blood film tests had been included in the analysis. Again, the results of this will be presented the critique of the manufacturer's economic evaluation.

5.2.5 Discounting

All costs and benefits were discounted at a rate of 3.5%.

5.2.6 Sensitivity analysis

No structural sensitivity analysis was performed on the economic model. The model did allow the option of the non-romiplostim arm starting on an active therapy rather than watch and rescue. No results for this potential situation are presented and no discussion is provided about why this particular situation is or is not relevant.

Uni-variate sensitivity analysis on the two main drivers of the economic model was performed. The costs of Romiplostim were initially varied form £[redacted] per ug. Secondly, the proportion of patients receiving rescue medication was varied from the lower bound (where only those with a hospital bleed are treated) to an upper bound (every patient with a platelet count of $<50 \times 10^9$/l receives rescue therapy).

Probabilistic sensitivity analysis (PSA) was undertaken. The distributions used in the sensitivity analysis are presented in Table 7.5 of the Manufacturer's submission. Distributions for the sensitivity analysis were either taken from the literature or from the trial data analysis. Distributions for the effectiveness comparators have were estimated due to low quality data being available. The robustness of this approach to PSA will be detailed further in the critique of the economic evaluation.

The proportion of patients responding to treatment has been adjusted by +/-30%. The durability of treatment response has also been adjusted by +/-30%. Bleeding risks adjusted by +/-30%. The proportion of patients suffering serious adverse events adjusted by +/-30%. Serious adverse event decrement adjusted by +/-30%. Mild/moderate adverse event rate adjusted by +/-30%. Mild/moderate adverse event disutility adjusted by +/-30%. Utilities for platelet <50 x 10^9/l and GI bleed were adjusted by +/-30% and platelet count <50 x 10^9/l and other bleed were adjusted by +/-30%. The proportion of patients that receive each intervention was also adjusted by +/-30%. The distributions used for sensitivity analyses have been estimated due to poor quality or limited data being available. The authors state that these estimates are based on 'reported values for a particular variable and assuming a distribution based on these values, or where only a point estimate was available this was varied by +/- 30%' (pg 143). As noted in Section 4.3.1 the total sample sizes available for each intervention were relatively small and the effect sizes were obtained by the crude aggregation of case series data. As a consequence it is highly unlikely that the distributions used adequately reflect the uncertainty surrounding estimates used within the model.

The ERG requested additional information on the probabilistic sensitivity analysis conducted by Amgen. In particular, for the proportion of patients on romiplostim responding to treatment a beta distribution using +/-30% is defined. The ERG requested to know why data directly from the RCT was not used to specify this distribution. In addition, the ERG requested clarification as to why differed distributions were used for some of the romiplostim parameters. In addition, no distributions were assigned to unit costs. The answers from Amgen to these questions will be detailed In the ERGs critique of the economic evaluation.

5.2.7 Model validation

On page 147 of the manufacturer's submission it is stated that use of IV immunoglobulin over the first 6 cycles of the model matched that from the placebo arms of the two romiplostim trials (the data from which were not otherwise used in the model). It is unclear whether these data were applicable to the UK. The estimated proportions receiving treatments within the

model were also checked against the survey data. Estimated mortality (assuming zero deaths from bleeding) were compared to all cause mortality data.

In addition checks were made of the model logic, although this did not cover the PSA.

5.2.8 Results

The results of the base case analysis from the economic model are presented on pages 147 to 150 of the Manufacturer's submission. A summary of the cost-effectiveness results are presented on page 147, Table 7.6 of the manufacturer's submission. A revised summary of the manufacturer's cost-effectiveness analysis with their revised cost of romiplostim included is presented on page 4 of the Manufacturer's revised submission. The original results from the base case analysis show that in non-splenectomised patients using romiplostim as a first option treatment results in an ICER of £[redacted]. In splenectomised patients this ICER rises to £[redacted]. A disaggregated breakdown of the results is presented by the manufacturer in tables 7.7a and 7.7b for splenectomised and non-splenectomised patients respectively.

The modeling of romiplostim's cost-effectiveness was re-run, correcting minor errors in the original submission and also assuming a revised acquisition price anticipated UK list price of £1.928 per mcg). The summary of ICERS given the change in price of romiplostim is provided below (presented in Table 1, pg 4 of the revised submission)

Table 15 Revised ICERs based on manufacturer's revised submission.

Treatment arm	Costs	QALYS	Marginal Costs	Marginal QALYs	Incremental Cost per QALY
Non-splenectomised					
Standard care	£409,037	10.94	£23,911	1.61	£14,840
Standard care + Romiplostim	£432,948	12.55			
Splenectomised					
Standard care	£616,915	11.98	£16,447	1.12	£14,655
Standard care + Romiplostim	£633,362	13.10			

The revised results from the base case analysis show that in non-splenectomised patients using romiplostim as a first option treatment results in a revised ICER of £14,840. In splenectomised patients this revised ICER is £14,655.

Results of sensitivity analysis

In the original submission Amgen provided sensitivity analysis on the effect of varying the price of romiplostim. Prices were varied form £[redacted]. The ERG requested that additional sensitivity analyses were provided, including sensitivity analysis of using the EQ-5D data available from the clinical trial to generate QALY scores. In addition, the ERG requested sensitivity analysis around the detriments to utility for serious adverse effects (AE).

Table 16 Summary of ICERs for analysis using utility values obtained from the clinical trials

Treatment arm	Costs	QALYS	Marginal Costs	Marginal QALYs	Incremental Cost per QALY
Non-splenectomised					
Standard care	£408,203	10.14			
Standard care + Romiplostim	£432,208	11.59	£24,005	1.45	£16,503
Splenectomised					
Standard care	£611,642	10.96			
Standard care + Romiplostim	£629,278	11.97	£17,636	1.00	£17,580

In addition, the ERG requested sensitivity analysis around the detriments to utility for serious adverse effects (AE). The manufacturer responded by performing sensitivity analysis on the utility detriment of serious adverse events by increasing/decreasing the values by 50% for all interventions. The results of this are presented in Table 42 of the manufacturer's revised submission is copied below as Table 17. Briefly, the changes result in only minor changes to the ICER, due to discounting effects.

Table 17 Summary of ICERs assuming a 50% increase and decrease in the utility detriment of serious adverse events

Treatment arm	Costs	QALYS	Marginal Costs	Marginal QALYs	Incremental Cost per QALY
Serious AE utility detriment increased 50%					
Non-splenectomised					
Standard care	£408,203	10.76	£24,005	1.64	£14,641
Standard care + Romiplostim	£432,208	12.40			
Splenectomised					
Standard care	£611,642	11.70	£17,636	1.13	£15,580
Standard care + Romiplostim	£629,278	12.83			
Serious AE utility detriment decreased 50%					
Non-splenectomised					
Standard care	£408,203	10.75	£24,005	1.45	£16,503
Standard care + Romiplostim	£432,208	12.39			
Splenectomised					
Standard care	£611,642	11.71	£17,636	1.13	£17,608
Standard care + Romiplostim	£629,278	12.83			

The ERG also requested to know why in the sensitivity analysis the proportion of patients on romiplostim responding to treatment a beta distribution using +/-30% was defined and why the data from the RCT was not used to calculate this probability distribution. Amgen responded to this query re-calculating the Beta distributions, amending the model and re-running the probabilistic sensitivity analyses. In addition, the ERG requested to know why there were no distributions assigned to unit costs. The results amendments by Amgen are shown below:

Confidence intervals have been added to the reference costs used in the model based on the reported interquartile ranges. The distributions used are shown in Table 18.

Table 18 Summary of reference cost values and distributions used in the PSA

Variable	Reference price	Lower Quartile	Upper Quartile	Assumed distribution
Other bleed	£1,718	£665	£1,745	Normal (1718,800)
GI bleed	£1,395	£895	£2,221	Normal (1395,982)
Clinician visit	£107	£79	£139	Normal (107,44)
Intracranial Haemorrhage	£3,680	£1,467	£5,414	Normal (3680,2923)
OP Bleed	£2,20	£172	£274	Normal (220,75)

The PSA has been rerun including the new romiplostim price and the variability around reference costs.

The results from the PSA were converted into cost-effectiveness acceptability curves (CEACs) showing the probability that romiplostim is cost effective at different acceptability threshold levels. These data are summarized in Table 19 below.

Table 19 Summary of results of PSA

Scenario	Mean ICER	Probability cost-effective at different threshold values		
		10,000	20,000	30,000
Non-splenectomised Patients	£14,633	10%	60%	81%
Splenectomised Patients	£15,595	25%	55%	77%

5.3.1 Critical appraisal of the manufacturer's submitted economic evaluation

The ERG has critically appraised the manufacturer's economic evaluation using the critical appraisal questions outlined in Table 20. The methods have also been compared to the criteria set out in reference case (Table 21).[201]

Table 20 Structured critical appraisal of manufacturer's economic model

Item	Critical Appraisal	Reviewer Comment
Is there a well defined question?	Yes	The model assessed the cost effectiveness of romiplostim for the treatment of adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP)
Is there a comprehensive description of alternatives?	Yes	The modelled alternatives were two pathways: a) standard-of-care pathway (with treatments and their ordering estimated from clinical guidelines and from a UK physician survey) and b) the same pathway with the addition of romiplostim as first line treatment
Is the perspective of the analysis clearly stated?	Yes	The manufacturer stated the perspective of the analyses was that of the NHS.
Is the perspective employed appropriate?	Yes?	The perspective did not include Personal Social Services. Given the nature of some of the treatments and the complications of the condition the costs falling on Personal Social Services have been omitted.
Has the correct patient group/ population of interest been clearly stated?	Yes?	Two populations of patients are modelled: a) Adult non-splenectomised chronic ITP patients who have had an inadequate response to or are intolerant of corticosteroids and immunoglobulins and in whom splenectomy is medically contraindicated and b) Patients refractory to splenectomy who are assumed to have received (and been refractory to or relapsed after) a course of oral corticosteroids and/or immunoglobulins before entering the model.

Item	Critical Appraisal	Reviewer Comment
Is the correct comparator used?	Yes?	The only comparator used was stated as standard care. As such, the model allows for the inclusion of romiplostim within the standard care pathway and not for direct comparison with any other medication. Moreover, splenectomy was not included as a relevant comparator due to the assumption made about the patient group entering the model. It was assumed throughout the manufacturer's submission that a patient receiving standard care would receive 'Watch and rescue' as their initial intervention. Patients in the romiplostim arm of the model would receive romiplostim on entry into the model. The results of the model are very sensitive to this decision and when patients in the non-romiplostim arm receive an active treatment initially the cost-effectiveness of romiplostim decreases.
Is the study type reasonable?	Yes	Cost-utility analysis
Is effectiveness of the intervention established?	Unclear	Source of effectiveness data were two RCT (24 weeks follow-up), open label study (follow-up 2 years), and model extrapolation for lifetime. Effectiveness data for comparators came from small non-randomised studies.
Has a lifetime horizon been used for analysis (has a shorter horizon been justified)?	Yes	The model allowed for lifetime time horizon
Are the costs and consequences consistent with the perspective employed?	Yes	The model included resources used from the NHS perspective and consequences were measured in QALYs based on responses by patients to a time trade off experiment

Item	Critical Appraisal	Reviewer Comment
Is differential timing considered?	Yes	Discounting was performed using a discount rate of 3.5% for costs and QALYs
Is incremental analysis performed?	Yes	Results were reported using incremental cost effectiveness ratios
Is sensitivity analysis undertaken and presented clearly?	Yes	One way sensitivity analyses were performed on key parameters (e.g. proportion of patients given rescue medication when under 50 x 10^9/l, rates and effects of adverse events, and utility values for QALYs). PSA was performed.

Table 21 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 routinely used in NHS	Possibly	The model considered one particular care pathway. There are differences in clinical practice and the data used to reflect this in the model comes from a relatively small survey that might not adequately reflect variations in practice.
Perspective -costs	NHS and PSS	Yes	Only NHS costs have been taken into account. Some costs to PSS might have been included. It is likely that they would have been reduced in the comparator experiencing better outcomes.
Perspective -benefits	All health effects on individuals	Probably	QALY benefits to treated individuals were considered. However, details of the time trade off scenarios used to obtain benefits were not provided.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	The economic model considered a lifetime time horizon. Alternative time horizons were explored in sensitivity analyses (page 152).
Synthesis of evidence	Literature review and indirect comparisons	No	Data on romiplostim came primarily from the romiplostim arms of 2 RCTs. Within the model it was used as observational data.

Attribute	Reference Case	Included in submission	Comment on whether de-novo evaluation meets requirements of NICE reference case
			The manufacturer used reviews obtained from the literature for effectiveness data for the comparators. The reviews used were not necessarily systematic, included studies not relevant to the decision problem. The estimation of relevant data from these studies involved crude summation across studies. Essentially within the model indirect comparisons between observational data were used to make comparisons. No attempt was made to explore potential modifying factors within the data and no attempt was made to explore the large biases likely to inherent with this approach.
Outcome measure	QALYs	Yes	The manufacturer considered a disease specific time trade off based utility measure to calculate QALYs.
Health states for QALY measurement	Described using a standardised and validated instrument	No	The manufacturer commissioned research to provide health utility values for the health states in the model. EQ-5D data were available from RCTs but were not used.
Benefit valuation	Time Trade Off or Standard Gamble	Yes	The manufacturer submission used Time Trade Off methods

Attribute	Reference Case	Included in submission	Comment on whether de-novo evaluation meets requirements of NICE reference case
			to develop model health states utility values.
Source of preference data	Sample of public	Yes	The manufacturer submission stated that members of the general public selected from a managed panel that included 300,000 individuals from the UK.
Discount rate	Health benefits and costs	Yes	Benefits and costs have both been discounted at 3.5%.
Equity	No special weighting	Yes	No special weighting was undertaken.
Sensitivity analysis	Probabilistic sensitivity analysis	Yes	Probabilistic sensitivity analysis was undertaken. Results presented graphically using cost effectiveness scatterplots and cost-effectiveness acceptability curves (CEACs).

5.3.1 Critical appraisal of economic evaluation methods

The ERG recognises that there is a trade-off between making the model user friendly and the transparency of the model. For an individual trying to obtain results from an economic model, such as the one submitted by the manufacturer, access to key parameters, assumptions and results are needed. However, to fully understand how the model works and how calculations are performed throughout the model, access to other sections is fundamental. The ERG feels that the model submitted by the manufacturer does lack transparency. This is a user friendly model rather than a transparent one (e.g. there are hidden calculation spreadsheets that need to be accessed through Visual Basic Editor and modifying spreadsheet preferences).

Decision problem, description of alternatives and perspective

The decision problem is outlined clearly on pages 12-16 of the original submission. Table 2.1 of this submission outlines the decision problem succinctly, with the intervention and the population in which romiplostim is to be used outlined. An overview of the comparators is also outlined in Table 2.1, along with outcomes to be assessed and the type of economic evaluation performed. A more detailed overview of the decision problem is outlined in the submission on pages 109-112. The authors performed a cost-utility analysis of romiplostim compared to a standard care pathway for the treatment of ITP. The manufacturer's economic model does provide a comprehensive description of the alternatives. Specifically, they modelled a standard of care pathway, based on clinical guidelines and their own commissioned survey of UK physicians and an alternative pathway, with the addition of romiplostim as the first line treatment. Whilst the decision problem, description of alternatives and perspective are all well outlined in the submission, there are some concerns as to the way the decision problem is addressed in the economic model, specifically relating to the structure of the economic model and whether patients enter the model on watch and rescue or an active treatment, this is critiqued in detail in later sections. In terms of the description of alternatives, again, whilst this is a clear description, the ERG does have some concerns as to the data used to populate the model.

The perspective of the analyses is that of the UK NHS and the outcomes are broadly consistent with this scope and objective. In the NICE reference case the recommended perspective is the NHS and personal and social services (PSS). The cost falling on PSS have not been included, however, taking the model results at face value it might be anticipated that they would be greater in non-romiplostim survivors than amongst romiplostim survivors. However, as patients who initially received romiplostim might survive longer then any costs falling on PSS would be incurred for longer. The net impact of this on cost-effectiveness is unclear.

5.4 Modelling methods

5.4.1 Modelling approach/model structure

Type of model used: is it justified for the purpose

The manufacturer submission included a cohort type model constructed in Microsoft Excel for the economic evaluation. The cohort of patients can move through eight health states and five treatments plus watch and rescue for the standard care pathway.

Treatment with romiplostim as first instance is the difference between standard care pathway and Romiplostim pathway. The selection of the model seems fair and appropriate. The assumption of lack of memory in these models is unlikely to have important effects on the cost-effectiveness results. Moreover, other options like individual simulation models are relatively more data demanding. The lack of data is obvious in the present model and this would have been potentially aggravated.

Rationale of the structure:

When examining the model structure there are a number of key issues to consider. Firstly, treatment with romiplostim is modelled in patients with a platelet count of less than 50 x 10^9/l rather than less than 30 x 10^9/l as stated in the final scope issued by NICE. For some patients, for example those who require an operation or those who have an active lifestyle, a target of <50 x 10^9/l might be adopted. The adoption of a lower target might reduce the drug costs of treatment and potentially lower the incidence and severity of side effects

Secondly, and importantly, the sequence of treatment has a significant effect on the economic modelling outcomes. For example, whether watch and rescue is the first point of entry into the model for the comparator arm, or whether it is more appropriate to have an active treatment as the fist option in the comparator arm. Both of these options can be considered to be clinically viable.

As an example, if watch and rescue is not the first line treatment in the comparator arm for non-splenectomised patients, the ICER moves significantly from £14,633 to £21,674. The model is sensitive to this regardless of the treatment efficacy of romiplostim. For example, if the proportion of patients responding to treatment is just 10% (arbitrarily chosen as an illustrative value) then under the model structure adopted as a base case analysis the ICER for non-splenectomised patients would be £15,152. However, if watch and rescue was not the first line intervention in the comparator arm the ICER would increase to £109,749

A final point to note when examining the model structure is that the structure of the model, primarily the frequency and use of drugs, is based on clinical guidelines.[3,7] Whilst these are the best available guidelines they were published in 1996 and 2003 respectively, and some may consider them to be out of date. In addition to these published guidelines Amgen used their commissioned survey of UK haematologists. Given that the response rate for this survey was [redacted] of all UK consultants and trainees haemotologists, it is questionable whether this can be seen as wholly reflective of current UK practice.

The model dichotomised individuals with platelet counts below or above 50 x 10^9/l. Treatment failure and decision on further treatment depend on this. Decisions on rescue treatment depend on platelets count below 50 x 10^9/l and severe bleeding event. Only a small proportion of not bleeding individuals with platelets counts below 50 x 10^9/l would receive rescue therapy.

Structural assumptions:

Transparent and justified?

The manufacturer submission addressed a series of assumptions and their justification for these assumptions (Manufacturer's submission, page 114-116). As noted above, one structural assumption likely to have an effect on the results is the cohort entering to watch and rescue at the beginning of the model run for the standard care strategy/pathway while going straight into romiplostim treatment for the romiplostim + standard care strategy. However, the model included an option to avoid this that would make the cohort start on rituximab treatment within the standard care strategy. As noted above the model results are highly sensitive to this assumption.

Table 22 Comparison of results of base case analysis for splenectomised patients with analysis based on the comparator cohort not starting on watch and rescue

	Intervention	Cost	QALYs	IC	IQ	ICER
Base case	Romiplostim	629,228	12.83	17,586	1.13	
	Without Romiplostim	611,642	11.70			15,595
Sensitivity analysis	Romiplostim	629,228	12.83	31,770	1.07	
	Without Romiplostim	597,458	11.76			29,771

IC = Incremental cost; IQ = Incremental QALYs

Table 23 Comparison of results of base case analysis for non-splenectomised patients with analysis based on the comparator cohort not starting on watch and rescue

	Intervention	Cost	QALYs	IC	IQ	ICER
Base case	Romiplostim	432,158	12.40	23,955	1.64	14633
	Without Romiplostim	408,203	10.76			
Sensitivity analysis	Romiplostim	432,158	12.40	33,929	1.57	21674
	Without romiplostim	398,229	10.83			

IC = Incremental cost; IQ = Incremental QALYs

Time horizon and cycle length

The base case analysis used a lifetime horizon and is likely to allow for all relevant consequences for the individuals. Cycle length was 4 weeks and seems appropriate to reflect relevant changes in patient conditions (e.g. differences in platelet counts that would have impact in events rates and quality of life).

Duration of treatment

Treatment effectiveness was considered within the model using three parameters: a) the percentage of patients having a platelet response, b) the time from treatment initiation to start of response, and c) the duration of response (time from treatment initiation to treatment withdrawal, "time to failure"). The parameter estimates for a) for romiplostim was obtained from the two phase 3 RCTs while for c) data were obtained from the two phase 3 RCT (follow-up 25 weeks), together with an open label extension study (follow-up 132 weeks). These data were extrapolated using regression analyses to an individual lifetime. For the comparator treatments data were obtained from existing reviews and supplementary information identified by the manufacturer. As noted in Chapter 4 there were some discrepancies between the data used within the model and that presented in the manufacturer's review of effectiveness. In addition, as noted in Chapter 4 some of the studies included by the manufacturer might not have been eligible for inclusion (e.g. they included data on children) while other potentially relevant data were excluded. The impact of including the potentially relevant data is explored later in Section 6.1.

Data:

Data identification process clear?

As described in Chapter 4 the process used to identify relevant studies could have been improved and some additional studies could have been identified. From the data provided in the manufacturer's submission document it is far from clear what data were used within the

economic model. Nevertheless, within the model a clear description of the source of the effectiveness data were provided. What was not clear was:

1. Why in some cases the data in the model did not match the data reported in the submission or where there was a choice why one source of data was used in preference to another source. These differences were not always in favour of romiplostim and from the data presented their net impact is unclear.
2. Whether the data that is available is sufficiently robust. As described in Chapter 4 and earlier in this chapter all the data used were treated as if it came from an observational sources and where data from more than one source is combined the model parameter value is based upon crude aggregation of data. Furthermore, the estimates used for some treatments are based on very sparse data – rarely more than 100 patients and in one case just 10 patients. This raises questions as to whether the data used provided reliable estimates of treatment efficacy.
3. The method of drawing comparisons between treatments may result in biased comparisons. As reported in Section 4.1.7 the indirect comparison of observational data may have produced biased estimates of relative effectiveness. The magnitude and direction of this bias is uncertain but its potential impact on cost-effectiveness has been ignored in the economic evaluation and the use of normal distributions with a standard deviation of 30% of the observed value in the probabilistic sensitivity analysis may not be sufficiently characterise the extent of the uncertainty.

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

There are a number of concerns raised by ERG about the pre-model data analyses and the statistical and epidemiological techniques employed. These concerns have been raised in Chapter 4. In short, the manufacturer appears not to have adjusted the findings for confounding factors (e.g. severity of ITP, age, number of previous treatments, concurrent treatments, and withdrawal rates) which may affect the reliability and size of the treatment effect. Assumptions have been made about the applicability of the data to the two patient populations, for example, in the economic model, most estimates were assumed to be the same between groups.

It is not clear how biased the estimates used by the manufacturer might be, but the ERG would suggest that this could be up to 100% in either direction. As described later (section 6.1.5) there are some data which the ERG identified but were not included as part of the manufacturer's submission. The impact of not including this data is described in that section.

Quality of life/Utilities:

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

As discussed in section 5.2.3 QALYS were used to measure the impact of ITP on health related quality of life. However, rather than using available data from the trials[11] and therefore the preferred measure of health related quality of life (EQ-5D) the authors commissioned their own research to provide information on health related quality of life using their own commissioned utility survey and the TTO method. Unfortunately, no examples of the TTO questions used in the utility survey were provided.

The ERG asked Amgen, in the matters for clarification, if they could provide justification for using their own survey and the TTO method, rather than the methods generally preferred by NICE. The manufacturer stated that the utility survey was used in the model instead of the RCT EQ-5D data as there was a lack of UK patients in the trials. The manufacturer did provide the ERG with the EQ-5D data analysed from the Phase III Studies 20030105 and 20030212 this was 'stratified by patients with a platelet count > 50 x 10^9/l and < 50 x 10^9/l and not currently suffering a bleeding event. The placebo arm (n=42) and romiplostim arm (n=83) are pooled as they assumed that the sole effect of treatments on utility would be related to the frequency of events. A total of 143 assessments were made for subjects > 50 x 10^9/l and 257 assessments were made for subjects < 50 x 10^9/l. There were insufficient data available to populate any of the other model states. This resulted in a utility score of 0.794*(SD: 0.194) for subjects > 50 x 10^9/l and 0.762 (SD: 0.217) for subjects < 50 x 10^9/l (clarification document page 67). This compares to values of [redacted] in the web based values and [redacted] in the face to face values from the TTO method for platelets >50 and no bleed. In patients with platelets < 50 and no bleed using the TTO method web based values produced a mean value of [redacted] in the web based survey and [redacted] in the face to face survey. Therefore the values obtained form the TTO method can be seen as being higher than the values obtained form the EQ-5D data available from the RCTs.

The results of using these values in the model are presented in the Table 5.11 (reproduced form the clarification document, Table 24).

Table 24 Summary of ICERs for analysis using utility values obtained from the clinical trials

Treatment arm	Costs	QALYS	Marginal Costs	Marginal QALYs	Incremental Cost per QALY
Non-splenectomised					
Standard care	£408,203	10.14	£24,005	1.45	£16,503
Standard care + Romiplostim	£432,208	11.59			
Splenectomised					
Standard care	£611,642	10.96	£17,636	1.00	£17,580
Standard care + Romiplostim	£629,278	11.97			

In terms of the QALY estimates, there is a small difference. The QALY estimates using the EQ-5D data are lower than using the TTO data, and the ICERS therefore are higher for both the splenectomised and non-splenectomised groups.

Data incorporation:

Is the process of data incorporation transparent?

The process of data incorporation in the economic model was clear. However, it was not clear how they moved from data reported in the Effectiveness section of the manufacturer's submission to the data included in the Economic sections. For example, there are some inconsistencies between these sections, with no rationale provided for this. This is highly likely to have introduced bias, both for and against romiplostim, however, we do not know the net impact of this.

5.4.2 Comment on validity of results presented with reference to methodology used

Given the methodology and assumptions adopted the results appear to be valid. As noted above concerns have been made about the need to consider alternative assumptions and give a fuller depiction of the uncertainty surrounding input parameters relating to the effectiveness of treatments.

5.4.3 Summary of uncertainties and issues

Were methodological, structural, heterogeneity, parameter uncertainties addressed?

With regard to methodological uncertainties, the type of utilities data used is of concern. As mentioned in previous sections, the manufacturer has not used the preferred method of obtaining utilities data in their base case analyses, even though this method was available to

them. As noted above this was explored in a uni-variant sensitivity analysis provided in response to points raised for clarification.

There are a number of concerns with regard to how structural uncertainty has been handled in the model. Firstly, one structural assumption likely to have an effect on the results is the cohort entering to watch and rescue at the beginning of the model run for the standard care strategy/pathway while going straight into romiplostim treatment for the romiplostim + standard care strategy. As noted previously, the model results are highly sensitive to this assumption. The second concern, with regard to structural uncertainty that the pathways that the cohort follow through the model has been defined by the survey of haematologists. These data may not be representative of UK practice and can not be readily changed within the economic model.

With regard to issues of heterogeneity and parameter uncertainty the ERG would like to highlight the potential bias estimates from observational data, which have been compared indirectly. With regard to sensitivity analysis to address some of these uncertainties, the manufacturer's submission recognised the limitations of their probabilistic sensitivity analysis as there were very limited data on which probability distributions could be based on and assumptions had to be made. The first model submitted had a few errors in the way the probability distribution parameters were selected. However, the main concern was about not using RCT available data to define a probability distribution for treatment response for romiplostim and on the fixed value for used for romiplostim treatment response duration (e.g. a probability distribution was attached but no sampling seem to have occurred). This was acknowledged within the clarification submission and a new version of the model with these issues addressed was included with the clarification submission. However, a simple inspection of the sampled values gave rise further concerns: namely, many of the sampled cells appear to result in values not suitable to feed the model. As such, it is unclear how much of the uncertainty that the authors wanted to spread throughout the model is actually being spread. Therefore, we believe the probabilistic analyses results should be taken with caution.

Furthermore, the assumption of 30% variation in estimates used in the probabilistic sensitivity analysis might not adequately reflect the degree of uncertainty. In addition, only one-way sensitivity analysis has been performed, the results of performing sensitivity analysis when the uncertainties in estimates are combined will be explored in the next section.

6 ADDITIONAL WORK UNDERTAKEN

6.1 Search strategy

6.1.1 Identification of systematic reviews

Literature searches were undertaken in MEDLINE (1966- wk2 Oct 2008), MEDLINE In process (20th Oct 2008), EMBASE (1980- Wk 42 2008), DARE and HTA Database (October 2008). The independent search strategies that were used are reported in Appendix 1. Searches were restricted to English language publications but no date restrictions were used. Fifty seven potential reviews were identified but only one was considered systematic. This review on IVIg was identified from the HTA Database search.[202]

6.1.2 Identification of Comparators

The ERG assessed the reviews and guidelines identified by the manufacturer as well as the systematic review on IVIg identified by the ERG. Only two were considered to be systematic and therefore likely to provide a comprehensive assessment. These were the reviews by Arnold and colleagues on rituximab[18] and the review by CADTH on IVIg.[202] Therefore independent searches were undertaken for these comparators with date restrictions to identify only studies published subsequently to these reviews; for IVIg studies published 2007-8 and for rituximab, studies published 2006-8. For all other comparators, no date restrictions were used. A restricted list of databases was searched due to the time available and included MEDLINE, MEDLINE In process, EMBASE, CINAHL, and CENTRAL. For all searches only English language publications were identified.

6.1.3 Inclusion and exclusion criteria

RCTs, non-randomised comparative studies, and case series with a sample size of at least five participants were included. Participants considered were adults (≥ 16 years old) with chronic ITP (≥ 6 months) in whom at least one prior treatment regimen has failed. Participants who were pregnant, or with secondary ITP or concurrent immune deficiency diseases such as SLE and HIV were excluded. We also excluded studies of participants with mean baseline platelet count more than 50 x 10^9/l. The cut-off used by the Final Scope issued by NICE was 30 x 10^9/l. We did not use this cut-off because only a small number of studies met this criterion.

Types of interventions considered were the same as those listed in the Final Scope issued by NICE, i.e. corticosteroids, IVIg, anti-D, rituximab, immunosuppressives (azathioprine, mycophenolate mofetil, ciclosporin), danazol, dapsone, and cytotoxic agents (cyclophosphamide, vinca alkaloids). There was no restriction on the dose and duration of the interventions. Studies reporting splenectomy were excluded as in the non-splenectomised

patients splenectomy is medically contraindicated, therefore it would not be considered as a comparator. Types of outcomes considered were the same as those listed in the final scope issued by NICE.

6.1.4 Quality assessment, data extraction, and data analysis

Two reviewers (GM, XJ) screened the titles (and abstracts where available) of all papers identified by the search strategy. The same reviewers assessed full-text copies of all reports deemed to be potentially relevant for inclusion. The screening results and full assessment results were cross-checked between reviewers and all inconsistencies were solved between reviewers. Quality of the additional studies was not assessed due to the time limit. One reviewer (XJ) extracted data on participant baseline information (platelet count, spleen status), dose and duration of intervention, initial response rate, time to response, and rate and duration of sustained response.

Data extracted from the additional studies (initial response rate, time to response, and rate and duration of sustained response) were compared with those used in the economic model (Table 7.1 in the submission, and the Excel file on mean response time in the submission). The difference in initial response rate was considered significant if the absolute difference was more than 5%. The difference in time to response was considered significant if the absolute difference is more than four weeks, i.e. one 4-week cycle. The difference in rate and duration of sustained response was considered significant if [redacted]

6.1.5 Number and type of additional studies

820 papers were identified, of which 168 were selected for full text assessment. Seventeen studies (16 papers, 1 conference abstract) not identified by manufacturer or included in any of the reviews met inclusion criteria. Appendix 2 provides details of the characteristics of these 17 additional studies.

All the additional studies were case series with sample size ranging from five to 38. In the studies reporting follow-up periods, they ranged from one month to 51 months. One study[203] reported corticosteroids, one[68] reported anti-D, three[204-206] reported rituximab, five[109,207-210] reported danazol, two[134,140] reported dapsone, one[209] reported Azathioprine, one[209] reported cyclophosphamide, five[167,168,173,176,211] reported vinca alkaloids, and no studies reported mycophenolate mofetil or cyclosporin.

6.1.6 Comparing results from additional studies and those in the submission

Differences were non-significant in all results except those listed in Table 25.

Table 25 Comparison of results from additional studies with those in the submission

Intervention	Outcomes	Reported in the submission	Reported in the additional studies
Danazol	Initial response rate	Non-splenectomised: 45.3%; Splenectomised: 60.0%	Non-splenectomised: 59.5% (22/37, 2 studies); Splenectomised: 42.9% (12/28, 2 studies)
Dapsone	Initial response rate	Non-splenectomised: 50.0%	Non-splenectomised: 61.0% (11/18, 2 studies)

Inclusion of these data within the economic model would change the mean initial response for both Danazol for non-splenectomised patients from 45% to 47% and for Dapsone from 54% to 55%. For splenectomised patients the response rates would change from 60% to 56% for danozol. Incorporation of these data into the economic model would have only a very small impact on the ICER regardless of whether it was assumed that patients in the non-romiplostim arm of the model started on watch and rescue or on an active treatment.

6.2 Additional sensitivity analyses conducted by the ERG

6.2.1 Impact of changes to model structure

The impact of not allowing watch and rescue to be the initial 'treatment' in the non-romplistom arm of the economic model is shown in Tables 26 (splenectomised patients) and 27 (non-splenectomised patients). As these tables illustrate and as has already been described in Chapter 5, the results are sensitive to the choice of initial management of non-romiplostim patients.

Table 26 Summary of sensitivity analyses – Splenectomy patient group

Scenario	ICER W&R is initial comparator intervention (Base case adopted by manufacturer)	W&R not initial comparator intervention
BASECASE RESULTS	£15,595	£29,771
1. Use of EQ-5D data from RCTs	£17,580	£33,558
2. Change in number of vials	£91,406	£109,802
Serious adverse events +50%	£15,580	£21,687
3. Serious adverse events -50%	£15,608	£29,796
4. Cost of bone marrow test included	£15,639	£29,817
5. Cost of blood assessment included	£22,068	£26,154
6. Reducing frequency of physician visits	£15,642	£29,803
7. Combining (1) to (6)	£110,352	£131,017
8. Response rate Romiplostim (worst case)	£17,501	£106,703
Response rate Romiplostim (Best case)	£15,367	£24,669
Combining (7) & (9)	£17,501	£106,703
Romiplostim effectiveness 0.25 of BC	£17,245	£446,204
Romiplostim effectiveness 0.75 of BC	£15,808	£39,268

W&R = watch and rescue; BC = base case

Table 27 Summary of sensitivity analyses – Non-splenectomised patient group

Scenario	ICER W&R is initial comparator intervention (Base case adopted by manufacturer)	W&R not initial comparator intervention
BASECASE RESULTS	£14,633	£21,674
1. Use of EQ-5D data from RCTs	£16,503	£24,426
2. Change in number of vials	£21,214	£28,556
Serious adverse events +50%	£14,623	£21,658
3. Serious adverse events -50%	£14,641	£29,741
4. Cost of bone marrow test included	£14,663	£21,706
5. Cost of blood assessment included	£19,230	£36,131
6. Reducing frequency of physician visits	£14,669	£21,701
7. Combining (1) to (6)	£29,179	£37,290
9. Response rate Romiplostim (worst case)	£16,258	£57,593
Response rate Romiplostim (Best case)	£14,152	£18,776
Combining (7) & (9)	£29,934	£76,728
Romiplostim effectiveness 0.25 of BC	£16,354	£165,129
Romiplostim effectiveness 0.75 of BC	£14,884	£26,439

W&R = watch and rescue; BC = base case

6.2.2 Estimation of cost and QALY thresholds

As part of the additional modelling to explore joint impact of uncertainties considered reported in the manufacturer's response to points for clarification the ERG first explored the magnitude of changes in costs and QALYs that would need to be observed before an ICER of £30,000 would be achieved for each patient group (Table 28 for splenectomised patients and Table 29 for non-splenectomised patients). What these data illustrate is that within the scenario chosen by the manufacturer as the base case large changes in marginal costs and QALYs would be needed before romiplostim would be associated with an ICER of greater than £30,000. Under the alternative assumption that watch and rescue was not the initial treatment for those not receiving romiplostim the magnitude of changes to marginal costs and marginal QALYs are relatively modest (especially for what is potentially the largest of the patient groups considered – splenectomised patients).

Table 28 Thresholds values for changes in marginal costs and marginal QALYS for splenectomised patients

Scenario	Change in value	% change	Change in value	% change
Additional cost	£16,245	92%	£13,035	0.77%
Reduction in QALYs	-0.8385 QALYs	-48%	-0.43 QALYs	-0.76%

Table 29 Thresholds values for changes in marginal costs and marginal QALYS for non-splenectomised patients

Scenario	W&R is initial comparator intervention		W&R not initial comparator intervention	
	Change in value	% change	Change in value	% change
Additional cost	£25,156	105%	£13,035	38%
Reduction in QALYs	-0.54 QALYs	-49%	-0.43 QALYs	-28%

6.2.3 Additional sensitivity analysis

Additional sensitivity analysis was conducted in these areas:

- **EQ-5D data**. This included EQ5D data the RCT data, where available. The only new available EQ-5D data was for patients with no bleed, with platelet counts <50 x 10^9/l and patients with no bleed and platelet counts > 50 x 10^9/l. The manufacturer re-submitted sensitivity analysis including this new EQ-5D data. In addition to the sensitivity analysis provided by the manufacturer, the ERG conducted additional sensitivity analysis using this new information, but also combining it with watch and rescue not being the first line treatment in the non-romiplostim arm.
- **Number of vials of Romiplostim**. The ERG requested clarification on the number of Vials of romiplostim used within the model. The ERG has conducted additional sensitivity analyses rounding up the number of vials used from 0.93 in the non-splenectomised group to 1, and rounding up from 1.38 in the splenectomised group to. In addition to these changes, the ERG also ran this analysis when watch and rescue was not the first line treatment in the non-romiplostim arm.
- **Changes in utility scores for adverse events**. The ERG requested that the manufacturer run sensitivity analysis of +/-50% decrements in serious adverse events. This information was supplied by the manufacturer. In addition to this the ERG also performed sensitivity analysis on these determents when watch and rescue was not the first line treatment in the non-romiplostim arm.

- **Additional costs of bone marrow tests**. This was also requested to be included in additional analysis. The manufacturer provided new sensitivity analysis where the additional costs (£100) of bone marrow tests were included in the analysis. In addition to the analysis submitted by the manufacturer, the ERG also completed this analysis when watch and rescue was not the first line treatment in the non-romiplostim arm.
- **Additional costs of blood film.** These additional costs were also assessed in sensitivity analysis, although no new sensitivity analysis was performed as these costs were assumed by the manufacturer to be the same as the ICERs generated in the bone marrow sensitivity analysis (approx £100). In addition to the sensitivity analysis provided by the manufacturer, the ERG also completed this analysis when watch and rescue was not the first line treatment in the non-romiplostim arm.
- **Physician visits**. The ERG requested clarification from the manufacturer as to whether drug cost calculations included physician visits, particularly, if the drugs were administered as a package these visits/costs might be double counted. The manufacturer responded by suggesting interventions that this assumption may affect. This included rituximab, cyclophosphamide and vinca alkaloids. The manufacturer investigated the sensitivity of this assumption in the revised economic model by performing uni-variant sensitivity analysis. To do this they reduced the number of clinician visits for these interventions. In addition to the sensitivity analysis performed by the manufacturer, the ERG re-ran this analysis when watch and rescue was not the first line treatment in the non-romiplostim arm.
- **Changes in the response rate for romiplostim.** The manufacturer in their response to points for clarification ran sensitivity analyses where it was assumed that all those patients that were censored in the romiplostim trials (a) ceased to respond to romiplostim once they were censored (a worst case analysis); and (b) continued to respond to romiplostim once they were censored (a best case analysis). Using the data provided by the manufacturer these analyses have been repeated under the scenario where all patients in the comparator arm initially receive watch and rescue (the manufacturer's base case) and where all patients in the comparator arm receive an active treatments initially.
- **Changes in relative effectiveness of treatments.** The results of the cost-effectiveness analysis are based on the indirect comparison of observational data. Such comparison may overestimate or underestimate the relative effectiveness of romiplostim. In this sensitivity analysis the ERG considers the implications when the data within the economic model overestimates the effectiveness of romiplostim. In these sensitivity analysis the proportion of people responding to romiplostim and the duration of response are reduced to 75% and 25% of the values used in the base case analysis.

6.2.4 Discussion of results of additional sensitivity analysis

Non-splenectomised group

In the non-splenectomised arm, the individual sensitivity analysis of making changes to (1) EQ-5D data, (2) Number of vials, (3) Adverse events, (4) bone marrow tests, (5) blood assessment, and (6) physician visits, can be said to have a limited impact on the ICER, with the exception of the number of vials used. This variable does have a moderate impact on the ICER, moving it from £14,633 to £21,214. Changing these effects individually has limited impact, however, making these changes together, in a combined sensitivity analysis provides far larger changes in the ICER. These combined changes resulted in a movement form the base case scenario of £14,633 to £29,179.

Of far greater importance with regard to the sensitivity analysis is whether individuals enter the model on watch and rescue or an active therapy. In the base case analysis, where watch and rescue is the first treatment results in an ICER of £14,633. If this assumption is altered, so that an active treatment is the fist line treatment, then the ICER increases to £21,674.

The incremental cost per QALY only slightly changes for both the best and worst case scenarios for censoring of patients in the romiplostim trials under the manufacturer's base case analysis. When patient do not receive watch and rescue as the initial treatment in the comparator arm the adoption of worst case scenario for censoring dramatically increases the incremental cost per QALY well beyond £30,000. A similar pattern emerged when it was assumed that the use of indirect observational data overestimated the relative effectiveness of romiplostim.

Splenectomised group

Similar results described above were found in the splenectomised group. In this group the base case analysis provided an ICER of £15,595. Changes in the number of vials used increased the ICER to £91,406. In addition, when the cost of blood film assessments was also included, this also increased the ICER significantly. The effect of combining all sensitivity analysis results in a change of ICER from a base case of £15,595 to an ICER of £110,352.

Once again, when the assumption that watch and rescue is the first line treatment is relaxed, in favour of an active treatment, these changes in the ICER are of greater magnitude, (£131,017 when combining all six separate sensitivity analyses, with the additional assumption that watch and rescue is not the first line treatment).

The results for splenectomised patients for changes in assumptions about censoring of patients in the romiplostim trials and assumptions about biases caused by using indirect observational data greatly increased the ICER. In both cases it observed that plausible changes in these parameters either alone or in combination with other parameters might increase the incremental cost per QALY well beyond £30,000.

6.3 Summary of results

What these additional analyses have demonstrated is that the results of the cost-effectiveness analyses are not generally altered to any appreciable extent by uni-variant changes in: Data available for the comparator interventions; Utilities; risk of serious adverse events; Changes in the frequency of tests and visits. The results are, however, very sensitive to:

1) The number of vials of romiplostim required per dose (splenectomy group only);
2) How censored data in the romiplostim trials is handled;
3) What the initial therapy is for the comparator arm; and
4) The potential bias that might exist from drawing indirect comparisons from non-randomised non comparative data.

One limitation of the industry submission was the failure to conduct multi-variant sensitivity analysis. Tables 26 and 27 illustrate that combining plausible changes in several parameters simultaneously lead to substantial increase in the incremental cost per QALY for both patient groups.

This chapter has concentrated on sensitivity analyses that make romiplostim appear less cost-effective. Plausible changes to some parameter values may lower the incremental cost per QALY of romiplostim below that reported in the industry submission but these have not been modelled. They would, however, strength the case for romiplostim. For example, patients censored in the romiplostim trial may be more likely to continue to respond and any bias caused by the indirect comparisons of treatments might lead to an underestimation of the effectiveness of romiplostim. In these situations the cost-effectiveness of romiplostim would be improved. The key issue is that the direction and magnitude of many of these uncertainties are unknown. Further data may become available from the romiplostim trials with respect to censoring but to overcome the limitations of he overall evidence base well designed and adequately powered RCTS of romiplostim against comparators relevant to the UK are required.

In summary the key questions for a decision-maker to ask are:

1) Will the use of romiplostim lead to wastage of the drug? At present within the base case industry submission it is assumed that there will be none but if there is, then the cost-effectiveness of romiplostim will be reduced.
2) Is the appropriate comparison for romiplostim with an active treatment rather than watch and rescue? If it is then the use of romiplostim is far less likely to be considered cost-effective.
3) Is it plausible that patients in the romiplostim trial who were censored were more likely to cease to respond to romiplostim? If it is plausible then the use of romiplostim is far less likely to be considered cost-effective.
4) What is the extent and direction of bias caused by the use of indirect comparisons of non comparative observational data? If the current data, as used in the manufacturer's submission, overestimates the relative effectiveness of romiplostim then romiplostim is far less likely to be considered cost-effective.

7 DISCUSSION

7.1 Summary of clinical effectiveness issues

A substantial amount of evidence presented in the manufacturer's submission came from existing reviews but these reviews were not quality assessed in the submission. A quality assessment conducted by the ERG showed that their quality was generally low. Some reviews did not even fully meet the inclusion criteria, e.g. included studies containing children,[95] containing patients with Evan's syndrome.[117] In addition, by undertaking independent searches, the ERG identified an additional high quality systematic review (on IVIg).[202]

The manufacturer's submission also included primary studies that were published after the existing reviews or identified from the literature in situations where there were no existing reviews available. None of these additional studies were quality assessed by the manufacturer. Furthermore, some primary studies included in the submission did not meet the inclusion criteria, e.g. studies containing HIV positive patients.[75] In the independent searches conducted by the ERG a total of 17 additional primary studies were identified. A couple of estimates were found to be different to the estimates reported in the manufacturer's submission by more than 5%, although included their data in the economic model had little impact on incremental cost-effectiveness.

Evidence from a survey on ITP treatment options conducted by the manufacturer was also used. However the response rate of this survey was only [redacted]%.

There were no RCTs comparing romiplostim with any of the comparator drugs available. Most of the evidence was from case series or reviews of case series. Case series are more prone to systematic biases than RCTs. In particular, selection bias in the type of participants included. Not adjusting findings for confounding factors (e.g. severity of ITP, age, number of previous treatments, concurrent treatments, and withdrawal rates) may also affect the reliability and size of the treatment effect in case series. Moreover, in the economic model, the submission calculated and used a single crude average value for each outcome based on this potentially biased evidence, while the use of alternative methods, e.g. median and range, could have been explored.

Although the evidence from case series is potentially biased, the efficacy and safety between romiplostim and comparator drugs could still have been compared indirectly using various statistical techniques and taking the bias into account, e.g. comparing median and range. However, the manufacturer did not attempt to use any indirect comparison techniques.

The submission did not follow the population definition in the Final Scope issued by NICE. In the scope, patient's baseline platelet counts should be < 30 x 10^9/l while the submission also included patients with platelet counts higher than this level. In the UK treatment is not typically required in patients with platelet counts > 30 x 10^9/l unless the patient experienced bleeding or is being prepared for an operation. The ERG did not calculate the percentage of patients with platelet count > 30 x 10^9/l. It is unclear what effect adopting a stricter threshold for treatment of 30 x 10^9/l would be and only very limited data would be available for a subgroup analysis. Secondly, one of the patient groups (non-splenectomised group) is, as is mentioned in the manufacturer's submission patients in whom splenectomy is medically contraindicated. It is likely that in practice this will be a very small patient group. Very few primary studies and reviews in the submission specified this as an inclusion criterion and the data that were used related to patients pre-splenectomy. It is likely that patients suitable for splenectomy were also included in these studies and hence their data might not be applicable to patients in whom splenectomy is medically contraindicated.

Evidence was not reviewed separately for non-splenectomised patients and splenectomised patients although in our report we have attempted to separate evidence on efficacy by patient group. In the economic model, most estimates were assumed to be the same between groups. This is probably because most of the reviews identified by the manufacturer did not report subgroups separately. However, the ERG discovered the subgroup information could be extracted from the primary studies in the reviews (and indeed this was performed for some treatments within the economic model submitted by the manufacturer). The estimates of efficacy and safety for each subgroup could be more precise if the evidence from all primary studies is synthesised separately by subgroup. It should be noted that given the very limited evidence base available for some treatments the quantity of data available by subgroup would be very sparse.

The treatment duration of romiplostim was 24 weeks in the RCTs by Kuter and colleagues.[11] This is longer than those of the comparator drugs which are usually administered at one or a few injections (e.g. steroids) or courses (e.g. 4 weeks for rituximab) in general practice. According to the literature, the remission after comparator drugs could be sustained at various rates even after discontinuing the drug. However the sustained remission after discontinuing romiplostim was reported poorly in the Kuter RCT.[11] However, patients may prefer a treatment with shorter duration and better long-term effects.

7.2 Summary of cost-effectiveness issues

The manufacturer submitted what might be described as a user friendly model rather than a transparent one. The economic model considered the cost-effectiveness of using romiplostim for the two patient groups: splenectomised and non-splenectomised patients (where patients were considered to be refractory to splenectomy). Two different care pathways were modelled: (i), a 'standard-of-care' pathway (ii) the same pathway with the addition of Romiplostim. The standard care pathway was informed by published clinical guidelines and the results of their own commissioned survey of haemotologists.

The ERG has noted a number of concerns with the manufacturer's economic evaluation. Firstly, with regard to methodological uncertainties, the type of utilities data used in the model does not meet the reference case requirements. One structural assumption likely to have an effect on the results is the cohort enters initially into to watch and rescue for the standard care pathway while going straight into romiplostim treatment for the romiplostim + standard care pathway. The model results are sensitive to this assumption. A second concern is that the pathways of care defined in the model are based primarily on the basis of the manufacturer's survey of haematologists. These data may not be representative of UK practice.

The ERG also has a number of concerns with regard to issues of heterogeneity and parameter uncertainty. Issues to highlight are the potential biased estimates obtained from observational data, which have been compared indirectly. In addition, the ERG has concerns with regard to the sensitivity analysis provided to address uncertainties within the model. The manufacturer's submission did recognise the limitations of their probabilistic sensitivity analysis, limitations which were difficult to avoid given the very limited evidence base. However, as part of the PSA many of the values were derived from the Monte Carlo simulation were not suitable to feed into the model. As such, it is unclear how much of the uncertainty that the authors wanted to spread throughout the model is actually being spread. Therefore, we believe the probabilistic analyses results should be taken with caution.

The additional sensitivity analyses conducted by the ERG show that the results are very sensitive to:

- The number of vials of romiplostim required per dose (splenectomy group only);
- How censored data in the romiplostim trials is handled;
- What the initial therapy is for the comparator arm; and

- The potential bias that might exist from drawing indirect comparisons from non-randomised non comparative data.

One limitation of the industry submission was the failure to conduct multi-variant sensitivity analysis. Plausible changes in several parameters simultaneously lead to substantial increase in the incremental cost per QALY for both patient groups. A key issue is that the direction and magnitude of many of these uncertainties are just not known. Further data may become available from the romiplostim trials with respect to censoring of patients but to overcome the limitations of he overall evidence base well designed and adequately powered RCTS of romiplostim against comparators relevant to the UK are required.

In summary the key questions for a decision-maker to ask are:

- Will the use of romiplostim lead to wastage of the drug? At present within the base case industry submission it is assumed that there will be none but if there is, then the cost-effectiveness of romiplostim will be reduced.
- Is the appropriate comparison for romiplostim with an active treatment rather than watch and rescue? If it is then the use of romiplostim is far less likely to be considered cost-effective.
- Is it plausible that patients in the romiplostim trial who were censored were more likely to cease to respond to romiplostim? If it is plausible then the use of romiplostim is far less likely to be considered cost-effective.
- What is the extent and direction of bias caused by the use of indirect comparisons of non comparative observational data? If the current data, as used in the manufacturer's submission, overestimates the relative effectiveness of romiplostim then romiplostim is far less likely to be considered cost-effective.

7.3 Overall summary

Based on the evidence submitted and the additional work conducted by the ERG the evidence available for romiplostim for both patient groups suggests that

1. Romiplostim appears to be a safe treatment for ITP
2. Romiplostim has short term efficacy for the treatment of ITP
3. There is no robust evidence on long-term efficacy of romiplostim
4. There is no robust evidence on long-term effectiveness of romiplostim compared to relevant comparators.
5. There is no robust evidence on long-term cost-effectiveness of romiplostim compared to relevant comparators.

7.4 Implications for research

To overcome the limitations of the evidence base further large randomised comparisons of romiplostim compared with comparators relevant to the UK are needed. These trials should:

1. Compare romiplostim to treatment pathways currently representative of the UK.
2. Compare romiplostim to alternative treatments such as Elthrombopag.
3. Compare treatments at thresholds more typically relevant to the UK (e.g. initiation of treatment when platelet counts fall below 30×10^9/l).
4. Include the measurement of relevant clinical outcomes (bleeding rates, response rates, duration of response, complication rates), resource use and health state valuations suitable for use in an economic evaluation conducted as part of the trial and within an economic model.

ITP is an uncommon condition and it would be helpful for a registry to be set up to identify: incidence; prevalence; treatments used; and long-term follow-up data.

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9 APPENDICES

Appendix 1 Additional searches undertaken by ERG

Search for Systematic Reviews for ITP treatments.

MEDLINE (1966-Wk 2Oct 2008), MEDLINE In process (20th October 2008), EMBASE (Wk 42 2008)

Ovid Multifile Search URL: http://gateway.ovid.com/athens

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. meta-analysis.pt.
12. review.pt.
13. meta-analysis/
14. systematic review/ use emez
15. randomized controlled trials/
16. (controlled or design or evidence or extraction).ab.
17. (sources or studies).ab.
18. or/11-17
19. 10 and 18
20. (letter or comment or editorial).pt.
21. 19 not 20

DARE and HTA Databases (October 2008)

NIHR Centre for Reviews & Dissemination

URL: http://www.york.ac.uk/inst/crd/crddatabases.htm

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

Search for Primary Studies for Comparator Treatments

MEDLINE (1966-Wk 2Oct 2008), MEDLINE In process (20th October 2008), EMBASE (Wk 42 2008), CINAHL 1982 - Oct Wk 2 2008)

Ovid Multifile Search URL: http://gateway.ovid.com/athens

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. idiopathic thrombocytopenic purpura/ use nursing
11. or/1-10
12. mmunoglobulins, intravenous/ use mesz,nursing
13. exp immunoglobin/iv use emez
14. (ivig or igiv or ivigg or igv).tw.
15. (gammaglobulin$ or gamma globulin$).tw.
16. (intravenous adj (immunoglobulin$ or immune globulin$ or ig)).tw.

17. (iv immunoglobulin$ or intravenous antibod$).tw.
18. (sandoglobulin or gamunex or Flebogamma or Gammagard or Octagam or Vigam).tw,rn.
19. or/12-18
20. 11 and 19
21. limit 20 to yr="2007 - 2008"
22. "RHo(D) Immune Globulin"/
23. Rhesus D Antibody/ use emez
24. Anti D.tw.
25. Anti Rh$.tw.
26. (rh$ adj3 (immune globulin$ or immunoglobulin$)).tw.
27. (winrho or rhophylac).tw.
28. or/22-28
29. 11 and 28
30. rituximab/
31. antigens, CD20/
32. rituximab.tw,rn.
33. rituxan.tw,rn.
34. mabthera.tw,rn.
35. anti-CD20.tw,rn.
36. or/30-35
37. 11 and 36
38. (2006$ or 2007$ or 2008$).em,ed.
39. (2007$ or 2008$).up. use prem
40. 37 and (38 or 39)
41. danazol.tw,rn.
42. danol.tw,rn.
43. danazol/
44. or/38-40
45. 11 and 44
46. exp dapsone/
47. dapsone.tw,rn.
48. 46 or 47
49. 11 and 48
50. azathioprine/
51. azathioprine.tw,rn.
52. imuran.tw,rn.

53. azamune.tw,rn.
54. or/50-53
55. 11 and 54
56. Mycophenolic Acid 2 Morpholinoethyl Ester/
57. mycophenolic Acid/ use mesz,nursing
58. myfortic.tw,rn.
59. cellcept.tw,rn.
60. mycophenolate mofetil.tw,rn.
61. mmf.tw.
62. or/56-61
63. 11 and 62
64. cyclosporine/
65. c?closporin$.tw,rn.
66. neoral.tw,rn.
67. sandimmun$.tw,rn.
68. or/64-67
69. 11 and 68
70. cyclophosphamide/
71. (endoxan$ or se?doxan$ or neosar$ or cytoxan$ or procytox$).tw,rn.
72. 70 or 71
73. 11 and 72
74. exp Vinca Alkaloids/
75. vinblastine/ or vinca alkaloid/ or vincristine/ or vindesine/
76. (vinblastine or vincristine or vindesine or vinorelbine).tw,rn.
77. or/74-76
78. 11 and 77
79. 20 or 29 or 40 or 45 or 49 or 55 or 63 or 69 or 73 or 78
80. randomized controlled trial.pt.
81. controlled clinical trial.pt.
82. clinical trials as topic/ use mesz
83. exp controlled clinical trials/ use emez
84. exp clinical trials/ use nursing
85. randomi?ed.ab.
86. placebo.ab.
87. randomly.ab.
88. trial.ti.
89. exp controlled study/ use emez

90. comparative study/ use mesz
91. follow-up studies/ use mesz
92. time factors/ use mesz
93. Treatment outcome/ use emez
94. major clinical study/ use emez
95. controlled study/ use emez
96. clinical trial/ use emez
97. (chang$ or evaluat$ or reviewed or baseline).tw.
98. (prospective$ or retrospective$).tw. use mesz
99. (cohort$ or case series).tw. use mesz
100. (compare$ or compara$).tw. use emez
101. or/90-101
102. case report/ use emez
103. (letter or comment or editorial or case reports).pt.
104. 101 not (102 or 103)
105. exp child/ or exp infant/
106. exp adult/
107. 105 not 106
108. 104 not 107
109. 79 and 108
110. (danazol or dapsone or azathioprine or mycophenolate mofetil or c?closporin$ or sandimmun$ or endoxan$ or se?doxan$ or neosar$ or cytoxan$ or procytox$ or vinblastine or vincristine or vindesine or vinorelbine).ti.
111. 11 and 110
112. 109 or 111
113. limit 112 to english
114. remove duplicates from 113

Cochrane Library (Issue4, 2008)

URL: http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME

#1 (itp):ti,ab,kw or (aitp):ti,ab,kw in Clinical Trials
#2 (idiopathic thrombocytop*):ti,ab,kw or (immune thrombocytop*):ti,ab,kw or (autoimmune thrombocytop*):ti,ab,kw in Clinical Trials
#3 MeSH descriptor Purpura, Thrombocytopenic, Idiopathic, this term only
#4 (#1 OR #2 OR #3)

Appendix 2 Additional studies identified and data extraction for initial response rate and sustained response rate

Study	Patients			Intervention		Initial response (platelet count ≥ 50)		Sustained response (platelet count ≥ 50)	
	N	Baseline platelet count	Spleen status	Dose & duration on drugs	Duration on drugs in cycle/4-wks	n/N, %	Responding time	n/N, %	Duration of remission
Steriods									
Zaja 2007	24	<20	Non-splenectomised	Dexamethasone 40mg/d x4d	0.14	15/24 (62.5%)	By day 30 after treatment	NR	NR
Anti-D									
Salama 1984	6	<30	Non-splenectomised			4/6 (66.7%)	NR	NR	NR
Rituximab									
Garcia-Chavez 2007	15	<30	Post-splenectomised	375 mg/m^2 weekly x 4wks	1	9/15 (60.0%)	Median (range): 14wk (4-32)	8/15 (53.3%)	>6m (off drugs)
Provan 2007	7	<30	Non-splenectomised	100mg/wk x 4 wks	1	4/7 (57.1%)	6-12wks	4/7 (57.1%)	6-14m
Schweizer 2007	10	2-69	Non-splenectomised	375 mg/m^2 weekly x median 4wk (range 2-4)	1	5/10 (50.0%)	Median (range): 2wk (1-4)	3/10 (30.0%)	Median (range): 8wk (2-59)
Danazol									
Ambriz-Fernandez 1985	12	Mean <50	Post-splenectomised	600mg/d x 4m	4.3	7/12 (58.3%)	NR	NR	NR
Edelmann 1990	7	<50	Non-splenectomised	800mg/d for ≥3m	3.2	5/7 (71.4%)	NR	3/7 (42.9%)	15-51m
Kaya 2007	16	Mean <30	Post-splenectomised	NR	NR	5/16 (31.3%)	NR	2/16 12.5%)	NR

Study	Patients			Intervention		Initial response (platelet count ≥ 50)		Sustained response (platelet count ≥ 50)	
	N	Baseline platelet count	Spleen status	Dose & duration on drugs	Duration on drugs in cycle/4-wks	n/N, %	Responding time	n/N, %	Duration of remission
Li 2005	30	Mean38	Non-splenectomised	NR	NR	17/30 (56.7%)	NR	NR	NR
Yagci 1999	7	Mean <50	Mixed (2 non-splenectomised & 5 post-splenectomised)	600mg/d x 3-19m	3.23-20	5/7 (71.4%)	NR	NR	NR
Dapsone									
Dutta 2001	6	<50	Non-splenectomised	100mg/d until response	NR	5/6 (83.3%)	NR	NR	NR
Godeau 1993	12	≤40	Non-splenectomised	NR	NR	6/12 (50.0%)	NR	NR	NR
Azathioprine									
Li 2005	13	Mean38	Non-splenectomised	100-200mg/d x 1-3m	4.3-3.23	7/13(53.8%)	NR	3/13 (23.1%)	≥24m
Mycophenolate mofetil (MMF) - No additional studies identified									
Cyclosporin - No additional studies identified									
Cyclophosphamide									
Li 2005	20	Mean38	Non-splenectomised	100-200mg/d x 2-6wk	0.5-1.5	14/20 (70.0%)	NR	8/20 (40.0%)	≥24m
Vinca alkaloids									
Cervantes 1980	8	≤30	Non-splenectomised	Vincristine 1mg/wk x 1-4wk	0.25-1	NR	NR	4/8 (50.0%)	1-20m
Fenaux 1990	24	<50	Mixed (7 non-splenectomised & 17	Vinblastine 0.1mg/kg·wk x 5wk →	4.48-9.85	14/24 (58.3%)	6-50d	2/24 (8.3%)	8m and 32m

Study	Patients			Intervention		Initial response (platelet count ≥ 50)		Sustained response (platelet count ≥ 50)	
	N	Baseline platelet count	Spleen status	Dose & duration on drugs	Duration on drugs in cycle/4-wks	n/N, %	Responding time	n/N, %	Duration of remission
			post-splenectomised)	same dose/2wks → same dose/m x 3-8m					
Kueh 1982	5	≤20	Mixed (3 non-splenectomised & 2 post-splenectomised)	Vincristine 1mg/wk x ≤3wks	0.25-0.75	2/5 (40.0%)	NR	0/5 by 10wks	NA
Nomura 1990	38	<30	Mixed (19 non-splenectomised & 19 post-splenectomised)	Vincristine 0.02-0.04mg/kg or vinblastine 0.1-0.2mg/kg	NR	21/38 (55.3%)	After 1-8 infusions	6/38 (15.8%)	NR, off drug
Simon 1987	9	<50	Post-splenectomised	Vinblastine 0.1mg/kg·2wk → same dose/m	NR	5/9 (55.6%)	6-21d	1/9 (11.1%)	>6m

NR: not reported

NA: not applicable

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