NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL (STA):

ROMIPLOSTIM FOR THE TREATMENT OF CHRONIC IMMUNE OR IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP)

INTERIM SUBMISSION OF EVIDENCE BY MANUFACTURER: AMGEN INC.

Contents

Instructions for manufacturers and sponsors

This specification for submission of evidence to the National Institute of Health and Clinical Excellence (NICE, or the Institute) as part of the single technology appraisal (STA) process is designed to indicate to manufacturers and sponsors the information required by the Institute and the format in which it should be presented. Use of the specification and completion of Appendices 9.1 to 9.3 are mandatory, and the format should be adhered to wherever possible. Reasons for not adhering to this format must be clearly stated. Sections that are not considered to be relevant should be marked 'N/A' and a justification given for this response. The specification should be completed with reference to the NICE document 'Guide to the methods of technology appraisal' (www.nice.org.uk), particularly with regard to the 'reference case'.

This updated specification aims to only reflect the new Guide to the Methods (2008); it is not the result of a full review of the specification.

If a submission is based on preliminary regulatory recommendations, the manufacturer or sponsor must advise the Institute immediately of any variation between the preliminary and final approval.

A submission should be as succinct and informative as possible. It is expected that the main body of the submission will not usually exceed 75 pages. The submission should be sent to the Institute electronically in Word or a compatible format, and not as a PDF file. A list of all references must be provided, together with paper or electronic copies.

For model-based economic evaluations, a transparent and fully executable (without password protection) electronic copy of the model should be submitted. The Evidence Review Group should have full access to the programming code, and running of the model should be unhindered. Please ensure that the submitted versions of the model program and the content of the submission match. The model should be constructed using standard software, such as Excel or DATA. If non-standard software is required for the construction of the model, please discuss this with the Institute at the earliest opportunity in advance of submission.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but which is considered to be relevant to the submission. Any additional appendices should be clearly referenced in the body of the submission and should not be used to present core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the efficacy section with 'see appendix X'. Clinical trial reports and protocols should not be submitted, but must be made available on request.

Trials should be identified by the first author or trial ID rather than relying on numerical referencing alone (for example, 'Trial 123/Jones et al. [126] found ABC' rather than 'One trial [126] found ABC').

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to the Institute at the time of submission. There will be no subsequent opportunity to submit information unless it has been specifically requested by the Institute.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to the Institute with all confidential information highlighted and underlined
- a fully executable electronic copy of the economic model has been submitted

- all key references have been made available (electronic or hard copy versions as appropriate)
- the checklist of confidential information has been completed and submitted.

Disclosure of information

To ensure that the appraisal process is as transparent as possible, the Institute considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. The Institute recognises, however, that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the Final Appraisal Determination (FAD) or Appraisal Consultation Document (ACD) to consultees and commentators, all the evidence seen by the Committee should ideally be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). As a minimum, a structured abstract will need to be made available for public disclosure, using a recognised format such as that provided by the CONSORT statement (www.consort-statement.org).

Where data are commercial in confidence or academic in confidence, it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The NICE checklist of confidential information should be completed. If no checklist of confidential information is provided, the Institute will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor will be requested to supply a second 'stripped' version of the submission from which any information that is to remain confidential has been removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear how much data have been removed and where they have been removed from.

The Institute will request the stripped version of the submission at least 2 weeks before the anticipated date of issue of the FAD or ACD to consultees and commentators. The stripped version will be issued to consultees and commentators along with the ACD or FAD, and made available on the Institute's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the stripped version of the submission does not contain any confidential information. No further amendments or corrections may be made to the submission at this stage. The NICE checklist of confidential information should be updated and submitted at the same time. The Institute will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for the Institute to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the Evidence Review Group and the Appraisal Committee. Confidential information may be distributed to consultees with the permission of the manufacturer or sponsor. The Institute will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by the Institute that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges the Institute to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to the Institute. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to

contact the designated company representative to confirm the status of any information previously deemed as commercial in confidence before making any decision on disclosure.

Equity and equality

The Institute is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the appraisal and reflect the diversity of the population. The Institute consults on whether there are any issues relevant to equalities within the scope of the appraisal, or if there is information that could be included in the evidence presented to the Appraisal Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by the Institute's responsibility in this respect; including in considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk)

Section A

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the 'Guide to the single technology appraisal process' – www.nice.org.uk). A (draft) Summary of Product Characteristics (SPC) for pharmaceuticals and a (draft) technical manual for devices should be provided (see appendix 1, section 9.1).

1 Description of technology under assessment

1.1 *Give the brand name, approved name and, where appropriate, therapeutic class. For devices please provide details of any different versions of the same device.*

Romiplostim is undergoing EMEA approval at present, the earliest estimated approval date being first quarter 2009; hence the brand name has not been approved. Amgen has asked for approval of the invented name Nplate for romiplostim. Romiplostim is a first in class thrombopoietin (TPO) mimetic. Romiplostim is a peptibody, an Fc-peptide fusion protein which works similarly to endogenous TPO and increases platelet production.

1.2 *Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, please give the date on which authorisation was received. If not, please state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).*

Romiplostim is currently under review by the EMEA. The earliest anticipated date of approval is Q1 2009.

1.3 *What are the (anticipated) indication(s) in the UK? For devices, please provide the (anticipated) CE marking, including the indication for use.*

The anticipated draft indication is as follows (please note that the indication is currently under negotiation with the EMEA):

- 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.

1.4 *To what extent is the technology currently being used in the NHS for the proposed indication? Include details of use in ongoing clinical trials. If the technology has not been launched, please supply the anticipated date of availability in the UK.*

Romiplostim is undergoing review by the EMEA hence is not approved for use at present. There is currently no use of romiplostim within the NHS. The earliest anticipated launch date of romiplostim for NHS use is the end of Q1 2009.

One global study, covering multiple countries, is currently active in the UK in which romiplostim is being administered to ITP patients. [redacted]

Amgen are in the process of setting up an additional study to examine the use of romiplostim in ITP patients, who are refractory to existing therapies. This study has received MHRA approval and site evaluation visits are currently being conducted.

1.5 *Does the technology have regulatory approval outside the UK? If so, please provide details.*

Romiplostim was approved by the Australian Therapeutic Goods Administration on 31 July 2008. It is approved for the treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who:

- Are non-splenectomised and have had an inadequate response, or are intolerant to both corticosteroids and immunoglobulins
- Are splenectomised and have had an inadequate response to splenectomy

Romiplostim was also approved by the US Drug and Food Administration on 22 August 2008. Romiplostim is approved in the US for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Romiplostim should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding. Romiplostim should not be used in an attempt to normalize platelet counts.

1.6 *Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?*

The appraisal by NICE will be the first HTA review of romiplostim as far as Amgen are aware. We anticipate submission to the Scottish Medicines Consortium in the second quarter of 2009 or within 6 months of UK launch.

1.7 *For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained-release tablet, strength(s) and pack size(s) will be available?*

Romiplostim will be supplied as a single use vial, sterile, preservative free, white lyophilised powder. The powder should be reconstituted with sterile water only. The vial sizes available at launch will be 250 and 500 micrograms. The drug should be stored in a refrigerator (2°C – 8°C) and in its original carton to protect it from light. Once reconstituted romiplostim should be administered within 24 hours.

[redacted]

1.8 *What is the proposed course of treatment? For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.*

Based upon recent regulatory approvals in the US, Australia, the submission to the EMEA, and the dosing used in clinical trials, the anticipated dosing in the UK is as follows:

The recommended initial dose for romiplostim is 1 µg/kg based on actual bodyweight, administered once weekly as a subcutaneous injection.

The dose should be adjusted by increments of 1 µg/kg until the patient achieves a platelet count ≥ 50 x 10^9/l. The maximum dose of 10 µg/kg should not be exceeded. Dose adjustments should be based on platelet counts, measured weekly until stable and ≥ 50 x 10^9/l. Thereafter, platelet counts should be measured at least monthly and appropriate dose adjustments made as per the dose adjustment guidance table in order to maintain platelet counts ≥ 50 x 10^9/l.

Regarding duration of therapy, the European SPC has not been finalised. Duration of treatment will depend on the patient's response as well as the natural history of the disease.

1.9 *What is the acquisition cost of the technology (excluding VAT)? For devices, provide the list price and average selling price. If the unit cost of the technology is not yet known, please provide details of the anticipated unit cost, including the range of possible unit costs.*

The UK acquisition cost of romiplostim will not be known until the product is launched. In the economic modelling, the price of romiplostim used is [redacted]

This was deemed an appropriate range for consideration until final CHMP opinion is received

1.10 *What is the setting for the use of the technology?*

Romiplostim will be initiated by hospital based physicians specializing in treating patients with ITP. The treatment will be supervised by the hospital specialist and they will be responsible for repeat prescribing of the product.

1.11 *For patients being treated with this technology, are there any other aspects that need to be taken into account? For example, are there additional tests or investigations needed for selection, or particular administration requirements, or is there a need for monitoring of patients over and above usual clinical practice for this condition? What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?*

During the treatment of ITP patients, rescue medications such as intravenous immunoglobulins (IVIg), anti-D and corticosteroids may be administered in conjunction with romiplostim.

If cellular morphological abnormalities are detected on a peripheral blood smear, a bone marrow biopsy with appropriate staining for reticulin should be considered.

If a patient has a loss of response or failure to maintain a platelet response with romiplostim within the recommended dosing range, a search for causative factors should be considered, including a blood test for antibodies to romiplostim and a bone marrow assessment for increased bone marrow reticulin.

2 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the Evidence Submission will address.

Overview of management of ITP

The management of ITP patients is complex and there is no single defined treatment pathway, with the only standard component of care being a course of oral corticosteroids or intravenous immunoglobulins at first diagnosis. A limited number of randomised trials investigating the efficacy and safety of current therapies have been published, and most of the available data are derived from case series. There are two sets of guidelines in existence, from the American Society of Hematology (ASH) in 1996,[1] and the British Committee for Standards in Haematology (BCSH) in 2003,[2] but due to lack of data these guidelines are based mainly on expert opinion. Both guidelines list treatment options but do not recommend a single strategy or pathway. These existing guidelines are somewhat outdated and likely to be revised in the near future; current management is described in recent reviews, such as that by Godeau et al 2007.[3] It is generally accepted that management of adult ITP should be tailored to the individual patient, depending on bleeding symptoms, platelet count, bleeding risk due to lifestyle, and adverse effects of therapies. Individual patient preference should also be taken into account. Patients are generally considered to require active treatment if they have a platelet count under 30 x 10^9/l or bleeding symptoms.[1-3]

Data from a physician survey conducted by Amgen and an advisory board held in January 2008 show that, within the UK, sequential medical therapies are often used followed by surgical therapy (splenectomy) within adult chronic ITP. Therefore, patients have a medical management phase and a surgical management phase. Management with medical therapies can be done within the pre- and post-surgical states, where applicable. Consistent with the management of ITP, the EMEA is considering romiplostim for patients for whom splenectomy has failed and also non-splenectomised patients where splenectomy is medically contraindicated.

The decision problem is shown in Table 2.1.

Table 2.1: Decision problem

	Final scope issued by NICE	**Decision problem addressed in the submission**
Population	*Adults with idiopathic thrombocytopenic purpura with platelet counts less than 30,000 per microlitre in whom at least one prior treatment regimen has failed*	Adults with chronic idiopathic (immune) thrombocytopenic purpura (ITP). Clinical guidelines and reviews as listed above suggest patients with platelet counts less than 30 x 10^9/l generally require treatment to prevent complications from the disease. The following subgroups will be 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*	Romiplostim is administered as a 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 (not exceeding a dose of 10 µg/kg). Dose adjustments are based on platelet counts, which should be measured weekly until stable within the above range and measured monthly thereafter. Romiplostim is being considered an alternative to other medical therapies and not as an alternative to surgery by EMEA.

	Final scope issued by NICE	Decision problem addressed in the submission
Comparator(s)	*People who have not had a splenectomy:* • *corticosteroids* • *intravenous normal immunoglobulin* • *intravenous anti-D immunoglobulin* • *rituximab* • *splenectomy* • *immunosuppressive agents* *People who have had a splenectomy:* • *corticosteroids* • *intravenous normal immunoglobulin* • *rituximab* • *immunosuppressive agents*	There is much practice variation in terms of which treatments are used for ITP, and in what order. For each population of patients (splenectomised and non-splenectomised), we are intending to model the sequence of treatments in the patient pathway based on existing ITP guidelines, recent reviews, and a physician survey of 169 clinicians involved in the management of ITP. We will screen medical therapies for inclusion as follows: 1) Available evidence that comparator is clinically used in the UK; 2) Comparators licensed in ITP; 3) If not licensed, availability of published evidence of studies in ITP which enable valid estimates of efficacy and safety. Consistent with medical practice of managing patients with medical therapies, treatment pathways with and without romiplostim will be compared. We intend to include the following comparator treatments in our analysis (assuming the existence of good-quality published data): • Corticosteroids • Watchful waiting with intravenous immunoglobulin (IVIg) as needed • Watchful waiting with anti-D immunoglobulin as needed (non-splenectomised patients only) • Splenectomy (recognized as a treatment option but it will not be included as a comparator in the non-splenectomy patient population because the proposed indication is for patients where splenectomy is medically contraindicated) • Rituximab • Immunosuppressives (azathioprine, mycophenolate mofetil, ciclosporin) • Danazol • Dapsone • Cytotoxic agents (e.g. cyclophosphamide, vinca alkaloids)

	Final scope issued by NICE	**Decision problem addressed in the submission**
Outcomes	*The outcome measures to be considered include:* *• platelet count* *• response rate* *• durable response* *• need for rescue treatments* *• use of concurrent treatments* *• reduction in symptoms (minor and/or severe)* *• adverse effects of treatment* *• mortality* *• health-related quality of life*	The following outcomes will be assessed where available: • 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 treatments • Mortality • Health-related quality of life
Economic Analysis	*The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The time horizon for the economic evaluation will be based on the appropriate time period over which costs and benefits can reasonably be expected to be experienced given the chronic nature of the condition. Costs will be considered from an NHS and Personal Social Services perspective.*	An economic model will be used to assess the cost-effectiveness of romiplostim compared to standard care in the treatment of ITP. Cost-effectiveness will be expressed in terms of incremental cost per quality-adjusted life year (QALY). The time horizon will be patient lifetime due to the chronic nature of the condition.

	Final scope issued by NICE	Decision problem addressed in the submission
Special considerations & other issues	*Those patients who have undergone splenectomy will not be offered treatment with anti-D. Therefore a separate consideration of the pathway of care, clinical and cost effectiveness is appropriate for this subgroup of patients.* *If the evidence allows, other subgroups may be identified for whom the technology may be particularly clinically and cost effective.* *Guidance will only be issued in accordance with the marketing authorisation.*	The cost-effectiveness of romiplostim will be assessed in both splenectomised and non-splenectomised populations.

Section B

3 Executive Summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based and clearly reference the relevant section of the submission. The summary should cover the following items.

- *The UK approved name, brand name, marketing status and principal pharmacological action of the proposed drug.*
- *The formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment and acquisition cost (see section 1.9).price.*
- *The indication(s) and any restriction(s).*
- *The recommended course of treatment.*
- *The main comparator(s).*
- *Whether the key clinical evidence in the submission comes from head to head randomised trials (RCTs), from an indirect comparison of two sets of randomised trials involving a common comparator (for example, placebo or other active therapy), or from non-randomised studies.*
- *The main clinical results of the randomised trials and any relevant non RCTs.*
- *In relation to the economic evaluation, details of:*
- *the type of economic evaluation and justification for the approach used*
- *the pivotal assumptions underlying the model/analysis*
- *the mean costs, outcomes and incremental ratios from the evaluation.*

Idiopathic (immune) thrombocytopenic purpura (ITP) is an orphan disease with an annual incidence of approximately 2,200 patients and a prevalence of approximately 9,000 patients in the UK.

ITP is an autoimmune disorder characterized by increased platelet destruction and suboptimal platelet production, which results in low platelet counts (thrombocytopenia) and mild (mucocutaneous) to more severe bleeding.

After initial diagnosis, patients exhibit a variety of bleeding-related symptoms, ranging from non life-threatening bleeding to severe and/or fatal haemorrhage. Lower platelet count is associated with increased risk of severe bleeding, and the risk of severe bleeding increases after each unique bleeding episode. Spontaneous remission among adults is unusual (occurring among 5% to 9% of patients), and the disease typically lasts several months to many years.

The management of ITP patients is complex and there is no single defined treatment pathway, with the only standard component of care being a course of oral corticosteroids or intravenous immunoglobulins at first diagnosis. A number of different medical therapies are included in the treatment of ITP, including cytotoxics and immunosuppressants. It is generally accepted that management of adult ITP should be tailored to the individual patient, depending on bleeding symptoms, platelet count, bleeding risk due to lifestyle, and adverse effects of therapies, and should take

patient preference into account. Patients are generally considered to require active treatment if they have a low platelet count or bleeding symptoms as recommended by guidelines.

There is still a significant unmet medical need for the treatment of ITP. Many current standard of care medical therapies are not approved for use in ITP, and are associated with significant side effects. The efficacy of currently available therapies for ITP has proven insufficient for many patients with chronic, refractory disease, and tolerability of treatments limits their ability to be used on a long-term basis.

Splenectomy is a potentially curative treatment option for approximately two thirds of ITP patients. Yet, evidence suggests that not all patients are eligible for splenectomy, nor is it free from problems. Surgical complication rates range from 16 percent for laparoscopic to 27 percent for open splenectomy and mortality rates range from 0.2 percent to 3.5 percent. Despite the use of vaccinations, life long or intermittent prophylactic oral antibiotic use, and less invasive approaches, splenectomy may result in early and late postoperative morbidity for patients with ITP.

Romiplostim is a novel thrombopoiesis-stimulating Fc-peptide fusion protein that works similarly to thrombopoietin (TPO), a natural protein in the body. TPO is the primary growth factor for the regulation of platelet production. Romiplostim stimulates thrombopoiesis through the same pathway as TPO, through binding to the TPO receptor on platelet progenitor cells. Romiplostim is administered as a once-weekly subcutaneous (SC) injection, at a starting dose of 1 µg/kg with dose adjustment to a maximum dose of 10 µg/kg to allow for maintenance of platelet counts above 50 x 10^9/l.

Romiplostim is currently under review by the EMEA and the proposed indication has yet to be finalised. The anticipated date of approval is in the first quarter of 2009. The draft indication is as follows:

- 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 are no head to head studies of romiplostim against any of the comparators individually; however, two randomised controlled phase 3 clinical trials of romiplostim-plus-standard-of-care versus placebo-plus-standard-of-care have been conducted, one in splenectomised (refractory) and one in non-splenectomised patient populations. The standard of care arm contained many of the comparators identified by NICE as options used by physicians in the trials. For both patient populations, romiplostim was statistically significantly superior to placebo for the primary efficacy endpoint (durable platelet response) and for all key secondary efficacy endpoints (including overall platelet response). Romiplostim was able to raise platelet counts, sustain platelet counts, improve quality of life, reduce the need for chronic concomitant ITP therapy, and reduce the need for rescue medications relative to placebo treated patients.

For the splenectomised patients, no subjects in the placebo group and 16 subjects (38.1%) in the romiplostim group achieved the rigorously defined endpoint of durable platelet response ($p = 0.0013$). No subjects in the placebo group and 33 subjects in the romiplostim group (78.6%) achieved an overall platelet response ($p < 0.0001$).

For the non-splenectomised patients, one subject (4.8%) in the placebo group and 25 subjects (61.0%) in the romiplostim group achieved a durable platelet response ($p <$

0.0001). A total of 3 subjects (14.3%) in the placebo group and 36 subjects (87.8%) in the romiplostim group achieved an overall platelet response ($p < 0.0001$).

In the phase 3 studies, the side effect profile was similar in both treatment arms. There was no marked difference in severe, life-threatening or fatal adverse events in each treatment group for both studies. The overall incidence of study duration-adjusted adverse events was lower in patients receiving romiplostim. In addition the bleeding event rate was lower in the romiplostim group.

Many of the comparators to romiplostim are not licensed for the treatment of ITP. As a consequence, there are very few randomised studies of the comparators in ITP, and little data or clinical consensus regarding the ideal patient pathway. ITP guidelines from the American Society of Hematology (ASH) and the British Committee for Standards in Haematology (BSCH) are largely based on evidence from case series and expert opinion and are outdated. The lack of randomised placebo-controlled trials, in addition to the complexity of the treatment paradigm for ITP and the heterogeneity of the data, means that it is not appropriate to undertake a formal indirect mixed treatment comparison (for example using Bayesian networks).

Bearing the above difficulties in mind, our approach to the economic evaluation is to compare two patient pathways:

1. A standard care pathway in which treatments used by clinicians and identified in the scoping process are ordered to match usual care as closely as possible (using information from the clinical guidelines together with an Amgen survey of expert clinicians);
2. A similar pathway which incorporates romiplostim. The data for this analysis is taken from the trial evidence relating to romiplostim and studies of all types that are available for each comparator; these are mainly single-arm studies such as cohort studies and case series. Much of this latter data is low-quality but is being used in the absence of higher-quality data.

The main uncertainties in the model relate to the efficacy and safety in the ITP population of the comparator drugs. The relative cost effectiveness estimates derived from our modelling are dependent on the assumptions we have made in relation to these dimensions, especially efficacy. We have made reasonable assumptions about the comparators and have tried to be as clear as possible where the information is derived from and the decisions we have made.

The cost-effectiveness analyses (Table 3.1) demonstrate that in non-splenectomised patients, a treatment pathway that has romiplostim as the first option post oral corticosteroids is [redacted] compared to a pathway without romiplostim, using a price which is equivalent [redacted]. The UK price will not be finalised until Amgen has received Marketing Authorisation for romiplostim.

In splenectomised patients, the ICER is higher at [redacted] reflecting the increased dose of romiplostim required to achieve clinical effectiveness and a slightly lower response rate, which is probably due to the more refractory disposition of the patients. In addition, the lack of evidence in assessing the efficacy of comparator treatments is particularly marked in the splenectomised population, as the available evidence tends to be in less refractory patients.

Since chronic adult ITP is an orphan disease the anticipated number of patients that will be treated with romiplostim is small. The anticipated budget impact for the NHS for 2009 is [redacted] for the non-splenectomised population ([redacted]) and [redacted] for splenectomised patients ([redacted]).

Table 3.1 ICER results

Treatment arm	Costs	QALYS	Marginal Costs	Marginal QALYs	Incremental Cost per QALY
Non-splenectomised					
Standard care	[redacted]	10.76	[redacted]	1.64	[redacted]
Standard care + Romiplostim	[redacted]	12.40			
Splenectomised					
Standard care	[redacted]	11.70	[redacted]	1.13	[redacted]
Standard care + Romiplostim	[redacted]	12.83			

4 Context

In this background section the manufacturer or sponsor should summarise and contextualise the evidence relating to the decision problem. The information provided will not be formally reviewed by the Evidence Review Group.

4.1 *Please provide a brief overview of the disease/condition for which the technology is being used. Provide details of the treatment pathway and current treatment options at each stage.*

ITP is an autoimmune disorder characterized by increased platelet destruction and suboptimal platelet production, which results in low platelet counts (thrombocytopenia) and mild (mucocutaneous) to more severe bleeding.[1;4-6]

Though the platelet destruction (due to presence of anti-platelet antibodies) has been implicated as the primary cause of ITP, recent data reveal suboptimal platelet production, due to a relative/functional thrombopoietin (TPO) deficiency, to be an important contributor.[7]

Adult ITP appears to be more prevalent among women, but this disparity is less pronounced as age increases. In a retrospective analysis conducted in Denmark, incidence of adult ITP was estimated to be 4.62 per 100,000 persons among those older than 60 years compared to 1.94 per 100,000 persons among those younger than 60 years.[8] Satia (2006) estimated the average ITP incidence in the UK to be 3 per 100,000 person-years.[9] The number of new patients diagnosed a year in the UK is estimated to be 2,243.[10]

Adult chronic ITP is heterogeneous both at initial presentation and throughout its disease course. Its onset may be insidious, in which case an initial diagnosis is made incidentally through routine blood counts.[1;2] Alternatively, patients may first present with dangerously low platelet counts necessitating hospitalisation. After initial diagnosis, patients exhibit a variety of bleeding-related symptoms, ranging from non life-threatening bleeding to severe and/or fatal haemorrhage. In contrast to ITP in children, spontaneous remission among adults is unusual (occurring among 5% to 9% of patients), and the disease typically lasts several months to many years.[1;11]

Such variability warrants individualised treatment planning and patient management to account for platelet response, lifestyle differences, and risk profiles (e.g. age and prior medical history).

Little data exists for bleeding risks for patients with platelet levels under 50 x 10^9/l. However, Cohen et al derived age-adjusted bleeding risk for patients with platelet levels under 30 x 10^9/l using a pooled analysis of ITP clinical series. Pooled estimates of fatal bleeding risk for ITP patients ranged from 1.6 to 4 percent for each year exposed to platelet counts < 30 x 10^9/l. Estimated age-adjusted annual risk for a major, nonfatal bleed for patients with platelet counts persistently lower than 30 x 10^9/l was 3 percent for patients under 40, 7 percent for patients 41 to 60, and 71 percent for patients over 60.[12]

Treatment pathways

There is no accepted single treatment algorithm for ITP patients. Please refer to section 4.6 for further details.

It is generally accepted that first line treatment can include watchful waiting if the patient has a satisfactory platelet count associated with no bleeding events and a lifestyle that will not put the patient at risk of bleeding events. If the patient needs treatment then a course of oral corticosteroids is the preferred initial therapeutic option.

For patients who are at risk of bleeding due to thrombocytopenia, IVIg or anti-D are recognised to be able to elevate platelet levels rapidly. The effects of intravenous immunoglobulin (IVIg) and anti-rhesus-D immunoglobulin (anti-D) are transient (1-4 weeks). Anti-D is not indicated in patients who are rhesus D negative or post-splenectomy.

If a patient does not respond to initial medical treatment or develops intolerant side effects, then there are limited options for the physician. Of the therapeutic options used by UK physicians, only corticosteroids, IVIg and anti-D have been approved by regulatory authorities to treat ITP. All the other drugs used are not licensed and the clinical evidence for use is based on case studies or experience from a small number of centres.

A physician survey conducted by Amgen highlights the complexity of the patient pathway and demonstrates that no consensus exists regarding a single pathway of care (Table 4.1.1).[13] When asked "For adults with ITP who you personally manage, please indicate your preferred line usage for each treatment option" (i.e. what lines of treatment do you consider in your patients), [redacted]

Table 4.1.1: Lines of therapy provided for ITP patients in the UK

	First Line (%)	Second Line (%)	Third Line (%)	Fourth Line (%)	Fifth Line (%)
Oral Steroids	[redacted]				
IV Steroids					
Watchful waiting					
Splenectomy					
IVIg					
Anti-D					
Mycophenolate mofetil					
Azathioprine					
Rituximab					
Dapsone					
Other					

Splenectomy is a potentially curative treatment option for ITP. Yet, evidence suggests that not all patients are eligible for splenectomy. There is no published data to suggest what proportion of patients this involves. Another physician survey conducted by Amgen involving [redacted] haematologists suggests that approximately [redacted] of newly diagnosed patients may not be eligible for splenectomy. The main potential reasons highlighted were advanced age and co-morbid conditions.[14]

In a multinational review of 14 case series of adult ITP patients with a minimum of 5 years' follow-up, 36 percent of adult ITP patients (251/707) failed to achieve complete response to splenectomy (median follow-up of 7 years). Complete response was defined as platelet count >150 x 10^9/l for at least 30 days without additional treatment.[15] Additional research suggests that approximately 30% of patients will still require additional medical treatment after splenectomy.[16]

4.2 *What was the rationale for the development of the new technology?*

In individuals not affected with ITP, thrombocytopenia typically induces thrombopoiesis (platelet production) through autoregulatory mechanisms that control circulating thrombopoietin (TPO) levels via production in the liver.[17] TPO binds to the TPO receptor on megakaryocytes, and promotes proliferation and maturation of

hematopoietic cells including megakaryocytes, which ultimately increases peripheral platelet counts.[18] Conversely, elevated platelet counts can reduce serum TPO levels via its removal from circulation.

This compensatory increase in platelet production is deficient in approximately two-thirds of patients with ITP, who have either reduced or normal platelet turnover.[4;19;20] ITP patients have a relative/functional TPO deficiency characterized by normal or near normal TPO concentration and platelet production, contrary to the increased platelet production that would be expected in response to peripheral thrombocytopenia.[5] As a result, inappropriately 'normal' circulating endogenous TPO concentration is below that required to keep pace with the rate of platelet destruction, resulting in persistent thrombocytopenia.[19-21]

An additional potential cause of inadequate platelet production in ITP is anti-platelet antibody binding to megakaryocytes. Ultrastructural studies of megakaryocytes taken from patients with ITP demonstrate evidence of apoptosis and cell damage, suggesting that anti-platelet antibodies may cause altered megakaryocyte morphology. This damage to megakaryocytes may contribute to suboptimal platelet production.[22]

These findings highlight the important role that suboptimal platelet production has in ITP, and establish a foundation for new therapeutic approaches to management of ITP that can increase platelet production.

4.3 *What is the principal mechanism of action of the technology?*

Romiplostim is a novel thrombopoiesis-stimulating Fc-peptide fusion protein that works similarly to thrombopoietin (TPO), a natural protein in the body. TPO is the primary growth factor for the regulation of platelet production.[7] Romiplostim stimulates thrombopoiesis through the same pathway as TPO, through binding to the TPO receptor on platelet progenitor cells. The active peptide component of romiplostim stimulates the TPO receptor, and the antibody Fc increases its circulatory half-life. Unlike most current ITP treatments that interfere with platelet destruction, romiplostim was designed to increase production of platelets at a rate that outpaces their destruction by the immune system.

Romiplostim has no amino acid sequence homology to endogenous TPO. This lack of sequence homology mitigates the risk that antibodies produced against romiplostim will cross react with endogenous thrombopoietin. To date, no neutralizing antibodies that cross-reacted to TPO have been identified in the romiplostim clinical development program.[23]

Substantial variability in platelet response and heterogeneity in disease course among adult chronic ITP patients warrant individualised patient management.

Romiplostim administration permits individual dose adjustments, with an initial weight-based dose and subsequent dose adjustments based on platelet counts. Romiplostim is administered as a once-weekly subcutaneous (SC) injection, without regard to food or medication, at a starting dose of 1 µg/kg with dose adjustment to a maximum dose of 10 µg/kg to allow for maintenance of platelet counts above 50 x 10^9/l.[24]

4.4 *What is the suggested place for this technology with respect to treatments currently available for managing the disease/condition?*

Romiplostim was approved by the Australian Therapeutic Goods Administration on 31 July 2008. It is approved for the treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who:

- Are non-splenectomised and have had an inadequate response, or are intolerant to both corticosteroids and immunoglobulins
- Are splenectomised and have had an inadequate response to splenectomy

Romiplostim was also approved by the US Drug and Food Administration on 22 August 2008. In the United States, romiplostim is approved for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Romiplostim should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding. Romiplostim should not be used in an attempt to normalise platelet counts.

Romiplostim is currently under review by the EMEA and the proposed indication has yet to be finalised. The anticipated date of approval is first quarter 2009. The draft indication is as follows:

- 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.

4.5 *Describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.*

Patient management

The management of ITP patients is complex and there is no single defined treatment pathway, with the only standard component of care being a course of oral corticosteroids or IVIg at first diagnosis. A limited number of randomised trials have been published, and most of the available data are derived from case series. It is generally accepted that management of adult ITP should be tailored to the individual patient, depending on bleeding symptoms, platelet count, bleeding risk due to lifestyle, and adverse effects of therapies, and should take patient preference into account. Patients are generally considered to require active treatment if they have a platelet count under 30 x 10^9/l or bleeding symptoms.[2;25]

In addition to the limited evidence base, another reason for the lack of consensus regarding a treatment pathway is that the use of the majority of current standard of care medical therapies can be associated with significant side effects. The efficacy of currently available therapies for ITP has proven insufficient for many patients with chronic, refractory disease, and tolerability of many treatments limits their ability to be used on a long-term basis.

Corticosteroid treatment

The British Committee for Standards in Haematology (BCSH) guidelines state that around two thirds of patients will respond to prednisolone initially but long term remission is only seen in 10-20% of patients when treatment is stopped.[26] Godeau et al state that a short term response to corticosteroids is seen in 60% of patients but only 30% have a prolonged response.[3] There are no randomised trials comparing corticosteroids to no treatment.[3] First line treatment is with corticosteroids in the vast majority of patients. As many as 75 percent of ITP patients receiving corticosteroids experience adverse effects, including nervousness/anxiety and weight gain in more than 20 percent of patients.[27;28] The long-term consequences of corticosteroid use are significant. Compared to non-users of corticosteroids, the one-year incidence is twice

as high for diabetes mellitus (DM), obesity, and gastrointestinal bleeding and three times as high for myocardial infarction (MI) for ITP corticosteroid users.[29]

Immunoglobulins

IVIg is effective in increasing the platelet count in 75% of patients. The effects usually last 1-4 weeks and platelet counts will return to pre-treatment level.[2] Anti-D quickly elevates platelet counts, resulting in short-term response (platelet count >20 x 10^9/l over baseline within 7 days of initial infusion) in approximately 75 percent of patients.[30] The mean time to response is approximately 3.1 ± 3.0 days and the mean duration of response is 19.2 ± 1.1 days.[31] IVIg and anti-D are effective at raising platelet counts quickly and are therefore recommended as emergency therapy to address or prevent acute bleeding.[30;32] However, they generally cannot sustain platelet counts at safe levels beyond one month.[2]

As many as 75 percent of ITP patients receiving IVIg experience adverse events, including mild headache, backache, nausea, cough, injection site reaction and fever.[1],[32] Approximately 20 percent and 5 percent of all adverse events experienced by ITP patients receiving IVIg are moderate and severe, respectively.[32] IVIg has been associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death.[32]

Anti-D includes a warning for potentially fatal (though uncommon) intravascular haemolysis, and is not approved for splenectomised patients.[33] Approximately 70 percent of patients receiving anti-D experience drug-related adverse events, most commonly mild to moderate in intensity.[31] Chills (34.7% of patients), pyrexia (26.5% of patients), increased blood bilirubin (21.4% of patients), and headache (14.3% of patients) are most common. Discontinuation rates as high as four percent have been reported.[30;34] Like IVIg, Anti-D is derived from human plasma. Such products may carry a risk of transmitting infectious agents, and, theoretically, Creutzfeldt-Jakob disease (CJD).[33]

Rituximab

Rituximab, a chimeric anti-CD20 monoclonal antibody, is not approved for ITP, but is used off-label for splenectomised and non-splenectomised patients.[35] Much of the published data on the effectiveness and safety of rituximab in ITP has been generated through low-quality, small sample, single-arm or retrospective analyses.

Data presented within a comprehensive literature review suggest that 46.3 percent (95% CI: 29.5-57.7) of ITP patients achieve complete response (> 150 x 10^9/l) and 62.5 percent (95% CI: 52.6-72.5) achieve overall response (> 50 x 10^9/l) to rituximab.[36] The highest response rates (> 60 percent) were reported in studies with small sample sizes (n < 20).[36] ITP patients included within the analysis were 16 to 89 years of age, had ITP for 1 to 360 months, and platelet counts ranging from 1 to 89 x 10^9/l. Approximately one-half of included patients were splenectomised.

Arnold et al call attention to a lack of robust data in support of rituximab use in ITP, and highlight a critical need for randomised, controlled trials of rituximab in ITP. Among 19 reviewed articles with comparable definitions of platelet response, 7 were prospective, 7 were retrospective, and 5 were of uncertain design. None were randomised controlled studies, and 9 were in abstract form only.[36]

In 2004, the US FDA reported that hepatitis B virus reactivation with fulminant hepatitis, hepatic failure, and death had been reported in some patients with haematologic malignancies treated with rituximab. In 2006, a retrospective review at

a single-centre found that one-third of patients with positive hepatitis B serology developed acute liver events when treated with rituximab alone or with chemotherapy. This correlation was more evident in patients with hepatitis B surface antigen (66% of these patients). Consequently, the authors concluded that hepatitis B serology screening should be performed prior to use of rituximab with or without chemotherapy treatment.[37] Rare cases of progressive multifocal leukoencephalopathy (PML) have been reported in NHL patients receiving rituximab. The extent to which these risks apply to the ITP population is unknown.

Splenectomy

A recent retrospective case series observed that five percent of patients relapse each year after successful splenectomy, corresponding to a 32 percent failure rate after five years.[38] Similarly, in a multinational review of 14 case series (N = 707) with a median follow-up of 7.25 years, 36 percent of adult ITP patients failed to achieve or sustain complete response (platelet count > 150 x 10^9/l for at least 30 days without additional treatment) after splenectomy. Splenectomy response rates are significantly lower for patients over the age of 60.[15]

Despite the use of vaccinations, prophylactic antibiotic use, and less invasive approaches, splenectomy may result in early and late postoperative morbidity for patients with ITP.[27]

Surgical complication rates range from 16 percent for laparoscopic splenectomy to 27 percent for open splenectomy. Mortality rates range from 0.2 percent to 3.5 percent.[39] In a study of 78 ITP patients who underwent splenectomy, 26 percent experienced early postoperative complications resulting in prolonged hospitalisation or re-admissions, and 5 percent had late complications.[40] Four percent of patients (n = 3) had septic events, one of which resulted in death.

Risk of bleeding and mortality

Patients with platelet counts below 50 x 10^9/l are susceptible to a number of bleeding complications, each with varying degrees of severity and mortality risk.[41] Lower platelet count is associated with increased risk of severe bleeding, and the risk of severe bleeding increases after each unique bleeding episode.[1;41;42] Major bleeding events regularly occur when platelet counts drop below 10 x 10^9/l, and a high risk of bleeding events of a severe nature has been described for patients with platelet counts between 20 - 30 x 10^9/l.[6;42;43]

Kaye et al (2007) reported that more than 90 percent of deaths among ITP patients occurred among those older than 45.[44] At equivalent platelet counts, the incidence of major haemorrhagic complications is significantly higher in older (>60 years) patients than in younger (<40 years) patients (10% vs. 0.4%; relative risk = 29, p < 0 .01).[41]

Cohen et al (2000) derived estimates of age-adjusted mortality risk through decision-analytic modelling informed by a pooled analysis of ITP clinical studies.[12] Seventeen case series were compiled, representing a total of 1,817 patients with ITP. The estimated age-adjusted annual risk for a major, nonfatal bleed for patients with counts persistently lower than 30 x 10^9/l was 3 percent for patients under 40 years of age, 7 percent for patients 41 to 60, and 71 percent for patients over 60 years of age. Predicted 5-year mortality (due to bleeding) ranged from 2 percent for ITP patients younger than 40 to 48 percent for patients older than 60.

McMillan and Durette (2004) examined the long-term outcomes of 105 adult chronic ITP patients refractory to splenectomy and medical therapy.[45] In total, 17 patients (16.2%) died for reasons related to ITP or its treatments. Eleven patients (10.5%) died from ITP-related bleeding after failing an average of 7.2 treatment regimens.

These patients had histories of multiple bleeding events (including mucosal bleeding episodes, buccal blisters, epistaxis, vaginal bleeding, gastrointestinal bleeding) requiring multiple hospitalisations. An additional six patients died as a direct result of ITP-treatment (3 sepsis associated with immunosuppression and asplenia, 1 post operative complications, 2 transfusion related hepatitis C and liver failure).

Immunosuppressants

Immunosuppressive drugs such as ciclosporin, azathioprine and mycophenolate mofetil are not licensed for the treatment of ITP. No randomised controlled trials have been conducted with these agents so the true safety profile for these drugs in ITP is unknown. All immunosuppressive drugs may increase the risk of infection.

Summary

Based on the above findings, uncertainty regarding best clinical practice in ITP can be attributed to a lack of robust clinical evidence guiding treatment, variable clinical effectiveness of current therapies, and significant morbidity associated with current therapies. Patients unable to maintain haemostatic platelet counts face a risk of clinically significant and even fatal bleeding, particularly among those with advanced age and those with persistent platelet counts <30 X 10^9. An unmet need exists for a well tolerated therapy that can be administered on a long-term basis, particularly among those ITP patients refractory to splenectomy.

For a detailed review of safety and efficacy data for all comparators considered in this submission please refer to section 6.7 and 6.8.

4.6 *Provide details of any relevant guidelines or protocols*

There are two sets of guidelines in existence, from the American Society of Hematology (ASH) in 1996[1] and the British Committee for Standards in Haematology (BCSH) in 2003,[2] but due to lack of data these guidelines are based mainly on expert opinion. Both guidelines list treatment options but do not recommend a single strategy or pathway. Current management is also described in recent reviews, such as that by Godeau 2007.[3] These existing guidelines have been published prior to knowledge of a drug that is able to increase platelet production such as romiplostim. Updated international guidelines will be published in the near future.

Both guidelines include the following recommendations:

- Treatment should focus on maintenance of safe platelet counts to prevent major bleeding episodes;
- Treatment should generally be initiated for patients with platelets counts < 30 x 10^9/l;
- Initial treatment should include corticosteroid use; and
- If treatment with corticosteroids is not successful, additional treatments should be considered for treatment of chronic ITP.

A brief description of the ASH and BCSH guidelines is provided below and in Table 4.6.1.

- ASH: Developed in 1996, the ASH guidelines[1] state that the diagnosis of ITP is based on patient history, physical examination, complete blood count, and examination of the peripheral smear, all which should exclude other causes of thrombocytopenia. ASH guidelines recommend treatment initiation for a)

patients with platelet counts < 50 x 10^9/l and significant mucosal bleeding, and b) for all patients with platelet counts <20 to 30 x 10^9/l. In addition, ASH guidelines suggest that patients with platelet counts <20 x 10^9/l and severe bleeding should be hospitalised.

- First Line: Glucocorticoids are the preferred first line of treatment for ITP, although IVIg may be recommended for patients with platelet counts < 30 x 10^9/l and patients with severe, life- threatening bleeding.
- Second Line: Splenectomy is not recommended as initial therapy in most cases, but may be considered for patients with platelet counts < 30 x 10^9/l as early as four to six weeks after medical treatment. Patients may be pre-treated with IVIg or oral glucocorticoid therapy if platelet counts are below 20 x 10^9/l.
- Persistent or Refractory Patients: Treatment options for patients who continue to have low platelet counts after glucocorticoid treatment and splenectomy include IVIg, glucocorticoids, and accessory splenectomy.
- At the time the ASH guidelines were published there was insufficient evidence to recommend Anti-D in the management pathway of an ITP patient.

The authors of the ASH guidelines recognised that at the time of their review, evidence based on case series without a control group (the weakest level of evidence) was the basis of most of their recommendations and weakness of these opinions were acknowledged as was the need for randomised clinical trials.

- BCSH guidelines were published in 2003. [2] Similar to ASH guidelines, these state that ITP treatment decisions should be individualised and consider clinical factors such as the presence of bleeding or bruising as well as platelet count. Treatment is not recommended for patients with platelet counts above 30 x 10^9/l unless blood loss from a surgical procedure, dental work, or labour is expected.

  - First Line: Oral corticosteroids and IVIg both are recommended as first-line therapy, although guidelines mention that there are no randomised studies assessing these treatments. BCSH guidelines also point out that IVIg is only effective for a duration of three to four weeks.
  - Second Line: BCSH also recommends splenectomy as second-line therapy, to be accompanied by lifelong or intermittant use of oral antibiotics for post-splenectomy infection prophylaxis.
  - Chronic Refractory ITP Patients: Patients who fail first- or second-line treatment or require high-dose corticosteroids to maintain safe platelet counts are defined as refractory. BCSH recommends additional courses of first-line therapies, although generally at a higher dose. If further treatment is needed, alternative treatments include methylprednisolone, IV anti-D, vinca alkaloids, danazol, immunosuppressive agents including azathioprine and cyclophosphamide, combination chemotherapy, dapsone, and rituximab.
  - Emergency Treatment: IVIg or IV methylprednisolone and/or IV cyclophosphamide are recommended. Transfusions with anonymous-donor platelets only are recommended for extreme emergencies.

Godeau et al (2007) recommend in their recent review that IVIg be reserved for patients with very low platelet count and significant bleeding. They also note that comparisons of case series show that the frequency of splenectomy has significantly decreased in the past 30 years, and they state: "As proposed by many experts, splenectomy is probably best reserved for patients with severe and symptomatic thrombocytopenia (<20-30 x 10^9/l) after at least 6 months' follow-up."[3]

Table 4.6.1: ASH (1996) and BCSH (2003) Adult ITP Treatment Guidelines

	ASH	BCSH
Warranting initiation of treatment	-Patients with platelet count < 50 x 10^9/l and significant mucosal bleeding or those who have risk factors for bleeding such as hypertension, peptic ulcer disease, and a vigorous lifestyle -All patients with platelet count < 20 x 10^9/l to 30 x 10^9/l	-Patients with platelet count < 30 x 10^9/l -Patients with platelet count ≥ 30 x 10^9/l if they are undergoing a procedure likely to induce blood loss
1st-line treatment	-Glucocorticoids -IVIg for patients with platelet counts < 30 x 10^9/l severe or life-threatening bleeding	-Oral corticosteroids -IVIg for immediate management of symptoms or signs of bleeding, and prior to anticipated blood loss (e.g. prior to surgery, labour etc.)
2nd-line treatment	-Splenectomy may be considered for patients with platelet count < 30 x 10^9/l 4-6 weeks after diagnosis and symptoms of bleeding	-Repeat 1st-line therapy (generally at a higher dose) -Splenectomy -Vinca alkaloids, anti-D, danazol, azathioprine, cyclosporine and dapsone
3rd-line treatment	-Accessory splenectomy, danazol, cyclophosphamide, vinca alkaloids or azathioprine	-Campath-1H -Rituximab -Mycophenolate mofetil
Additional treatments	-Recommendations depend on individual patient characteristics	-Agents such as high-dose IVIg, vinca alkaloids, anti-D, danazol, azathioprine, and cyclosporine may be considered when there is a non-urgent or semi-urgent need to elevate platelet count
Emergency interventions	-Hospitalisation -High-dose parenteral glucocorticoid therapy and/or IVIg and platelet transfusion	-Transfusion of random donor platelets -IVIg and/or IV methylprednisolone and/or IV cyclophosphamide

5 Equity and equality

The Institute considers equity in terms of how the effects of a health technology may deliver differential benefits across the population. Evidence relevant to equity considerations may also take a variety of forms and come from different sources. These may include general-population-generated utility weightings applied in health economic analyses, societal values elicited through social survey and other methods, research into technology uptake in population groups, evidence on differential treatment effects in population groups, and epidemiological evidence on risks or incidence of the condition in population groups. Evidence submitters are asked to consider whether the chosen decision problem could be impacted by the Institute's responsibility in this respect; including in considering subgroups and access to recommendations that use a clinical or biological criterion.

5.1 Identification of equity and equalities issues

5.1.1 *Are there any issues relating to equity or equalities (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?*

ITP is an orphan disease and the low frequency of occurrence means there are fewer patients over whom investment in R&D for treatment of ITP may be recouped. This tends to push up cost of treatment per patient and, given the use by NICE of cost-effectiveness thresholds, makes it harder to gain support for new, efficacious treatment. Equity requires that this be taken into account in making reimbursement decisions.

Whether orphan diseases should be given special consideration in economic evaluations is controversial.[46;47] Options include flexible cost-effectiveness thresholds and employing a rule of rescue. We recognize that there is currently a debate whether the cost-effectiveness threshold should be adjusted for orphan diseases, and we encourage NICE to consider flexibility in this regard, as well as the rule of rescue, as it evaluates novel and innovative therapies for an orphan disease like chronic ITP.

The poor quality of life of patients, the range of universally toxic and unpleasant treatments available as alternatives to romiplostim, and the high mortality risks make some of the more refractory ITP patients comparable to many cancer patients in the later stages of their disease. Similarly, the difficulty in assessing the relative effectiveness of a new drug because of poor evidence on effectiveness of a wide variety of unlicensed alternatives is comparable to many cancer appraisals. Some of the same kind of uncertainties will need to be accepted.

Alternatives to surgical therapy are needed, as are alternatives to current drug treatments and their long-term toxicities. In a recent survey of 1,000 patients of the Platelet Disorder Support Association (PDSA), a major global ITP patient advocacy group, 37% of patients were splenectomised and, of these, 62% reported having been pressured into accepting this surgical treatment as opposed to (or due to the lack of) drug therapy alternatives.[48]

Amgen is unaware of any specific issues relating to treatment of ITP in the context of equalities legislation.

5.1.2 How has the analysis addressed these issues?

As with orphan drugs, and cancer drugs used for salvage, greater than usual uncertainties exist around the exact size of the estimate of relative effectiveness. In this case the cause is not that the trials conducted on romiplostin are too small to demonstrate efficacy, but that the evidence relating to the comparator drugs is poor. This has been addressed in the analysis by making reasonable judgements on effect sizes, based on the literature, whilst at the same time demonstrating the effect of varying those assumptions either singly or together through appropriate sensitivity analyses, trying to be as transparent as possible about the assumptions made.

In addition, the model does not take into account the long-term failure rate or the rate of long term adverse events of therapies such as corticosteroids and splenectomy. Hence the true cost of current standard of care is probably underestimated, making the current model more conservative in favour of standard of care when compared with romiplostim.

6 Clinical evidence

Manufacturers and sponsors are required to submit a systematic review of the clinical evidence that relates directly to the decision problem. Systematic and explicit methods should be used to identify, select and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Where appropriate, statistical methods (meta-analysis) should be used to analyse and summarise the results of the included studies. The systematic review should be presented in accordance with the QUORUM statement checklist (www.consort-statement.org/QUOROM.pdf).

The systematic review is not required to be exhaustive (that is, it is not necessary to include all evidence relating to the use of the technology), but justification needs to be provided for the exclusion of any evidence. Where manufacturers have identified a study but do not have access to the level of detail required, this should be indicated.

The Institute has a strong preference for evidence from 'head-to-head' randomised controlled trials (RCTs) that directly compare the technology and the appropriate comparator(s). Wherever such evidence is available, and includes relevant outcome evidence, this is preferred over evidence obtained from other study designs. When head-to-head RCTs exist, evidence from mixed treatment comparison analyses may be presented if it is considered to add information that is not available from the head-to-head comparison. If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used. Formal assessments of heterogeneity should be included.

In the absence of valid RCT evidence, evidence from other study designs will be considered, with reference to the inherent limitation inferred by the study design. The Institute also recognises that RCT data are often limited to selected populations, short time spans and selected comparator treatments. Therefore good-quality observational studies may be submitted to supplement RCT data. Any potential bias arising from the design of the studies used in the assessment should be explored and documented.

6.0 Approach to analysis

Challenges and overall approach

In ITP, there are very few randomised studies comparing one treatment to another, and little data or clinical consensus regarding the ideal patient pathway. ITP treatment guidelines from ASH and BCSH are largely based on evidence from case series and expert opinion and are somewhat outdated.

Due to the lack of clinical guidance on which ITP therapy patients should receive at each "line" of treatment, it would have been difficult to design an RCT to compare romiplostim directly with each of the specific comparator treatments in the decision problem. However, there are two phase 3 RCTs comparing romiplostim to placebo in ITP patients. These RCTs were designed to evaluate the efficacy and safety of romiplostim in a "real world" clinical context, and patients in both the romiplostim and placebo arms could receive concurrent chronic ITP therapies and rescue medications at the discretion of the investigator (see below for rationale for design of these studies). Hence these RCTs could be considered to compare romiplostim plus standard-of-care to placebo plus standard-of-care.

In terms of the comparator treatments, several are not licensed for ITP, and there are very few RCTs comparing these treatments to placebo (either for efficacy or safety). This lack of placebo-controlled trials, in addition to the complexity of the

treatment paradigm for ITP and the heterogeneity of the data, means that it is not possible to undertake a formal indirect mixed treatment comparison (for example using Bayesian networks). In addition, the studies which have been conducted are small and of poor quality. Efficacy data taken from unblinded, uncontrolled studies have been shown to overestimate effect sizes.[49;50]

It is difficult to obtain comparable outcome data from the studies of the various comparators. The studies discussed above do not generally present data on bleeding rates. Instead, the main outcomes reported are the proportions of patients reaching a certain platelet threshold. This threshold is generally defined as 50 x 10^9/l which is widely accepted as a conservative measure of efficacy; however this causes difficulties for the economic modelling since current guidelines suggest only treating patients whose platelet count falls to less than 30 x 10^9/l with a treatment goal of establishing a platelet count > 50 x 10^9/l. In addition, many existing ITP treatments are strongly immunosuppressive and have unpleasant and potentially harmful short- and long-term side effects. However, it is difficult to obtain accurate estimates of adverse effects from uncontrolled studies. Also, many studies of the comparators are in ITP patients who are much less refractory (and more likely to respond to treatment) than those enrolled in the phase 3 RCTs of romiplostim, which may overestimate the effect of the comparators in relation to romiplostim.

Bearing the above difficulties in mind, our approach to this assessment is to compare two patient pathways: 1) a standard care pathway in which treatments are ordered to match usual care as closely as possible (using information from the clinical guidelines together with a survey of expert clinicians); and 2) a similar pathway which incorporates romiplostim. The data for this analysis is taken from the study types that are available for each comparator; these are mainly single-arm studies such as cohort studies and case series. Much of this data is low-quality but is being used in the absence of higher-quality data.

Rationale for concurrent therapies permitted in the romiplostim pivotal ITP studies

The romiplostim phase 3 ITP studies were designed to evaluate the efficacy and safety of romiplostim in a “real world” clinical context. As such, the studies evaluated romiplostim in the context of administration of a number of medical therapies that represent the standard of care in the medical management of ITP.

The pivotal studies allowed patients to enrol while receiving a constant dose and schedule of prednisone, azathioprine, and danazol. These medications have the potential to be administered on a chronic basis, and their use during the study was permitted to fulfil the therapeutic needs of patients who were requiring ongoing therapy for thrombocytopenia at the time of enrolment. Additionally, concurrent use of these medications during the study enabled an assessment of the ability of romiplostim to reduce the need for standard of care medications whose use can be associated with significant side effects.

In addition to the above, patients enrolled in the pivotal studies were also eligible to receive rescue medications at the discretion of each investigator to prevent or to treat bleeding. Allowed rescue medications included corticosteroids (oral or intravenous), intravenous immunoglobulin (IVIg), and intravenous anti-D. These medications are commonly used in the management of ITP on an as needed basis to prevent or to treat haemorrhage.

While the pivotal studies allowed use of many standard of care therapies, the use of either alkylating agents (i.e. cyclophosphamide) or rituximab was prohibited on the basis of practical considerations and regulatory agency interactions. Although these medications do not have marketing authorisation in the United Kingdom, they are

indeed part of the current standard of care in the treatment of ITP. As a cytotoxic agent that has the potential to destroy platelet forming cells (megakaryocytes), cyclophosphamide was prohibited based on the theoretical possibility that it could undermine the effect of a platelet producing agent like romiplostim that works by stimulating cells of the megakaryocyte lineage to proliferate, differentiate and mature.

Although it is less likely that the mechanism of action of rituximab would conflict with that of romiplostim, its use was proscribed given the concern that it could potentially confound an efficacy assessment of romiplostim. Both response to rituximab and time to response are relatively unpredictable, making it difficult to adjust for its impact on platelet counts among study participants.

Importantly, despite the lack of use of these medications during the pivotal studies, a significant number of phase 3 patients had received these therapies prior to enrolment. Approximately half (63/125; 50.4%) of all enrolled patients had received rituximab, and approximately one third (48/125; 38.4%) had received cyclophosphamide.[51] The fact that patients had a mean and median platelet count $<20 \times 10^9$/l at enrolment (16.5 and 16.0 $\times 10^9$/l, respectively) suggests that they had either previously failed or been intolerant these therapies.

Therefore, based on the above, the efficacy and safety of romiplostim were evaluated against a background of use of the majority of medications that compose the current standard of care in the medical management of ITP.

The choice of concomitant ITP therapies permitted in the pivotal studies reflects the current guidelines and UK practice. IVIg, anti-D, corticosteroids and danazol are all used in the UK and represent part of the current standard of care in the treatment of ITP. Azathioprine, also used in the UK, was the immunosuppressant therapy chosen for the studies. Cyclophosphamide use in the UK seems minimal so its exclusion as a rescue therapy in this study does not impact the relevance of the results for UK physicians.

6.1 Identification of studies

Describe the strategies used to retrieve relevant clinical data both from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in appendix 2, section 9.2.

As noted in the decision problem, there are a large number of comparator treatments used to treat ITP. Whilst there has been a large number of studies published over recent years relating to these comparator treatments, little or no clinical evidence exists from head-to-head randomised clinical trials (RCTs). Instead, much of the clinical evidence would be considered low quality by QUORUM standards, e.g. single arm case series involving small patient numbers, and where the evidence was published some time ago. Due to the diversity of the clinical evidence for all the comparator treatments, it was not feasible to conduct an extensive and full systematic search and identify all studies for all comparator treatments. Therefore a pragmatic approach has been used to identify relevant studies that provide valid clinical evidence to address the decision problem, described as follows:

1) The current clinical guidelines (ASH and BCSH) were used to identify clinical studies:
    - British Committee for Standards in Haematology (BCSH) Guideline for Management of ITP (Provan et al 2003)[2]
    - American Society of Hematology (ASH) Practice Guideline for ITP (George et al 1996)[1]

2) Recent reviews of ITP and systematic reviews of specific treatments were used to ensure the clinical evidence included most recent estimates of efficacy and safety for those outcomes noted in the decision problem; key reviews included:
    - Vesely 2004 systematic review of treatments post-splenectomy[52]
    - Godeau 2007 literature review of ITP treatments[3]
    - Cines & Bussel 2005 review of ITP treatments[6]
    - Cines & Blanchette 2002 review of ITP treatments[43]
    - Arnold 2007 systematic review of rituximab for ITP[36]
    - Zhou 2008 systematic review of rituximab for ITP[53]
    - Maloisel 2004 literature review of danazol for ITP[54]
    - Bierling & Godeau 2004 & 2005 reviews of IVIg safety[55;56]

3) Clinical evidence reported from the original studies included in these reviews and guidelines have been obtained.

4) In addition, a literature search has been undertaken to identify any key clinical studies in the relevant comparators published since the review by Godeau et al 2007[3] (or since the most relevant review for each individual treatment; please see Section 6.8.1 for further details). Please see Appendix 2 for details of the search terms and databases searched. Studies were excluded if they related to secondary thrombocytopenia associated with other conditions, ITP in childhood or pregnancy, or if they included less than 5 patients.

6.2 Study Selection

6.2.1 Complete list of RCTs

Provide a list of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the assessors.

Where data from a single study have been drawn from more than one source (for example, a poster and a published report) and/or where trials are linked (for example, an open-label extension to an RCT), this should be made clear.

The following section relates to RCTs of romiplostim in ITP. Studies of comparator treatments in ITP are almost all non-randomised and so are described in Section 6.8.

The main source of the clinical evidence of efficacy and safety data for romiplostim (the intervention) are two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials, as published by Kuter et al.[23] In both trials, patients were randomised to receive either romiplostim-plus-standard-of-care or placebo-plus-standard-of-care over a 24-week period. Patients in both groups could receive concurrent or rescue ITP medications at the investigator's discretion. The two phase 3 trials are:

1) Study 20030212: A Randomised, Placebo-Controlled Study Evaluating the Efficacy and Safety of AMG 531 (Romiplostim) Treatment of Thrombocytopenic Subjects with Immune (Idiopathic) Thrombocytopenic Purpura (ITP) Prior to Splenectomy
2) Study 20030105: A Randomised, Placebo-Controlled Study Evaluating the Efficacy and Safety of AMG 531 (Romiplostim) Treatment of Thrombocytopenic Subjects with Immune (Idiopathic) Thrombocytopenic Purpura (ITP) Refractory to Splenectomy

A phase 2 dose-finding RCT has also been carried out (study 20000137B: Phase 2, Multicenter, Randomised, Dose-Finding, Placebo-Controlled Study Evaluating Safety, PK/PD, and Efficacy of Romiplostim in Thrombocytopenic Subjects with ITP). In this study, 17 patients received various set doses of romiplostim (rather than 1 µg/kg followed by dose titration as specified in the product label) and 4 patients received placebo (Bussel 2006). This study is not used in the efficacy analysis as its dosing algorithm does not match that in the pivotal phase 3 studies and the draft SPC.

There are also two ongoing RCTs. The first is a phase 3b study (study 20060131) entitled "A Randomised, Controlled, Open-label Study Evaluating the Efficacy and Tolerability of AMG 531 versus Medical Standard of Care as Chronic Therapy for Non-splenectomised Subjects with Immune (Idiopathic) Thrombocytopenic Purpura." No efficacy data and only very limited safety data is currently available for this study. The second is a phase 3 Japanese study (study 20060216) entitled "A Randomised, double blind, placebo-controlled phase 3 study to assess efficacy (platelet response) and safety of romiplostim in Japanese subjects with ITP." No data is currently available for this study.

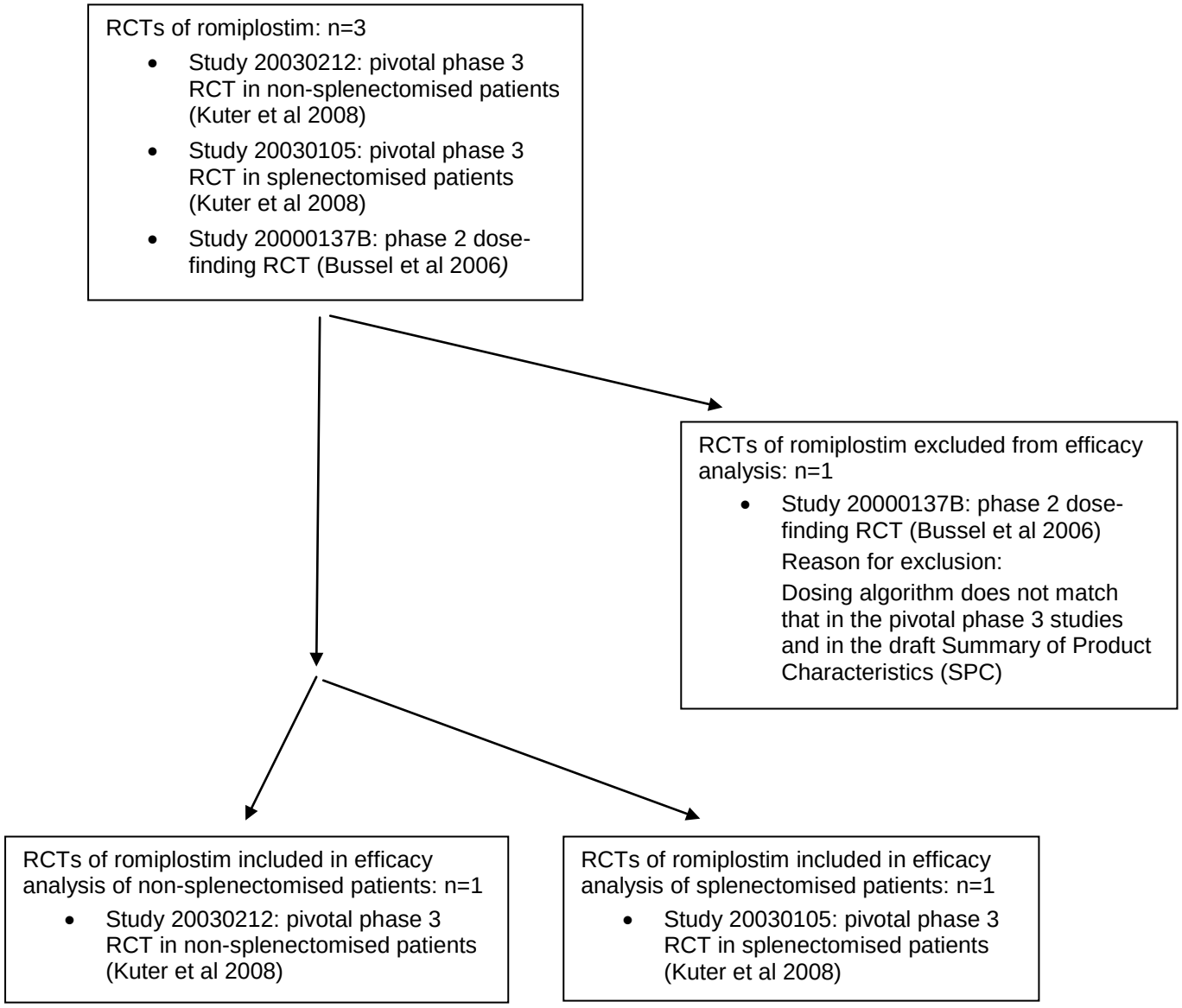
6.2.2 Inclusion and exclusion criteria

State the inclusion and exclusion criteria that were used to identify the studies detailed in the list of relevant RCTs. If additional inclusion criteria were applied to select studies that have been included in the systematic review, these need to be listed separately.

Only romiplostim 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) were used as the basis for the clinical evidence of efficacy. This consisted of the two phase 3 romiplostim RCTs (Section 6.2.1). Dose-finding studies were not included in the analysis of efficacy. Included romiplostim RCTs are shown in Figure 6.2.2.

Figure 6.2.2: Flow diagram of romiplostim RCTs



6.2.3 List of relevant RCTs

List all RCTs that compare the technology directly with the appropriate comparator(s) with reference to the specification of the decision problem. If there are none, state this. Where studies have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. A flow diagram of the numbers of studies included and excluded at each stage should be provided at the end of section 6.2, as per the QUORUM statement flow diagram (www.consort-statement.org/QUOROM.pdf). The total number of studies in the

QUORUM statement should equal the total number of studies listed in section 6.2.1. Where data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or where trials are linked (for example, an open-label extension to an RCT), this should be made clear.

There are no RCTs that compare romiplostim directly with each of the specific comparator treatments specified in the decision problem. The two phase 3 RCTs (studies 20030212 and 20030105; Kuter et al, 2008)[23] were designed to evaluate the safety and efficacy of romiplostim in a "real world" clinical context, as described in Section 6.0. Patients in both the romiplostim and placebo arms could receive concurrent chronic ITP therapies and rescue medications at the discretion of the investigator, allowing assessment of the ability of romiplostim to reduce the need for such therapies. These pivotal phase 3 RCTs formed the basis of the prescribing information. Therefore these two phase 3 RCTs will be used to obtain efficacy data on romiplostim. This will be used together with efficacy data on the comparator treatments to model two pathways: current standard of care, and current standard of care with romiplostim.

6.2.4 List of relevant non-randomised controlled trials

Provide details of any non-randomised controlled trials that are considered relevant to the decision problem. Provide justification for their inclusion.

There are no non-randomised trials that compare romiplostim with any of the specific comparator treatments specified in the decision problem.

Non-RCT studies of romiplostim are as follows:

- Study 20030213: An Open Label Study Evaluating the Safety and Efficacy of Long-Term Dosing of AMG 531 in Thrombocytopenic Subjects with Immune (Idiopathic) Thrombocytopenic Purpura (ITP).[57-61] Long-term uncontrolled clinical evidence of safety and efficacy of romiplostim is available from this study. Romiplostim- or placebo-treated patients completing the phase 3 studies, whose platelet counts subsequently fell to below 50 x 10^9/l after discontinuation of investigational product, were eligible to enrol in study 20030213 and receive open-label romiplostim on an ongoing basis; this study is still in progress. Patients completing other romiplostim studies (20000137A, 20000137B, 20010218, 20040209, 20060131) were also eligible to enrol. As described in Section 6.4, data from phase 3 patients going onto study 20030213 were used to calculate time-to-failure on romiplostim (this could not be calculated from the phase 3 studies alone, since the interventions in the phase 3 studies ended after 24 weeks). Only those patients entering study 20030213 from the phase 3 studies were included in this analysis, because these patients received the dosing described in the decision problem and the draft label.

The following studies provide safety data (see section 6.7):

- Study 20000137A: Phase 1-2, Multicenter, Open-Label, Dose-Finding, Sequential-Cohort Study Evaluating the Safety and Efficacy of Romiplostim in Thrombocytopenic Subjects with ITP
- Study 20010218: Phase 1-2, Multicenter, Open-Label, Sequential-Cohort, Unit Dose-Finding Study of Safety and Efficacy of Romiplostim in Adult Thrombocytopenic Subjects with ITP
- Study 20040209: An Open Label Individual Patient Protocol of AMG 531 in Severely Refractory Thrombocytopenic Subjects with Immune (Idiopathic) Thrombocytopenic Purpura (ITP)

- Study 20050123: The Effects of Long-Term Dosing of AMG 531 on Bone Marrow Morphology in Thrombocytopenic Subjects with Immune (Idiopathic) Thrombocytopenic Purpura (ITP) (sub-study of the pivotal studies and the open label extension study)
- Study 20050162: Phase 2, multicenter, open-label, dose-escalation, sequential-cohort, safety and efficacy (platelet response) in thrombocytopenic subjects with ITP in Japan

6.2.5 Ongoing studies

Provide details of relevant ongoing studies from which additional evidence is likely to be available in the next 12 months.

The following studies of romiplostim in ITP are ongoing:

The open-label extension study of romiplostim described above (study 20030213).

Study 20060131: a randomised, controlled, open-label study evaluating the efficacy and tolerability of romiplostim versus medical standard of care as chronic therapy for non-splenectomised ITP patients.

Study 20060113: Open-label extension study to assess long-term dosing of romiplostim in Japanese subjects with ITP who previously participated in romiplostim studies. Preliminary data for this study may be available within 12 months of submission, but this is dependent on internal timelines and is subject to potential change.

Study 20060216: Randomised, double blind, placebo-controlled phase 3 study to assess efficacy (platelet response) and safety of romiplostim in Japanese subjects with ITP (note that the Japanese programme of studies use a different starting dose of romiplostim of 3 ug/kg). Preliminary data for this study is likely to be available within 12 months, but these timelines are subject to potential change.

In addition, the following studies of ITP patients are ongoing (but do not involve administration of romiplostim):

Study 20050237: A Prospective Observational Descriptive Study and Retrospective Chart Review of Subjects with Immune (Idiopathic) Thrombocytopenic Purpura (ITP).

[redacted]

6.3 Summary of methodology of relevant RCTs

As a minimum, the summary should include information on the following aspects of the RCT, but the list is not exhaustive. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (http://www.consort-statement.org/). The methodology should not be submitted in confidence without prior agreement with NICE. Where there is more than one RCT, the information should be tabulated.

6.3.1 Methods

Describe the RCT design (for example, duration, degree and method of blinding, and randomisation) and interventions.

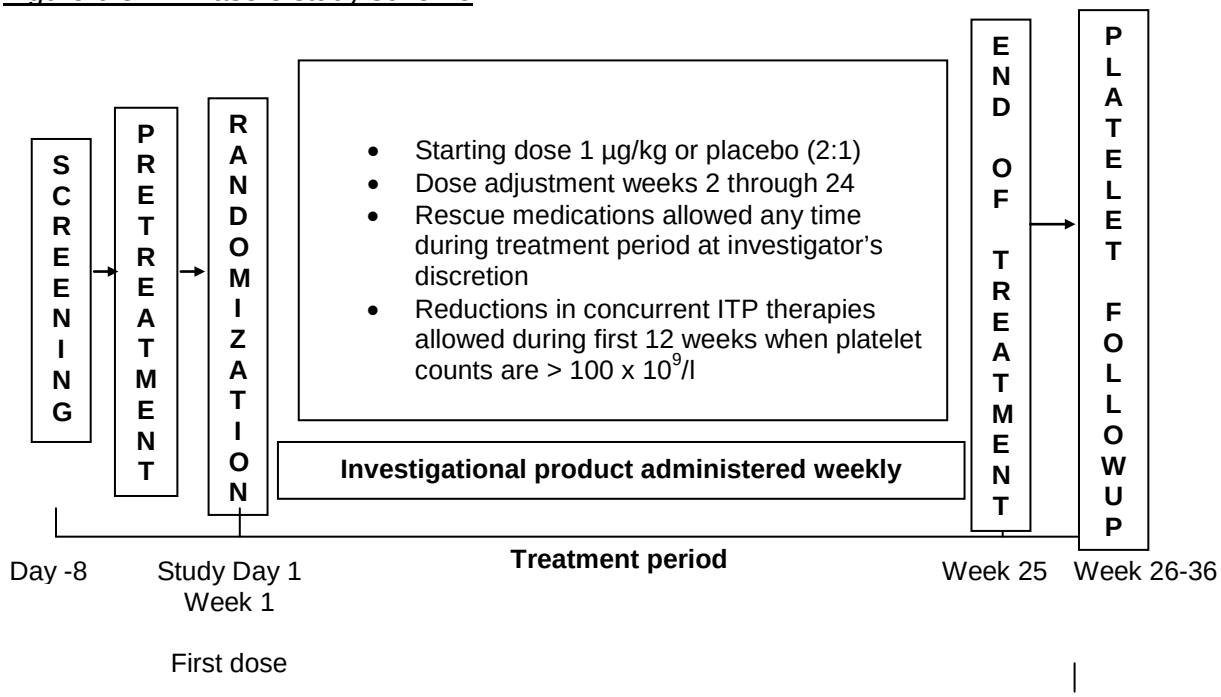
The two phase 3 romiplostim ITP studies were identical in design, except that one recruited splenectomised patients and one non-splenectomised. Both studies were randomised, double blind, placebo-controlled, 24-week trials.

The primary objective of both studies was to evaluate the efficacy of romiplostim in the treatment of thrombocytopenia in adult subjects with ITP, as measured by durable platelet response during the last 8 weeks of treatment, and other platelet response parameters. The secondary objectives were to evaluate the overall safety of romiplostim; to evaluate possible reductions in concurrent ITP therapies while receiving romiplostim; and to evaluate changes in Patient Reported Outcomes (PROs) and Health Resource Utilization due to treatment with romiplostim.

Each study planned to enrol approximately 60 subjects, randomised in a 2:1 ratio to romiplostim or placebo (40 and 20, respectively). Randomisation was stratified by baseline concurrent ITP therapy (yes or no) within each study. The randomisation list was generated by Amgen and patients were randomised using a central telephone (IVRS) system. To maintain the blind, romiplostim and placebo were supplied in identical vials. Patients received subcutaneous injections of romiplostim or placebo once per week for 24 weeks, starting with a dose of 1 ug/kg. Doses were subsequently adjusted based on platelet counts to maintain platelet counts in the range of 50 to 200 x 10^9/l (maximum romiplostim dose 15 ug/kg). Concurrent ITP therapies (corticosteroids, azathioprine or danazol) were permitted if at a constant dose and schedule; reductions in these could occur during the first 12 weeks of treatment when platelet counts were >100 x 10^9/l. Rescue therapies (corticosteroids, immunoglobulins or platelet transfusions) were permitted for the intended purpose of raising platelet counts at any time at the investigator's discretion; any increase in the dose of a baseline concurrent ITP therapy was also defined as rescue medication. After 24 weeks of treatment, investigational product was withdrawn and patients were monitored until platelet counts fell to ≤ 50 x 10^9/l or until week 36, whichever occurred first. Patients whose platelet counts fell to ≤ 50 x 10^9/l were eligible to enrol into an open label extension study (20030213).

The study schema for the phase 3 studies is shown in Figure 6.3.1.

Figure 6.3.1: Phase 3 study scheme



6.3.2 Participants

Provide details of the inclusion and exclusion criteria, and describe the patient characteristics at baseline. Highlight any differences between study groups.

Eligible patients were recruited from centres in the United States and Europe. Patients were required to be at least 18 years of age with a diagnosis of ITP according to ASH guidelines and required adequate liver and renal function and haemoglobin >9.0 g/dL. Enrolled patients had completed at least 1 previous treatment for ITP with an inadequate platelet response, defined as a mean of 3 platelet counts during screening and pre-treatment ≤ 30 x10^9/l, with no individual count >35 x10^9/l. Patients older than 60 years required a documented history of chronic ITP confirmed by bone marrow biopsy. For study 20030105, splenectomy must have occurred at least 4 weeks before study entry. Subjects enrolled into study 20030212 were not permitted to have had a splenectomy for any reason.

Patients' baseline characteristics are summarised in Table 6.3.2. Demographic characteristics were well balanced between the treatment groups in both trials and were reflective of the ITP population. As expected, splenectomised patients were more refractory than those who had not undergone splenectomy. Moreover, it is important to note that both the splenectomised and non-splenectomised patients in these studies were more refractory than patients included in many of the single-arm studies of other treatments included in the economic model. The median durations of ITP (romiplostim and placebo groups) were 7.8 and 8.5 years in the study of splenectomised patients and 2.2 and 1.6 years in the study of non-splenectomised patients. In the study of splenectomised patients, 93% in the romiplostim group and 95% in the placebo group had received at least three previous ITP treatments prior to enrolment, compared to 37% and 24%, respectively, in the study of non-splenectomised patients. The median baseline platelet count was 14-15 x 10^9/l in the study of splenectomised patients and 19 x 10^9/l in the study of non-splenectomised patients. The median age across all groups in the two studies was 52 years (range 21-88).

Table 6.3.2: Patient demographics and baseline characteristics

	Non-splenectomised		Splenectomised		All patients from both studies		
	Romi-plostim (n=41)	Placebo (n=21)	Romi-plostim (n=42)	Placebo (n=21)	Romi-plostim (n=83)	Placebo (n=42)	Total (n=125)
Age (years)	52 (21-80)	46 (23-88)	51 (27-88)	56 (26-72)	52 (21-88)	52 (23-88)	52 (21-88)
Women	27 (66%)	16 (76%)	27 (64%)	11 (52%)	54 (65%)	27 (64%)	81 (65%)
Race White	31 (76%)	18 (86%)	34 (81%)	19 (91%)	65 (78%)	37 (88%)	102 (82%)
Black or African American	3 (7%)	1 (5%)	3 (7%)	2 (10%)	6 (7%)	3 (7%)	9 (7%)
Hispanic or Latino Other*	3 (7%) 4 (10%)	2 (10%) 0 (0%)	3 (7%) 2 (5%)	0 (0%) 0 (0%)	6 (7%) 6 (7%)	2 (5%) 0 (0%)	8 (6%) 6 (5%)
Weight (kg)	78 (44-134)	71 (52-123)	77 (45-138)	89 (57-169)	78 (44-138)	81 (52-169)	79 (44-169)
Duration of ITP (years since diagnosis)	2.20 (0.1-31.6)	1.60 (0.1-16.2)	7.75 (0.6-44.8)	8.50 (1.1-31.4)	N/A	N/A	N/A
≥3 previous treatments	15 (37%)	5 (24%)	39 (93%)	20 (95%)	54 (65%)	26 (60%)	79 (63%)
Platelet count (10^9/l)†	19 (2-29)	19 (5-31)	14 (3-29)	15 (2-28)	16 (2-29)	18 (2-31)	16 (2-31)
Thrombopoietin concentration (pg/mL)‡	94 (31-1228)	81 (31-1848)	113 (31-586)	124 (31-744)	102 (31-1228)	108 (31-1848)	103 (31-1848)
Receiving concurrent ITP therapy at baseline	11 (27%)	10 (48%)	12 (29%)	6 (29%)	23 (28%)	16 (38%)	39 (31%)

Data are median (minimum–maximum) or number (%). ITP=immune (idiopathic) thrombocytopenic purpura. N/A=not applicable. *Includes Asian and native Hawaiian or other Pacific Islander. †Baseline platelet count=mean of platelet counts at days –8, –2, and predose on day 1. ‡Normal thrombopoietin concentrations range from 32 to 246 pg/mL.

6.3.3 Patient numbers

Provide details of the numbers of patients who were eligible to enter the RCT, randomised, and allocated to each treatment. Provide details of and the rationale for patients who crossed over treatment groups and/or were lost to follow up/ withdrew from the RCT. This information should be presented as a CONSORT flow chart.

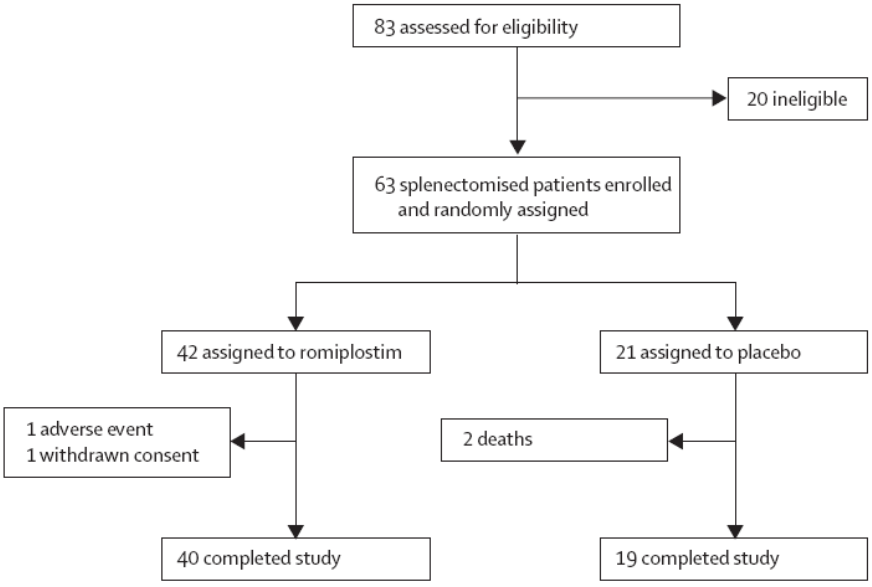
The patient numbers for the two romiplostim phase 3 studies are shown in the flow chart in Figure 6.3.3 (as in Kuter 2008). Eighty-three patients were screened for the study of splenectomised patients; 42 of these were randomised to romiplostim (40 completed study) and 21 to placebo (19 completed study). Eighty-five patients were screened for the study of non-splenectomised patients; 41 of these were randomised to romiplostim (39 completed study) and 21 to placebo (17 completed study). One patient randomised to the placebo group in the non-splenectomy study received three doses of romiplostim in error (weeks 19, 22 and 24). All randomised patients were included in an intention-to-treat analysis according to their randomised treatment group. Hence the placebo patient who received romiplostim in error was included in the placebo group. For study 20030212, the first subject was enrolled on 4 April 2005

and the last subject visit was 21 December 2006. For study 20030105, the first subject was randomised on 29 March 2005 and the last subject visit was 5 September 2006.

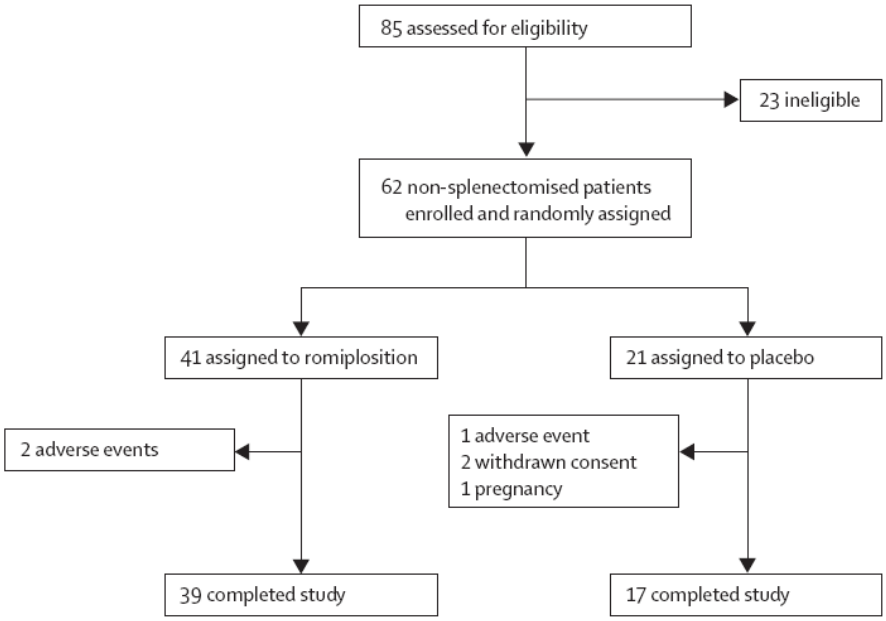
[redacted]

Figure 6.3.3: Flow chart: trial profile for splenectomised patients (A) and non-splenectomised patients (B):

A



B



6.3.4 Outcomes

Provide details of the outcomes investigated and the measures used to investigate those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the specification of the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of quality of life and social outcomes, and any arrangements to measure concordance. Data provided should be from prespecified outcomes rather than post-hoc analyses. Where appropriate, also provide details of the principal outcome measure(s), including details of length of follow-up, timing of assessments, scoring methods, evidence of reliability/validity, and current status of the measure (such as approval by professional bodies or licensing authority).

In the two romiplostim phase 3 studies, all primary and secondary efficacy outcome measures, and safety outcome measures (with the exception of bleeding rates; see below) were prospectively defined before patient enrolment began. The analysis methods to be used for these endpoints were also prospectively defined. One additional outcome measure (time to failure) was defined post-hoc for this decision problem (described below).

Primary Efficacy Outcome Measure

In current guidelines, management of ITP is dictated by platelet count and/or severity of bleeding (as defined in the ASH and BCSH guidelines) and treatment recommended at a platelet level of ≤30 x 10^9/l to avoid clinical sequelae related to thrombocytopenia such as bruising and bleeding. To be conservative, a target platelet count of 50 x 10^9/l was prospectively defined for both studies. This target was developed in conjunction with regulatory authorities and is generally recognised as a conservative effective therapeutic level, at which the risk of spontaneous bleeding is minimal. Using this target level the primary endpoint in the two studies was prospectively defined as:

Incidence of durable response: achieving at least 6 weekly platelet responses (platelets ≥ 50 x 10^9/l) during the last 8 weeks of treatment with no rescue medications administered at any time during the 24 week treatment period.

This primary endpoint was also developed in conjunction with regulatory authorities and is more stringent than the outcome measures used in most studies of other ITP therapies (see section 6.8.4).

Secondary Efficacy Outcome Measures

Secondary endpoints which were prospectively defined for both studies are listed below:

- Incidence of transient platelet response: four or more weekly platelet responses (platelets ≥ 50 x 10^9/l) without a durable response (excluding platelet responses within 8 weeks after rescue medications)
- Incidence of overall platelet response (either a durable response or a transient response)
- Time to first weekly platelet response (platelets ≥ 50 x 10^9/l)
- Number of weekly platelet responses (platelets ≥ 50 x 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 8 weeks of treatment)

Patient Reported Outcome (PRO) Measures

- Change from baseline for the EQ-5D.[62] The EQ-5D includes dimensions of mobility, self-care, usual activities (role activities), pain/discomfort, and anxiety/depression. The EQ-5D visual analogue scale (VAS) contains one item that assesses self-rated health status. EQ-5D index values range from -.59 to 1.00 and EQ-5D VAS scores range from 0 to 100, with higher scores representative of better health status. Effect sizes were estimated using linear regression, adjusting for baseline scores, as well as age and gender. Baseline data were available for 76 of 84 romiplostim patients and 40 of 41 placebo patients. Missing data were imputed using the last value carried forward, unless a subject died, in which zero was imputed. Change from baseline was a pre-specified secondary endpoint with predefined scheduled assessment and analysis methods. Additional outcomes were identified post-hoc and are described in Section 6.4.
- Change from baseline for the ITP-Patient Assessment Questionnaire (ITP-PAQ). ITP-PAQ is a disease-specific instrument to assess HRQoL in ITP patients. [63;64]

Safety Outcomes

- Incidence of adverse events (including clinically significant changes in laboratory values and incidence of antibody formation)

Outcomes defined retrospectively

- Bleeding: this was assessed as a retrospective analysis of bleeding events reported as safety adverse events

[redacted]

Time to failure outcome

6.3.5 Statistical analysis and definition of study groups

State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were preplanned or post-hoc.

In each of the romiplostim phase 3 studies, the hypothesis to be tested was that the rate of durable platelet response in the romiplostim group was greater than in the placebo control group. (It was anticipated that the true difference between the two groups would be 40%.) For each study, a sample size of 60 patients with a 2:1 randomisation ratio (40 romiplostim, 20 placebo) was chosen to provide adequate power to demonstrate that efficacy, measured by durable platelet response of romiplostim, was significantly better than that of placebo. The probability of achieving durable response with romiplostim and placebo was estimated at 50% and 10%, respectively. The sample size was chosen to have approximately 87% power to detect the difference in the incidence of durable response between romiplostim and placebo using a 2-sided Fisher's exact test at a significance level of 5%. Efficacy

analyses were performed on an Intention to Treat (ITT) population which included all randomised subjects, analysed according to randomised treatment groups.

[redacted]

In each study, the primary analysis compared the incidence of durable response in the treatment groups using the Cochran-Mantel-Haenszel test for the odds ratio of two groups, with adjustment for baseline concurrent ITP therapy. Exact 95% Confidence Intervals (CIs) for the incidence were calculated for each treatment group and normal approximated 95% CIs calculated for the difference between treatment groups.

The following secondary endpoints were analysed using methodology similar to that for the primary endpoint: incidence of transient response, incidence of overall response, proportion of subjects who required rescue medication, and incidence of achieving durable platelet response with stable dose.

The number of weekly platelet responses was compared across treatment groups using an analysis of variance model which included treatment and baseline ITP therapy as predictor variables.

Kaplan-Meier estimates were used to analyse the median time to first weekly platelet response. Descriptive statistics were calculated for weekly platelet counts.

[redacted]

Changes from baseline in EQ-5D and ITP-PAQ were analysed using general linear models adjusting for baseline covariates.

6.3.6 Critical appraisal of relevant RCTs

The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study meeting the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. If there is more than one RCT, tabulate the responses, highlighting any 'commercial in confidence' data. The critical appraisal will be validated by the Evidence Review Group. The following are suggested criteria for critical appraisal, but the list is not exhaustive.

- *How was allocation concealed?*
- *What randomisation technique was used?*
- *Was a justification of the sample size provided?*
- *Was follow-up adequate?*
- *Were the individuals undertaking the outcomes assessment aware of allocation?*
- *Was the design parallel-group or crossover? Indicate for each crossover trial whether a carry-over effect is likely.*
- *Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?*
- *How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.*
- *For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?*

- *Were the study groups comparable?*
- *Were the statistical analyses used appropriate?*
- *Was an intention-to-treat analysis undertaken?*
- *Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?*

General Considerations of Study Quality:

There are two relevant randomised controlled studies evaluating the efficacy and safety of romiplostim treatment in thrombocytopenic subjects with ITP. The two romiplostim phase 3 ITP 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. Therefore, the critical appraisal of each study is identical.

The 2 pivotal studies were designed and reviewed with input from regulatory authorities through the Special Protocol Assessment (US FDA) and Committee for Orphan Medicinal Products (COMP) Protocol Assistance (EMEA) processes, respectively. Moreover, the pivotal clinical studies were conducted according to ICH Tripartite E6 guideline on Good Clinical Practice and the principles set forth in the Declaration of Helsinki (2000).

Each pivotal study was a randomised, double blind, placebo controlled, 24-week study. The 24 week duration of treatment met criteria for assessment of the efficacy and safety of romiplostim as a chronic ITP therapy. Approximately 60 subjects were enrolled in a 2:1 ratio to receive romiplostim or matching placebo (40 romiplostim and 20 placebo). Blinded randomisation occurred via an interactive voice response system (IVRS), and the identity of investigational product was concealed by the identical appearance of vials of placebo and romiplostim. Investigational product was administered by subcutaneous injection once per week at a starting dose of 1 µg/kg with weekly dose adjustments based on platelet count; a similar dosage regimen is also contained in the draft Summary of Product Characteristics. Randomisation was stratified to balance treatment groups by whether or not patients were receiving baseline concurrent ITP therapy (yes or no). This stratified randomisation helped to insure the comparability of treatment groups; the fact that baseline demographic characteristics (age, sex, race, baseline platelet count, etc) were well balanced between the placebo and romiplostim groups within both pivotal studies provided evidence for the comparability of the treatment groups.

Statistical Robustness of the RCTs:

The pivotal studies used common and well-established statistical approaches with adequate sample sizes and power that were consistent across studies.

For each study, the sample size of 60 subjects with a 2:1 randomisation ratio was chosen to provide adequate power to demonstrate that the efficacy, measured by the durable platelet response of romiplostim, was significantly better than placebo. The probability of achieving durable platelet response with romiplostim and placebo was estimated at 50% and 10%, respectively. The chosen sample size had approximately 87% power to detect the difference in the incidence of durable platelet response between romiplostim and placebo using a two-sided Fisher's exact test at a significance level of 0.05.

The primary efficacy analysis in the phase 3 studies was based on the full analysis set, consisting of all randomised subjects analyzed according to their randomised treatment group. Hence an intent-to-treat analysis, considered to be the most conservative approach for superiority trials, was undertaken.

The incidences of durable and overall platelet responses, proportion of subjects requiring rescue medication, and incidence of subjects achieving durable platelet response with stable dose were compared between the romiplostim and placebo groups by using the Cochran Mantel-Haenszel test stratified by baseline concurrent ITP therapy (yes/no) and by study when data were combined. This test is appropriate when comparing frequencies across groups when randomisation is stratified and is valid even when some or all of the strata have small frequencies.

[redacted]

To minimize the potential for bias in study conduct or analysis, access to blinded data was restricted to a minimum number of individuals who required access for data capture, validation, and preparation for the reporting of the results. In addition, these individuals remained blinded to the treatment allocation of individual patients until all patients had completed or withdrawn from the study, all patient data had been entered into the clinical trial database and data quality checks had been applied to this data. Also, the statistical methods to be used in the analysis of the trial data were prospectively defined while the data remained blinded.

Potential Confounders that May Impact Interpretation of Study Results:

[redacted]

Relevance of the RCTs to the United Kingdom:

[redacted]

Conclusions

Overall, the quality and control of the pivotal clinical studies was high and enabled a robust assessment of the efficacy and safety of romiplostim. The randomised, double-blind, placebo-controlled design of the pivotal romiplostim studies is superior to the non-randomised studies and case series available for many of the comparator treatments. The pivotal clinical studies included patients from the United Kingdom, and one would expect a high degree of overlap between RCT participants and patients in the UK who would be likely to receive romiplostim.

6.4 Results of the relevant comparative RCTs

Provide the results for all relevant outcome measure(s) pertinent to the decision problem. If there is more than one RCT, tabulate the responses, highlighting any 'commercial in confidence' data. The information may be presented graphically to supplement text and tabulated data. Data from intention-to-treat analyses should be presented wherever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given.

For each outcome for each included RCT the following information should be provided.

- *The unit of measurement.*
- *The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.*
- *A 95% confidence interval.*
- *The number of patients included in the analysis.*
- *The median follow-up time of analysis*
- *State whether intention-to-treat was used for the analysis and how data were imputed if necessary.*
- *Discuss and justify definitions of any clinically important differences.*
- *Where interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.*
- *If the RCT measures a number of outcomes, discuss whether and how an adjustment was made for multiple comparisons in the analysis.*
- *Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.*

Efficacy Results for the Splenectomised Population

Among splenectomised patients, romiplostim was statistically significantly superior to placebo for the primary efficacy endpoint and for all key secondary efficacy endpoints. Romiplostim was able to raise platelet counts, sustain platelet counts, reduce the need for chronic concomitant ITP therapy, and reduce the need for rescue medications relative to placebo treated patients (see Table 6.4.1).

No subjects in the placebo group and 16 subjects (38.1%) in the romiplostim group achieved the rigorously defined endpoint of durable platelet response ($p = 0.0013$). The analyses of additional secondary efficacy endpoints and descriptive secondary endpoints also demonstrated the efficacy of romiplostim. No subjects in the placebo group and 33 subjects in the romiplostim group (78.6%) achieved an overall platelet response ($p < 0.0001$). Based on these results, romiplostim treated patients were more readily able to raise and sustain platelet counts than placebo treated patients. Notably, these increases in platelet response occurred relatively quickly. The Kaplan-Meier estimated median time to the first platelet response was 3.0 weeks for splenectomised subjects. The number of weeks with platelet response was also significantly greater for the romiplostim group: mean 0.2 weeks, SD 0.5 weeks for placebo; mean 12.3 weeks, SD 7.9 for romiplostim ($p < 0.0001$).

[redacted]

A total of 13 (31.0%) subjects were able to achieve a durable platelet response at a stable dose of romiplostim (no subject in the placebo group) (p = 0.0046) ("stable dose" was defined as a dose maintained within ± 1 µg/kg during the last 8 weeks of treatment).

Six subjects in the placebo group and 12 subjects in the romiplostim group were receiving concurrent ITP therapies at baseline. At week 25 of the study, 1 placebo subject (16.7%) had a > 25% reduction in concurrent ITP treatment, while 4 romiplostim subjects (33.3%) had a > 25% reduction and an additional 8 romiplostim subjects (66.7%) had discontinued all concurrent ITP therapies. In the splenectomised population, romiplostim demonstrated an ability to reduce the need for concomitant ITP therapy, predominantly corticosteroids.

Efficacy Results for the Non-Splenectomised Population

As in splenectomised patients, among non-splenectomised patients romiplostim was statistically significantly superior to placebo for the primary efficacy endpoint and for all key secondary efficacy endpoints. Once again, romiplostim was able to raise platelet counts, sustain platelet counts, reduce the need for chronic concomitant ITP therapy, and reduce the need for rescue medications relative to placebo treated patients (see Table 6.4.1).

One subject (4.8%) in the placebo group and 25 subjects (61.0%) in the romiplostim group achieved a durable platelet response (p < 0.0001). The analyses for additional secondary efficacy endpoints and descriptive secondary endpoints also demonstrated the efficacy of romiplostim. A total of 3 subjects (14.3%) in the placebo group and 36 subjects (87.8%) in the romiplostim group achieved an overall platelet response (p < 0.0001). Among non-splenectomised patients, these increases in platelet response occurred rapidly. The Kaplan-Meier estimated median time to the first platelet response was 2.0 weeks for non-splenectomised subjects. The number of weeks with platelet response was also significantly greater for the romiplostim group: mean 1.3 weeks, SD 3.5 weeks for placebo; mean 15.2 weeks, SD 7.5 for romiplostim (p < 0.0001).

A total of 13 subjects (61.9%) in the placebo group and 8 subjects (20%) in the romiplostim group received rescue medication during the treatment period (p = 0.0010).

[redacted]

Ten subjects in the placebo group and 11 subjects in the romiplostim group were receiving concurrent ITP therapies at baseline. At week-25 of the study, 2 placebo subjects (20.0%) had a > 25% reduction in dose of at least one concurrent ITP treatment and an additional 3 placebo subjects (30.0%) discontinued all concurrent ITP therapies, while 4 romiplostim subjects (36.4%) had a > 25% reduction in dose of at least one concurrent ITP treatment and an additional 4 romiplostim subjects (36.4%) had discontinued all concurrent ITP therapies. In the non-splenectomised population, romiplostim once again demonstrated an ability to reduce the need for concomitant ITP therapy, predominantly corticosteroids.

Time to failure on romiplostim

[redacted]

Table 6.4.1: Efficacy results from phase 3 studies of romiplostim in ITP

	Splenectomised			Non-splenectomised			Total		
	Romiplostim (n=42)	Placebo (n=21)	p-value	Romiplostim (n=41)	Placebo (n=21)	p-value	Romiplostim (n=83)	Placebo (n=42)	p-value
Overall platelet response[1] [95% CI]	33/42 (79%) [63.2, 89.7%]	0/21 (0%) [0.0, 16.1%]	<0.0001	36/41 (88%) [73.8, 95.9%]	3/21 (14%) [3.0, 36.3%]	<0.0001	69/83 (83%) [73.3,90.5%]	3/42 (7%) [1.5, 19.5%]	<0.0001
Durable platelet response[2] [95% CI]	16/42 (38%) [23.6, 54.4%]	0/21 (0%) [0.0, 16.1%]	0.0013	25/41 (61%) [44.5, 75.8%]	1/21 (5%) [0.1, 23.8%]	<0.0001	41/83 (49%) [38.2, 60.6%]	1/42 (2%) [0.1, 12.6%]	< 0.0001
Durable response with stable dose[3] [95% CI]	13/42 (31%) [17.6, 47.1%]	0/21 (0.0%) [0.0, 16.1%]	0.0046	21/41 (51%) [35.1, 67.1%]	0/21 (0.0%) [0.0, 16.1%]	< 0.0001	34/83 (41%) [30.3, 52.3%]	0/42 (0.0%) [0.0, 8.4%]	< 0.0001
Median time to first platelet response [95% CI]	3 weeks [2, 5 weeks]	N/A		2 weeks [1,3 weeks]	N/A	N/A	3 weeks [2,3 weeks]	N/A	
Mean [SD] number of weeks with platelets ≥50 x 10^9/l (of 24 weeks on study)[4]	12.3 [7.9]	0.2 [0.5]	<0.0001	15.2 [7.5]	1.3 [3.5]	<0.0001	13.8 (0.9)	0.8 (0.4)	<0.0001
Proportion of patients receiving rescue therapies at any point during study[5] [95% CI]	11/42 (26%) [13.9, 42.0%]	12/21 (57%) [34.0,78.2%]	0.0175	[redacted]	13/21 (62%) [38.4,81.9%]	0.0010	[redacted]	25/42 (60%) [43.3, 74.4%]	<0.0001
Proportion of patients discontinuing all concurrent ITP therapies[6]	8/12 (67%)	0/6 (0%)	n/a	4/11 (36%)	3/10 (30%)	n/a	12/23 (52%)	3/16 (19%)	n/a
Patients discontinuing all concurrent ITP therapies or reducing at least one by >25%[6]	12/12 (100%)	1/6 (17%)	n/a	8/11 (73%)	5/10 (50%)	n/a	20/23 (87%)	6/16 (38%)	n/a

[1]Overall platelet response is defined as achieving durable or transient platelet responses. Transient platelet response was defined as weekly platelet count ≥ 50 x 10^9/l for 4 or more times during study weeks 2-25 but without durable platelet response. Patient may not have a weekly response within 8 weeks after receiving any rescue medicines.
[2]Durable platelet response was defined as weekly platelet count ≥ 50 x 10^9/l for 6 or more times for study weeks 18-25 in the absence of rescue therapies any time during the treatment period.
[3]Stable dose was defined as a dose maintained within ± 1 µg/kg during the last 8 weeks of treatment.
[4]Number of weeks with platelet response is defined as number of weeks with platelet counts ≥50 x 10^9/l during study weeks 2-25. Patient may not have a weekly response within 8 weeks after receiving any rescue medicinal products.
[5]Rescue therapies defined as any therapy administered to raise platelet counts. Patients requiring rescue medicinal products were not considered for durable platelet response. Rescue therapies allowed in the study were IVIg, platelet transfusions, anti-D immunoglobulin, and corticosteroids.
[6]Patients reducing or discontinuing concurrent therapies (corticosteroids, azathioprine, and/or danazol) shown as percentage of patients receiving these therapies at baseline.
N/A: not applicable; n/a: test of statistical significance not performed (descriptive secondary efficacy endpoint)
[redacted]

Table 6.4.2: Subject disposition by study period, used to calculate time to failure on romiplostim

Weeks	Subjects who started this period	Subjects censored at the end of this period	Subjects who withdrew during this period	Proportion of patients continuing to respond
1-12	[redacted]	[redacted]	[redacted]	[redacted]
12-24	[redacted]	[redacted]	[redacted]	[redacted]
24-36	[redacted]	[redacted]	[redacted]	[redacted]
36-48	[redacted]	[redacted]	[redacted]	[redacted]
48-60	[redacted]	[redacted]	[redacted]	[redacted]
60-72	[redacted]	[redacted]	[redacted]	[redacted]
72-84	[redacted]	[redacted]	[redacted]	[redacted]
84-96	[redacted]	[redacted]	[redacted]	[redacted]
96-108	[redacted]	[redacted]	[redacted]	[redacted]
108-120	[redacted]	[redacted]	[redacted]	[redacted]
120-132	[redacted]	[redacted]	[redacted]	[redacted]

Bleeding Events in the Pivotal phase 3 ITP Studies

Bleeding events were not prospectively assessed but were instead analysed retrospectively as bleeding events reported as safety adverse events (Table 6.4.3). The overall incidence of bleeding events in the pivotal studies was similar between romiplostim and placebo treated patients. Forty-five (54%) romiplostim treated patients experienced at least one bleeding event of any severity, and 25 (61%) placebo treated patients experienced such a bleeding event.

An analysis of serious bleeding events and clinically relevant, higher severity bleeding events demonstrates a consistent trend in favour of a lower incidence of such events occurring among romiplostim treated patients. Serious bleeding events were those that met the protocol defined regulatory definition of seriousness. In both Phase 3 studies combined, a serious bleeding event was reported for 9 patients [5 (6%) romiplostim, 4 (10%) placebo]. Across both pivotal studies, bleeding events that were grade 3 severity or higher occurred in 6 (7%) patients treated with romiplostim and 5 (12%) patients treated with placebo. Bleeding events that were grade 2 (moderate) severity or higher occurred in 12 (15%) patients treated with romiplostim and 14 (34%) patients treated with placebo.

Table 6.4.3: Post-hoc analysis of reported safety adverse events of bleeding from phase 3 studies of romiplostim in ITP

	Romiplostim (n=83)	Placebo (n=42)
Overall bleeding events	45/84 (54%)[2]	25/41 (61%)[2]
Serious bleeding events[1]	5/84 (6%)[2]	4/41 (10%)[2]
Grade 2 or higher bleeding events (moderate, severe, life-threatening or fatal)[3]	12/84 (15%)[2]	14/41 (34%)[2]
Grade 3 or higher bleeding events (severe, life-threatening or fatal)[3]	6/84 (7%)[2]	5/41 (12%)[2]

[1]A serious adverse event is defined by regulatory agencies as one that suggests a significant hazard or side effect, regardless of the investigator or sponsor's opinion on the relationship to investigational product. This includes, but may not be limited to, any event that: is fatal, is life threatening (places the subject at immediate risk of death), requires in-patient hospitalisation or prolongation of existing hospitalisation, is a persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

[2] Denominators in the safety analysis set differ from those in the efficacy analysis set because 1 patient randomly assigned to placebo received 3 doses of romiplostim in error, and was included in the intention-to-treat efficacy analysis placebo group, but in the safety analysis romiplostim group

[3]The severity of bleeding events was determined by study investigators who reported bleeding events as adverse safety events. The Amgen adverse event grading scale was used for bleeding events where 1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening and 5 = fatal; a clinically significant bleeding event was defined as a bleeding event that met the Amgen adverse event grading scale criteria as grade 3 or higher.

[redacted]

Table 6.4.4: Rates of all bleeding events by platelet level and treatment group

Placebo					
Platelet Count	Number of Events	Person weeks of follow-up	Rate per person-month	Rate per 100 person months	Monthly probability
<50,000	[redacted]				
>50,000					
missing					
Total					
Romiplostim					
Platelet Count	Number of Events	Person weeks of follow-up	Rate per person-month	Rate per 100 person months	Monthly probability
<50,000	[redacted]				
>50,000					
missing					
Total					

Table 6.4.5: Rates of bleeding-related hospitalisation by platelet level and treatment group

Placebo					
Platelet Count	Number of Events	Person weeks of follow-up	Rate per person-month	Rate per 100 person months	Monthly probability
<50,000	[redacted]				
>50,000					
missing					
Total					
Romiplostim					
Platelet Count	Number of Events	Person weeks of follow-up	Rate per person-month	Rate per 100 person months	Monthly probability
<50,000	[redacted]				
>50,000					
missing					
Total					

Table 6.4.6: Bleeding-related hospitalisations in the pooled registration trials

	Romiplostim		Placebo	
Event	Events	%	Events	%
Intracranial hemorrhage				
GI bleed				
Other bleeding hospitalization				
Total				

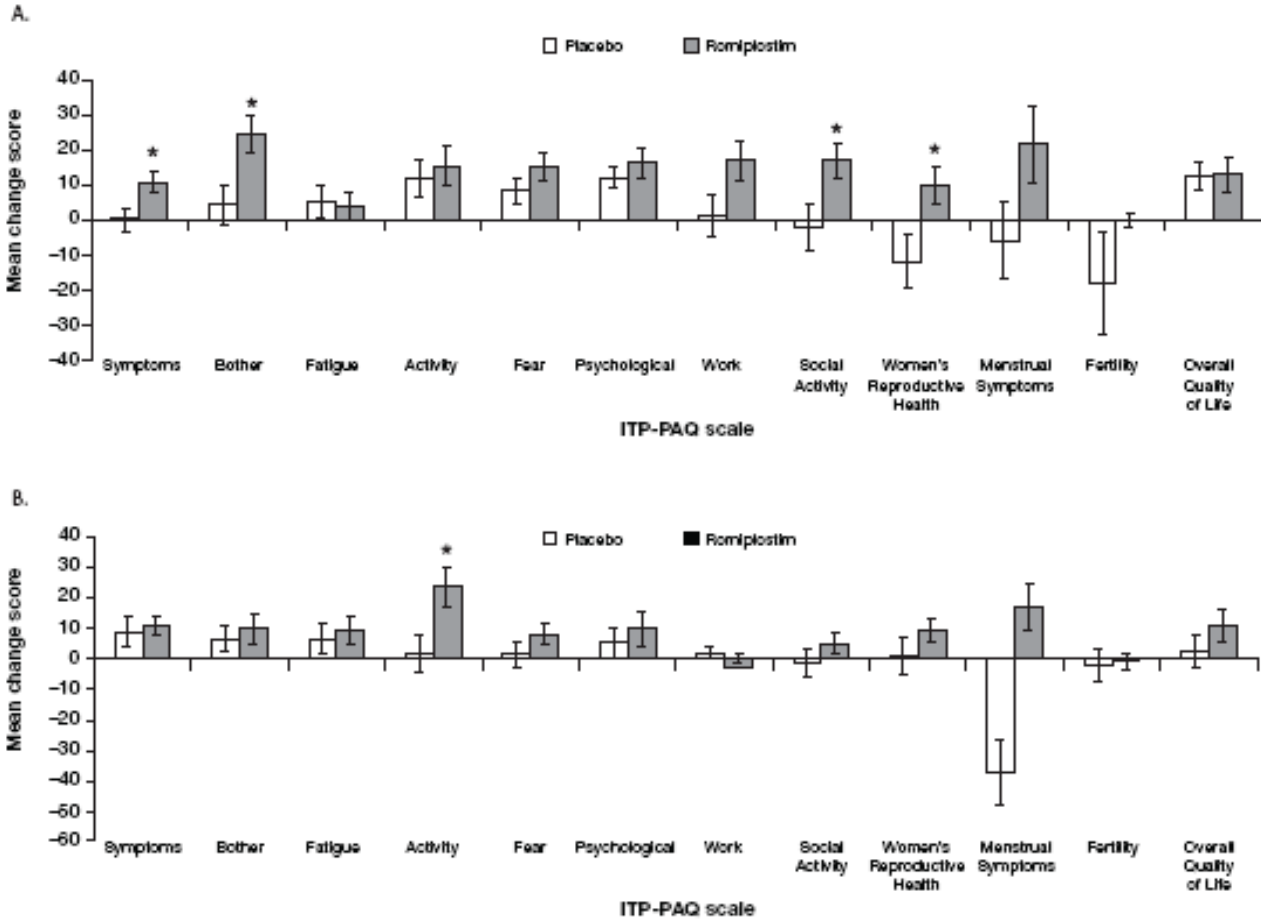
Patient-reported outcome (PRO) results

ITP-PAQ change from baseline results

Splenectomised patients treated with romiplostim had significantly greater improvement in HRQoL than those treated with placebo (ITP-PAQ scales: Symptoms, Bother, Social Activity, and Women's Reproductive Health scales, Figure 6.4.1; P = 0.0337, 0.0126, 0.0145, 0.0184, respectively). Non-splenectomised patients treated with romiplostim showed significantly greater improvement in HRQoL than those treated with placebo in the Activity scale (Figure 6.4.1; P = 0.0458).

Fig 6.4.1. Mean ITP-PAQ change scores from baseline to week 24 for splenectomised (A) or non-splenectomised (B) patients. Error bars represent standard error (SE); menstrual symptoms and fertility are subscales of the Women's Reproductive Health scale; *p < 0.05. (George J., et al. 2008, British Journal of Hematology: Improved quality of life for romiplostim-treated patients with chronic immune thrombocytopenic purpura: results from two randomised, placebo-controlled trials, manuscript accepted for publication, expected in print November 2008)

Figure 6.4.1: ITP-PAQ results



A post hoc repeated measures analysis on the ITP-PAQ using general linear models was performed with pooled data from the two trials. Results from this analysis are provided in Table 6.4.7 and confirm that HRQoL benefits (differences in between-group change scores) of romiplostim occur regardless of splenectomy status (George et al., 2008). The reported F and P values and associated least square means were generated upon comparing data from romiplostim and placebo treated patients (Table 6.4.7). Results

indicate that, compared with placebo, romiplostim patients experience statistically significant improvements on seven of 10 ITP-PAQ scales. Compared with placebo, the romiplostim-treated patients showed significantly greater improvement ($p < 0.05$) in HRQoL on three of four physical health scales (Symptoms, Bother, and Activity), on two of two emotional health scales (Fear and Psychological), and on Social Activity, and Women's Reproductive Health scales (Menstrual Symptoms subscale). No differences in improvement between romiplostim and placebo groups were found for Fatigue, Overall QoL, Work, and Fertility.

Table 6.4.7. Mean ITP-PAQ change scores from baseline to week 24 using GLM repeated measure mixed models and pooled data to compare romiplostim- (n = 84) and placebo-treated patients (n = 41).

ITP-PAQ Scale	F	P	Least Square Means Estimate	Standard Error
Symptoms	12.96	0.0005	7.48	2.08
Bother	10.52	0.002	8.94	2.76
Fatigue	0.40	0.53	1.78	2.83
Activity	6.04	0.016	8.52	3.47
Fear	12.90	0.0005	7.13	1.99
Psychological	4.25	0.042	5.71	2.77
Work	0.05	0.82	1.11	4.79
Social Activity	9.57	0.0025	9.66	3.12
Women's Reproductive Health	10.98	0.002	12.88	3.89
Menstrual Symptoms	17.07	0.0001	24.23	5.86
Fertility	0.01	0.90	0.39	3.40
Overall Quality of Life	1.82	0.18	4.14	3.07

General linear models (GLM) analysis utilized ITP-PAQ data collected at baseline and weeks 4, 12, and 24. Age, gender, splenectomy status, and the use of baseline ITP medications were controlled for in these analyses. P values < 0.05 indicate that romiplostim-treated patients had significantly higher mean change scores (F value) than the placebo-treated patients.

EQ-5D change from baseline post-hoc results

A post-hoc analysis of the combined phase 3 clinical trial data revealed that changes in mean EuroQol (EQ-5D) Index and EuroQol visual analogue scale (EQ-5D VAS) scores were significantly higher from baseline to week 24 for patients receiving romiplostim versus placebo (Table 6.4.8).

EQ-5D scores for romiplostim patients improved from baseline to week 24, and differences in mean change-scores were statistically significant between romiplostim and placebo patients (Table 6.4.8). Additionally, adjusted-mean changes from baseline for patients with platelet counts > $50x10^9$/l or > $30x10^9$/l (responders) during the last 4 weeks of the study were significantly higher than those with platelet counts < $50x10^9$/l or < $30x10^9$/l (non-responders) during the same trial period.

Table 6.4.8. EQ-5D Change Scores, Baseline to Week 24

		Mean (SD) Change from Baseline[a]				
	N	Romiplostim (n = 84)	N	Placebo (n = 41)	Difference between Groups	P value[b,c]
EQ-5D INDEX	76	0.03 (0.17)	41	-0.03 (0.16)	0.06	0.017
EQ-5D VAS	73	6.01 (16.15)	41	1.10 (18.14)	4.91	0.041
		Mean (SE) Change from Baseline[a]				
		Responders, platelets > $50x10^9$/l (N = 62)		Non-responders, platelets < $50x10^9$/l (N = 63)		
EQ-5D INDEX	60	0.05 (0.02)	57	-0.01 (0.02)	0.06	0.055
EQ-5D VAS	58	6.75 (2.53)	56	0.79 (2.35)	5.96	0.015
		Responders, platelets > $30x10^9$/l (N = 85)		Non-responders, platelets < $30x10^9$/l (N = 40)		
EQ-5D INDEX	81	0.03 (0.02)	36	-0.01 (0.03)	0.04	0.065
EQ-5D VAS	78	6.87 (2.08)	36	-3.29 (2.88)	10.16	0.001

[a] For responder vs. non-responder analyses, adjusted for age (<40, 40-65, >65 years) and gender.

[b] For placebo vs. romiplostim analysis, linear regression using final score as dependent variable adjusted for ntent-to-treat analysis by treatment.

[c] For responder vs. non-responder analyses, linear regression using final score as dependent variable eline score, age (<40, 40-65, >65 years), and gender.

6.5 Meta-analysis

Where more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. If a meta-analysis is not considered appropriate, the rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal. If any of the relevant RCTs listed in response to section 0 are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored. The following steps should be used as a minimum.

- *Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.*
- *Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).*
- *Provide an adequate description of the methods of statistical combination and justify their choice.*
- *Undertake sensitivity analysis where appropriate.*
- *Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).*

There is one phase 3 RCT for romiplostim-plus-standard-of-care versus placebo-plus-standard-of-care in each of the key ITP populations: non-splenectomised patients and splenectomised patients. Therefore no meta-analysis is required for romiplostim.

Data on the comparator treatments is derived from single-arm studies and so no formal meta-analysis can be done. Where there is more than one relevant study for a treatment, estimates of efficacy are combined by taking a weighted average, weighting by sample size.

6.6 Indirect / mixed treatment comparisons

Data from head-to-head RCTs should be presented in the reference-case analysis, if available. If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used. An 'indirect comparison' refers to the synthesis of data from trials in which the technologies of interest have not been compared in head-to-head trials, but have been compared indirectly using data from a network of trials that compare the technologies with other interventions.
When head-to-head RCTs exist, evidence from mixed treatment comparison analyses may be presented if it is considered to add information that is not available from the head-to-head comparison. A 'mixed treatment comparison' refers to an analysis that includes trials that compare the interventions of interest head-to-head and trials that compare them indirectly. This mixed treatment comparison must be fully described and presented as additional to the reference-case analysis (a 'mixed treatment comparison' includes trials that compare the interventions head-to-head and indirectly).

When multiple technologies are being appraised that have not been compared within a single RCT, data from a series of pairwise head-to-head RCTs should be presented. Consideration should also be given to presenting a combined analysis using a mixed treatment comparison framework if it is considered to add information that is not available from the head-to-head comparison.

The principles of good practice for standard meta-analyses should also be followed in mixed and indirect treatment comparisons.

- *When evidence is combined using indirect or mixed treatment comparison frameworks, trial randomisation must be preserved. Where this is not possible the data should be treated as observational.*
- *Provide a clear description of the methods of synthesis*
- *Provide a rationale for the identification and selection of the RCTs, including the rationale for the selection of treatment comparisons that have been included.*
- *Perform a statistical assessment of heterogeneity. The degree of, and the reasons for, heterogeneity should be explored as fully as possible*
- *The methods and results of the individual trials should be documented. If there is doubt about the relevance of a particular trial, sensitivity analysis should also be presented in which these trials are excluded.*
- *The heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies should be reported.*
- *Evidence from a mixed treatment comparison may be presented in a variety of ways such as in tables or diagrams.*

As discussed in Section 6.0, with the exception of romiplostim phase 3 trials, there are no RCTs assessing comparator treatments, other than a small number of studies comparing IVIg or anti-D to corticosteroid strategies (see Section 6.8 for details). This lack of placebo-controlled trials involving other ITP treatments, in addition to the complexity of the treatment paradigm for ITP and the heterogeneity of the data, makes it difficult to undertake a formal indirect mixed treatment comparison (for example using Bayesian networks).

Therefore, our approach to the economic evaluation is to compare two treatment pathways: 1) a standard care pathway in which treatments are ordered to match usual care as closely as possible (using information from the clinical guidelines together with a survey of expert clinicians); and 2) a similar pathway which incorporates romiplostim.

Data used in the base-case cost-effectiveness analysis is taken from the study types that are available for each comparator; these are mainly single-arm studies such as cohort studies and case series. Sensitivity analyses have been used adjusting estimates obtained from the various data sources to account for the uncertainty in the data.

6.7 Safety

This section should provide information on the safety of the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, they may demonstrate that the technology shows a relative lack of adverse effects commonly associated with the comparator, or the occurrence of adverse effects not significantly associated with other treatments.

If any of the main trials are designed primarily to assess a safety outcome (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse effect), these should be reported here in the same detail as described in the previous sections relating to the efficacy trials.

Give a brief overview of the safety of the technology in relation to the decision problem. Give incidence rates of adverse effects if appropriate.

Executive summary for safety of romiplostim

The adverse event profile of romiplostim has been reviewed in the two phase 3 randomised controlled studies. Long term assessment of adverse events has been performed on patients that have participated in the open label extension (20030213) study.

6.7.1 Safety of romiplostim

Pivotal Phase 3 RCTs of Romiplostim

Safety data from the pivotal phase 3 RCTs of romiplostim (Section 6.3) are summarised below:

Splenectomised patients (Study 20030105): Similar proportions of patients experienced adverse events (100% romiplostim of 42 patients, 95% placebo of 21 patients). Severe adverse events occurred in a similar percentage of patients in each group (36% romiplostim, 33% placebo); 2 patients (5%) receiving romiplostim and no patients receiving placebo experienced life-threatening adverse events (GI haemorrhage and a suicide attempt) (Table 6.7.1).

Non-splenectomised patients (Study 20030212): The percentage of patients experiencing adverse events was similar in the 2 treatment groups: 100% of the romiplostim group (n=42 patients) and 95% of the placebo group (of 20 total patients). Adverse events that were graded severe or life threatening occurred in a similar percentage of patients in each group (severe – 19% romiplostim, 25% placebo, life threatening – 2 (5%) romiplostim, 1 (5%) placebo (romiplostim: CVA and B-cell lymphoma; placebo: autoimmume haemolytic anaemia) – Table 6.7.1).

Table 6.7.1 Adverse Event Severity (Phase 3 Studies)

	20030105		20030212		Both	
Subject Reporting:	Romiplostim N=42 n (%)	Placebo N=21 n (%)	Romiplostim N=42 n (%)	Placebo N=20 n (%)	Romiplostim N=84 n (%)	Placebo N=41 n (%)
Any Adverse Event	42(100)	20(95)	42(100)	19(95)	84(100)	39(95)
AE with Severity of:						
Severe	15(36)	7(33)	8(19)	5(25)	23(27)	12(29)
Life-threatening[a]	2(5)	0(0)	2(5)	1(5)	4(5)	1(2)
Fatal [a]	0(0)	3(14)	1(2)	0(0)	1(1)	3(7)

AE = Adverse Event. A subject can be counted in more than one category of severity grade. Only adverse events starting after the first dose of investigational product are tabulated.

[a]One subject receiving romiplostim (6051, study 20030212) had both a life-threatening adverse event (cerebrovascular accident) and a fatal adverse event (haemorrhage intracranial).

One patient in the 20030212 study randomised to placebo received 3 doses of romiplostim and was included in the romiplostim group regarding the safety endpoints.

Sources: Amgen. Clinical Summary of Safety 2007;[67] Amgen Study Report 20030212;[66] Amgen Study Report 20030105;[65] Data on file, Amgen.

The most common adverse events and adverse events with a ≥ 10 percent higher incidence in the pooled romiplostim treatment group are shown in Table 6.7.2 below.

Table 6.7.2 Pooled Adverse Event Summary (Phase 3 Studies)

Adverse Event (AE)	Romiplostim N=84 n (%)	Placebo N=41 n (%)
Most Common AEs		
Headache	29(35)	13(32)
Fatigue	28(33)	12(29)
Epistaxis	27(32)	10(24)
AEs with > 10% difference		
Dizziness	14(17)	0(0)
Myalgia	12(14)	1(2)
Abdominal pain	9(11)	0(0)

AE = Adverse Event
Source: Amgen Clinical Summary of Safety 2007; Data on file, Amgen[67]

[redacted]

Table 6.7.3 Treatment-Related Adverse Events (Phase 3 Studies)

	20030105		20030212		Both	
	Romiplostim N=42 n (%)	Placebo N=21 n (%)	Romiplostim N=42 n (%)	Placebo N=20 n (%)	Romiplostim N=84 n (%)	Placebo N=41 n (%)
Patients Reporting Any Treatment-Related AE	[redacted]					
Patients Reporting Treatment-Related AE with Severity of:						
Severe	[redacted]					
Life-threatening	[redacted]					
Fatal	[redacted]					

AE = Adverse Event

Sources: Amgen. Clinical Summary of Safety 2007;[67] Amgen Study Report 20030212;[66] Amgen Study Report 20030105;[65] Data on file, Amgen.

Adverse Drug Reactions - Phase 3 studies

Adverse drug reactions (ADRs) are defined in 21 CFR 201.57(c) (7) as undesirable effects reasonably associated with use of a drug, which may occur as part of the pharmacological action of the drug or be unpredictable in occurrence. Adverse events with ≥ 5 percent difference between romiplostim and placebo groups were considered ADRs in romiplostim phase 3 clinical trials.[67]

Headache was considered an ADR even though it did not meet criteria for ≥ 5 percent difference between romiplostim and placebo groups. It was the most common adverse drug reaction among romiplostim patients, was usually mild to moderate in severity and typically relieved by non-narcotic medications.36 Arthralgia, dizziness and insomnia were most common ADRs with ≥ 5% difference between romiplostim and placebo (Table 6.7.4).[67]

Table 6.7.4 Adverse Drug Reactions (Phase 3 Studies)

Adverse Drug Reaction	Romiplostim n=84 (%)	Placebo n=41 (%)
Headache	29(35)	13(32)
Arthralgia	22(26)	8(20)
Dizziness	14(17)	0(0)
Insomnia	13(15)	3(7)
Myalgia	12(14)	1(2)
Pain in Extremity	11(13)	2(5)
Abdominal Pain	9(11)	0(0)
Shoulder Pain	7(8)	0(0)
Dyspepsia	6(7)	0(0)
Paraesthesia	5(6)	0(0)

Source: Amgen Clinical Summary of Safety 2007; Data on file, Amgen[67]

Less common adverse drug reactions included recurrent thrombocytopenia after cessation of treatment, increased bone marrow reticulin and thrombocytosis (increased platelet count above the normal range).[68] These adverse drug reactions are discussed more specifically later in this section.

Serious adverse events, fatalities and withdrawals - Phase 3 studies

In the pivotal studies, a numerically higher percentage of placebo patients had serious and fatal adverse events compared with romiplostim patients (Table 6.7.5). As discussed previously, two patients in the romiplostim group reported 3 serious adverse events that were considered related to investigational product; bone marrow disorder, peripheral embolism, and peripheral ischaemia. No placebo treated patients reported a treatment-related serious adverse event.

One placebo treated patient withdrew from the study because of metastases to the liver. Three (4%) romiplostim-treated patients withdrew from a phase 3 study; 1 each due to a B-cell lymphoma, bone marrow disorder, or an intracranial haemorrhage (fatal).

Table 6.7.5 Serious Adverse Events, Fatalities, and Withdrawals (Phase 3 Studies)

	20030105		20030212		Both	
	Romiplostim N=42 n (%)	Placebo N=21 n (%)	Romiplostim N=42 n (%)	Placebo N=20 n (%)	Romiplostim N=84 n (%)	Placebo N=41 n (%)
Patients Reporting Any Serious Adverse Events	9(21)	5(24)	5(12)	3(15)	14(17)	8(20)
Fatal	0(0)	3(14)	1(2)	0(0)	1(1)	3(7)
Patients Reporting Any Treatment-Related Serious Adverse Events	2(5)	0(0)	0(0)	0(0)	2(2)	0(0)
Patients Who Withdrew from Study Due to AE	1(2)	0(0)	2(5)	1(5)	3(4)	1(2)

Sources: Amgen Clinical Summary of Safety,[67] Amgen Study Report 20030212;[66] Amgen Study Report 20030105.[65] Data on file, Amgen

Deaths - Phase 3 studies

Among phase 3 study participants, three splenectomised patients in the placebo group and one non-splenectomised patient in the romiplostim group died. The causes of death were pneumonia (after the end of study and more than 30 days after the last dose of investigational product), pulmonary embolism, and cerebral haemorrhage for placebo patients, and intracranial haemorrhage (two weeks after discontinuation of study drug) for the romiplostim treated patient.

[redacted]

Table 6.7.6. Number of Patients Exposed to Romiplostim by Duration of Overall Exposure (ITP Safety Set)

Duration of Overall Exposure	Romiplostim N =204 n (%)
1 wk to < 26 wks	76 (37)
≥ 26 wks to < 52 wks	54 (26)
≥ 52 wks	74 (36)

The ITP safety set consists of all patients who received investigational product in an ITP study (20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050123, or 20050162).
Duration of overall exposure (weeks) = (last dose date - first dose date + 7) / 7. If a subject is enrolled in multiple studies, this is the sum of treatment durations of individual studies.

[redacted]

[redacted]

Table 6.7.7. Overall Summary of Adverse Events (ITP Safety Set)

	Placebo (N = 46) n (%)	Romiplostim (N = 204) n (%)
Patients Reporting Any Adverse Events	[redacted]	[redacted]
Patients Reporting Adverse Events with Severity of		
Severe Life-threatening Fatal	[redacted]	[redacted]
Patients Reporting Any Serious Adverse Events	[redacted]	[redacted]
Patients Reporting Any Treatment-Related Adverse Events	[redacted]	[redacted]
Patients Reporting Treatment-Related Adverse Events with Severity of		
Severe Life-threatening Fatal	[redacted]	[redacted]
Patients Reporting Any Treatment-Related Serious Adverse Events	[redacted]	[redacted]
Patients Who Withdrew from Study Due to Adverse Events	[redacted]	[redacted]

The ITP safety set consists of all patients who received investigational product in an ITP study (20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050123, or 20050162).

N = number of patients who received at least one dose of investigational product over the course of all ITP studies.

Thirty-five patients who started on placebo and later received romiplostim were counted in both treatment groups. Adverse events were assigned to treatment group by start date of the event.

A subject can be counted in more than one category of severity grade.

[redacted]

[redacted]

For serious adverse events, thrombocytopenia and platelet count decrease had the highest study duration-adjusted event rates. Thrombocytopenia had a rate of 0 for patients who received placebo compared with 8.6/100 subject-years on study for patients who received romiplostim while platelet count decrease had a rate of 40.4/100 subject-years on study for patients who received placebo compared with 2.1/100 subject-years on study for the patients who received romiplostim.[redacted]

[redacted]

Deaths

Eight patients died during a romiplostim ITP clinical study; 3 (7%) placebo patients and 5 (2%) romiplostim patients; none of the deaths were considered treatment-related. These incidence rates correspond to a study duration-adjusted event rate for fatal adverse events of 15.2/100 subject-years on study and 2.7/100 subject-years on study for subjects while receiving placebo and romiplostim, respectively. Causes of death among placebo patients included primary atypical pneumonia, pulmonary embolism, and cerebral haemorrhage. Among romiplostim patients, causes of death included intracranial haemorrhage, pneumococcal pneumonia, cardiac arrest, hepatic failure/renal failure, and acute respiratory distress syndrome.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Special Warning and Precautions

The following special warnings and precautions are topics covered in the draft Summary of Product Characteristics. They have either actually been observed or are potential class effects based on the pharmacological mechanism of action of thrombopoietin (TPO) receptor stimulators.

Identified Risks

Reoccurrence of thrombocytopenia and bleeding after cessation of treatment

Thrombocytopenia is likely to reoccur upon discontinuation of treatment with romiplostim. There is an increased risk of bleeding if romiplostim treatment is discontinued in the presence of anticoagulants or anti-platelet agents. Patients should be closely monitored for a decrease in platelet count and medically managed to avoid bleeding upon discontinuation of treatment with romiplostim. It is recommended that, if treatment with romiplostim is discontinued, ITP treatment be restarted according to current treatment guidelines. Additional medical management may include cessation of anticoagulant and/or antiplatelet therapy, reversal of anticoagulation, or platelet support.

Increased Reticulin in the Bone Marrow[67;68]

Increased bone marrow reticulin is believed to be a result of TPO receptor stimulation, leading to an increased number of megakaryocytes in the bone marrow, which may subsequently release cytokines. Increased reticulin may be suggested by morphological changes in the peripheral blood cells and can be detected through bone marrow biopsy. Therefore, examinations for cellular morphological abnormalities using peripheral blood smear and complete blood counts (CBC) prior to and during treatment with romiplostim are recommended.

[redacted]

If a loss of efficacy and abnormal peripheral blood smear is observed in patients, administration of romiplostim should be discontinued, a physical examination should be performed, and a bone marrow biopsy with appropriate staining for reticulin should be considered. If available, comparison to a prior bone marrow biopsy should be made. If efficacy is maintained and abnormal peripheral blood smear is observed in patients, the physician should follow appropriate clinical judgment, including consideration of a bone marrow

biopsy, and the risk-benefit of romiplostim and alternative ITP treatment options should be re-assessed.

Potential Risks

Thrombotic/Thromboembolic Complications

[redacted]

Platelet counts above the normal range may present a theoretical risk for thrombotic / thromboembolic complications. The incidence of thrombotic / thromboembolic events observed in clinical trials was similar between romiplostim and placebo and an association between these events and elevated platelet counts was not observed. Dose adjustment guidelines should be followed.[68]

Progression of Existing Myeloid Malignancies or Myelodysplastic Syndromes (MDS)

TPO receptor stimulators are growth factors that lead to thrombopoietic progenitor cell expansion, differentiation, and platelet production. The TPO receptor is predominantly expressed on the surface of cells of the myeloid lineage. For TPO receptor stimulators there is a theoretical concern that they may stimulate the progression of existing haematopoietic malignancies or MDS.

Romiplostim is not indicated for the treatment of thrombocytopenia due to MDS or any other cause of thrombocytopenia other than ITP. The risk-benefit profile for romiplostim has not been established in MDS or other non-ITP patient populations. In a single-arm, open-label clinical study of treatment with romiplostim in patients with MDS, there were reported cases of progression to acute myeloid leukaemia (AML), however this is an expected clinical outcome of MDS and the relationship to romiplostim treatment is unclear. In addition, cases of transient blast cell increases were observed in this study. The transient blast cell increases were reversible upon discontinuation of romiplostim. Therefore this observation is inconsistent with progression to AML. It is not possible to distinguish leukaemic blasts from normal blasts.

[redacted]

6.7.2 Safety of comparator treatments

Corticosteroids

Corticosteroids are licensed for use in ITP.

Adverse events or long-term complications affect nearly three-quarters of ITP patients receiving corticosteroids.[27;28] Adverse events and complications attributable to corticosteroids include: diabetes, hypertension, osteoporosis, anxiety, insomnia, gastritis, infections, fractures, obesity and excessive weight gain, psychosis, depression, headache, cramps, and alopecia.[1;11;28;29;41;70-75] In a study of 201 ITP patients receiving corticosteroids for an average of 2 ± 0.7 months, 70 percent had at least one adverse event, among which nervousness/insomnia and weight gain were most common (Table 6.7.8). The mean age of the treated patients was 43 years, and more than 2/3 of patients were female. Initial daily dose was 1.5 mg/kg followed by tapering after a month.[28]

Table 6.7.8 Corticosteroid-related Adverse Events in Adult ITP (N = 118)

Corticosteroid-related Adverse Events	
Nervousness/insomnia (23%)	Acne (8%)
Weight gain (20%)	Hypertension (3%)
Epigastralgia (15%)	Psychiatric complications (3%)
Bacterial infections (14%)	Myopathy (2%)
Muscle pain and weakness (13%)	Gastrointestinal haemorrhage (1%)

Zimmer et al, 2004[28]

ITP patients who receive corticosteroids are at higher risk for serious co-morbidities than those who do not receive corticosteroids. The one-year incidence is twice as high for diabetes mellitus (DM), obesity, and gastrointestinal (GI) bleeds and three times as high for myocardial infarction (MI) for ITP corticosteroid users compared to non-users. These findings are based on an analysis of medical claims for 2,454 adult ITP patients, 618 who were corticosteroid users, compared to age-and gender-matched non-ITP controls (N = 21,196).[29]

Oral corticosteroid use among ITP patients also is associated with increased risk of cataracts. Among 760 ITP patients studied between 1992 and 2005, the incidence of cataracts among corticosteroid users was 14.0 per 1,000 person-years, compared to 6.1 per 1,000 person years for non-users.[76]

The risk of complications increases as the duration of corticosteroid use increases. For each additional day of corticosteroid use, there is a 0.5 percent increased risk of osteoporosis, hypertension (HTN), DM, and anxiety/depression. ITP patients receiving > 60 days of corticosteroids are over twice as likely to develop osteoporosis, DM, and HTN than ITP patients using corticosteroids for less than 60 days, and the incidence of co-morbid conditions increases with each additional corticosteroid treatment (Table 6.7.9).[29;77]

Table 6.7.9 Odds Ratios for Corticosteroid-related Complications in Adult ITP

Condition	Increased Risk (%)	Odds Ratio (OR)
Myocardial Infarction	14	OR=1.14, 1.01-1.30
Osteoporosis	14	OR=1.14, 1.06-1.22
Diabetes Mellitus	12	OR=1.12, 1.04-1.20
Hypertension	12	OR=1.12, 1.05-1.19
Obesity	11	OR=1.11, 1.01-1.21
Anxiety/Depression	7	OR=1.07, 1.00-1.14

Aledort et al, 2006[29]

Long-term use of systemic, high-dose corticosteroids may result in corticosteroid-induced lipodystrophy (CIL), categorized by adipose-tissue accumulation in the face ("moon face"), dorsocervical region ("buffalo hump"), and abdomen, and/or reduced subcutaneous fat thickness in the limbs.[78] In a prospective study of 88 patients who received 20 mg/day or higher doses of corticosteroids for a minimum of three months, the cumulative incidence of CIL at months 3 and 12 was 61% ±8% and 69% ± 9%, respectively. The risk of CIL at the third month was higher in women (OR: 10.87), patients younger than 50 years of age (OR: 11.11), patients with a high baseline body mass index (OR: 1.56), and patients with high energy intake (OR: 6.11).[78]

IVIg

IVIg is licensed for use in ITP.

As many as 75 percent of ITP patients experience adverse events, including mild headache, backache, nausea, cough, injection site reaction and fever.[25;32] Approximately 20 percent and 5 percent of adverse events experienced by ITP patients receiving IVIg are moderate and severe, respectively.[32]

US Food and Drug Administration (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.[32] 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. Finally, as a blood-derived product, IVIg may transmit infectious agents. 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.[79]

Anti-D

Anti-D is licensed for use in ITP.

In a single arm study of 98 ITP patients receiving a single dose of anti-D, approximately 70 percent of patients experience drug-related adverse events, most commonly mild to moderate in intensity.[31] Chills (34.7% of patients), pyrexia (26.5% of patients), increased blood bilirubin (21.4% of patients), and headache (14.3% of patients) are most common. Discontinuation rates as high as four percent have been reported.[30;34]

Among patients receiving anti-D, serious adverse reactions have been observed in ITP patients.[33] The available clinical literature and FDA prescribing information caution that the potential benefit of treatment with anti-D must be weighed against the risk of hypersensitivity reactions. FDA prescribing information for anti-D includes a black-box warning for potentially fatal (though uncommon) intravascular haemolysis (IVH) 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. Like IVIg, anti-D is derived from human plasma. Such products may carry a risk of transmitting infectious agents, and, theoretically, Creutzfeldt-Jakob disease (CJD).

Rituximab

Rituximab is not licensed for use in ITP. The long-term effects of rituximab in ITP patients have not been assessed in randomised controlled trials.

In a report across 19 studies including 306 ITP patients, approximately 22 percent of patients receiving rituximab experienced mild to moderate adverse events. The most common were infusion-related (17.9%). Ten patients experienced severe or life-threatening adverse events (3.7%).[36] Nine deaths (2.9%) were temporally associated with rituximab use, including three cases of fatal bleeding and one case of postoperative fatal pulmonary embolism, though causality was not determined. A summary of adverse events is provided in Table 6.7.10.

Table 6.7.10 Adverse Events (AEs) Associated with Rituximab Use in Adult ITP

Grade 1 or 2		Grade 3 or 4		Grade 5	
Rash or allergic reaction	2%	Pneumonia	1.3%	Respiratory failure	0.3%
Infusion-related	18%	Bronchospasm	0.3%	Pneumonia	0.3%
Serum sickness	0.3%	Anaphylactic reaction	0.3%	Haemorrhage	0.7%
Thrombocytosis	0.3%	Muscle pain	0.3%	Unknown	0.3%
Panniculitis	0.3%	Meningitis	0.3%	Hepatic failure	0.3%
Leg cramp/ diarrhoea	0.3%	Retinal artery thrombosis	0.3%	Infection	0.7%
		Pulmonary embolism	0.3%	Pulmonary embolism	0.3%

Adapted from Arnold, et al, 2007.[36]

In 2004, the US FDA reported that hepatitis B virus reactivation with fulminant hepatitis, hepatic failure, and death had been reported in some patients with haematologic malignancies treated with rituximab (FDA 2004). In 2006, a retrospective review at a single-centre found that one-third of patients with positive hepatitis B serology developed acute liver events when treated with rituximab alone or with chemotherapy. This correlation was more evident in patients with hepatitis B surface antigen (66% of these patients). Consequently, the authors concluded that hepatitis B serology screening should be performed prior to use of rituximab with or without chemotherapy treatment.[37] The extent to which these risks apply to the ITP population is

unknown. Rare cases of progressive multifocal leukoencephalopathy have been reported in NHL patients receiving rituximab, but the potential impact on ITP patients is unknown.[80]

Other treatments

For the following drugs, an extensive literature search has been performed and no randomised controlled clinical trials were found for these drugs in ITP:

- Danazol
- Azathioprine
- Ciclosporin
- Mycophenolate mofetil
- Cyclophosphamide
- Vincristine
- Dapsone

The publications described in this section are based on non-randomised studies and on a small number of patients from a single or a small number of centres. As a result, the adverse event data is not that of a modern randomised clinical trial where all events are captured, but instead only states events that led to discontinuation of the drug or more severe events. Therefore this data is subject to more variability and of lower quality compared to RCT data.

Danazol

Danazol is a synthetic steroid derived from ethisterone. It is licensed for the treatment of endometriosis and benign fibrocystic breast disease. Danazol is not licensed in ITP.

In a study reviewing 57 ITP patients treated with danazol, 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%).112 Danazol also may cause cytopenias, gastrointestinal symptoms, and acute thrombocytopenia.[81]

The adverse events listed in the danazol (Danol) SPC include the following:[82]

- androgenic effects – weight gain, acne
- hirsutism, hair loss
- menstrual disturbances, amenorrhoea which can be persistent
- backache and muscle cramps can be severe
- hypertension and tachycardia
- benign intracranial hypertension.

The frequency of these events were not listed.

Dapsone

Dapsone is indicated for the treatment of leprosy, dermatitis hepatiformis, and prophylactic prevention of malaria and pneumocystis carinii in combination with other drugs. Dapsone is not licensed for use in ITP.[83]

Damodar et al published a retrospective review on 55 adult ITP patients treated with dapsone. An overall response rate of 61.8% was observed in adults. Only 9 patients had a response greater then 6 months. Side effects requiring discontinuation of therapy were observed in three patients (note this figure may include children receiving dapsone).[84]

Godeau et al published results on 66 patients. A response was seen in 50%. Side effects were seen in 16 (24%) patients. Seven patients had to stop treatment due to methaemoglobinaemia (1 patient), rash (1), nausea and vomiting (2), haemolysis (1), headache and vomiting (1), and mild hepatitis (1). Other adverse events that did not require treatment to be stopped were nausea (7) and rash (4).[85]

The SPC states the following adverse events:[83]

- Haemolysis and methaemoglobinaemia are the most frequently reported adverse effects of dapsone and occur in most subjects given more than 200mg daily; doses of up to 100mg daily do not cause significant haemolysis
- Agranulocyctosis (rare)
- Stevens-Johnson syndrome (rare)
- A “dapsone syndrome” may occur after 3-6 weeks therapy; symptoms include rash, which is always present, fever, and eosinophilia. If dapsone is not stopped immediately, the syndrome may progress to exfoliative dermatitis, hepatitis, albuminuria and psychosis. Deaths have been recorded.
- Peripheral neuropathy

Azathioprine

Azathioprine is an immunosuppressant and is licensed to enhance organ survival in transplant patients. Azathioprine is not licensed for use in ITP.[86] Patients that receive immunosuppressants are at increased risk of infection. Use of azathioprine in ITP patients may cause weight gain, fluid retention, GI symptoms, leukopenia, thrombocytopenia, and lymphomas.[87;88]

The azathioprine SPC states that adverse events that are very common (i.e. occurring in >10% of patients) include:[86]

- Viral, fungal and bacterial infections
- Myelosuppression.

Ciclosporin

Ciclosporin is an immunosuppressant and is licensed to prevent graft rejection, psoriasis, atopic dermatitis, rheumatoid arthritis and nephritic syndrome. Ciclosporin is not licensed for use in ITP.[89]

Emilia et al[90] describe 12 ITP patients (8 had been treated by splenectomy) who were treated with ciclosporin 2.5-3 mg/kg per day for a median of 40 months. Two patients failed to respond. Side effects were reported to be moderate and transient. Side effects included moderate hypertension (3), fatigue (2), paraesthesia (2) gingival hyperplasia (3), myalgia (2), dyspepsia (2), hypertrichosis (1) and tremor (1). One patient developed candidiasis of the oropharynx and ciclosporin had to be discontinued.

Kappers-Klunne et al 2001[91] gave ciclosporin 5 mg/kg/day with prednisolone to twenty patients. Overall 6 (30%) patients discontinued ciclosporin due to side effects which were – hypertension, severe headache, muscle ache, raised creatinine, fatigue and nausea. Only 3 patients did not report any toxicity. Of the 11 patients who did not stop ciclosporin but did have adverse events they were as follows – hypertension (5), muscle ache (5, 2 patients had severe pain), headache (2), raised serum creatinine (2), gum hyperplasia (1), nausea (1) and paraesthesia (2).

Ciclosporin is associated with the following adverse events according to the SPC:[89]

- renal impairment, tends to occur in the first few weeks of treatment and is usually reversible on dose reduction. Particular care has to be take in elderly patients
- predisposes patients to infection
- increases risk of malignancies including lymphoma and skin cancer
- very common side effects (>10%) include – hyperlipidaemia, hypercholesterolaemia, tremor, hypertension and renal dysfunction.
- common side effects (1-10%) include – nausea, vomiting, diarrhoea, hepatic dysfunction, hyperkalaemia, hypomagnesaemia, myalgia, paraesthesia

Ciclosporin interacts with a large number of drugs which may increase or decrease its levels and hence may cause increased toxicity or reduced efficacy, that latter which could potentially put the patient at risk of a severe bleed. Drugs which increase plasma levels include oral contraceptives, danazol and high dose methylprednisolone which ITP patients may receive.

Mycophenolate mofetil (MMF)

Mycophenolate mofetil is an immunosuppressant and is licensed to be used in conjunction with ciclosporin and corticosteroids to prevent acute transplant rejection. MMF is not licensed for use in ITP.[92]

Provan et al administered MMF at an initial dose of 250mg bd gradually titrated up to 1g bd to 18 patients (1 patients was 4 years old). All but 1 of the patients had undergone a splenectomy. No severe toxicity was seen, although two of the 18 patients discontinued MMF within the first month of treatment because of side effects, i.e., headache. Another patient could not tolerate the 1g bd dose due to headaches.[93]

Hou et al gave MMF 1.5-2 g/day to 21 patients. MMF was well tolerated with only slight nausea and diarrhoea recorded in 3 of 21 cases. No premature withdrawal was found in this study.[94]

MMF is indicated to be used in combination with ciclosporin and prednisolone to prevent acute rejection in patients receiving an allogeneic transplant. Therefore adverse events as a single agent have not been reported in the

SPC. The SPC states that MMF therapy is associated with the following adverse events:[92]

- increases risk of malignancies including lymphoma and skin cancer
- bone marrow suppression
- predisposes patients to infection which may be fatal
- cases of progressive multifocal leukoencephalopathy which can be fatal

Cyclophosphamide

Cyclophosphamide is an alkylating agent and is not licensed for use in ITP.

Reiner et al gave pulsed cyclophosphamide to 20 patients with refractory ITP (patients had failed to achieve remission after a mean of 4.8 prior treatments). Patients received 1-4 doses (mean 2) of 1-1.5g/m2 IV cyclophosphamide. Adverse events included neutropenia (three patients, one of whom developed staphylococcal sepsis), acute deep venous thrombosis (two patients), and psoas abscess (one patient). No patients had developed a secondary malignancy after a median follow up of 2 years.[95]

Cyclophosphamide is an alkylating agent which is frequently used in combination with other chemotherapy agents to treat various cancers. Cyclophosphamide is associated with:[96]

- myelosuppression which can lead to neutropenic sepsis which may be fatal
- amenorrhoea and azoospermia which may not be reversible
- haemorrhagic cystitis
- alopecia
- mucositis
- nausea and vomiting

Secondary malignancies such as acute myeloid leukaemia have been reported in breast cancer patients, usually within 5 years of administration post cyclophosphamide with an anthracycline.[97]

Vincristine

Vincristine is a vinca alkaloid and is not licensed for use in ITP.

Linares et al. published a letter involving 8 patients who were refractory to steroids but not splenectomised that were given vincristine 1mg every week for 4 weeks. Four patients had a response for more then 3 months, 3 patients had a response less then 3 months, and 1 patient did not respond. The letter states that all patients tolerated the treatment without side effects.[98]

In a collective review by Pizzuto 19 patients received vincristine 1-2 mg every 1-2 weeks for a minimum of four doses. All these patients had been previously treated with steroids and splenectomy. Fifteen patients (79%) did not respond, 2 patients responded then relapsed after 3 months, and 2 patients responded and relapsed within 3 months. Six patients (32%) developed neuropathy although the severity is not recorded.[99]

Vincristine is a vinca alkaloid that is a chemotherapy agent which is often used in combination with other chemotherapy drugs to treat various cancers.

The vincristine SPC states the following adverse events when used as a single weekly agent including:[100]

- leucopenia
- neuritic pain
- alopecia
- paraesthesia
- muscle wasting

Adverse events relating to the splenectomised population

Surgical complication rates range from 16 percent for laparoscopic to 27 percent for open splenectomy and mortality rates range from 0.2 percent to 3.5 percent.[39] In a study of 78 ITP patients who underwent splenectomy, 26 percent experienced early postoperative complications resulting in prolonged hospitalisation or re-admissions, and 5 percent had late complications.[40] Three patients (4%) had septic events, one of which resulted in death. Despite the use of vaccinations, prophylactic antibiotic use, and less invasive approaches, splenectomy may result in early and late postoperative morbidity for patients with ITP.[27]

Complications among splenectomised patients are significantly higher among patients older than 60.[101] In a retrospective review of 55 patients, the majority of patients (9/12) who experienced complications were older than 60 ($p < 0.02$), and all elderly patients reported complications after splenectomy.[101]

All studies considered regarding adverse event data for the comparators has been recorded in a separate excel file (not part of this document) sent to NICE with this submission.

6.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available.

Inferences about relative treatment effects drawn from non-RCT evidence will necessarily be more circumspect than those from RCTs with properly controlled evidence. The bias that may be present in non-randomised data means the results should be interpreted cautiously. When possible, the use of more than one independent source of such evidence needs to be examined to gain some assurance of the validity of any conclusions drawn.

Executive summary for non-RCT evidence

Studies assessing comparator treatments in ITP were identified via a literature review plus references from existing ITP guidelines and reviews. Most studies were uncontrolled studies such as case series (level 3 evidence). There were also a small number of RCTs comparing IVIg or anti-D to corticosteroids. Most studies assessed overall platelet response, generally defined only using a platelet threshold of 50 x 10^9/l, although a few studies used different thresholds. Some studies also reported duration of response, or the proportion of patients still responding at a later time point. Data from these studies was synthesised in order to model the efficacy of the various treatments in the patient pathway.

6.8.1 Details of how the relevant non-RCTs have been identified and selected

As discussed in Section 6.0, with the exception of romiplostim phase 3 trials, there are very few RCTs comparing ITP treatments to placebo. Therefore, a search was undertaken for any type of study assessing the effectiveness of the comparators in ITP.

Due to the diversity of the clinical evidence for all the comparator treatments, it was not feasible to conduct an extensive and full systematic search and identify all studies for all comparator treatments. Therefore a pragmatic approach has been used to identify relevant studies that provide valid clinical evidence to address the decision problem, described as follows:

1) The current clinical guidelines (ASH and BCSH) were used to identify clinical studies:
    - British Committee for Standards in Haematology (BCSH) Guideline for Management of ITP (Provan et al 2003)[2]
    - American Society of Hematology (ASH) Practice Guideline for ITP (George et al 1996)[1]

2) Recent reviews of ITP and systematic reviews of specific treatments were used to ensure the clinical evidence included most recent estimates of efficacy and safety for those outcomes noted in the decision problem; key reviews included:
    - Vesely 2004 systematic review of treatments post-splenectomy[52]
    - Godeau 2007 literature review of ITP treatments[3]
    - Cines & Bussel 2005 review of ITP treatments[6]

- Cines & Blanchette 2002 review of ITP treatments[43]
- Arnold 2007 systematic review of rituximab for ITP[36]
- Zhou 2008 systematic review of rituximab for ITP[53]
- Maloisel 2004 literature review of danazol for ITP[54]
- Bierling & Godeau 2004 & 2005 reviews of IVIg safety[55;56]

3) Clinical evidence reported from the original studies included in these reviews and guidelines have been obtained.

4) In addition, a literature search has been undertaken to identify any key clinical studies in the relevant comparators published since the review by Godeau et al 2007[3] (or since the most relevant review for each individual treatment; see below). Please see Appendix 2 for details of the search terms and databases searched. Studies were excluded if they related to secondary thrombocytopenia associated with other conditions, ITP in childhood or pregnancy, or if they included less than 5 patients.

The specific approaches for identifying relevant studies for each individual comparator treatment vary according to the systematic reviews already in existence, and are described for each treatment as follows.

IVIg

The ASH guidelines (1996)[25] included a literature search undertaken in April 1994. In addition, the efficacy of IVIg has been described in the BCSH guidelines[2] and other recent reviews. We hand-searched the reference lists of the other reviews and guidelines listed above, and undertook a literature search of papers published from 1994 onwards (including those published in abstract form only).

Anti-D

The ASH guidelines (1996)[25] undertook a literature search in April 1994. In addition, the efficacy of anti-D has been described in the BCSH guidelines[2] and other recent reviews. We hand-searched the reference lists of the other reviews and guidelines listed above, and undertook a literature search from 2006 onwards to identify any papers published since the Godeau et al (2007)[3] review.

Rituximab

There are a number of recent reviews assessing the efficacy and safety of rituximab in ITP. These include the systematic review by Arnold et al (2007),[36] a review of all studies of 10 or more patients by Zhou et al (2008),[53] and the systematic review of ITP treatments post-splenectomy by Vesely et al (2004).[52] We undertook a literature search for papers published since Arnold et al undertook their search in 2006.

Danazol

Maloisel et al (2004),[54] in addition to undertaking a study of danazol in ITP, also conducted a literature search of previous studies of danazol in ITP. In addition, use of danazol post-splenectomy was assessed in the systematic review by Vesely et al (2004).[52] We also hand-searched the reference lists of the other reviews and guidelines listed above, and undertook a full literature search for additional papers.

Dapsone

Published literature searches for studies of dapsone in ITP were undertaken by Godeau et al (2007)[3] and in the post-splenectomy setting by Vesely et al (2004). We hand-searched the reference lists of the other reviews and guidelines listed above, and undertook a literature search from 2006 onwards to identify any papers published since the Godeau et al (2007) review.

Azathioprine

Vesely et al (2004)[52] undertook a review of post-splenectomy patients receiving azathioprine. We hand-searched the reference lists of the other reviews and guidelines listed above, and undertook a full literature search for additional papers.

Mycophenolate mofetil

Published literature searches for studies of mycophenolate mofetil in ITP were undertaken by Godeau et al (2007)[3] and in the post-splenectomy setting by Vesely et al (2004).[52] We hand-searched the reference lists of the other reviews and guidelines listed above, and undertook a literature search from 2006 onwards to identify any papers published since the Godeau et al (2007) review.

Ciclosporin

Published literature searches for studies of ciclosporin in ITP were undertaken by Godeau et al (2007)[3] and in the post-splenectomy setting by Vesely et al (2004).[52] We hand-searched the reference lists of the other reviews and guidelines listed above, and undertook a literature search from 2006 onwards to identify any papers published since the Godeau et al (2007) review.

Cyclophosphamide

We hand-searched the reference lists of the reviews and guidelines listed above, and undertook a literature search of papers published from 2006 onwards to identify any papers published since the Godeau et al (2007)[3] review.

Vinca alkaloids

We hand-searched the reference lists of the reviews and guidelines listed above, and undertook a literature search of papers published from 2006 onwards to identify any papers published since the Godeau et al (2007)[102] review.

6.8.2 Summary of methodology of relevant non-RCTs

Data on most of the comparator treatments is derived from single-arm case series and cohort studies. Most of the relevant studies are unblinded and have no control group. It has been shown that unblinded studies tend to overestimate the efficacy outcomes (Shultz 1995, Chalmers 1983). Therefore, the efficacy of the comparators may be overestimated compared to the efficacy of romiplostim reported in the RCTs discussed in Section 6.4.

The outcomes used and the exact definitions of these outcomes vary between studies. Results of the primary efficacy outcome endpoint used in the romiplostim trials (percentage of patients with a platelet response in 6 of the last 8 weeks of treatment in the absence of administration of rescue therapy

during the entire 24 treatment period) were not available for any of the comparator interventions.

However most studies present data on the following outcomes, and these are used in the economic modelling:

- Percentage of patients with overall platelet response, where platelet response is generally defined as reaching a threshold; the platelet threshold reported is generally 50 x 10^9/l. Some studies use 30 x 10^9/l or other thresholds. However, most studies do not report response rates based on a threshold of 30 x 10^9/l or 20 x 10^9/l, and therefore it is very difficult to compare data on anything but the 50 x 10^9/l threshold. (This outcome most closely but not exactly resembles the outcome of overall response defined in the romiplostim trials)
- Time from treatment initiation to platelet response
- Proportion of patients with durable or long-term response, and/or duration of response (only available from studies with long-term follow-up)

A small number of studies report data on number of repeat treatments or on reduction in other therapies, but these outcomes are not consistently reported. Very few studies report the incidence of bleeding events (although this is a clinically relevant outcome, numbers of bleeding events in small studies are likely to be low, and so platelet response is generally used as a proxy outcome).

In addition, some studies report on adverse effects of treatment and mortality, although the quality of reporting of safety data is variable. It is not clear whether estimates of adverse effects are accurate, and it is possible that older publications and publications based on small case series may under-report adverse effects in comparison to more recent publications based on larger RCTs.

The methodology of studies for each comparator is described under Section 6.8.4 below. Few RCTs were found.

6.8.3 Critical appraisal of relevant non-RCTs

There are few reliable methods for critically appraising studies such as case series. Rather than attempting to undertake a formal critical appraisal on all studies, our approach is to try to take account of the fact that efficacy data on comparator treatments is only available from unblinded, uncontrolled studies. These studies are frequently of poor quality, and this type of study is likely to overestimate treatment effects while under-reporting safety data.[49;50] However, this is the only type of data available for most of the comparator interventions.

6.8.4 Results of the relevant non- RCTs

A summary of results of studies for the comparator treatments included in this assessment are shown in Table 6.8.3 below. Please see the Excel file "Efficacy data on ITP comparator treatments" for full details of all included studies on comparators. Adverse events are not discussed here; they are described in Section 6.7.

Overall summary of results

For the majority of comparator treatments, there are no RCTs or controlled studies of any kind in ITP, and the literature consists mainly of a number of uncontrolled case series. For IVIg and anti-D, there are a few RCTs comparing to corticosteroid treatment strategies (see below). The levels of evidence for intervention studies, as described in the NICE Guideline Development Methods document,[103] are shown in Table 6.8.1. The level of evidence available for each comparator, as identified in our literature review, is shown in Table 6.8.2.

Table 6.8.1: Levels of evidence for intervention studies, as defined by NICE[103]

Level of evidence	**Type of evidence**
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*
2++	High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2-	Case–control or cohort studies with a high risk of confounding bias, or chance and a significant risk that the relationship is not causal*
3	Non-analytic studies (for example, case reports, case series)
4	Expert opinion, formal consensus

*Studies with a level of evidence '–' should not be used as a basis for making a recommendation

Table 6.8.2: Levels of evidence for comparator treatments in ITP

Comparator treatment	**Level of evidence of studies in ITP**
IVIg	Level 1+ (two RCTs of IVIg vs. various corticosteroid strategies) Plus several level 3 studies (case series)
Anti-D	Level 1+ (one RCT of anti-D plus corticosteroids vs. corticosteroids) Plus several level 3 studies (case series)
Rituximab	Level 3 studies (case series)

Danazol	Level 3 studies (case series)
Dapsone	Level 3 studies (case series)
Azathioprine	Level 3 studies (case series)
Mycophenolate mofetil	Level 3 studies (case series)
Ciclosporin	Level 3 studies (case series)
Cyclophosphamide	Level 3 studies (case series)
Vinca alkaloids	Level 3 studies (case series); also one RCT comparing two vinblastine regimens

Corticosteroids

Initial treatment for ITP is generally a course of corticosteroids, generally prednisolone (IVIg or anti-D may be used in patients for whom steroid treatment is contraindicated). Corticosteroid treatment produces an initial platelet response in approximately two-thirds of patients, but remission is only sustained in approx 10-20% once steroids are reduced or stopped.[11;104] In this assessment, all patients are assumed to receive a course of corticosteroids prior to all treatment pathways modelled (i.e. all patients entering the economic models are refractory to or relapsed after steroid treatment). Therefore, papers on corticosteroid use have not been reviewed in detail in the tables below.

IVIg

Included studies

We summarise the results from the ASH guidelines based on the 14 case series identified in their 1994 literature search.[1] The BCSH guidelines[2] and recent reviews[3] reported similar efficacy data to the ASH guidelines. In addition, from our own search of publications from 1994 onwards, 26 relevant studies were identified. 17 of these are described in Table 6.8.3, while an additional 9 could not be sourced in time for this review. All were single-arm studies or trials comparing different administrations of IVIg, with the exception of two studies: a small RCT by Jacobs et al[105] comparing IVIg vs prednisolone vs both, and an RCT by Godeau et al[70] comparing 4 groups: IVIG then placebo, IVIg then oral prednisolone, high-dose methylprednisolone then placebo, or high-dose methylprednisolone then oral prednisolone. Overall, the studies described support the data reported in the guidelines and reviews in terms of the efficacy of IVIg.

Summary of efficacy data

High-dose immunoglobulin can be given to quickly raise platelet counts. The dose given is generally either 0.4g/kg/day for 5 days, or 1g/kg/day for either 1 day or 2 days. In the review of 14 case series in the ASH guidelines, approximately 75% of patients had a platelet response. Pooling data across the several studies we reviewed, 80.5% of patients had a platelet response $\geq 50 \times 10^9$/l. The response generally occurs within a few days but is generally transient, lasting 3-4 weeks on average. These response data are agreed upon in the BCSH guidelines[2] and in recent reviews (Godeau 2007). The additional studies described in our table support these data. IVIg treatment can be repeated a number of times, with a proportion of patients eventually

becoming refractory.[106;107] A small RCT comparing prednisolone to IVIg showed a trend for higher initial responses and longer times to splenectomy with prednisolone, though these differences were not significant.[105]

Anti-D

Included studies

We summarise the results from the ASH guidelines based on the 5 case series identified in their 1994 literature search.[1] The BCSH guidelines[2] and recent reviews[3] reported similar efficacy data to the ASH guidelines. In addition, 7 further studies of anti-D (those referenced in any of the guidelines and reviews listed in Section 6.1) are summarised in Table 6.8.3. They were all single-arm studies, with the exception of an RCT by George et al[108] comparing anti-D plus prednisolone to prednisolone alone.

Summary of efficacy data

Anti-D may be given as an alternative to IVIg, but is not suitable for use in rhesus D-negative patients or post-splenectomy.[30] Studies have tested doses of 50-75 µg/kg, generally given as a single infusion. The review of case series in the ASH guidelines and the studies described in Table 6.8.3 suggested that approximately 46% of non-splenectomised patients reach a platelet count of ≥50 x 10^9/l, with higher numbers of patients reaching a platelet threshold of 20 or 30 x 10^9/l.[30;31;109] A dose of 75 ug/kg may give higher response rates.[34] Splenectomised patients have been found to respond poorly to anti-D.[1;30] As with IVIg, the response is generally transient, lasting approx 2-3 weeks, or slightly longer with the 75 ug/kg dose.[1;110] In a study of 28 non-splenectomised patients, intermittent treatment with anti-D as required repeatedly increased counts in 68% of patients, and 25-30% of pts showed responses lasting longer than 1 year.[34] An RCT of intermittent anti-D plus prednisolone vs. prednisolone alone in non-splenectomised patients showed slightly more splenectomies in the anti-D group; some splenectomies were carried out earlier than advised in the protocol, indicating that compliance with this anti-D regimen may not be feasible for some patients & physicians.[108] Overall, the individual studies reviewed support the data reported in the guidelines and reviews in terms of the efficacy of anti-D.

Rituximab

Included studies

We summarise the data from three recent reviews assessing the efficacy and safety of rituximab in ITP: the systematic review by Arnold et al,[36] a review of all studies of 10 or more patients by Zhou et al,[53] and the systematic review of ITP treatments post-splenectomy by Vesely et al.[52] A literature search identified 31 potentially-relevant publications for rituximab in ITP published since Arnold et al undertook their search in 2006. Many of these were small studies published in abstract form only, were not peer-reviewed, and some were likely to be duplicate publications. Since there were already very recent systematic reviews in existence which had undertaken a full search and applied consistent inclusion and exclusion criteria, it was decided that the best approach to minimise bias was to use the data from these reviews rather than incorporating data from additional small non-peer-reviewed studies. However, to reflect ongoing research in this area, additional studies recently published in peer-reviewed journals were included in the analysis.[102;111;112] All studies

identified were single-arm studies; no RCTs of rituximab in ITP have been undertaken.

Summary of efficacy data

Rituximab has recently begun to be tested as a treatment for ITP, but is not yet licensed for use in this setting, with no randomised controlled trials yet undertaken. Long-term adverse effects of rituximab treatment are not yet known.[3] Rituximab is generally given as a weekly infusion of 375 mg/m2 for 4 consecutive weeks, although lower doses of 100mg per infusion have recently been studied.[111] The three recent reviews estimate the overall platelet response as 62.5%,[36] 52.9%[53] and 58.5%[52] (post-splenectomy for the latter estimate). Results of recent studies not included in these reviews are similar (see Table 6.8.3).[102;111;112] Arnold et al reported a median time from first dose to response of 5.5 weeks, and a median response duration of 10.5 months.[36]

Danazol

Included studies

We summarised the efficacy data from the Maloisel 2004 study[54] and from the 13 studies identified in their literature review, and the data on post-splenectomy patients from the review by Vesely 2004.[52] In addition, a further 10 publications were identified from our literature review and from other reviews and guidelines.

Summary of efficacy data

Danazol (an attenuated androgen) is generally given as 4-800 mg orally, daily, for a number of months. Maloisel et al reported an overall platelet response of 67% in their study of 57 patients, and also undertook a literature review of prior studies, across which the average overall response was 40%.[54] Vesely et al reported a rate of 60% post-splenectomy.[52] It has been suggested that danazol if given for longer than a year may induce remissions lasting for years after discontinuation, whereas if given for less than 6 months, early relapses are frequent.[25;113] Maloisel et al reported a median time to response of 3 months.[54] This study reported that 47% of patients were still responding after 119 months, while other studies have reported fewer long-term responses (see Table 6.8.3; for example, the percentage of patients still responding after 2 or 3 months was reported as 9%, 12%, 21%, 34%, 47%, and 60% in various studies; these differences may reflect length of time on danazol and severity of ITP in the patients studied). In the study by Maloisel et al, 16% of patients discontinued due to severe adverse effects.

Dapsone

Included studies

Godeau et al[3] in their literature search identified three key studies of dapsone in ITP (they excluded two further studies with very small patient numbers). We describe these studies, plus the post-splenectomy data analysed by Vesely et al 2004.[52] Our literature search did not identify any further relevant studies published from 2006 onwards (i.e. since the review by Godeau et al 2007).

Summary of efficacy data

Dapsone is not licensed for ITP and there do not appear to be any randomised controlled trials of dapsone in this setting. Godeau 2007 reviewed

three studies of dapsone in ITP (most patients in these studies were non-splenectomised). Overall response rates were 40%, 50% and 62%.[84;85;114] The analysis of post-splenectomy patients by Vesely et al indicated an overall response rate of 47% in this population.[52] Godeau et al reported a median time to response of 3 weeks.[85] In this study, 30% of patients were still responding at 1 year, all but one on continuous treatment (while most patients who discontinued treatment then relapsed). Damodar et al reported that 16% of patients still had a platelet count $\geq 100 \times 10^9$/l at 6 months.[84] 11% of 66 patients discontinued dapsone due to adverse events in one study,[85] while 27% of 15 discontinued in another study[114] and 3% of 90 discontinued due to treatment-related serious adverse events in a further study.[84]

Azathioprine

Included studies

From our literature search and hand-searching of reviews and guidelines, 18 potentially relevant papers were identified. For 10 of these, the post-splenectomy data was analysed by Vesely et al[52] and we summarise this here. Six additional papers identified from other reviews and from our search are described in Table 6.8.3; these include studies with reasonably large numbers of patients (a few smaller studies identified in our search could not be obtained in time for this review).

Summary of efficacy data

Azathioprine is an immunosuppressant and is not licensed for use in ITP. When used in this setting, it is generally given orally each day for a number of months. Studies in splenectomised patients suggested an overall response rate of approximately 60%,[52;115-117] while the rate in non-splenectomised patients was reported as 50%.[115] The time to response is approx 4 months.[116] The ASH guidelines reported that, across a number of case series, approximately 20% of patients sustained a normal platelet count for months to years off-treatment. For example, one study of 53 patients reported long-term responses in 40% at 1 year and 32% at 2 years; approximately half of these patients were still on-treatment at the times of follow-up.[116]

Mycophenolate mofetil

Included studies

Godeau et al[3] in their literature search identified four studies of mycophenolate mofetil in ITP. We describe these studies, plus the post-splenectomy data analysed by Vesely et al.[52] Our literature search did not identify any further relevant studies published from 2006 onwards (i.e. since the review by Godeau et al 2007).

Summary of efficacy data

Mycophenolate mofetil (MMF) is an immunosuppressant and is not licensed for use in ITP. When used in this setting, it is generally given orally each day for a number of months. Studies involving small numbers of patients (n=7 to 18) have reported overall response rates of 50% and 67% pre-splenectomy[94;118] and 39% and 57% post-splenectomy.[93;94] It took 4-5 months to reach the maximum platelet count.[94;118] One study reported that 6 of 9 patients (67%) were still responding at a median follow-up of 35 months while still on-treatment, [118] while another study reported that 38% of 21 patients

were still responding at a median follow-up of 6 months, half still on-treatment.[94] In one study, 2/18 (11%) of patients discontinued MMF due to adverse effects. [93]

Ciclosporin

Included studies

Godeau et al[3] in their literature search identified four relevant studies. We describe these studies, plus the post-splenectomy data analysed by Vesely et al.[52] Our literature search did not identify any further relevant studies published from 2006 onwards (i.e. since the review by Godeau et al 2007).

Summary of efficacy data

Ciclosporin is an immunosuppressant and is not licensed for use in ITP. When used in this setting, it is generally given orally each day for a number of months. Studies involving small numbers of patients (n=6 to 21) have reported overall response rates of 50% pre-splenectomy,[91] while post-splenectomy rates are reported as 45%[119], 50%[120] and 76% (Vesely 2004 analysis of three studies).[90;91;121] Regarding long-term response, 2 of 10 pre-splenectomy patients were still responding off-treatment at 2 years in one study, with 9 of 10 eventually undergoing splenectomy (analysis of pre-splenectomy patients).[91] In studies where all or most patients were splenectomised, response rates off-treatment were 17% at 18 months,[120] 27% at 1 year and 18% at 2 years,[119] 42% at 3 years,[90] and 20% at 2 years (analysis of post-splenectomy patients).[91] In a study of 20 patients, 30% of patients discontinued ciclosporin due to adverse effects.[91]

Cyclophosphamide

Included studies

Both sets of guidelines plus recent reviews such as that by Godeau et al describe published studies of cyclophosphamide in ITP. The ASH guidelines describe 5 case series, and Vesely et al (2004) analyse post-splenectomy data from 5 studies. Godeau et al also list key studies. Our literature search did not identify any further relevant studies published from 2006 onwards (i.e. since the review by Godeau et al). We summarise the results from the reviews above, and also describe key papers to provide further detail on outcomes.

Summary of efficacy data

Cyclophosphamide is a cytotoxic alkylating agent and is not licensed for use in ITP. When used in this setting, it is generally given as a series of approximately 4 weekly infusions. A summary of case series described in the ASH guidelines reports an overall response in 60-80% of non-splenectomised patients; 20-40% of these patients sustained a normal platelet count for 2-3 years after discontinuing treatment.[25] As noted in the review by Godeau et al, some of these case series include patients with recently-diagnosed ITP, which may overestimate the effectiveness (since currently, cytotoxic agents would generally only be considered in refractory patients).

Vinca alkaloids

Included studies

Both sets of guidelines plus recent reviews such as that by Godeau et al describe published studies of vinca alkaloids in ITP. The ASH guidelines describe 12 case series, and Vesely et al analyse post-splenectomy data from 12 studies. Godeau et al also list key studies. Our literature search did not identify any further relevant studies published from 2006 onwards (i.e. since the review by Godeau et al). We summarise the results from the reviews above, and also describe key papers to provide further detail on outcomes.

Summary of efficacy data

The vinca alkaloids (vincristine and vinblastine) are cytotoxic agents and are not licensed for use in ITP. They have been studied in this setting as weekly infusions given for 4-6 weeks. The ASH guidelines summarise 13 studies, in which the initial response rate was approximately 67%.[25] A response is generally seen within 1-3 weeks. Vesely et al showed that splenectomised patients across these studies had a response rate of 53%.[52] Across these case series, less than 10% of patients sustained a normal count requiring no further treatment for at least 3 months (further detail on these studies is shown in Table 6.8.3). Twenty-one percent of 19 patients in one study[122] and 21% of 42 patients in another study[123] discontinued due to adverse events.

Table 6.8.3: Summary of efficacy data for ITP comparator treatments (see Excel file for full details of studies)

Treatment type	Interventions (& dose & duration)	Proportion with initial platelet response (generally >50 x 10^9/l unless otherwise stated). N.B. platelet counts shown as e.g. "50" refer to a count of 50 x 10^9/l	Proportion with durable or long-term response (define threshold and whether on repeat / continuous treatments), and/or duration of response	Time to response	Number of new courses of same treatment permissible (repeat courses, number of patients refractory or intolerant)	Reduction in other therapies
IVIg	IVIg 0.4g/kg/d for 5d or 1g/kg/d for 2d	Pre- and post-splenectomy: The 14 case series in ASH guidelines: Approx 75% had a platelet response initially. This is supported by the study results below: The average of the following data for platelets >50 (weighting by sample size) is a response for platelets >50 of **80.5%:** Platelets >50: 46/57 (81%) (Robak 2007)[124] 14/19 (74%) (Julia 2006)[125] 15/21 (71.4%) (Leibl 2005)[126] 11/18 (61%) (Unsal 2004)[109] 24/33 (73%) (Milligan 2004)[127] 55/61 (90%) (Bussel 2004)[128] 22/26 (85%) (Wolf 2003)[129] 22/24 (91.7%) (Colovic 2003)[130] 4/5 (80%) (Pugina 1999)[131] 6/6 (100%) (Altintop 1997)[132] 7/13 (54%) (Jacobs 1994)[105] 18/20 (90%) (Godeau 1993)[107] Platelets >30: 15/20 (75%) (Newland 2001)[133] 14/14 (100%) (Schiavotto 1995)[106]	For each infusion, response generally transient. 3-4 weeks after each infusion (14 case series in ASH guidelines, Godeau 2007 review)[3;25] Data from individual studies supports this: Median: 15.4 days (Robak 2007) [124] 25 days (Leibl 2005)[126] 25.5 days (Colovic 2003)[130] 2-3 weeks (Schiavotto 1995)[106] Mean: 10 days (range 1-29) in one group, 18 days (range 2-29) in other group (Wolf 2003)[129]	Within 1-5 days depending on schedule (1-2 days for 2-day schedule or 1-5 days for 5-day schedule) (Bierling & Godeau 2004 and 2005 reviews)[55;56]	Newland 2001[133]: 8 of 15 responders had further treatment when platelets later fell <30, for up to 4 courses, on a total of 14 occasions. This consisted of another 3 days or single dose of 0.8 g/kg. This was effective on 8/14 occasions. Schiavotto 1995[106]: At least 3 courses per patient. All pts had initial response but 2/14 (14%) became refractory to IVIg after 16 and 20 courses. Godeau 1993[107]: 2/18 did not need repeat courses as had prolonged CR. Of 16 pts attempting repeat courses, 13/16 had 6 courses as planned, and 3/18 (17% of total), i.e. 3/16 (19% of those who attempted repeat courses), became refractory after 1 or 2 courses.	Jacobs 1994[105] (RCT of corticosteroids vs. IVIg): Time to splenectomy 339d (prednisolone group, n=17), 59d (IVIg group, n=13), and 98d (prednisolone + IVIg group, n=13) but numbers small and difference not significant. At minimum of 2 yrs follow-up, platelets >100 (therefore no requirement for splenectomy) in 29% (prednisolone), 15% (IVIg) and 8% (both).

Treatment type	Interventions (& dose & duration)	Proportion with initial platelet response (generally >50 x 10^9/l unless otherwise stated). N.B. platelet counts shown as e.g. "50" refer to a count of 50 x 10^9/l	Proportion with durable or long-term response (define threshold and whether on repeat / continuous treatments), and/or duration of response	Time to response	Number of new courses of same treatment permissible (repeat courses, number of patients refractory or intolerant)	Reduction in other therapies
Anti-D	Anti-D, generally 50-75 µg/kg	Pre-splenectomy: Transiently increases platelet counts to >50 in approx 50% of non-splenectomised patients (ASH guidelines 1996).[1] The following data from individual papers supports this: Platelets >50 initially: The values below give an average of **46.0%**: - 5/11 (45%) platelets >50 (Unsal 2004, 50 ug/kg)[109] - 120/261 (46%) platelets >50 (Scaradavou 1997, dose unclear)[30] Platelets >30 initially: - 26/28 (93%) platelets >30 (Cooper 2002, 50-75 ug/kg)[34] Platelets >20 initially: - 188/261 (72%) platelets >20 (Scaradavou 1997, dose unclear)[30] - 66% had platelets >20 (Aledort 2007, 50 ug/kg)[31] Post-splenectomy: Minimal or no response in 11 splenectomised pts (Scaradavou 1997)[30]	For each infusion, response generally transient. 50 ug/kg dose: approx 2-3 weeks (5 case studies in ASH guidelines),[1] 21 days (Newman 2001),[133] 19 days (Aledort 2007)[31] 75 ug/kg dose: 45 days (Newman 2001)[110]	Mean time to response approx 3 days (Aledort 2007).[31]	George 2003 (intermittent anti-D as required):[108] in anti-D group, of 32 pts, 13 pts received only 1 infusion and 19 pts received 2-10 infusions Cooper 2002 (intermittent anti-D as required):[34] anti-D increased counts repeatedly in 68% patients (median follow-up of 26 months) and 25-30% of pts showed responses lasting longer than 1 year	George 2003 (intermittent anti-D as required):[108] splenectomy rate at median follow-up of 1.3 years: 14/33 (42%) (steroids + anti-D group) vs 14/37 (38%) (steroids only). Median time to splenectomy: 112 days (steroids + anti-D) vs 36 days (steroids only). Some splenectomies earlier than advised in protocol, indicating that compliance with this anti-D regimen is not feasible for some patients & physicians. Cooper 2002 (intermittent anti-D as required):[34] 29% underwent splenectomy (median follow-up 2.2 yrs). 43% not required any treatment or splenectomy for >6 months

Treatment type	Interventions (& dose & duration)	Proportion with initial platelet response (generally >50 x 10^9/l unless otherwise stated). N.B. platelet counts shown as e.g. "50" refer to a count of 50 x 10^9/l	Proportion with durable or long-term response (define threshold and whether on repeat / continuous treatments), and/or duration of response	Time to response	Number of new courses of same treatment permissible (repeat courses, number of patients refractory or intolerant)	Reduction in other therapies
Rituximab	Rituximab, generally as weekly infusion of 375 mg/m2 for 4 consecutive weeks	Pre-splenectomy and post-splenectomy: Use average of the estimates from the reviews by Arnold 2007[36] (62.5%) and Zhou 2008[53] (52.9%). These reviews incorporate many of the same but a few different studies, and approx half of included patients in the Arnold review were splenectomised. This gives an average of 58%. This is similar to the 58.5% from the Vesely 2004[52] individual patient analysis of splenectomised patients. A recent study of 60 pts reported an overall response rate of 60% (Godeau 2008)[102] and another study of 28 pts a response rate of 75% (Zaja 2008, 100mg dose).[111]	Cooper 2004:[134] platelets >50 in 18/57 (32%) after median of 72.5 wks. Godeau 2008:[102] platelets >50 in 24/60 (40%) at 1 year and 20/60 (33%) at 2 years. Zaja 2008[111] (100mg dose): 14/28 (50%) still responding (with initial level of response) at 11 months Assume this data for pre- and post-splenectomy pts	Median time to response 5.5 weeks from first dose (IQR 3.0 to 6.6, range 2 to 18) (Arnold 2007)[36]	Assume 1 course (of 4 weekly treatments) since little published data on further courses	Little data

Treatment type	Interventions (& dose & duration)	Proportion with initial platelet response (generally >50 x 10^9/l unless otherwise stated). N.B. platelet counts shown as e.g. "50" refer to a count of 50 x 10^9/l	Proportion with durable or long-term response (define threshold and whether on repeat / continuous treatments), and/or duration of response	Time to response	Number of new courses of same treatment permissible (repeat courses, number of patients refractory or intolerant)	Reduction in other therapies
Danazol	Danazol, generally 4-800 mg daily for a number of months	Pre-splenectomy: 38/57 (67%) in Maloisel 2004 study and 87/219 (40%) in Maloisel 2004 review of prior studies.[54] Pool these data. Post-splenectomy: 54/90 (60%) from Vesely 2004 systematic review.[52] Godeau 2007[3] suggests may be overestimated since often not severe ITP.	If given for longer than a year, induced remissions lasting for years after discontinuation; however if given for less than 6 months, early relapses were frequent (Ahn 1989 and ASH guidelines)[1;113] The following are estimates from studies below (still need to check full texts for many of them): - 27/57 (47%) for ≥119 months (Maloisel 2004)[54] - 19/56 (34%) for ≥2 months (McMillan 2004)[45] - 2/17 (12%) for ≥3 months (Schiavotto 1993)[122] - 2/22 (9%) for ≥3 months (Fenaux 1990)[135] - 7/18 (39%) for ≥1 year, 2 still on-treatment (Majer 1990)[136] - No more than 1/17 (6%) (Nozaki 1990)[137] - 60% for >2 months (Ahn 1989)[113] - 7/15 (47%) for ≥2 months (Mylvaganam 1989)[138] - 0/10 (0%) (Mazzucconi 1987)[139] - 3/14 (21%) ≥3 months (Buelli 1985)[140] - 1/10 (10%) sustained response (McVerry 1985)[141]	Median time to response 3.1 months (SD 3.9 months, range 2 weeks to 3.2 months) (Maloisel 2004)[54]	Not applicable - 1 course only	Little data

Treatment type	Interventions (& dose & duration)	Proportion with initial platelet response (generally >50 x 10^9/l unless otherwise stated). N.B. platelet counts shown as e.g. "50" refer to a count of 50 x 10^9/l	Proportion with durable or long-term response (define threshold and whether on repeat / continuous treatments), and/or duration of response	Time to response	Number of new courses of same treatment permissible (repeat courses, number of patients refractory or intolerant)	Reduction in other therapies
Dapsone	Dapsone, generally 75-100mg/day orally for a number of months	Pre-splenectomy: Pool data from 3 papers identified in Godeau 2007 literature review:[3] Overall response (usually platelets >50) in 34/55 (62%) (Damodar 2005),[84] 33/66 (50%) (Godeau 1997),[85] 6/15 (40%) (Hernandez 1995).[114] Most but not all pts in these studies non-splenectomised. Pool these numbers. Post-splenectomy: 7/15 (47%) from Vesely 2004 systematic review.[52] Godeau 2007[3] suggests may be overestimated since often not severe ITP.	Godeau 1997: 20/66 (30%) sustained response at median of 12.5 months follow-up, 19 of these still on treatment.[85] Seems to require continuous treatment. 9/55 (16%) platelets >100 for >6 months with or without dapsone therapy (Damodar 2005)[84]	Response seen after a median of 21d (range 8-90) (Godeau 1997)[85]	Not applicable - 1 course only	Little data
Azathioprine	Azathioprine, oral daily dose for a number of months	Pre-splenectomy: 30/60 (50%) (pre-splenectomy in Vianelli 2001)[115] Post-splenectomy: Pool the following figures: 69/109 (63%) (Vesely 2004 systematic review),[52] 13/22 (59%) (post-splenectomy in Vianelli 2001),[115] 34/53 (64%) (Quiquandon 1990, majority splenectomised),[116] 11/17 (65%) (Bouroncle 1969)[117]	Quiquandon 1990: 21/53 (40%) had responses lasting 1 year or more and 17/53 (32%) lasting 2 years or more (10 after stopping treatment and 7 still on treatment).[116] ASH guidelines: approx 20% sustain normal count for months to years off-treatment)[25]	Median time to response 4 months (Quiquandon 1990)[116]	Not applicable - 1 course only	Little data
Mycophenolate mofetil (MMF)	Mycophenolate mofetil (MMF) 0.5-3g/day orally for a number of months	Pre-splenectomy: pool the following: - 6/9 (67%) (Kotb 2005, most non-splenectomised)[118] - 7/14 (50%) (Hou 2003, non-splenectomised pts)[94] Post-splenectomy: pool the following: - 7/18 (39%) (Provan 2006, all but 1 splenectomised)[93] - 4/7 (57%) (Hou 2003 and Vesely review, splenectomised pts)[52;94]	6/9 (67%) still responding at a median follow-up of 35 months (range 5-50) while still on-treatment (Kotb 2005)[118] 8/21 (38%) still responding at median of 22 weeks follow-up, 5/21 (24%) on-treatment and 3/21 (14%) after treatment cessation (Hou 2003)[94]	Median time to maximum platelet count 5.3 or 4.2 months (Kotb 2005; Hou 2003)[94;118] Time to response >50 not reported; assume 4 months as for azathioprine	Not applicable - 1 course only	Little data

Treatment type	Interventions (& dose & duration)	Proportion with initial platelet response (generally >50 x 10^9/l unless otherwise stated). N.B. platelet counts shown as e.g. "50" refer to a count of 50 x 10^9/l	Proportion with durable or long-term response (define threshold and whether on repeat / continuous treatments), and/or duration of response	Time to response	Number of new courses of same treatment permissible (repeat courses, number of patients refractory or intolerant)	Reduction in other therapies
Ciclosporin	Ciclosporin, oral daily dose for a number of months	Pre-splenectomy: - 5/10 (50%) (Kappers-Klunne 2001 non-splenectomy pts)[91] Post-splenectomy: pool the following: - 16/21 (76%) (Vesely 2004, includes splenectomised pts from Emilia 2002, Kappers-Klunne 2001 & Emilia 1996)[52;90;91;121] - 3/6 (50%) (Zver 2006)[120] - 5/11 (45%) (Peng 2003)[119]	Pre-splenectomy: - 2/10 (20%), 2 years follow-up off-treatment; 9/10 eventually had splenectomy (Kappers-Klunne 2001)[91] Post-splenectomy (all/most splenectomised): - 1/6 (17%), 18 months follow-up, off-treatment (Zver 2006)[120] - 3/11 (27%) had response up to 1 year off-treatment and 2/11 (18%) still responding off-treatment after 2 years follow-up (Peng 2003)[119] - 9/12 (75%) still responding at median of 37 months follow-up, 5/12 (42%) off-treatment and 4/12 (33%) on continuous treatment (Emilia 2002; received long-term ciclosporin)[90] - 2/10 (20%), 2 years follow-up off-treatment (Kappers-Klunne 2001)[91]	Not clear - estimate 2 months from Emilia 2002 (counts began to increase after 3-4 weeks)[90]	Assume generally 1 course only. Some pts in Zver 2006[120] received a second course	Little data
Cyclo-phosphamide	Cyclophosphamide, generally as a series of approx 4 weekly infusions	Pre-splenectomy: - ASH guidelines[1] summarise 5 case series: overall response 60-80%, therefore average = 70% Post-splenectomy: - 51/83 (61%) (Vesely 2004 review)[52] Godeau 2007 review:[3] case series include pts with recently-diagnosed ITP which may overestimate effectiveness	ASH guidelines: 20-40% pts (average 30%) sustained normal count for 2-3 yrs after discontinuing treatment[1]	Responses typically require 1-3 months (Cines & Bussel 2005 review)[6]	Assume generally 1 course only	Little data

Treatment type	Interventions (& dose & duration)	Proportion with initial platelet response (generally >50 x 10^9/l unless otherwise stated). N.B. platelet counts shown as e.g. "50" refer to a count of 50 x 10^9/l	Proportion with durable or long-term response (define threshold and whether on repeat / continuous treatments), and/or duration of response	Time to response	Number of new courses of same treatment permissible (repeat courses, number of patients refractory or intolerant)	Reduction in other therapies
Vinca alkaloids	Vinca alkaloids: generally vincristine 1-2mg IV or vinblastine 5-10mg IV weekly for 4-6 weeks	Pre-splenectomy: - ASH guidelines summarise 12 case series (plus 1 RCT comparing two vinblastine regimens): overall response approx two-thirds i.e. 67%[1] Post-splenectomy: - 55/103 (53%) (Vesely 2004 review)[52] (Also ASH guidelines state approx 50% patients respond initially)[1]	Use the following: - ASH and BSH guidelines: [1;2] 12 case series (plus 1 RCT comparing two vinblastine regimens): <10% have sustained normal platelet count requiring no further treatment for at least 3 months As an illustration, the following data are from some of the studies examined in the ASH and BSH guidelines: - 3/17 (18%) platelets >50 at 1 year (of pts with ITP >6 months, Facon 1994)[123] - 0/14 (0%) sustained platelets >50 for at least 2 months without maintenance therapy, and 2/14 (14%) sustained platelets >100 with repeated maintenance therapy (of pts with ITP >6 months, Manoharan 1991)[142] - 4/8 (50%) still responding (platelets >50) at 3, 5, 9 and 10 months (Linares 1988)[98] - 0/19 (0%) had complete remission for at least 6 months (Pizzuto 1984)[99]	1-3 weeks (ASH guidelines)[1]	Assume generally 1 course only	Little data

N.B. Platelet counts shown as e.g. "50" refer to a platelet count of 50 x 10^9/l.

6.9 Interpretation of clinical evidence

6.9.1 *Provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.*

As discussed in Section 6.0, clinical data on the efficacy, safety and optimum sequence of treatments in the management of ITP is severely lacking.

The two phase 3 RCTs that compare romiplostim-plus-standard-of-care to placebo-plus-standard-of-care were designed to evaluate the efficacy and safety of romiplostim in a "real world" clinical context, and patients in both the romiplostim and placebo arms could receive baseline concurrent chronic ITP therapies and rescue medications at the discretion of the investigator (see below for rationale for design of these studies). Due to the lack of clinical guidance on what treatment ITP patients should receive at each "line" of treatment, it would have been difficult to design an RCT to compare romiplostim directly with each of the specific comparator treatments in the decision problem.

In terms of the comparator treatments, several are not licensed for ITP Also, as discussed in Section 6.0, with the exception of romiplostim phase 3 trials, there are very few RCTs comparing ITP treatments to placebo. This lack of placebo-controlled trials, in addition to the complexity of the treatment paradigm for ITP and the heterogeneity of the data, makes it difficult to undertake a formal indirect mixed treatment comparison (for example using Bayesian networks). Many existing studies of comparators are small and of poor quality. Efficacy data taken from unblinded, uncontrolled studies has been shown to overestimate the effect size.[49;50]

It is difficult to obtain comparable outcome data from the studies of the various treatments. Comparator treatments do not generally present data on bleeding rates. Instead, the main outcomes reported are the proportions of patients reaching a certain platelet threshold. This threshold is generally defined as 50 x 10^9/l which is generally accepted as a conservative measure of efficacy; however this causes difficulties for the economic modelling since recent guidelines suggest generally treating patients whose platelet count falls to less than 30 or 50 x 10^9/l if concurrent risk factors for bleeding exist.

Many existing ITP treatments are strongly immunosuppressive and have unpleasant and potentially harmful short- and long-term side effects but it is difficult to obtain comparable estimates of adverse effects from uncontrolled studies.

However, despite these limitations we have used the available information to try to model the patient pathway for ITP treatment as closely as possible. A range of sensitivity analyses test the robustness of the results and how the cost-effectiveness is impacted by the uncertainty in the data.

6.9.2 *Identify any factors that may influence the applicability of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select suitable patients based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the Summary of Product Characteristics?*

Many studies of comparator treatments, especially older studies, enrolled ITP patients who were much less refractory (and more likely to respond to treatment) than those enrolled in the phase 3 RCTs of romiplostim. Some studies included recently-

diagnosed patients who, according to current practice, would be likely to be managed by watchful waiting with intermittent treatment if needed. Some of these patients may have undergone spontaneous remission rather than developing chronic ITP. Therefore, many studies of comparator treatments are likely to overestimate the efficacy, in relation to that which might be observed in a more refractory population.

The populations and dosages used in the romiplostim phase 3 RCTs reflect those in the draft SPC and would be relevant to clinical practice.

[redacted]

As discussed in Section 6.0, the phase 3 trials were designed to evaluate the efficacy and safety of romiplostim in a "real world" context. The fact that concurrent medications and rescue medications were permitted in both arms of the trials increases the applicability of the results to clinical practice. However, alkylating agents (i.e. cyclophosphamide) and rituximab were not permitted on the basis of practical considerations. As a cytotoxic agent that has the potential to destroy platelet forming cells (megakaryocytes), cyclophosphamide was prohibited based on the theoretical possibility that it could undermine the effect of a platelet producing agent like romiplostim that works by stimulating cells of the megakaryocyte lineage to proliferate, differentiate and mature. The use of rituximab was prohibited given the concern that it could potentially confound an efficacy assessment of romiplostim, since both response to rituximab and time to response are relatively unpredictable, making it difficult to adjust for its impact on platelet counts among study participants.

Overall, the demographics, epidemiology, and disease severity of participants in the romiplostim RCTs should be quite similar to that of patients in the UK who are likely to receive romiplostim. The romiplostim pivotal studies enrolled an adult splenectomised and non-splenectomised ITP population that had received considerable prior ITP treatment and still had a baseline platelet count $<30 \times 10^9$/l. Perhaps the only expected difference between RCT participants and patients in the UK who would be likely to receive romiplostim relates to the non-splenectomised patient population. Whereas study 20030212 enrolled a broad population of adult non-splenectomised ITP patients, the final clinical indication statement in the Summary of Product Characteristics may limit use of romiplostim to a subgroup of non-splenectomised patients for whom splenectomy is medically contraindicated.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

7.1.1 Identification of studies

Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided in appendix 3, section 9.3.

A literature search was undertaken for all publications relating to romiplostim (see Appendix 3 for details of the search terms and databases searched).

7.1.2 Description of identified studies

Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. Where studies have been identified and not included, justification for this should be provided.

The literature search did not identify any published studies assessing the cost-effectiveness of romiplostim in ITP.

7.2 De novo economic evaluation(s)

In the absence of a relevant published economic evaluation, manufacturers or sponsors should submit their own economic evaluation. When estimating cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal'). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	Reference case	Section in 'Guide to the methods of technology appraisal'
Defining the decision problem	The scope developed by the institute	5.2.5 & 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 & 5.2.6
Perspective costs	NHS and Personal Social Services	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 to 5.2.12
Synthesis of evidence on outcomes	Systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12

HRQL, health related quality of life; NHS, National Health Service; QALYs, quality-adjusted life years

7.2.1 Technology

7.2.1.1 *How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use.*

Indication

The indication for romiplostim in the economic evaluation is adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP). Two populations 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. This population will be referred to as "non-splenectomised" patients.

b) Patients refractory to splenectomy. These are patients who have had a splenectomy but are in a continued need of treatment due to low platelet count and/or bleeding risk. This population will be referred to as "splenectomised" patients.

Modelled patients are assumed to have an initial platelet count of $<50 \times 10^9$/l. A platelet threshold of $<50 \times 10^9$/l is used because most studies of comparator treatments only present platelet response rates using this threshold, with little data on other platelet thresholds such as $<30 \times 10^9$/l. Most patients in the romiplostim trials however were initially at a level of $<30 \times 10^9$/l which reflects treatment guideline recommendations for the initiation of treatment.

Dose, frequency and duration of use

Using the dosing data in the phase 3 trials, the average dose per kilogram (kg) bodyweight per week was calculated for non-splenectomised and splenectomised patients, in order to calculate the average dose per 4-week period. This calculation is described in more detail in section 7.2.9.2. As shown in Table 7.1, non-splenectomised patients were found to receive on average [redacted] vials (equivalent to 0.93 x 250 ug vials) per kg bodyweight, and splenectomised patients were found to receive on average [redacted] vials (equivalent to 1.38 x 250 ug vials) per kg bodyweight.

Patients were assumed to receive this average weekly dose every week they remained on treatment.

The duration of romiplostim treatment (time to failure) was calculated as the time from first exposure to romiplostim treatment to the time of discontinuation. Some patients had a last visit and were not recorded as being withdrawn from therapy; these patients are considered censored.

Concomitant treatments

Throughout the patient pathway, patients were assumed to be eligible to receive intravenous rescue medications (IVIg, anti-D or IV corticosteroids) whenever the platelet count fell to below 50×10^9/l and received rescue therapy whenever they experienced a bleed that resulted in hospitalisation.

7.2.1.2 *Has a treatment continuation rule been assumed? Where the rule is not stated in the SmPC this should be presented as a separate scenario, by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.*

- *the costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required)*
- *the robustness and plausibility of the endpoint on which the rule is based*
- *whether the 'response' criteria defined in the rule can be reasonably achieved*
- *the appropriateness and robustness of the time at which response is measured*
- *whether the rule can be incorporated into routine clinical practice*
- *whether the rule is likely to predict those patients for whom the technology is particularly cost effective*
- *issues with respect to withdrawal of treatment from non-responders and other equity considerations.*

In patients receiving romiplostim, platelet counts should be assessed weekly until a stable platelet count (≥ 50 x 10^9/l for at least 4 weeks) has been achieved. Platelet counts should be assessed monthly thereafter. The cost of this assessment is included in the model. This kind of monitoring is currently part of normal clinical practice for most patients and so the addition of romiplostim would be readily achievable. The point of discontinuation assumed in the model is clinically relevant because it is based on clinical data relating to patients discontinuing after receiving romiplostim.

The average duration of platelet response (i.e. time until a platelet response was no longer maintained) is an important and relevant outcome. It is poorly defined in the literature but results based on various definitions of "long term response" were available for the majority of the comparator treatments (see Section 6.8). Typically response is reported as the number of patients still responding at a given time. However this outcome was not a prospective outcome defined for romiplostim in the pivotal phase 3 studies, where treatment ended after 24 weeks in these studies. Therefore, to allow comparison with data available for the comparator treatments, this outcome has been calculated retrospectively (see section 6.3.4)

7.2.2 Patients

7.2.2.1 *What group(s) of patients is/are included in the economic evaluation? Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of* the decision problem?

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.

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.

This reflects the decision problem and the draft label (which is still being discussed with CHMP). The final clinical indication statement in the Summary of Product Characteristics may limit use of romiplostim to a subgroup of non-splenectomised patients for whom splenectomy is medically contraindicated.

7.2.2.2 *Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified? If subgroups are based on differences in relative treatment effect, what clinical information is there to support the biological plausibility of this approach? For subgroups based on differences in baseline risk of specific outcomes, how were the data to quantify this identified? How was the statistical analysis undertaken?*

No further subgroups were identified beyond the two patient groups specified above.

7.2.2.3 *Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Refer to the subgroups identified in the scope.*

No.

7.2.2.4 *At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?*

Patients entering the evaluation have either had an inadequate response to, or are intolerant to corticosteroids and immunoglobulins, or are refractory to splenectomy. Patients exit the model when they die.

7.2.3 Comparator technology

What comparator(s) was/were used and why was it/were they chosen? The choice of comparator should be consistent with the summary of the decision problem (Section A).

As described in Section 6.0, there is little consensus among experts or clinical guidelines on a definitive patient pathway for ITP, so there are no defined comparator treatments for a particular "line" of treatment. Therefore, the approach to this analysis is to model two pathways: a) a standard-of-care pathway (with the treatments and their ordering estimated as accurately as possible from clinical guidelines and from a physician survey of 169 UK haematologists conducted by Amgen) and b) the same pathway with the addition of romiplostim.

As listed in the decision problem (Section A part 2), the following treatments are modelled in the pathway:

- Watchful waiting 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)

Non-splenectomised patients have previously had an inadequate response to or are intolerant of corticosteroids and immunoglobulins, therefore the initial courses of these treatments are not modelled.

Splenectomy is recognized as a treatment option but it is not modelled as a comparator in the non-splenectomised patient population because the expected indication is for patients for whom splenectomy is contra indicated.

7.2.4 Study perspective

If the perspective of the study did not reflect NICE's reference case, provide further details and a justification for the approach chosen.

The perspective is that of the NHS.

7.2.5 Time horizon

The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared.

What time horizon was used in the analysis, and what was the justification for this choice?

The model has a lifetime horizon because adult ITP is a chronic disease which most patients have for life. Furthermore, to fully capture patient experiences as they progress through the treatment pathway, a long term model is required. There are difficulties however in modelling the long term experiences of patients who are refractory to treatments. These patients have progressed down the treatment pathway and have failed on all the available treatments and the only option left for them is long term 'watch and rescue'. These patients become a major driver of cost effectiveness as their long term use of expensive rescue therapies adds a significant cost burden. However, exactly what is their usage is not well known and it is not easy to model long term rescue of refractory patients, using medications with significant side effects as if these late treatments were cost effective and clinically desirable choices. Current use of these treatments only as a last resort makes it clear that it is not the case in the view of physicians. It does pose problems for modelling in the absence of any robust data for this part of the treatment pathway. A sensitivity analysis of the effect of varying the time horizon of the model is therefore of major significance as when shorter time frames are considered, the long term impact of treatment of refractory patients is reduced.

7.2.6 Framework

The purpose of this section is to provide details of the framework of the analysis. Section a) below relates to model-based evaluations, and section b) below relates to evaluations conducted alongside clinical trials. Please complete the section(s) relevant to the analysis.

a) Model-based evaluations

7.2.6.1 *Please provide the following.*

- *A description of the model type.*
- *A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.*
- *A list of all variables that includes their value, range (distribution) and source.*
- *A separate list of all assumptions and a justification for each assumption.*

Description of the model type

The model is constructed using a life time cohort based methodology. The model is divided into discrete time intervals of 4 weeks. The model consists of 8 health states between which the cohort can transition. The modelled health states are:

- Platelet > 50 x 10^9/l and no bleed
- Platelet > 50 x 10^9/l and minor bleed treated as an outpatient
- Platelet < 50 x 10^9/l and no bleed
- Platelet < 50 x 10^9/l and minor bleed treated as an outpatient
- Platelet < 50 x 10^9/l and intracranial haemorrhage
- Platelet < 50 x 10^9/l and GI bleed
- Platelet <50 x 10^9/l and other bleed requiring hospitalisation
- Death

Patient pathway for ITP

As described in Section 4 and Section 6.0, there is no definitive treatment pathway for ITP. However, based on the best information available from the two sets of guidelines, recent reviews, plus an Amgen-commissioned survey of 169 haematologists, the pathway is assumed to be as shown in Figure 7.1.

Schematic of the model

A schematic of the model is shown in Figure 7.2

List of all variables in the model

A list of all the variables in the model is shown in Table 7.1.

Assumptions (A) and justifications (J)

A. Patients enter the model on the comparator treatment arm with a regime of 'watch and rescue' (i.e. watchful waiting with IVIg, anti-D or IV corticosteroids as needed) followed by the treatment path in Figure 7.1, and in arm 2 treated with romiplostim followed by a regime of 'watch and rescue' and then the treatment path. Patients have previously had an inadequate response to or are intolerant of corticosteroids and immunoglobulins. Patients enter the model with a platelet count of $< 50 \times 10^9$/l.
J. We are demonstrating the modelled cost effectiveness of romiplostim as the first choice therapy after first line failure, reflecting the expectation that the first line treatment of choice will remain corticosteroids. Patients starting treatment are first line failures and thus have a low platelet count.

A. The patient pathway consists of active therapies and 'watch and rescue'. When a patient becomes refractory to an active therapy they move to 'watch and rescue'. In 'watch and rescue', once they bleed or fail to respond to rescue therapy then they are moved to the next active treatment in the pathway. Once all active therapies have been tried, the patient remains on 'watch and rescue'.
J. It is assumed that this patient pathway, although a simplification, reflects current UK practice as closely as possible.

A. When moving to the next active therapy, only a proportion of the cohort receives the therapy. The probability of this occurring for each treatment is based on an Amgen-commissioned UK physician survey into the usage of each comparator. If a patient does not receive the therapy, they then move to the next active therapy based on their distribution of use. All patients are assumed to move in a linear sequence through the patient's pathway.
J. Not all therapies are routinely used in the UK and the use of some of them is quite scarce (particularly the more toxic therapies further down the pathway). There is no defined pathway in the UK and all treatments are available to a clinician as a 'basket' of options. The approach adopted here results in an overall comparator treatment usage by the cohort that reflects current UK practice as closely as we are able to judge and reproduce. The ordering of treatment best reflects that shown from a physician survey.

A. Patients starting a new therapy have a maximum period in which they can respond. During this period the proportion of the cohort that responds reflects the overall response rate for the therapy as identified from reviews of the relevant literature. After the maximum period has passed without response they are assumed to be refractory to this treatment and move to 'watch and rescue'.
J. Patients do not immediately respond to treatment (apart from rescue therapy) and therefore may have a period of a low platelet count before response. The literature results are difficult to interpret as evidence for comparators is not well controlled and rarely in patients with an appropriate degree of refractoriness to therapy. Assumptions on comparator efficacy rates have been guided both by evidence from the literature and by clinical advice. We have tried to adopt a fair, even generous, interpretation of comparator efficacy evidence.

A. Response to therapy is assumed to equate to achieving a platelet count $>50 \times 10^9$/l. It is assumed that this level is maintained throughout the period of response.
J. A platelet count $>50 \times 10^9$/l is the most common response threshold reported in the literature. There is scarce data for the comparator treatments on the proportion of patients reaching other thresholds (such as 20 or 30×10^9/l) and so we use a platelet count of $>50 \times 10^9$/l in order to allow comparison between treatments.

A. Patients on 'watch and rescue' receive rescue medication if their platelet count falls below 50 x 10^9/l and they have a bleed involving hospitalisation. A proportion of patients also have a probability of receiving rescue medication if their platelet count is below 50 x 10^9/l and they have not had a bleed requiring hospitalisation. This proportion of patients is calibrated so that the total use of immunoglobulin rescue medication in the first 24 weeks of the model reflects the rescue medication use in the trials (1.86 administrations in the non-splenectomy group and 2.67 in the splenectomised arm). This calibration is performed against a treatment arm with only 'watch and rescue' patients (no active therapies), fully reflecting the patients in the trial. In the non-splenectomised patients, this results in 20% of non severe bleeding patients receiving IVIg, 7% receiving Anti-D and 6% IV steroids per 4 week cycle. In the splenectomised patients 43% of non severe bleeding patients receive IVIg and 25% receive IV steroids per 4 week cycle.
J. These rules reflect current treatment guidelines which suggest that patients should be considered to require active treatment if they have a platelet count under 30 x 10^9/l or bleeding symptoms. In the health state <50 x 10^9/l patients platelet levels will be distributed over a range of levels. A proportion of these will be at a low level which will require rescue therapy. Treatment decisions are tailored to individual patients often depending on a clinician's particular preference. Whilst the percentage figures used in this assumption are based on the modelled calibration, the resulting modelled rescue therapy use is the same as the rescue medication used in the trial. By reflecting the use of rescue medication in the trial, we represent the rescue medicine treatment requirements of patients who are candidates for romiplostim.

A. In the base case we assume that patients that are refractory to all active medication continually receive rescue medication as defined in the rules above. This use of immunoglobulins reflects that observed in the trial.
J. This assumption is based on the results of the clinical trials which give us the best available evidence of rescue therapy utilisation.

A. Patients that are refractory to all active medication are likely to have a low platelet count and be at a higher risk of bleeding than those responding to medication. There is no available data on the platelet distribution of these patients. We therefore assume that once a patient enters the final 'watch and rescue' state their risk of suffering a serious bleed resulting in hospitalisation, doubles.
J. Not adjusting the risk of bleed in very refractory patients could be a potent source of underestimation of the cost effectiveness of romiplostim because there is a built in tendency to underestimate the resource use in the non romiplostim arm. We have tried to make some idea allowance for this in our base case estimates

A. Patients responding to an active treatment and who have a minor outpatient bleed do not receive rescue medication.
J. The patient incurs costs associated with an outpatient visit that reflect the mild treatment such as oral steroids required to treat a minor bleed in the >50 x 10^9/l state. It is not expected that these patients would receive any expensive IV rescue therapies.

A. Patients that receive rescue medication in cycle t can receive rescue medication in cycle t+1. Therefore they will potentially have 2 consecutive 4 week cycles with a platelet count >50 x 10^9/l.
J. There were patients in the trial that received frequent redosing of rescue therapy.

A. Patients can only have one bleed (outpatient or hospitalisation) per cycle.
J. It is judged that the probability of having more that one bleed episode in a 4 week period is low. This is a conservative assumption that biases in favour of the

comparator arm since there are more patients with a platelet count <50 x 10^9/l in the comparator arm and thus they are at greater risk of bleeding.

A. We assume that the distribution of the platelet count of patients in the <50 x 10^9/l health state remains the same throughout the model. Lower platelet counts are associated with an increased risk of bleeding and as a consequence of this assumption, the risk of bleeding does not change in the <50 x 10^9/l state throughout the model. This is biased in favour of those treatments with poorer efficacy since it is likely that patients on these medications will have a lower platelet distribution than romiplostim. This is turn means that they would have a higher risk of bleeding.
J. The only available data on the risk of bleeding was from the romiplostim trials. No data was available either on the distribution of platelets or the risk of bleeds for the comparators. It is therefore not of any use to look at the change in risk of bleed as the platelet count drops (when below 50 x 10^9/l) as there will be no marginal effect difference observed between comparators.

A. Adverse event rates for comparators are reported as total incidence. It is assumed that a patient's exposure to the adverse event is over the entire response period and so the incidence rate is thus distributed.
J. There is insufficient literature available to model a credible time-dependent adverse event rate.

A. Excess mortality risk in ITP only results from bleeding events requiring hospitalisation. Unless hospitalized, patients die at their age- and gender-specific rates.
J. This may understate the risk but we have no credible data to allow us to make a reasonable alternative estimate.

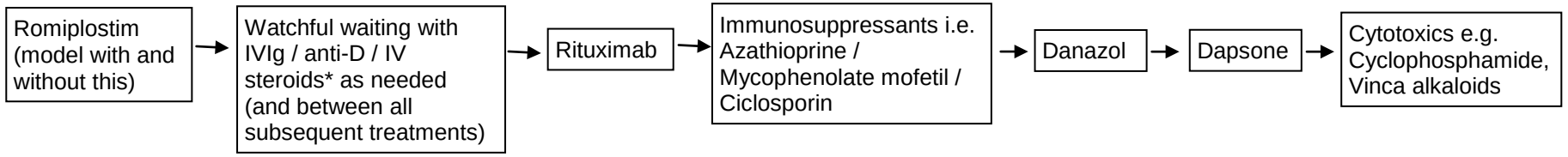
A. Patients are compliant with their treatments (no additional discontinuation or poor compliance is modelled).
J. There is no data with which to model compliance. Discontinuations due to reasons other than failed platelet response are assumed to have been captured by the overall response period. This is limited by the quality of the reporting of the comparator data.

A. Utility decrements for adverse events and bleeds are assumed to be limited to the cycle in which they occur.
J. Generally, the time period in which a patient suffers these events is not expected to be more than 4 weeks. There will be some rare events that have an increased decrement (e.g. stroke following intracranial haemorrhage), but the increased modelling complexity of including model memory (i.e. an individual patient model) was not considered appropriate given the expected benefits of inclusion. This is a conservative assumption, biased against romiplostim, since the comparator therapies are likely to have patients with lower platelet counts and thus higher risk of bleed.

Figure 7.1: Patient pathway for ITP

Patients enter the evaluation having either had an inadequate response to or who are intolerant of corticosteroids and immunoglobulins or are refractory to splenectomy.

Patients are assumed to have a period of watchful waiting, receiving IVIg and/or anti-D and/or IV steroids as needed, between each treatment.



**Anti-D not indicated in splenectomised setting*

Figure 7.2: Schematic of model structure

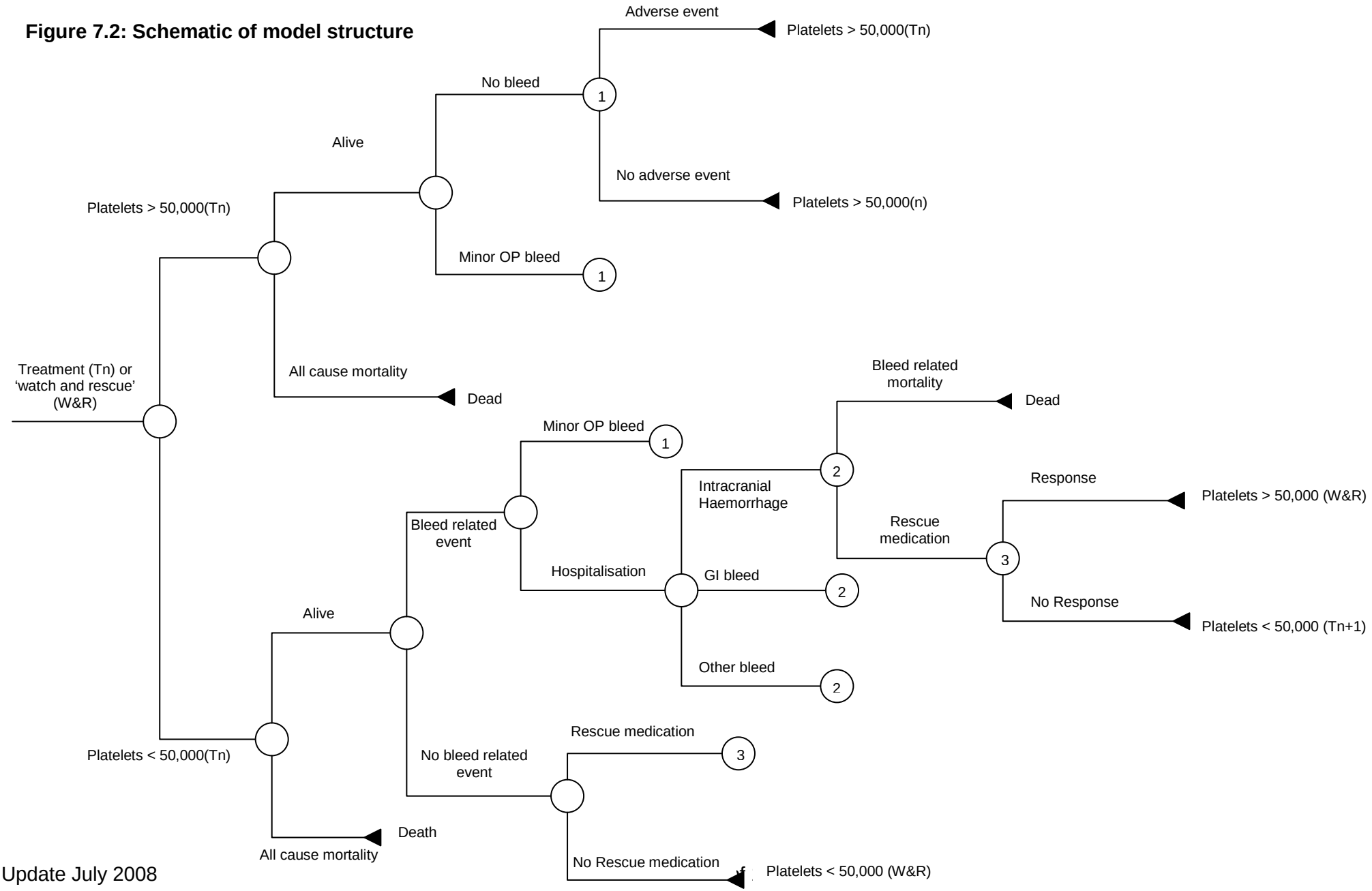


Table 7.1: Variables included in the model

Variable	Value non-splenectomised	Value splenectomised (if different)	Source
General			
Discounting rates for costs and QALYs	3.5%		NICE reference case
Patient demographics			
Age: mean (SD)	52.2		Romiplostim phase 3 trials (Kuter 2008)
Male / female ratio	35% / 65%		Romiplostim phase 3 trials (Kuter 2008)
Treatment pathway (at certain points in the pathway patients are assumed to receive one of a class of drugs in the following ratios)			
Azathioprine	59%		Amgen UK physician survey
Mycophenolate mofetil	37%		Amgen UK physician survey
Ciclosporin	4%		Amgen UK physician survey
Dapsone	*48%*		Amgen UK physician survey
Danazol	*7%*		Amgen UK physician survey
Cyclophosphamide	2%		Amgen UK physician survey
Vinca alkaloids	5%		Amgen UK physician survey
Percentage of patients receiving each rescue medication:			
IVIg	59%	64%	Amgen UK physician survey
Anti-D	25%	0%	Amgen UK physician survey
IV Steroid	16%	36%	Amgen UK physician survey
Treatment efficacy			
Probability of initial platelet response:			
Treatments:			
Romiplostim	87.8%	78.6%	Romiplostim phase 3 trials (Kuter 2008)
Rituximab	57.7%		Arnold 2007, Zhou 2008 (average of 2 reviews)

Variable	Value non-splenectomised	Value splenectomised (if different)	Source
Azathioprine	50.0%	62.8%	Non-splenectomised: Vianelli 2001 Splenectomised: Vesely 2004, Vianelli 2001, Bouroncle 1969
Mycophenolate mofetil	56.52%	44.0%	Non-splenectomised: Kotb 2005, Hou 2003 Splenectomised: Provan 2006, Hou 2003
Ciclosporin	50.0%	63.2%	Non-splenectomised: Kappers-Klunne 2001 Splenectomised: Vesely 2004, Zver 2006, Peng 2003
Danazol	45.3%	60.0%	Non-splenectomised: Maloisel 2004 (own study and review of prior studies) Splenectomised: Vesely 2004
Dapsone	50.0%	46.7%	Non-splenectomised: Damodar 2005, Godeau 1997, Hernandez 1995 Splenectomised: Vesely 2004
Cyclophosphamide	70.0%	61.4%	Non-splenectomised: ASH guidelines (George 1996) Splenectomised: Vesely 2004
Vinca alkaloids	67.0%	53.4%	Non-splenectomised: ASH guidelines (George 1996) Splenectomised: Vesely 2004
Rescue medications:			
IVIg	80.5%	78.6%	Various IVIg papers: see Section 6.8
Anti-D	46.0%	Not indicated for use in splenectomised	Unsal 2004, Scaradavou 1997
IV Steroid	46.0%	46.0%	Assumed to be the same as Anti-D
Average response rate to rescue medications (response rate * % receiving each)	68.1%	66.2%	
Mean response duration (from treatment initiation) (number of 4-week cycles) These have been either been calculated from median response or from the proportion of patients responding at a reported time			
Treatments:			

Variable	Value non-splenectomised	Value splenectomised (if different)	Source
[redacted]	[redacted]		[redacted]
Rituximab	18.9		Cooper 2004, Godeau 2008, Zaja 2008
Azathioprine	20.3		Quiquandon 1990
Mycophenolate mofetil	5.7		Hou 2003
Ciclosporin	16.2	12.91	Kappers-Klunne 2001
Danazol	147.35	145.4	Various danazol papers reporting long-term response; see Section 6.8
Dapsone	20.3		Godeau 1997
Cyclophosphamide	27.0		ASH guidelines (George 1996)
Vinca alkaloids	1.4		ASH guidelines (George 1996)
Rescue medications:			
IVIg	1		ASH guidelines (George 1996)
Anti-D	1	Not indicated for use in splenectomised	ASH guidelines (George 1996)
IV Steroid	1		ASH guidelines (George 1996)
Max time from treatment initiation to initial response (number of 4-week cycles)			
Treatments:			
Romiplostim	1		Romiplostim phase 3 trials (Kuter 2008)
Rituximab	2		Arnold 2007
Azathioprine	4		Quiquandon 1990
Mycophenolate mofetil	4		Kotb 2005, Hou 2003
Ciclosporin	2		Emilia 2002
Danazol	4		Maloisel 2004
Dapsone	1		Godeau 1997
Cyclophosphamide	2		Cines & Bussel 2005
Vinca alkaloids	1		ASH guidelines (George 1996)
Rescue medications:			
IVIg	0		Bierling & Godeau 2004
Anti-D	0		ASH guidelines (George 1996)
IV Steroids	0		ASH guidelines (George 1996)

Variable	Value non-splenectomised	Value splenectomised (if different)	Source
Bleeding and platelet counts			
[redacted]	[redacted]	[redacted]	[redacted]
Probability of bleed for patients with platelet count >50 x 10^9/l, per cycle			
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]		
[redacted]			
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]		
[redacted]			
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]		
[redacted]	[redacted]		
Mortality rates			
Mortality associated with bleed treated as outpatient	0%		
Mortality associated with bleed-related hospitalisations, per cycle, for the following:			
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]		
[redacted]	[redacted]		
All-cause mortality	Dependent on patient current age in the model		UK government actuary department 2006 interim life tables
Adverse events (AEs)			
% of patients experiencing serious/severe AEs or discontinuations:			

Variable	Value non-splenectomised	Value splenectomised (if different)	Source
Romiplostim	3% (range 2-4%)†		Kuter 2008 (†These values are the treatment-related serious AEs (2%) and AEs leading to discontinuation (4%) from the romiplostim arms of the Phase 3 trials. These values were thought to be most comparable to values in the literature for the comparator treatments.)
IVIg	2.1% (range 0.5-3.8%)		Gamunex prescribing information, ASH guidelines
Anti-D	2.8%		Scaradavou 1997, Aledort 2007
Corticosteroids	3%		Matzdorff 2007, Zimmer 2004, Aledort 2006
Rituximab	3.3%		Arnold 2007
Immunosuppressants (azathioprine, mycophenolate mofetil, ciclosporin)	15% (range 11%-30%)		Sternthal 2008, Provan 2006, Kappers-Klunne 2001, Zwerner 2007
Danazol	16%		Maloisel 2004
Dapsone	11% (range 3%-27%)		Godeau 1997, Damodar 2005, Hernandez 1995
Cytotoxics (cyclophosphamide, vinca alkaloids)	21%		Schiavotto 1993, Facon 1994
% of patients experiencing other AEs:			
Romiplostim	31%		Kuter 2008
IVIg	0%*		Gamunex prescribing information, ASH guidelines (*Conservative estimate; these treatments are associated with a number of infusion reactions but these were not thought likely to last for a 4-week cycle and so were not modelled)
Anti-D	0%*		Scaradavou 1997, Aledort 2007 (*Conservative estimate; these treatments are associated with a number of infusion reactions but these were not thought likely to last for a 4-week cycle and so were not modelled)

Variable	Value non-splenectomised	Value splenectomised (if different)	Source
Corticosteroids	70%		Matzdorff 2007, Zimmer 2004, Aledort 2006
Rituximab	0%*		Arnold 2007 (*Conservative estimate; these treatments are associated with a number of infusion reactions but these were not thought likely to last for a 4-week cycle and so were not modelled)
Immunosuppressants (azathioprine, mycophenolate mofetil, ciclosporin)	12-36%		Sternthal 2008, Provan 2006, Kappers-Klunne 2001, Zwerner 2007
Danazol	35%		Maloisel 2004
Dapsone	24%		Godeau 1997, Damodar 2005, Hernandez 1995
Cytotoxics (cyclophosphamide, vinca alkaloids)	30%‡		Schiavotto 1993, Facon 1994 (‡Cytotoxic treatments are known to have several unpleasant adverse effects but there is little incidence data on most. The percentage of patients experiencing any AEs during/following cytotoxic treatment has been estimated as 30%, which is thought to be a conservative estimate)
1 cycle utility decrement due to serious AEs			
Romiplostim	0.10		Estimated
Rituximab	0.10		Estimated
Azathioprine	0.40		Estimated
Mycophenolate mofetil	0.40		Estimated
Ciclosporin	0.40		Estimated
Danazol	0.40		Estimated
Dapsone	0.40		Estimated
Cyclophosphamide	0.40		Estimated
Vinca alkaloids	0.40		Estimated
IVIg	0.10		Estimated
Anti-D	0.10		Estimated
IV Steroids	0.10		Estimated

Variable	Value non-splenectomised	Value splenectomised (if different)	Source
Utility decrement due to other AEs	0.10		Estimated
Cycle total treatment cost (see cost section below for further detail)			
[redacted]	[redacted]	[redacted]	[redacted]
Rituximab	£6,300.90		British National Formulary + NHS Reference Costs
Azathioprine	£274.29		British National Formulary + NHS Reference Costs
Mycophenolate mofetil	£408.71		British National Formulary + NHS Reference Costs
Ciclosporin	£302.04		British National Formulary + NHS Reference Costs
Danazol	£287.88		British National Formulary + NHS Reference Costs
Dapsone	£488.12		British National Formulary + NHS Reference Costs
Cyclophosphamide	£682.16		British National Formulary + NHS Reference Costs
Vinca alkaloids	£1,082.16		British National Formulary + NHS Reference Costs
Watchful waiting	£262.00		British National Formulary + NHS Reference Costs
IVIg	£7,112.74		British National Formulary + NHS Reference Costs
Anti-D	£5,666.66		British National Formulary + NHS Reference Costs
IV Steroids	£651.90		
Bleed Costs			
Outpatient bleed	£220.00		Reference Costs (general surgery)
Other bleed requiring hospitalisation	£1,718.00		NHS Reference Costs (cost of inpatient bleeding event)
Gastrointestinal bleed	£1,395.00		NHS Reference Costs (cost of HRG F62)
Intracranial haemorrhage	£3,680.00		NHS Reference Costs (cost of HRG A19)
Utility values for health states			
Platelet > 50,000 and no bleed	0.91		Amgen UK ITP TTO utility study
Platelet > 50,000 and OP bleed	0.81		Amgen UK ITP TTO utility study
Platelet < 50,000 and no bleed	0.89		Amgen UK ITP TTO utility study

Variable	Value non-splenectomised	Value splenectomised (if different)	Source
Platelet < 50,000 and OP bleed	0.77		Amgen UK ITP TTO utility study
Platelet < 50,000 and IH bleed	0.28		Amgen UK ITP TTO utility study
Platelet < 50,000 and GI bleed	0.54		Regier DA, et al Cost-effectiveness of self-managed versus physician managed oral anticoagulation therapy
Platelet < 50,000 and other bleed	0.54		Regier DA, et al Cost-effectiveness of self-managed versus physician managed oral anticoagulation therapy

7.2.6.2 *Why was this particular type of model used?*

There is no requirement for memory within the model beyond the previous health state the patient was in and therefore a cohort based model is appropriate. Furthermore a lifetime individual patient model with frequently occurring events would require an unfeasibly large processing time.

7.2.6.3 *What was the justification for the chosen structure? How was the course of the disease/condition represented? Please state why any possible other structures were rejected.*

Please see below.

7.2.6.4 *What were the sources of information used to develop and inform the structure of the model?*

The structure of the model was informed by clinical guidelines for ITP (ASH 1996[1] and BCSH 2003)[2] and recent reviews of ITP (for instance Godeau et al 2007,[3] Cines & Bussel 2005,[6] Cines & Blanchette 2002).[43]

7.2.6.5 *Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?*

All relevant features of the condition are considered.

7.2.6.6 *For discrete time models, what was the model's cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?*

The model's cycle length is 4 weeks. The draft SPC states that platelet counts should be assessed weekly until a stable platelet count ($\geq$ 50 x 10^9/l for at least 4 weeks without dose adjustment) has been achieved. Platelet counts should be assessed monthly thereafter. Therefore once stability has been achieved, patient's platelet counts are assessed monthly and thus a 4 week time cycle is appropriate.

7.2.6.7 *Was a half-cycle correction used in the model? If not, why not?*

Yes. A half cycle value was subtracted from the costs and QALYs of each patients starting state to account for the half cycle shift. There is no adjustment on exit from the model as it is a lifetime model and the cohort is absorbed before the end of the model. Also, the model cycle (4 weeks) is small relative to overall survival in the model.

7.2.6.8 *Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about*

the longer-term difference in effectiveness between the technology and its comparator?

For each treatment modelled, the time to failure is taken where possible from the literature. The literature often reports a percentage of patients that are still responding to treatment after a certain amount of time. Those data points are used to estimate treatment durability curves from which the mean time to treatment failure is estimated.

For romiplostim, the time to failure is taken from the reported number of patients still on therapy at 12 week intervals from the 24 week trial and the long-term open-label extension study. A curve is fitted to these data and the mean duration on treatment estimated.

It is assumed that a patient's initial response to treatment is independent of the time in which they start treatment and is independent of how many treatments the patient has previously failed. There is considerable heterogeneity in the patient populations observed in the literature. Patients range from those that are newly diagnosed and thus are likely to respond well to treatment to those who have failed on previous therapies and thus are likely to be poor responders. Due to the poor quality of the data it has not been possible to account for the heterogeneity and thus we have to assume that the benefits are independent of the underlying patient disposition. This is likely bias towards comparator treatments which are further down in the treatment pathway and are given to severely refractory patients, but in the literature are often assessed among less refractory patients who respond better.

b) Non-model-based economic evaluations

7.2.6.9 *Was the evaluation based on patient-level economic data from a clinical trial or trials?*

This approach was not used.

7.2.6.10 *Provide details of the clinical trial, including the rationale for its selection.*

N/A

7.2.6.11 *Were data complete for all patients included in the trial? If not, what were the methods employed for dealing with missing data for costs and health outcomes?*

N/A

7.2.6.12 *Were all relevant economic data collected for all patients in the trial? If some data (for example, resource-use or health-related utility data) were collected for a subgroup of patients in the trial, was this subgroup prespecified and how was it identified? How do the baseline characteristics and effectiveness results of the subgroup differ from those of the full trial population? How were the data extrapolated to a full trial sample?*

N/A

7.2.6.13 *Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about any longer-term differences in effectiveness between the technology and its comparator?*

N/A

7.2.7 Clinical evidence

Where relevant, answers to the following questions should be derived from, and consistent with, the clinical evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided and a justification for the approach provided.

7.2.7.1 *How was the baseline risk of disease progression estimated? Also state which treatment strategy represents the baseline.*

Since ITP treatments are generally not thought to be curative (except in the case of splenectomy, not modelled here), it is assumed that patients' platelet counts may only increase when they receive treatment, for the defined length of time appropriate for that treatment. Disease progression occurs, with the patient's platelet count dropping below 50 x 10^9/l.

7.2.7.2 *How were the relative risks of disease progression estimated?*

As described in Section 6.0, it was not possible to estimate a relative risk since most of the comparator data is derived from single-arm uncontrolled studies. The romiplostim phase 3 trials compare romiplostim-plus-standard-of-care to placebo-plus-standard-of-care, but romiplostim has not been compared individually to each potential comparator treatment.

Therefore, for each treatment, three parameters have been estimated from the available clinical data (see Sections 6.4 and 6.8): a) percentage of patients having a platelet response, b) time from treatment initiation to start of response, and c) duration of response (time from treatment initiation to treatment withdrawal, "time to failure").

7.2.7.3 *Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?*

Data from the romiplostim phase 3 trials was used to indicate what proportion of patients with platelets under or over 50 x 10^9/l experienced a bleeding event. For patients with platelets under 50 x 10^9/l, data from the romiplostim phase 3 trials was used to indicate what proportion of bleeding events led to hospitalisation and, for bleeds requiring hospitalisation, what proportion of each type of bleed occurred (intracranial haemorrhage, gastrointestinal bleed, or other bleeding-related hospitalisation). The same relationship of bleeding to other events was assumed in the non romiplostim arm.

The mortality risks and utility decrements associated with each type of bleed are based on an analysis of the Nationwide Inpatient Sample (NIS) from 2003 to 2006. The NIS is a 20% random sample of all inpatient discharges in the United States across all ages and payers. It provides information on diagnoses, procedures, costs, length of stay, and disposition upon discharge (including death). Based on information from 29,518 discharges across 4 years in patients with diagnosis codes indicating ITP, we calculated the following population-based mortality rates used in the model: gastrointestinal bleed (3.6%), intracranial haemorrhage (13.2%), other bleeding hospitalisation (1.7%). The mortality rate for each event was applied in the month during which the event took place.

In addition, adverse event data for each treatment was taken from a variety of sources (see Table 7.2)

7.2.7.4 *Were the health effects or adverse effects associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?*

The adverse effects associated with romiplostim and with the comparator treatments were included in the economic evaluation, as many ITP treatments are immunosuppressive and are associated with serious adverse effects. Data on adverse events and the rate of occurrence is extremely underreported in the literature, reflecting the unlicensed nature of many of the comparators. We have modelled adverse events from the best estimates we can get of the rate of serious AEs or the rate of discontinuation due to AEs and less severe AEs.

We take the reported risk of severe AE incidence for each intervention and evenly distribute the probability over the mean response time for the intervention. A utility decrement is estimated for the adverse events. The same technique is used for less severe AEs using a smaller estimated utility decrement. There is a paucity of data on the utility decrement associated with the AEs and therefore these have had to be estimated to reflect the unpleasant treatments available as alternatives.

The effect of varying the AE rates and related utility decrements is examined in sensitivity analysis and show that the cost effectiveness is not particularly sensitive to these assumptions.

Full details of adverse events are provided in section 6.7 and also in an Excel document submitted as an Appendix.

Table 7.2: Adverse event data and sources used in the model

Treatment	Serious AEs or discontinuations	Other AEs lasting for a 4-week cycle	References
Romiplostim	3% (range 2-4%)†	31%	Kuter 2008
IVIg	2.1% (range 0.5-3.8%)	0%*	Gamunex prescribing information, ASH guidelines
Anti-D	2.8%	0%*	Scaradavou 1997, Aledort 2007
Corticosteroids	3%	70%	Matzdorff 2007, Zimmer 2004, Aledort 2006
Rituximab	3.3%	0%*	Arnold 2007
Immunosuppressants (azathioprine, mycophenolate mofetil, ciclosporin)	15% (range 11%-30%)	12-36%	Sternthal 2008, Provan 2006, Kappers-Klunne 2001, Zwerner 2007
Danazol	16%	35%	Maloisel 2004
Dapsone	11% (range 3%-27%)	24%	Godeau 1997, Damodar 2005, Hernandez 1995
Cytotoxics (cyclophosphamide, vinca alkaloids)	21%	30%‡	Schiavotto 1993, Facon 1994

*Conservative estimate; these treatments are associated with a number of infusion reactions but these were not thought likely to last for a 4-week cycle and so were not modelled
†These values are the treatment-related serious AEs (2%) and AEs leading to discontinuation (4%) from the romiplostim arms of the Phase 3 trials. These values were thought to be most comparable to values in the literature for the comparator treatments.
‡Cytotoxic treatments are known to have several unpleasant adverse effects but there is little incidence data on most. The percentage of patients experiencing any AEs during/following cytotoxic treatment has been estimated as 30%, thought to be a conservative estimate.

7.2.7.5 *Was expert opinion used to estimate any clinical parameters? If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?*

N/A

7.2.7.6 *What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?*

With a variety of poor quality research available to inform the model about the efficacy and side effect profile of comparator treatments, it has inevitably been necessary to make judgements about which figures to use. We have tried to indicate what the issues are in these choices both in this section and in section 6.

7.2.8 Measurement and valuation of health effects

The value of health effects should be expressed in terms of QALYs for the appropriate time horizon. For the reference case, the measurement of changes in HRQL should be reported directly from patients and the value of changes in patients' HRQL (that is, utilities) should be based on public preferences using a choice-based method. The EQ-5D is the preferred measure of HRQL in adults. The methods to elicit EQ-5D utility values should be fully described. When EQ-5D data are not available or are inappropriate for the condition or effects of treatment, the valuation methods should be fully described and comparable to those used for the EQ-5D. Data collected using condition-specific, preference-based measures may be presented in separate analyses. The use of utility estimates from published literature must be supported by evidence that demonstrates that they have been identified and selected systematically.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

7.2.8.1 *If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?*

QALYs were used to express health effects.

7.2.8.2 *Which health effects were measured and valued? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.*

Health effects measured and valued were: having ITP (with or without low platelet counts and with or without minor or severe bleeding); various types of bleeding; and adverse effects of treatments.

7.2.8.3 *How were health effects measured and valued? Consideration should be given to all of the following:*

- *State whether the EQ-5D was used to measure HRQL or provide a description of the instrument/s used.*
- *Provide details of the population in which health effects were measured. Include information on recruitment of sample, sample size, patient characteristics and response rates.*
- *Were the data collected as part of a RCT? Refer to section 5.3 as necessary and provide details of respondents.*
- *How were health effects valued? If taken from the published literature, state the source and describe how and why these values were selected. What other values could have been used instead?*
- *Was a mapping mechanism (or 'cross-walk') generated to estimate health-related utilities of patients in the trials? Provide details of the rationale for the analysis, the instruments used, the sample from which the data were derived and the statistical properties of the mapping mechanism.*

- *Were health states directly valued? If so, provide details of the rationale for the analysis, the HRQL measures that were valued, the population who produced the values and full details of the methods used. Explain the rationale for the analysis and the choice of instruments used.*

There is a paucity of data available in the literature describing the utility associated with ITP. We have therefore commissioned research to provide estimate of health utility values in certain ITP related health states.

Five distinct ITP health states were identified for the cost-effectiveness model by Amgen based on data from the romiplostim clinical trials and input from internal and external clinical experts consulted by Amgen. Health states were defined based on platelet levels, risk of bleeding events, characteristics of bleeding events, and key adverse events:

1. Sufficient platelets, no outpatient bleed
2. Sufficient platelets, outpatient bleed
3. Low platelets, no outpatient bleed
4. Low platelets, outpatient bleed
5. Intracranial hemorrhage (2-6 months)

A stand alone utility survey was conducted with the primary objective to directly measure health utility values for these ITP health states as perceived by members of the UK general public.
A mixture of sources was used to *identify key attributes* along which to describe the 5 ITP health states, included published literature, romiplostim clinical trial data, and patient focus group discussion in the UK. The following key attributes were identified to describe the ITP health states:

- Experiencing a bleeding or bruising episode
- Emotional health: fear of bleeding or dying
- Physical health: physical and sporting activities
- Social activities and usual activities
- Emotional, psychological health
- Women's reproductive health

The *development of exact descriptions* was based on actual romiplostim clinical trial data on AE bleed characteristics and ITP-PAQ quality of life data. Specifically, four patient groups were identified based on AE bleed status and platelet levels. Corresponding median group scores on the ITP-PAQ questionnaire were then used to describe the reported levels of problems in each attribute. The descriptions for the intracranial hemorrhage and the steroid AE health states were primarily based on the literature and expert opinion. Health state descriptions were validated by clinical experts. Further detail on the development and validation of the ITP-PAQ can be found at Appendix 4.

A pilot survey was administered to a random sample of 135 members of the UK general public selected from a managed panel that includes 300,000 individuals in the UK. Sixty-three respondents completed the face-to-face administration of the survey and 72 respondents completed the web-based survey. The purpose of this pilot survey was to compare health utility values

elicited through the web-based utility data collection method and standard face-to-face utility data collection, and improve the final web survey approach.

359 new respondents completed the main web-based survey selected from the same managed panel. The 2001 UK census data were used in the sampling methodology to ensure representativeness by age, gender, and education level. Each respondent completed the following survey questions:

- Evaluation of the 5 ITP health states on the visual analogue scale and using the time trade-off (TTO) method
- Comprehension questionnaire
- Socio-demographic questionnaire

In the TTO part of the survey, respondents were presented with descriptions of each ITP health state. They were then led by a process of 'bracketing' to find their point of indifference between alternatives:

- In case of states regarded better than dead, respondents were asked to select a length of time (X) in 'perfect health' that they regarded as equivalent to 10 years in the ITP state in question. Utility scores were anchored on the Perfect Health and Dead scale: X/10.
- In case of states regarded as worse than dead, the choice was between dying immediately vs. spending a length of time (x) in the target state followed by (10-x) years in the perfect health state. States regarded worse than dead were calculated as X/10-1, so as scores were bounded by -1.

The web survey included verification questions and the time spent on the survey was also measured.

The Wilcoxon rank-sum test was used to compare utility scores for each health state between administration methods. Descriptive statistics were used to evaluate utility scores and results of the questionnaire on ease of administration and comprehension. The two sample t-test was used to compare age and the Chi-squared test was used to compare all categorical variables across the two pilot samples. Wilcoxon signed rank test was used to compare each pair of health state.

In the base case the TTO utility values used were those from the web survey as it was felt that this gave the best representative responder sample. Sensitivity analysis is performed to examine the effect of using the face-to-face set. Utility values are shown in Table 7.3.

Values that were not estimated from the above research were extracted from the literature.

Table 7.3: 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				
Platelets <50 and outpatient bleed				
Platelets <50 and intracranial haemorrhage				
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.	

7.2.8.4 *Were any other generic or condition-specific preference based measures used in the clinical trials? Provide a description of the data below. The results should be considered in a sensitivity analysis (see Section 6.2.11).*

No

7.2.8.5 *Were any health effects excluded from the analysis? If so, why were they excluded?*

No

7.2.9 Resource identification, measurement and valuation

For the reference case, costs should relate to resources that are under the control of the NHS and PSS when differential effects on costs between the technologies under comparison are possible. These resources should be valued using the prices relevant to the NHS and PSS. Evidence should be presented to demonstrate that resource use and cost data have been identified systematically.

Some technologies may have a substantial impact on the costs (or cost savings) to other government bodies. In these exceptional circumstances, costs to other government bodies may be included if this has been specifically agreed with the Department of Health, usually before referral of the topic. When non-reference-case analyses include these broader costs, explicit methods of valuation are required. In all cases, these costs should be reported separately from NHS/PSS costs. These costs should not be combined into an incremental cost-effectiveness ratio (ICER; where the QALY is the outcome measure of interest).

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

7.2.9.1 *What resources were included in the evaluation? (The list should be comprehensive and as disaggregated as possible.)*

The resources included in the evaluation are shown in Table 7.4.

Table 7.4: Summary of costs included in the model

Variable	Description	Cost	Source
Treatment costs			
Romiplostim cost per vial*	[redacted] per ug; [redacted] this equates to [redacted] per ug. Therefore the cost of a [redacted] is priced at [redacted] and a 250ug vial is taken as being [redacted].	[redacted] [redacted]	[redacted]
Romiplostim cost per patient per 4-week cycle, non-splenectomised	Mean dose 242 μg, therefore patients use on average [redacted] (or 0.93 of the 250 μg) vials. Cost per 4-week cycle: (4 * 0.93 * [redacted]) +4 lab tests (£48) + 2 physician appointments (£214) = [redacted]	[redacted]	Romiplostim phase 3 trials (Kuter 2008)
Romiplostim cost per patient per 4-week cycle, splenectomised	Mean dose 388 μg, therefore patients use on average [redacted] (or 1.38 of the 250 μg) vials. Cost per 4-week cycle: (4 * 1.38 * [redacted]) + 4 lab tests (£48) + 2 physician appointments (£214) = [redacted].	[redacted]	Romiplostim phase 3 trials (Kuter 2008)

Variable	Description	Cost	Source
Rituximab cost per 4-week course	Total dose for 4 weeks = (375 mg/m^2 * average body surface area of 2 m^2 * 4 weekly doses) = 3,000 mg. Cost = (£174.63 per 100 mg or £1.75/mg * 3,000 mg) + cost of 4 administrations (£800) + 4 lab tests (£48) + 2 physician appointments (£214) = £6,300.90	£6,300.90	British National Formulary + NHS Reference Costs
Azathioprine cost per 4-week cycle	Total dose = (1.5 mg/kg/day * average weight of 83.7 kg * 28 days) = 3,515.4 mg per cycle. Cost per pack = £9.79 (56 * 50 mg tablets). Tablets per cycle = 70.3. Cost per cycle = (£9.79 / 56 tablets * 28 days) + 4 lab tests (£48) + 2 physician appointments (£214) = £274.29	£274.29	British National Formulary + NHS Reference Costs
Mycophenolate mofetil cost per 4-week cycle	Dose = 1.5 g/day. Cost per pack = £87.33 (50 * 500 mg tablets). Cost per day = (£87.33 / 50 * 3) = £5.24. Cost per 4-week cycle = £5.24 * 28+ 4 lab tests (£48) + 2 physician appointments (£214) = £408.71	£408.71	British National Formulary + NHS Reference Costs
Ciclosporin cost per 4-week cycle	Total dose = (5 mg/kg/day * average weight of 83.7 kg * 28 days) = 11,718 mg/cycle. Cost per pack = £57.89 (30 * 100 mg tablets). Cost per mg = £0.02. Cost per cycle = (£0.02/mg * 11,718 mg) + 4 lab tests (£48) + 2 physician appointments (£214) = £488.12	£488.12	British National Formulary + NHS Reference Costs
Danazol cost per 4-week cycle	Dose = 300 mg/day. Cost per pack = £64.18 (56 * 200 mg tablets) or £17.04 (60 * 100 mg tablets). Cost per day (i.e. for 300 mg) = (£64.18/56 + £17.04/60) = £1.43. Cost per 4-week cycle = £1.43 * 28+ 4 lab tests (£48) + 2 physician appointments (£214) = £302.04	£302.04	British National Formulary + NHS Reference Costs
Dapsone cost per 4-week cycle	Dose = 75 mg/day. Cost per pack = £17.25 (28 * 50 mg tablets). Cost per day = (£17.25 / 28 * 1.5) = £0.92. Cost per 4-week cycle = £0.92 * 28 + 4 lab tests (£48) + 2 physician appointments (£214)= £287.88	£287.88	British National Formulary + NHS Reference Costs

Variable	Description	Cost	Source
Cyclophosphamide cost per course	Total dose = (1 g/m^2/dose * average body surface area 2m^2 * mean of 2 doses [Reiner 1995]) = 4 g per course. Cost = (£5.04/g * 4 g) + cost of 2 administrations (£400) + 4 lab tests (£48) + 2 physician appointments (£214)= £682.16	£682.16	British National Formulary + NHS Reference Costs
Vinca alkaloids	No clear dosing information. Assume cost of cyclophosphamide (since drug cost is minimal compared to administration cost). Recommended 4-6 weeks dosing. Assume 4 weeks. therefore cost per course + 4 lab tests (£48) + 2 physician appointments (£214) = £1082.16.	£1082.16	British National Formulary + NHS Reference Costs
Watchful waiting: cost per 4-week cycle	Cost = 4 lab tests (£48) plus 2 consultant visits (£214) = £262.00	£262.00	British National Formulary + NHS Reference Costs
IVIg cost per infusion	Total dose = 1 g/kg/day * 2 days * average weight 83.7 kg = 167.4g. Cost = (£40.10/g * 167.4g) + administration cost of 2-day infusion (£400) = £7,112.74	£7,112.74	British National Formulary + NHS Reference Costs
Anti-D	Dose = (average of 50 ug/kg and 75 ug/kg) = 62.5 ug/kg. Total dose = 62.5 ug/kg * average weight 83.7 kg = 5,231 ug = 5.231 mg. Cost = (£1,045/mg * 5.231 mg) + administration cost of 1-day infusion (£220) = £5,666.66	£5,666.66	British National Formulary + NHS Reference Costs
IV Steroids	Dose = 1g administered 3 times over 3 days. Cost per gram = £17.30. 3 administrations of £200 each.	£651	British National Formulary + NHS Reference Costs
Costs of managing bleeds			
Outpatient bleed	"General surgery" cost	£220.00	British National Formulary + NHS Reference Costs (general surgery)
Other bleed requiring hospitalisation	Cost of inpatient bleeding event	£1,718.00	British National Formulary + NHS Reference Costs
Gastrointestinal bleed	Cost of HRG F62	£1,395.00	British National Formulary + NHS Reference Costs
Intracranial haemorrhage	Cost of HRG A19	£3,680.00	British National Formulary + NHS Reference Costs

*Please note that the cost of romiplostim has not yet been finalised.

7.2.9.2 *How were the resources measured?*

During the conduct of romiplostim clinical studies, only 500µg single use vials have been available for use. Analyses from Phase 1 and 2 studies involving mostly splenectomised patients had suggested that 500µg vials of romiplostim would often be required to treat the ITP population. However, the Phase 3 studies included both splenectomised and non-splenectomised patients, the latter group requiring lower doses of romiplostim. Based upon the analysis of dosing data from the Phase 3 studies, including non-splenectomised patients, it was recognized that smaller vial sizes should be available. Subsequently, a [redacted] and 250µg single use vial has been planned. The 250µg vial and 500µg vial will be available at launch; and the [redacted]. Given the close proximity in time between the estimated availability of the [redacted] and the potential approval of romiplostim by the EMEA, the economic model assumes the availability of the smaller vial size.

We analyzed the dosing data in the phase 3 trials, as well as in the phase 3 participants in the open-label extension trial using a separate, Excel-based model with Monte Carlo sampling. We used the actual baseline weights in the trial, as well as the actual doses administered each week from week 13 to the end of the study (to avoid the initial titration period for romiplostim). Based on the mean dose administered during this time interval, we calculated an average dose per kilogram (kg) for each patient. These dose/kg estimates were used, along with the baseline weight distribution, to generate a sample of 10,000 hypothetical patient doses (i.e., a random dose/kg was combined with a random weight to generate a dose). Several assumptions were used in estimating the expected dosing

1. We assumed no relationship between body weight and dose/kg
2. We assumed that the trial participant weights are a reasonable sample of patient weights for the refractory population of ITP patients.
3. We assumed that providers would use the most economically advantageous dosing given the overfill of the vials.
4. We assumed a maximum dose of 10 µg/kg.

Based on these analyses, we estimated that non-splenectomised patients would use [redacted] (or equivalent to 0.93 of the 250 µg) vials and splenectomised patients would use [redacted] (or equivalent to 1.38 of the 250 µg) vials. The mean doses were 242 µg and 388 µg, respectively.

Treatment doses for comparators were taken from the British National Formulary (BNF). Where comparator dose is based on body weight we assume the average body weight from the trial (83.7kg) and assume a body surface area of $2m^2$ where required.

Rates and types of bleeding and number of doses of rescue medication for patients with platelets under or over 50 x 10^9/l were taken from the romiplostim phase 3 trials. Number of treatment associated lab tests and physician visits etc are taken from the trial protocol for romiplostim and similar assumptions made for comparator interventions.

7.2.9.3 *Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?*

The rates of use of romiplostim, rescue medication and rates and types of bleeding were taken from the romiplostim phase 3 trials, as was clinical data on the efficacy of romiplostim. Efficacy of comparator treatments was estimated based on published literature

7.2.9.4 *Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)? Provide details and a justification for any assumptions that were made (for example, assumptions regarding types of subsequent treatment).*

Patients are treated continually in the model as they progress through the patient pathway. The resource use for each patient is not assumed to change over time and is driven by the patient's platelet count and treatment pathway position.

7.2.9.5 *What source(s) of information were used to value the resources? Were alternative sources of information available? Provide a justification for the preferred source and explain any discrepancies between the alternatives.*

Drug costs were taken from the British National Formulary (BNF).[143] NHS costs were taken from NHS reference costs as shown in Table 7.4.

7.2.9.6 *What is the unit cost (excluding VAT) of the intervention(s) included in the analysis? Does this differ from the (anticipated) acquisition cost reported in section 1? If price discounts are presented in sensitivity analyses provide details of formal agreements regarding the discount including the period over which the discount is agreed and confirmation of national organisations with which the discount has been agreed for the whole of the NHS in England and Wales.*

The final pricing of romiplostim will not take place until receipt of the final CHMP opinion.

[redacted]

For the economic evaluation, an exchange rate of [redacted]. Therefore the cost [redacted].

All resource costs are shown in Table 7.4 in section 7.2.9.1

7.2.9.7 *Does the technology require additional infrastructure to be put in place? Provide details of data sources used to inform resource estimates and values.*

No additional infrastructure is required.

7.2.9.8 *Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?*

Yes

7.2.9.9 *Were resource values indexed to the current price year?*

Yes.

7.2.9.10 *Provide details of and a justification for any assumptions that were made in the estimation of resource measurement and valuation.*

The average dose per patient is described in section 7.2.9.2

7.2.10 Time preferences

Were costs and health benefits discounted at the rates specified in NICE's reference case?

Yes. An annual discount rate of 3.5% was used for costs and for health benefits.

7.2.11 Sensitivity analysis

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

7.2.11.1 *Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated including a description of alternative scenarios included in the analysis.*

No structural sensitivites were considered.

7.2.11.2 *Which variables were subject to sensitivity analysis? How were they varied and what was the rationale for this?*

The two main drivers of cost effectiveness are the price of romiplostim and the proportion of patients under 50 x 10^9/l that are treated with rescue medication.

[redacted]

The proportion of patients given rescue medication when under 50 x 10^9/l was varied from a lower bound where only those who have a hospitalised bleed are treated, to an upper bound where every patient with a platelet count < 50 x 10^9/l receives rescue therapy.

An area of uncertainty in the model is in the rates and effect of the adverse events for the modelled treatments. These have largely been estimated in the model due to a paucity of any evidence in the literature. We show the effect of varying these estimates, by assuming a lower bound of zero adverse events up to an upper bound which is 50% higher that that we have estimated.

Utility values taken from the UK survey that are used in the base case are taken from a web based questionnaire. A second set of utilities is presented for surveys conducted face-to-face and generally are higher in value. A sensitivity analysis is performed using this set.

7.2.11.3 *Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.*

A PSA has been undertaken. Where available, distributions have been used from the literature or from trial data analysis and these are shown in Table 7.1. Due to the poor quality of the available comparator data, there are very few distributions available for us to use. We have therefore had to estimate a majority of those used in the PSA. This was done by taking the range of reported values for a particular variable and assuming a distribution based on these values, or where only one point estimate was available this was varied by $\pm$ 30% to give an approximation of the uncertainty. A full list of variables and the assumed distribution is given in Table 7.5.

We appreciate that this is not an ideal way to perform a PSA, however it was felt that an approach of estimating distributions and providing an idea of how the variables in the model interact was superior to not providing a PSA at all.

Table 7.5: Summary of values and distributions used in PSA.

Variable	Assumed distribution	Calculated from data or ±30% estimate
Proportion of patients responding to treatment		
Romiplostim	Beta (18.13 , 2.52)	±30% estimate
Rituximab	Beta (17.48 , 12.81)	±30% estimate
Azathioprine	Beta (20.84 , 20.84)	Calculated from data
MMF	Beta (9.44 , 7.26)	Calculated from data
Ciclosporin	Beta (20.84 , 20.84)	Calculated from data
Dapsone	Beta (10.65 , 9.19)	Calculated from data
Danazol	Beta (22.9 , 27.66)	±30% estimate
Cyclophosphamide	Beta (12.11 , 5.19)	±30% estimate
Vinca alkaloids	Beta (13.42 , 6.61)	±30% estimate
IVIg	Beta (6.54 , 1.72)	Calculated from data
Anti-D	Beta (22.61 , 26.59)	±30% estimate
Durability of treatment response		
Romiplostim	Lognormal	Calculated from data
Rituximab	Normal (0.05 , 0.01)	Calculated from data
Azathioprine	Normal (0.05 , 0.02)	Calculated from data
MMF	Normal (5.68 , 0.87)	±30% estimate
Ciclosporin	Normal (16.15 , 2.47)	±30% estimate
Dapsone	Normal (19.39 , 2.97)	Calculated from data
Danazol	Normal (0.01 , 0.01)	Calculated from data
Cyclophosphamide	Normal (26.99 , 4.13)	±30% estimate
Vinca alkaloids	Normal (1.4 , 0.21)	±30% estimate
Bleeding risks		
Probability of bleed: platelets > 50,000 – outpatient	Beta (39.58 , 517.75)	±30% estimate
Probability of bleed: platelets < 50,000 – inpatient	Beta (40.83 , 919.83)	±30% estimate
Probability of bleed: platelets < 50,000 – outpatient	Beta (22.81 , 27.32)	±30% estimate
Proportion of patients that are treated with rescue therapy	Beta (27.64 , 52.61)	±30% estimate
Bleed death - Other Bleed	Beta (41.94 , 2425.22)	±30% estimate
Bleed death - GI Bleed	Beta (41.11 , 1100.88)	±30% estimate
Bleed death - IH Bleed	Beta (36.92 , 242.76)	±30% estimate
% of patient suffering serious AE		
Romiplostim	Beta (41.37 , 1337.76)	±30% estimate
Azathioprine	Beta (36.13 , 204.75)	±30% estimate
MMF	Beta (36.13 , 204.75)	±30% estimate
Danazol	Beta (36.13 , 204.75)	±30% estimate
Dapsone	Beta (37.88 , 306.48)	±30% estimate
Ciclosporin	Beta (35.69 , 187.4)	±30% estimate
Cyclophosphamide	Beta (33.51 , 126.06)	±30% estimate
Vinca alkaloids	Beta (33.51 , 126.06)	±30% estimate
Serious AE utility decrement		
Romiplostim	Beta (42.65 , 50790.11)	±30% estimate
Rituximab	Beta (42.44 , 7581.53)	±30% estimate
Azathioprine	Beta (41.6 , 1636.02)	±30% estimate
MMF	Beta (38.93 , 414.02)	±30% estimate
Danazol	Beta (42.53 , 12247.5)	±30% estimate
Dapsone	Beta (41.6 , 1636.02)	±30% estimate
Ciclosporin	Beta (41.32 , 1286.33)	±30% estimate
Cyclophosphamide	Beta (41.87 , 2191.47)	±30% estimate
Vinca alkaloids	Beta (29.33 , 66.65)	±30% estimate
Mild/Moderate AE rate		

Variable	Assumed distribution	Calculated from data or ±30% estimate
Romiplostim	Beta (29.14 , 64.87)	±30% estimate
Rituximab	Beta (0 , 0)	±30% estimate
Azathioprine	Beta (32.2 , 101.97)	±30% estimate
MMF	Beta (32.2 , 101.97)	±30% estimate
Danazol	Beta (32.2 , 101.97)	±30% estimate
Dapsone	Beta (32.2 , 101.97)	±30% estimate
Ciclosporin	Beta (27.39 , 50.88)	±30% estimate
Cyclophosphamide	Beta (29.58 , 69.02)	±30% estimate
Vinca alkaloids	Beta (29.58 , 69.02)	±30% estimate
Mild/moderate AE disutility		
Romiplostim	Beta (42.65 , 50790.11)	±30% estimate
Rituximab	Beta (42.44 , 7581.53)	±30% estimate
Azathioprine	Beta (41.6 , 1636.02)	±30% estimate
MMF	Beta (38.93 , 414.02)	±30% estimate
Danazol	Beta (42.53 , 12247.5)	±30% estimate
Dapsone	Beta (41.6 , 1636.02)	±30% estimate
Ciclosporin	Beta (41.32 , 1286.33)	±30% estimate
Cyclophosphamide	Beta (41.87 , 2191.47)	±30% estimate
Vinca alkaloids	Beta (29.33 , 66.65)	±30% estimate
Utilities		
Platelet > 50,000 and no bleed	Beta (4.1 , 1.2)	Calculated from data
Platelet > 50,000 and OP bleed	Beta (3 , 1.1)	Calculated from data
Platelet < 50,000 and no bleed	Beta (4.8 , 1.2)	Calculated from data
Platelet < 50,000 and OP bleed	Beta (3.5 , 1.1)	Calculated from data
Platelet < 50,000 and IH bleed	Beta (3 , 1.1)	Calculated from data
Platelet < 50,000 and GI bleed	Beta (19.09 , 16.27)	±30% estimate
Platelet < 50,000 and other bleed	Beta (19.09 , 16.27)	±30% estimate
Proportion of patients that receive each intervention		
Rituximab	Beta (16.97 , 11.87)	±30% estimate
Azathioprine	Beta (16.97 , 11.87)	±30% estimate
MMF	Beta (26.64 , 45.92)	±30% estimate
Danazol	Beta (40.75 , 880.16)	±30% estimate
Dapsone	Beta (21.76 , 23.67)	±30% estimate
Ciclosporin	Beta (39.63 , 526.47)	±30% estimate
Cyclophosphamide	Beta (41.91 , 2318.96)	±30% estimate
Vinca alkaloids	Beta (40.36 , 717.48)	±30% estimate

7.2.12 Statistical analysis

7.2.12.1 *How were rates or probabilities based on intervals transformed into (transition) probabilities?*

Probabilities that occur over a fixed time period in the model are assumed to be distributed evenly over the time period using the formula

$$1-(1-\text{probability})^{\wedge(1/\text{number of cycles})}$$

to calculate the cycle transition probability. Where a mean time to an event is given then the rate 1/(number of cycles) is used to calculate the transition probability

7.2.12.2 *Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.*

Patients who fail on a number of treatments are seen as being increasingly refractory and are less likely to respond to further treatments. This is not included in the model due to lack of published evidence. The romiplostim phase 3 pivotal trials recruited patients who were quite refractory, with 94% of splenectomised patients and 32% of non-splenectomised patients having received at least 3 prior ITP treatments.

7.2.13 Validity

Describe the measures that have been undertaken in order to validate and check the model.

The model has been calibrated to ensure that the amount of IV immunoglobulin use over the first 24 weeks by the comparator arm in the model matched that reported by the placebo plus standard of care arms of the two trials (1.8 for non-splenectomised and 2.6 administrations for splenectomised patients).

The proportion of patient receiving each treatment generated by the model has been checked against the Amgen-commissioned physician survey data for each treatments UK usage.

To check that there are at no point any negative values for the proportion of the cohort in a health state, each variable has been set to its maximum and minimum value and the effect on the model monitored.

For each cycle and each treatment sheet in the model a check cell is included which adds up all the movements for the cycle and ensures that the overall cohort value always adds up to 1.

The increased mortality rates for bleeds have been set to zero and the resultant cohort mortality validated against expected all-cause mortality rates.

Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following:

- costs, QALYs and incremental cost per QALY
- disaggregated results such as life years gained, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a statement as to whether the results are based on a probabilistic sensitivity analysis
- cost-effectiveness acceptability curves including a representation of the cost-effectiveness acceptability frontier
- scatterplots on cost-effectiveness quadrants
- a tabulation of the mean results (costs, QALYs, ICERs) the probability that the treatment is cost-effectiveness a thresholds of £20,000-£30,000 per QALY gained and the error probability.

7.2.14 Base-case analysis

7.2.14.1 *What were the results of the base-case analysis?*

Results for non-splenectomised and splenectomised patients are run at the point estimates of each variable, presented in Table 7.6. A detailed breakdown of these results is presented in Table 7.7. These show that in non-splenectomised patients, a treatment pathway that has romiplostim as the 1st option post oral corticosteroids is [redacted] compared to a pathway without romiplostim. In splenectomised patient's, the ICER is higher at [redacted] reflecting the increased dose of romiplostim required to achieve clinical effectiveness and a possible underestimation of costs in the comparator arm.. These results are based on the efficacy point estimates and not on the results of the probabilistic sensitivity analysis (PSA) as there were not sufficient data on the distribution of each of the input variables to use the output from the PSA.

Table 7.6: Summary of cost effectiveness results

Treatment arm	Costs	QALYS	Marginal Costs	Marginal QALYs	Incremental Cost per QALY
Non-splenectomised					
Standard care	[redacted]	10.76	[redacted]	1.64	[redacted]
Standard care + Romiplostim	[redacted]	12.40			
Splenectomised					
Standard care	[redacted]	11.70	[redacted]	1.13	[redacted]
Standard care + Romiplostim	[redacted]	12.83			

Table 7.7a: Disaggregated breakdown of the cost effectiveness results for non-splenectomised patients

Variable	Treatment path with romiplostim	Treatment path without romiplostim	Marginal difference
Treatment costs			
Romiplostim	[redacted]	[redacted]	[redacted]
Rituximab	£2,696	£3,644	-£948
Azathioprine	£1,409	£1,942	-£533
MMF	£608	£837	-£230
Danazol	£130	£181	-£51
Dapsone	£931	£1,300	-£369
Ciclosporin	£561	£837	-£276
Cyclophosphamide	£138	£196	-£57
Vinca alkaloids	£68	£95	-£27
'watch and rescue'	£243,083	£372,290	-£129,208
Bleed and associated costs	£17,249	£26,879	-£9,630
Total Costs	[redacted]	[redacted]	[redacted]
Life years	23.14	20.22	2.92
Total QALYs	**12.40**	**10.76**	**1.64**

Table 7.7b: Disaggregated breakdown of the cost effectiveness results for non-splenectomised patients

Variable	Treatment path with romiplostim	Treatment path without romiplostim	Marginal difference
Treatment costs			
Romiplostim	£260,471	£0	£260,471
Rituximab	£2,839	£3,689	-£850
Azathioprine	£1,763	£2,332	-£570
MMF	£605	£799	-£195
Danazol	£142	£189	-£47
Dapsone	£1,010	£1,349	-£339
Ciclosporin	£802	£1,134	-£331
Cyclophosphamide	£135	£182	-£47
Vinca alkaloids	£67	£89	-£22
'watch and rescue'	£397,926	£582,144	-£184,219
Bleed and associated costs	£13,104	£19,734	-£6,630
Total Costs	[redacted]	[redacted]	[redacted]
Life years	24.05	22.02	2.03
Total QALYs	**12.83**	**11.70**	**1.13**

A PSA has been performed sampling 1000 sets of input variables from the estimated distributions shown in 7.2.11.3. The results of this analysis are represented as a scatter plot in Figure 7.3a and 7.3b.

Figure 7.3a: Scatter plot of the cost effective quadrants for non-splenectomised patients

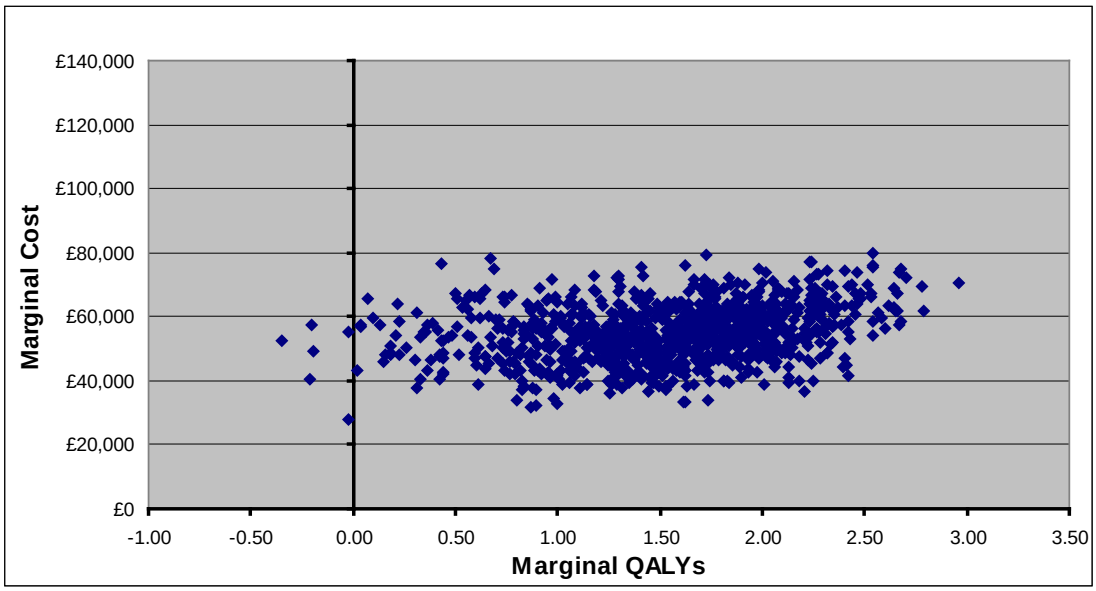
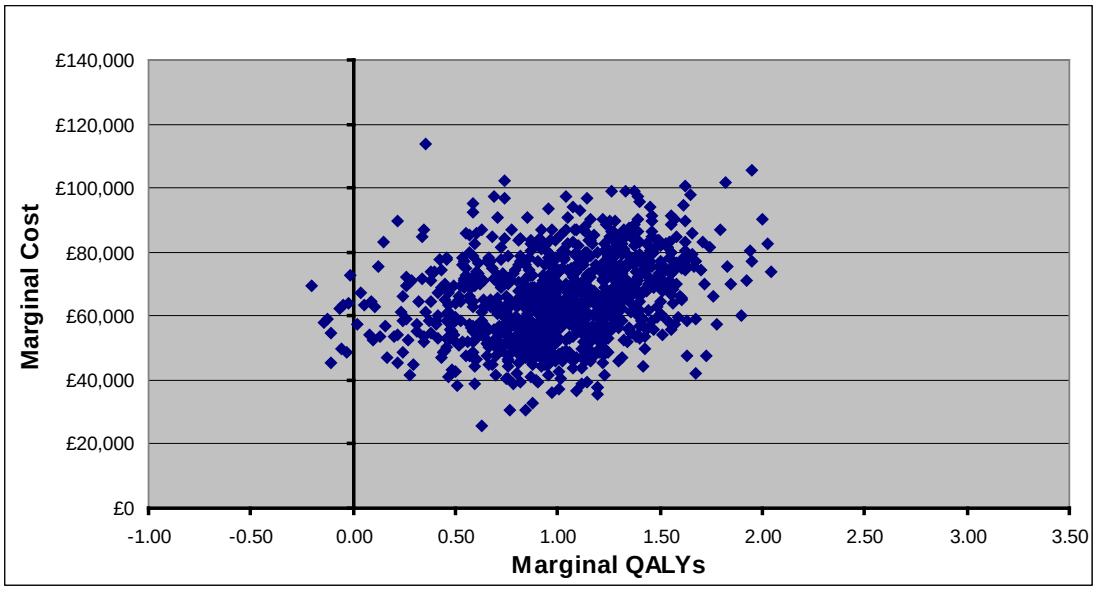


Figure 7.3b: Scatter plot of the cost effective quadrants for splenectomised patients



The results from the PSA are converted into cost-effectiveness acceptability curves (CEACs) which shown the probability that romiplostim is cost effective at different acceptability threshold levels. These curves are shown in Figure 7.4a and 7.4b. The CEACs show that for non-splenectomised patients there is

a 1.1% chance that a treatment arm with romiplostim in is cost effective at an acceptability threshold of £20,000 and a 31.7% chance at a £30,000 threshold. In splenectomised patients this is considerably lower with a 0.8% chance of cost effectiveness at a £30,000 threshold.

Figure 7.4a: Cost Effectiveness Acceptability Curve for Non-splenectomised patients

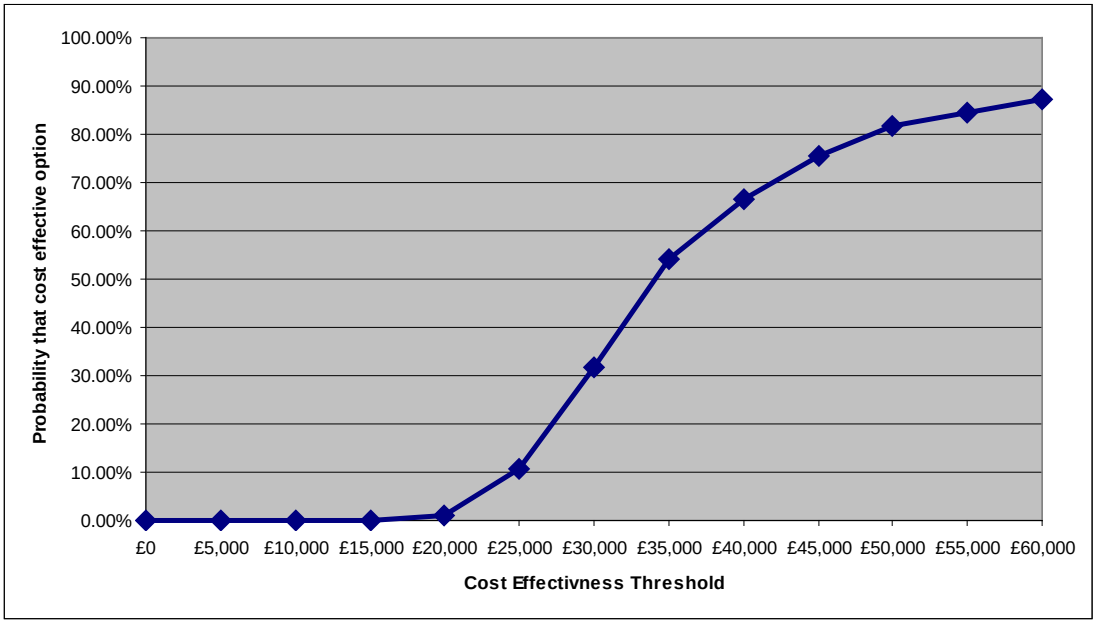
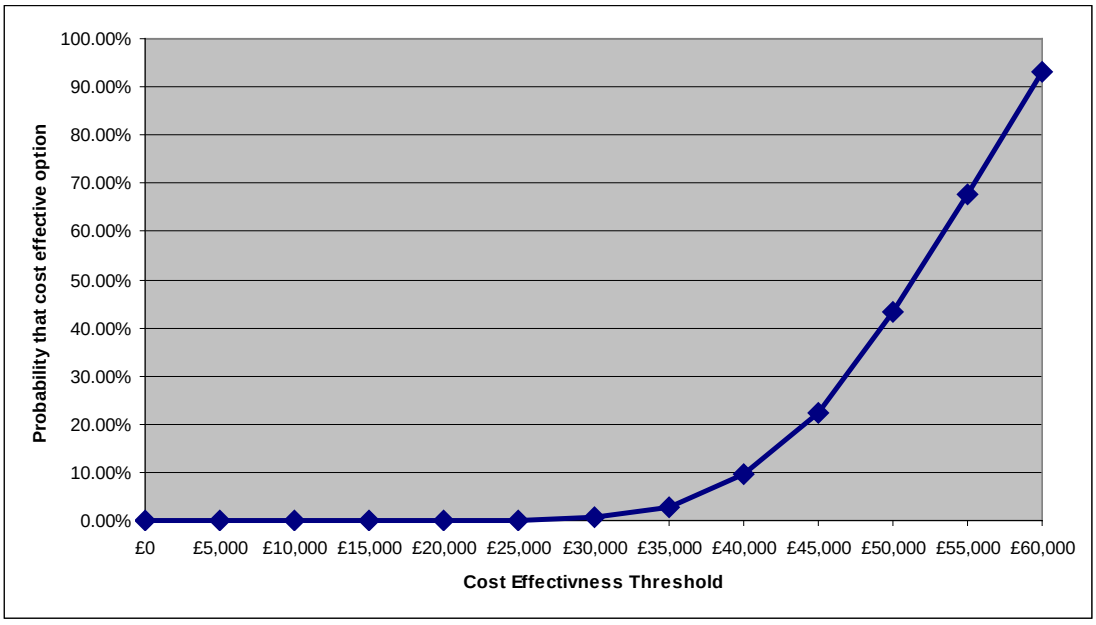


Figure 7.4b: Cost Effectiveness Acceptability Curve for Splenectomised patients



Subgroup analysis

7.2.14.2 *What were the results of the subgroup analysis/analyses if conducted?*

No further subgroups were analysed, in addition to the non-splenectomised and splenectomised populations described above.

7.2.15 Sensitivity analyses

7.2.15.1 *What were the main findings of the sensitivity analyses?*

Price Sensitivity

An analysis was performed examining the effect on the ICER of varying the price of romiplostim. The price used in the basecase analysis [redacted] is based on the US acquisition price. A range of prices is shown varying from [redacted] per ug. The results of the analysis are shown in Figure 7.5 and show that the ICER is strongly driven by the acquisition price of romiplostim and the lower price ranges result in an ICER below £30,000 for the splenectomised patients.

Figure 7.5: A sensitivity analysis investigating the relationship between romiplostim acquisition price and the ICER

[redacted]

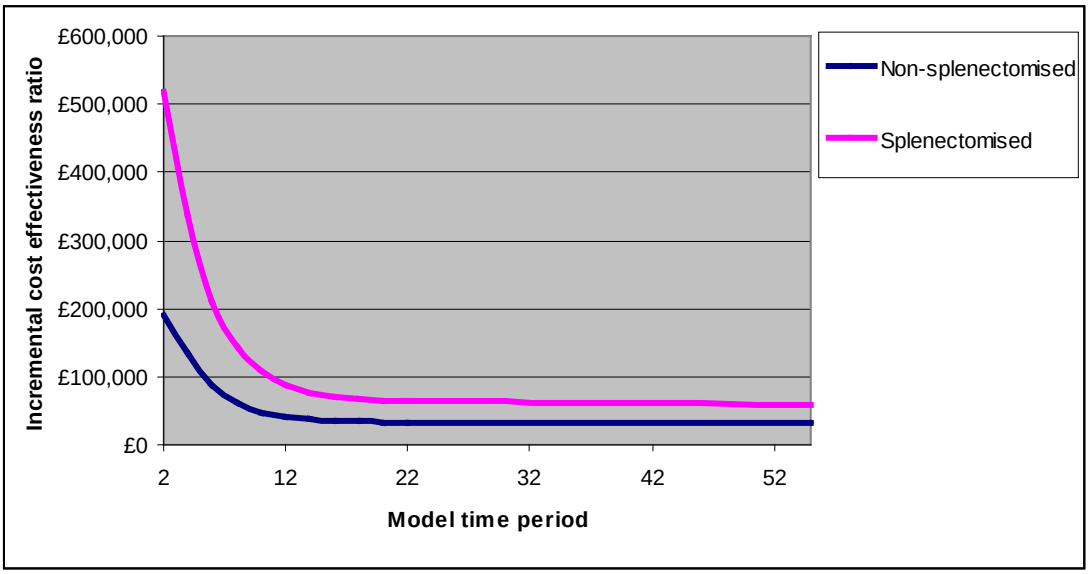
Time period over which the model is run

The model is assumed to be a lifetime model. However, as patients progress down the patient pathway, they eventually reach the stage where they are refractory to all treatments and the only option is 'watch and rescue'. In a lifetime model the majority of patients spend a considerable time in this state. Furthermore, the way in which these patients are treated, their platelet levels and the associated risk of bleed, morbidity and mortality are unknown. By running the model over shorter time periods, the amount of time in which this state contributes to the overall cost effectiveness is reduced, which in turn reduces the long term uncertainty relating to patient epidemiology. However, at the same time, it reduces the reflection of the value that romiplostim brings.

A sensitivity analysis is performed, truncating the run of the model at different time periods to investigate the build up in costs and QALYs over time. This is shown in Figure 7.6. This analysis shows that the cost effectiveness results stabilise after approximately 20 years.

If we were to consider the modelled time period to be 15 years then the ICERs would be £35,963 in the non-splenectomised patients and £73,572 in the splenectomised patients. Although the uncertainty associated with estimating the consequences of treating completely refractory patients would be reduced, this would be at the loss of reality. This sensitivity shows that exactly what happens to patients at this stage is a major determinant of the cost effectiveness of romiplostim. Naïve application of treatment rates derived from observation of much less refractory and severe patients can be misleading.

Figure 7.6: A sensitivity analysis examining the relationship between modelled period and the ICER



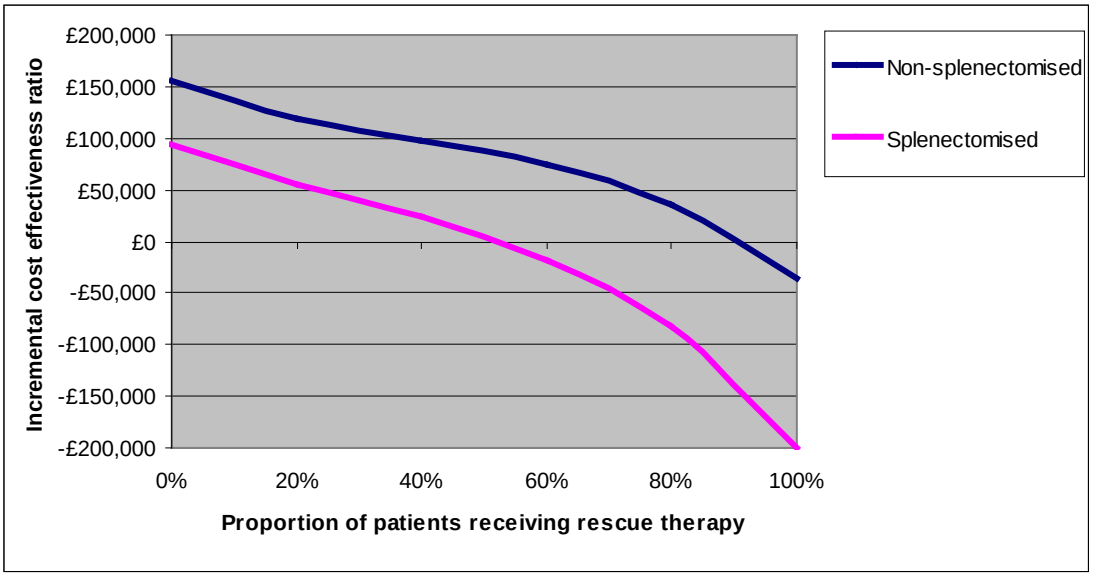
Proportion of non bleeding and minor bleed patient under <50 x 10^9/l that receive rescue medication

The proportion of patients with a platelet count of <50 x 10^9/l that receive rescue medication in the model is calibrated against the trial immunoglobulins usage so that in the first 24 weeks of the model patients have the same rescue therapy usage as observed in the clinical trials (calibrated using a pathway of only 'watch and rescue')

The proportion of patients with a platelet count of <50 x 10^9/l is subject to a sensitivity analysis, varying the rate from 0% (where only patients who suffer a severe bleed resulting in hospitalisation are treated with rescue therapy) to all patients with a platelet count <50 x 10^9/l (Figure 7.7). Ideally, we would like to know the distribution of the proportions of patients by platelet level below 50 x 10/l but in the absence of this information we can only assess plausible

assumptions. The sensitivity analysis shows that once again this is an important area of uncertainty, which we have dealt with conservatively.

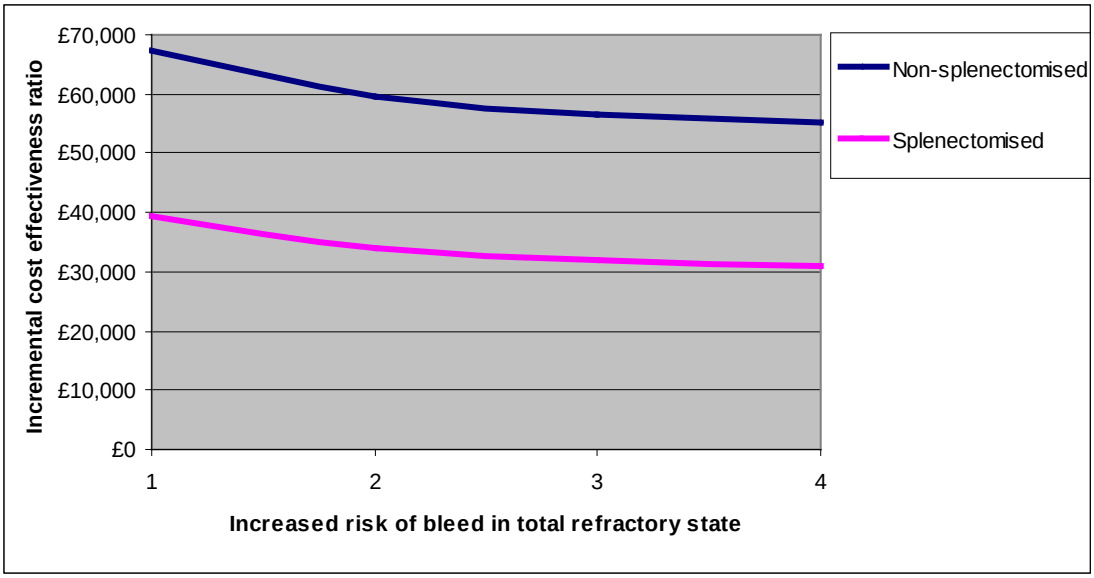
Figure 7.7: A sensitivity analysis investigating the effect of varying the proportion of patients <50 x 10^9/l that receive rescue medication on the ICER



Risk of bleed of refractory patients

In the basecase patients that have failed on all available treatment option and are very refractory are assumed to have double the risk of severe bleed. The effect of varying this assumption is analysed in a sensitivity analysis by assuming a range of 0 increased risk to 4 times the risk. The result of this analysis are shown in figure 7.8.

Figure 7.8: A sensitivity analysis investigating the effect of varying the risk of bleeding in the final refractory state



Utility values

The research investigating the utility values for patients with ITP reported 2 sets of results. The first was based on a web survey which selected a broad cross section of society. The second set of utility values was acquired from face-to-face surveys.

- The face-to-face and the web survey participants were similar in terms of age, gender, employment status, and living status. This was due to that the stratified random sampling aimed to reflect the 2001 UK census population data on key characteristics in both surveys.
- People with primary education level were not present in the face-to-face sample.
- The face-to-face sample included people from two geographical locations (Greater London and Leeds area), while the web sample included all regions of the UK.

The two sets of utility values are shown in Table 7.9. The result of this analysis shows that in the non-splenectomised patients, the utility gain of including romiplostim in the treatment pathway improves with the face-to-face survey values from 1.64 to 1.76 which reduces the ICER from £33,885 to £31,475. In the splenectomised patients the utility gain improves from 1.13 to 1.21 with a reduction in the ICER from £59,611 to £55,376.

This analysis shows that using the face-to-face utility survey values improves the ICER and so using the web based survey in the base case is conservative.

Table 7.9: Utility values used in the base case and the sensitivity analysis

Health state	Web based survey (base case)	Face-to-face survey
Platelets >50 and no bleed	[redacted]	[redacted]
Platelets >50 and outpatient bleed	[redacted]	[redacted]
Platelets <50 and no bleed	[redacted]	[redacted]
Platelets <50 and outpatient bleed	[redacted]	[redacted]
Platelets <50 and intracranial haemorrhage	[redacted]	[redacted]

Adverse events

There is a paucity of available data on the frequency, severity and detrimental effect on utility of adverse events. In the basecase the rates have been extracted as best as possible from the data and the utility detriment values have been estimated. The sensitivity of the cost effectiveness analysis to these values is investigated by reducing the occurrence of adverse events to 0% This only has a small increase on the ICER from £33,885 to £33,907 in the non-splenectomised patients and from £59,611 to £59,645 demonstrating the rate of adverse events in the comparators is not a major driver of cost effectiveness.

7.2.15.2 *What are the key drivers of the cost effectiveness results?*

The key drivers of cost effectiveness are the acquisition price of romiplostim; the time period over which the disease is modelled; the assumptions around the percentage of patients that receive rescue medication when suffering low platelet counts with either no bleed or a minor bleed; and exactly what happens to patients who become completely refractory to treatment other than with rescue medication.

7.2.16 Interpretation of economic evidence

7.2.16.1 *Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?*

No published economic evaluations of romiplostim in ITP were identified.

7.2.16.2 *Is the economic evaluation relevant to all groups of patients who could potentially use the technology?*

Yes; the economic evaluation covers ITP patients who are either non-splenectomised or splenectomised.

7.2.16.3 *What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?*

The main strength of the evaluation lies in its careful reflection of the issues involved, even if there are no good data to allow estimation of the magnitude of effects of use of many of the comparator treatments. We have searched diligently through masses of poor quality evidence relating to comparators to sift out information of relevance and have tried to provide the Appraisal Committee with a sense of the issues involved and what we think is the most reasonable use of the evidence that is available. We have tried to treat frankly the uncertainties involved.

An inescapable weakness is that the data quality on comparators, which is self evidently important in trying to assess the relative effectiveness of romiplostim, is poor. The efficacy we have used for the comparators is likely to be an overestimate since there are no published placebo controlled trials. Most of the published evidence consists of single arm studies.

However, our analysis has shown that the cost effectiveness results are reasonably robust, despite this.

7.2.16.4 *What further analyses could be undertaken to enhance the* robustness/completeness of the results?

Without further well-controlled studies on comparators at appropriate points in the treatment pathway, which are unlikely to be conducted unless they are funded publicly, there are few further analyses which could be undertaken.

8 Assessment of factors relevant to the NHS and other parties

8.1 What is the estimated annual budget impact for the NHS in England and Wales?

Chronic adult ITP is an orphan disease; hence the anticipated number of patients that will require romiplostim is small. The estimated net budget impact for the NHS in the first year is [redacted] for non-splenectomised patients ([redacted] patients) and [redacted] for splenectomised patients ([redacted] patients).

Table 8.1 Budget impact calculation for the NHS in England and Wales

UK population including N.Ireland and Scotland	61Million		
ITP prevalence (no. of patients)	9,949 patients		From Ref 10.
Proportion not needing treatment / acute ITP / responding to steroids	[redacted]		Ref 14.
Chronic ITP prevalence (no. of patients)	[redacted]		[redacted]
Proportion to undergo splenectomy	[redacted]		Ref 13.
→ non splenectomised patient base	[redacted]		[redacted]
→ splenectomised patient base	[redacted]		[redacted]

	Non splenectomised	Splenectomised	Comments
Proportion of eligible patients as per draft indication	[redacted]*	[redacted]	*Proportion of non splenectomised patients with medical contra-indication[14]
Total Eligible patients in UK	[redacted]	[redacted]	
Expected market penetration year 1	[redacted]	[redacted]	
Romiplostim treated patients in year 1 in UK	[redacted]	[redacted]	
Correction to exclude patients from N.Ireland and Scotland	[redacted]	[redacted]	Estimated 10% of total UK
Romiplastim treated patients in year 1 in England and Wales	[redacted]	[redacted]	
Estimated annual drug acquisition cost per patient	[redacted]	[redacted]	[redacted]
Cost offset vs. Standard Care	[redacted]	[redacted]	Cost offset of IVIg, other rescue medications, hospitalisations

			etc.
Marginal (or Net) annual drug cost per treated patient	[redacted]	[redacted]	
Estimated Net Budget impact for the NHS in England and Wales	[redacted]	[redacted]	
Total year 1 impact for NHS in England & Wales	[redacted]		

8.2 *What number of patients were assumed to be eligible? How was this figure derived?*

Assuming market authorization is granted in line with the draft indication, the estimated numbers of patients eligible for treatment with romiplostim for the first year are [redacted] non-splenectomised patients and [redacted] splenectomised patients respectively, as per table 8.1.

Amgen assumes that approximately [redacted]

8.3 *What assumption(s) were made about current treatment options and uptake of technologies?*

The key assumption is that romiplostim will reduce the need for use of rescue medication such as IVIG and anti-D. The economic model fully accounts for the cost offsets of romiplostim (see section 7)

8.4 *What assumption(s) were made about market share (where relevant)?*

We assume a market penetration of [redacted] in the first year in non-splenectomised patients, and [redacted] in the eligible splenectomised patient population.

8.5 *What unit costs were assumed? How were these calculated?*

In the economic modelling we use the [redacted]. This is translated into GBP [redacted]. All other comparator costs are detailed in section 7.2.9.1.

8.6 *In addition to drug costs, consider other significant costs associated with treatment. What is the recommended treatment regime – for example, what is the typical number of visits, and does treatment involve daycase or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a need for other treatments in combination with the technology?*

Romiplostim will be administered as a weekly subcutaneous injection. Upon initiation of therapy patients will undergo a dosage titration phase until platelet

counts are stable above $50x10^9$/l. This will occur in the haematology outpatient clinic. It is expected that this phase will take 4 to 8 weeks. After titration the patients will have the opportunity to administer the subcutaneous injection in the home setting. No other significant costs are anticipated.

8.7 *Were there any estimates of resource savings? If so, what were they?*

The key assumption is that romiplostim will reduce the need for use of rescue medication such as IVIg and anti-D. In the pooled phase 3 trials we observed an average reduction of [redacted] per patient of IVIg/Anti-D rescue medication during the first 24 weeks. The economic model fully accounts for the cost offsets of romiplostim (see section 7)
Cost offset vs. Best Standard Care in non-splenectomised patients is [redacted]
The cost offset in splenectomised patients is [redacted] per patient treated.

8.8 *Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?*

There is an opportunity to reduce the costs and consequences of adverse events due to long term use of steroids and immunosuppressive agents. In addition the reduced occurrence of severe bleeding events implies a potential positive impact on capacity in the NHS.

9 References

Please use the Vancouver style (that is, consecutive numbering throughout the main text). In the reference list, the names of up to six authors should be given, followed by et al.; for example:

1. Chalmers TC, Smith H, Blackburn B, Silverman B, Schroeder B, Reitmen D et al. (1981) Method for assessing the quality of randomized controlled trials. Controlled Clinical Trials 2: 31–9.

(1) George JN, Woolf SH, Raskob GE, Wasser JS, Aledort LM, Ballem PJ et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology.[see comment]. [Review] [295 refs]. Blood 1996; 88(1):3-40.

(2) Provan D, Newland A, Norfolk D, Bolton-Maggs P, Lilleyman J, Greer I et al. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. British Journal of Haematology 2003; 120(4):574-596.

(3) Godeau B, Provan D, Bussel J, Godeau B, Provan D, Bussel J. Immune thrombocytopenic purpura in adults. [Review] [157 refs]. CURR OPIN HEMATOL 2007; 14(5):535-556.

(4) Ballem PJ, Segal GM, Stratton JR, Gernsheimer T, Adamson JW, Slichter SJ. Mechanisms of thrombocytopenia in chronic autoimmune thrombocytopenic purpura. Evidence of both impaired platelet production and increased platelet clearance. J Clin Invest 1987; 80(1):33-40.

(5) Chang M, Nakagawa PA, Williams SA, Schwartz MR, Imfeld KL, Buzby JS et al. Immune thrombocytopenic purpura (ITP) plasma and purified ITP monoclonal autoantibodies inhibit megakaryocytopoiesis in vitro. Blood 2003; 102(3):887-895.

(6) Cines DBB. How I treat idiopathic thrombocytopenic purpura (ITP). Blood 2005; 106(7):2244-2251.

(7) Nichol JL. Endogenous TPO (eTPO) levels in health and disease: possible clues for therapeutic intervention. Stem Cells 1998; 16(Suppl 2):165-175.

(8) Frederiksen H, Schmidt K. The incidence of idiopathic thrombocytopenic purpura in adults increases with age. Blood 1999; 94(3):909-913.

(9) Satia JA. Epidemiology of Immune Thrombocytopenic Purpura in the United Kingdom, Germany, and the Netherlands. 2006. Data on file, Amgen. Ref Type: Report

(10) Satia JA, Acquavella J, Hollowell J. Descriptive Epidemiology of Immune thrombocytopenic Purpura in Three European Countries. 11th conference of the European Hematology Association; Amsterdam 2006;Abstract 936.

(11) Stasi R, Stipa E, Masi M. Long-term observation of 208 adults with chronic idiopathic thrombocytopenic purpura. American Journal of Medicine 1995; 98(5):436-442.

(12) Cohen YC, Djulbegovic B, Shamai-Lubovitz O, Mozes B. The bleeding risk and natural history of idiopathic thrombocytopenic purpura in patients with persistent low platelet counts. Arch Intern Med 2000; 160(11):1630-1638.

(13) Physician survey conducted by Amgen, Zug. 2008.
Ref Type: Report

(14) Physician survey conducted by Amgen, UK. 2008.
Ref Type: Report

(15) Kojouri K, Vesely SK, Terrell DR, George JN. Splenectomy for adult patients with idiopathic thrombocytopenic purpura: a systematic review to assess long-term platelet count responses, prediction of response, and surgical complications. Blood 2004; 104(9):2623-2634.

(16) McMillan R. Therapy for adults with refractory chronic immune thrombocytopenic purpura. ANN INTERN MED 1997; 126(4):307-314.

(17) Szilvassy SJ. Haematopoietic stem and progenitor cell-targeted therapies for thrombocytopenia. Expert Opinion on Biological Therapy 2006; 6(10):983-992.

(18) Deutsch VR, Tomer A. Megakaryocyte development and platelet production. Br J Haematol 2006; 134(5):453-466.

(19) Heyns AP, Badenhorst PN, Lotter MG, Pieters H, Wessels P, Kotze HF. Platelet turnover and kinetics in immune thrombocytopenic purpura: results with autologous 111In-labeled platelets and homologous 51Cr-labeled platelets differ. Blood 1986; 67(1):86-92.

(20) Stoll D, Cines DB, Aster RH, Murphy S. Platelet kinetics in patients with idiopathic thrombocytopenic purpura and moderate thrombocytopenia. Blood 1985; 65(3):584-588.

(21) Aledort LMH. Prospective screening of 205 patients with ITP, including diagnosis, serological markers, and the relationship between platelet counts, endogenous thrombopoietin, and circulating antithrombopoietin antibodies. American Journal of Hematology 2004; 76(3):205-213.

(22) Houwerzijl EJ, Blom NR, van der Want JJ, Esselink MT, Koornstra JJ, Smit JW et al. Ultrastructural study shows morphologic features of apoptosis and para-apoptosis in megakaryocytes from patients with idiopathic thrombocytopenic purpura. Blood 2004; 103(2):500-506.

(23) Kuter DJ, Bussel JB, Lyons RM, Pullarkat V, Gernsheimer TB, Senecal FM et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial.[see comment]. Lancet 2008; 371(9610):395-403.

(24) Amgen Clinical Summary of Efficacy for studies 20030105, 20030212 and 20030213: Data on File, Amgen, Aug 9. 2007.
Ref Type: Report

(25) George JNW. Idiopathic thrombocytopenic purpura: A practice guideline developed by explicit methods for the American Society of Hematology. Blood 1996; 88(1):3-40.

(26) Bussel J, Provan A, Shamsi T, Cheng G, Kovaleva L, Stone N et al. Eltrombopag raises platelet count and reduces bleeding compared with placebo during short-term treatment in chronic idiopathic thrombocytopenic purpura: A phase III study. Haematologica-the Hematology Journal 2007; 92:143.

(27) Matzdorff A, Arnold G, Matzdorff A, Arnold G. Treatment of chronic immune thrombocytopenic purpura: the patients' perspective. European Journal of Haematology 2007; 78(5):381-388.

(28) Zimmer J, Andres E, Noel E, Koumarianou A, Blickle JF, Maloisel F et al. Current management of adult idiopathic thrombocytopenic purpura in practice: a cohort study of 201 patients from a single center. Clinical & Laboratory Haematology 2004; 26(2):137-142.

(29) Aledort LM, Lyons RM, Okano G. Retrospective matched cohort study of immune thrombocytopenic purpura (ITP): complications related to corticosteroid (CS) use. Blood (ASH Annual Meeting Abstracts) 2006; 108(11):Abstract 3295.

(30) Scaradavou A, Woo B, Woloski BM, Cunningham-Rundles S, Ettinger LJ, Aledort LM et al. Intravenous anti-D treatment of immune thrombocytopenic purpura: experience in 272 patients. Blood 1997; 89(8):2689-2700.

(31) Aledort LM, Salama A, Kovaleva L, Robak T, Newland AC, Nugent DJ et al. Efficacy and safety of intravenous anti-D immunoglobulin (Rhophylac) in chronic immune thrombocytopenic purpura. Hematology 2007; 12(4):289-295.

(32) Talecris-Biotherapeutics. Gamunex (immune globulin intravenous) prescribing information. http://www.fda.gov/cber/label/igivbay082703LB.pdf. Accessed Oct 5, 2007. 2007.
Ref Type: Report

(33) Baxter Healthcare Corporation. WinRho SDF Efficacy Information http://www.winrho.com/isi.html. Accessed Jun 28, 2006. 2006.
Ref Type: Report

(34) Cooper N, Woloski BM, Fodero EM, Novoa M, Leber M, Beer JH et al. Does treatment with intermittent infusions of intravenous anti-D allow a proportion of adults with recently diagnosed immune thrombocytopenic purpura to avoid splenectomy?[see comment]. Blood 2002; 99(6):1922-1927.

(35) United States Pharmacopeia Drug Information (USPDI). Drug Information for the Health Care Professional: Drug Point Summary - Rituximab. Vol 1. 27th ed. 2007. Greenwood Village, CO: Thomson Micromedex, Greenwood Village, CO: Thomson Micromedex.
Ref Type: Report

(36) Arnold DM, Dentali F, Crowther MA, Meyer RM, Cook RJ, Sigouin C et al. Systematic review: efficacy and safety of rituximab for adults with idiopathic

thrombocytopenic purpura.[see comment]. [Review] [57 refs]. ANN INTERN MED 2007; 146(1):25-33.

(37) Hanbali A, Khaled Y, Ajrouche H, Ansari S, Janakiraman N. Incidence of hepatitis B reactivation in association with rituximab therapy. Blood 2006; 108(11, Part 1).

(38) Mikhael J, Kessler C, Danese M, Deuson R. Initial and Long-Term Outcomes of Splenectomy in Adult Immune Thrombocytopenic Purpura (ITP) Patients: A Systematic Review and Meta-Analysis. Blood 2007; 110(11):Abstract 1321.

(39) Winslow ER, Brunt LM. Perioperative outcomes of laparoscopic versus open splenectomy: a meta-analysis with an emphasis on complications. Surgery 2003; 134(4):647-653.

(40) Portielje JE, Westendorp RG, Kluin-Nelemans HC, Brand A. Morbidity and mortality in adults with idiopathic thrombocytopenic purpura. Blood 2001; 97(9):2549-2554.

(41) Cortelazzo S, Finazzi G, Buelli M, Molteni A, Viero P, Barbui T. High risk of severe bleeding in aged patients with chronic idiopathic thrombocytopenic purpura. Blood 1991; 77(1):31-33.

(42) Lacey JV, Penner JA. Management of idiopathic thrombocytopenic purpura in the adult. Semin Thromb Hemost 1977; 3(3):160-174.

(43) Cines DB, Blanchette VS. Immune thrombocytopenic purpura.[see comment]. [Review] [103 refs]. N ENGL J MED 2002; 346(13):995-1008.

(44) Kaye J, Schoonen M, Fryzek J. ITP Incidence and Mortality in UK General Practice Research Database (GPRD). 12th conference of the European Hematology Association, Vienna 2007.

(45) McMillan R, Durette C. Long-term outcomes in adults with chronic ITP after splenectomy failure. Blood 2004; 104(4):956-960.

(46) National Institute for Health and Clinical Excellence (NICE): Social Value Judgements, Principles for the development of NICE guidance, second edition. 2005.
Ref Type: Report

(47) McCabe C, Claxton K, Tsuchiya A. Orphan drugs and the NHS: should we value rarity? BMJ 2005; 331(7523):1016-1019.

(48) Berti D, Moons P, Dobbels F, Deuson R, Janssens A, De GS. Impact of corticosteroid-related symptoms in patients with immune thrombocytopenic purpura: results of a survey of 985 patients. Clin Ther 2008; 30(8):1540-1552.

(49) Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995; 273(5):408-412.

(50) Chalmers TC, Celano P, Sacks HS, Smith H, Jr. Bias in treatment assignment in controlled clinical trials. N Engl J Med 1983; 309(22):1358-1361.

(51) AMG 531 Clinical Summary of Efficacy, Amgen data on file. 2007.
Ref Type: Report

(52) Vesely SK, Perdue JJ, Rizvi MA, Terrell DR, George JN, Vesely SK et al. Management of adult patients with persistent idiopathic thrombocytopenic purpura following splenectomy: a systematic review.[see comment]. [Review] [99 refs]. ANN INTERN MED 2004; 140(2):112-120.

(53) Zhou Z, Yang R, Zhou Z, Yang R. Rituximab treatment for chronic refractory idiopathic thrombocytopenic purpura. [Review] [134 refs]. Critical Reviews in Oncology-Hematology 2008; 65(1):21-31.

(54) Maloisel F, Andres E, Zimmer J, Noel E, Zamfir A, Koumarianou A et al. Danazol therapy in patients with chronic idiopathic thrombocytopenic purpura: long-term results. Am J Med 2004; 116(9):590-594.

(55) Bierling P, Godeau B. Intravenous immunoglobulin for autoimmune thrombocytopenic purpura. [Review] [47 refs]. Human Immunology 2005; 66(4):387-394.

(56) Bierling P, Godeau B. Intravenous immunoglobulin and autoimmune thrombocytopenic purpura: 22 years on. Vox Sanguinis 2004; 86(1):8-14.

(57) Kuter D, Bussel J, George J, Aledort L, Lichtin A, Lyons R et al. Long-term dosing of AMG 531 in thrombocytopenic patients with immune thrombocytopenic purpura: 48-week update. Blood (ASH Annual Meeting Abstracts) 2006; 108(11):144A, Abstract 511.

(58) Bussel JB, Kuter DJ, de Wolf JTM, Guthrie TH, Newland A, Wasser JS et al. Long-term dosing of AMG 531 in thrombocytopenic patients with immune thrombocytopenic purpura: 2-year update. Blood (ASH Annual Meeting Abstracts) 2007; 110(11):174A-175A.

(59) Bussel JB, Kuter DJ, George JN, Aledort LM, Lichtin AE, Lyons RM et al. Long-term dosing of AMG 531 is effective and well tolerated in thrombocytopenic patients with immune thrombocytopenic purpura. Blood (ASH Annual Meeting Abstracts) 2005; 106(11):68A, Abstract 220.

(60) Tarantino MD, Henry DH, Go RS, Lefrere F, Lichtin AE, Terebelo HR et al. Health-related Quality of Life (HRQoL) in patients with chronic immune thrombocytopenic purpura (ITP): Interim results from an open-label study of AMG 531. Blood (ASH Annual Meeting Abstracts) 2007; 110(11):399A.

(61) Newland AC, Sanz MA, Bourgeois E, Grande C, te Boekhorst PAW, Vellenga E et al. Evaluating the long-term efficacy of romiplostim (AMG 531) in patients with chronic immune thrombocytopenic purpura (ITP) during an open-label extension study. Haematologica (13th Congress of the European Hematology Association) 2008; 93(Suppl 1):377, Abstract 0945.

(62) Sanz M. The Impact of Romiplostim on Patient-Reported Outcomes Measured by the EUROQOL (EQ-5D). ISPOR-EU November 8-11, 2008 (accepted for poster presentation) 2008;Abstract #20713.

(63) Mathias SD, Bussel JB, George JN, McMillan R, Okano GJ, Nichol JL et al. A disease-specific measure of health-related quality of life in adults with chronic

immune thrombocytopenic purpura: psychometric testing in an open-label clinical trial. CLIN THER 2007; 29(5):950-962.

(64) Mathias SD, Bussel JB, George JN, McMillan R, Okano GJ, Nichol JL. A disease-specific measure of health-related quality of life for use in adults with immune thrombocytopenic purpura: its development and validation. Health Qual Life Outcomes 2007; 5:11.

(65) Amgen. A Randomized, Placebo Controlled Study Evaluating the Efficacy and Safety of AMG 531 Treatment of Thrombocytopenic Subjects with Immune (Idiopathic) Thrombocytopenic Purpura (ITP) Refractory to Splenectomy (Protocol 20030105 Study Report). Data on file, Amgen; Jun 12, 2007. 2007.
Ref Type: Report

(66) Amgen. A Randomized, Placebo Controlled Study Evaluating the Efficacy and Safety of AMG 531 Treatment of Thrombocytopenic Subjects with Immune (Idiopathic) Thrombocytopenic Purpura (ITP) Prior to Splenectomy (Protocol 20030212 Study Report). Data on file, Amgen; Jun 26, 2007. 2007.
Ref Type: Report

(67) Amgen. Clinical Summary, Summary of Clinical Safety (CSS) for Amgen studies 20030105, 20030212 and 20030213: Data on file, Amgen; Aug 7, 2007. 2007.
Ref Type: Report

(68) Amgen. Romiplostim Core Data Sheet-Annotated: Data on file, Amgen; Sep 17, 2007. 2007.
Ref Type: Report

(69) Amgen. Romiplostim Clinical Summary of Safety. 2007.
Ref Type: Report

(70) Godeau B, Chevret S, Varet B, Lefrere F, Zini JM, Bassompierre F et al. Intravenous immunoglobulin or high-dose methylprednisolone, with or without oral prednisone, for adults with untreated severe autoimmune thrombocytopenic purpura: a randomised, multicentre trial.[see comment]. Lancet 2002; 359(9300):23-29.

(71) Berti D, Moons P, Dobbels F. Which Symptoms Related to Corticosteroid use do patients with Immune Thrombocytopenic Purpura experience? Data on file, Amgen. 2007.
Ref Type: Report

(72) Gutierrez-Espindola GR, Morales-Polanco MR, Guerrero-Rivera S, Talavera JO, Sanchez-Valle E, Gomez-Morales E et al. High doses of dexamethasone in adult patients with idiopathic thrombocytopenic purpura. Arch Med Res 2003; 34(1):31-34.

(73) Lukert BP, Raisz LG. Glucocorticoid-induced osteoporosis: pathogenesis and management. Ann Intern Med 1990; 112(5):352-364.

(74) Reid IR. Glucocorticoid osteoporosis--mechanisms and management. Eur J Endocrinol 1997; 137(3):209-217.

(75) Stasi R, Brunetti M, Pagano A, Stipa E, Masi M, Amadori S. Pulsed intravenous high-dose dexamethasone in adults with chronic idiopathic thrombocytopenic purpura. Blood Cells Mol Dis 2000; 26(6):582-586.

(76) Feudjo-Tepie MA, Hall SA, Logie JW. Risk of Cataracts among Idiopathic Thrombocytopenic Purpura (ITP) Patients in the UK General Practice Research Database (GPRD). Blood (ASH Annual Meeting Abstracts) 2007; 110(11):Abstract 3922.

(77) Smith JA, Gadberry TD, Okano GJ. Corticosteroid therapy for immune thrombocytopenic purpura: Assessing the risks. Spring Practice and Research Forum; Apr 21 - 25, 2007 2007.

(78) Fardet L, Cabane J, Lebbe C, Morel P, Flahault A. Incidence and risk factors for corticosteroid-induced lipodystrophy: a prospective study. J Am Acad Dermatol 2007; 57(4):604-609.

(79) Sandoglobulin SPC. Accessed from www.medicines.org 19 Sep 2008. 2008.
Ref Type: Report

(80) Rituximab SPC. Accessed from www.medicines.org 19 Sep 2008. 2008.
Ref Type: Report

(81) George JN. Management of patients with refractory immune thrombocytopenic purpura. Journal of Thrombosis and Haemostasis 2006; 4(8):1664-1672.

(82) Danazol (Danol) SPC. Accessed from www.medicines.org 19 Sep 2008. 2008.
Ref Type: Report

(83) Dapsone SPC. Accessed from http://www.actavis.co.uk/en/products/products_list.htm 19 Sep 2008. 2008.
Ref Type: Report

(84) Damodar S, Viswabandya A, George B. Dapsone for chronic idiopathic thrombocytopenic purpura in children and adults - A report on 90 patients. European Journal of Haematology 2005; 75(4):328-331.

(85) Godeau B, Durand JM, Roudot-Thoraval F, Tenneze A, Oksenhendler E, Kaplanski G et al. Dapsone for chronic autoimmune thrombocytopenic purpura: a report of 66 cases. Br J Haematol 1997; 97(2):336-339.

(86) Azathioprine SPC. Accessed from www.medicines.org 19 Sep 2008. 2008.
Ref Type: Report

(87) Cines DB, McMillan R. Management of adult idiopathic thrombocytopenic purpura. Annual Review of Medicine 2005; 56:425-442.

(88) Huber MRK. Treatment advances in adult immune thrombocytopenic purpura. Annals of Hematology 2003; 82(12):723-737.

(89) Ciclosporin SPC. Accessed from www.medicines.org 19 Sep 2008. 2008.
Ref Type: Report

(90) Emilia G, Morselli M, Luppi M, Longo G, Marasca R, Gandini G et al. Long-term salvage therapy with cyclosporin A in refractory idiopathic thrombocytopenic purpura. Blood 2002; 99(4):1482-1485.

(91) Kappers-Klunne MC, van't Veer MB. Cyclosporin A for the treatment of patients with chronic idiopathic thrombocytopenic purpura refractory to corticosteroids or splenectomy. Br J Haematol 2001; 114(1):121-125.

(92) Mycophenolate SPC. Accessed from www.medicines.org 19 Sep 2008. 2008.
Ref Type: Report

(93) Provan D, Moss AJ, Newland AC, Bussel JB, Provan D, Moss AJ et al. Efficacy of mycophenolate mofetil as single-agent therapy for refractory immune thrombocytopenic purpura. American Journal of Hematology 2006; 81(1):19-25.

(94) Hou M, Peng J, Shi Y, Zhang C, Qin P, Zhao C et al. Mycophenolate mofetil (MMF) for the treatment of steroid-resistant idiopathic thrombocytopenic purpura. Eur J Haematol 2003; 70(6):353-357.

(95) Reiner A, Gernsheimer T, Slichter SJ. Pulse cyclophosphamide therapy for refractory autoimmune thrombocytopenic purpura. Blood 1995; 85(2):351-358.

(96) Cyclophosphamide SPC. Accessed from www.medicines.org 19 Sep 2008. 2008.
Ref Type: Report

(97) Hershman D, Neugut AI, Jacobson JS, Wang J, Tsai WY, McBride R et al. Acute myeloid leukemia or myelodysplastic syndrome following use of granulocyte colony-stimulating factors during breast cancer adjuvant chemotherapy. Journal of the National Cancer Institute 2007; 99(3):196-205.

(98) Linares M, Cervero A, Sanchez M, Garcia S, Miguel-Sosa A, Miguel-Garcia A et al. Slow infusion of vincristine in the treatment of refractory thrombocytopenic purpura. Acta Haematol 1988; 80(3):173-174.

(99) Pizzuto J, Ambriz R. Therapeutic experience on 934 adults with idiopathic thrombocytopenic purpura: Multicentric Trial of the Cooperative Latin American group on Hemostasis and Thrombosis. Blood 1984; 64(6):1179-1183.

(100) Vincristine SPC. Accessed from www.medicines.org 19 Sep 2008. 2008.
Ref Type: Report

(101) Andres E, Zimmer J, Noel E, Kaltenbach G, Koumarianou A, Maloisel F et al. Idiopathic thrombocytopenic purpura: a retrospective analysis in 139 patients of the influence of age on the response to corticosteroids, splenectomy and danazol. [Review] [25 refs]. DRUGS AGING 2003; 20(11):841-846.

(102) Godeau B, Porcher R, Fain O, Lefrere F, Fenaux P, Cheze S et al. Rituximab efficacy and safety in adult splenectomy candidates with chronic immune thrombocytopenic purpura - results of a prospective multicenter phase 2 study. Blood 2008; 112(4):999-1004.

(103) NICE Guideline Development Methods 2005, http://www.nice.org.uk/niceMedia/pdf/GDM_Chapter7_0305.pdf. Accessed 15 Oct 2008. 2005.
Ref Type: Report

(104) Ben-Yehuda D, Gillis S, Eldor A. Clinical and therapeutic experience in 712 Israeli patients with idiopathic thrombocytopenic purpura. Israeli ITP Study Group. Acta Haematol 1994; 91(1):1-6.

(105) Jacobs P, Wood L, Novitzky N. Intravenous gammaglobulin has no advantages over oral corticosteroids as primary therapy for adults with immune thrombocytopenia: a prospective randomized clinical trial. American Journal of Medicine 1994; 97(1):55-59.

(106) Schiavotto C, Ruggeri M, Rodeghiero F, Schiavotto C, Ruggeri M, Rodeghiero F. Failure of repeated courses of high-dose intravenous immunoglobulin to induce stable remission in patients with chronic idiopathic thrombocytopenic purpura. Annals of Hematology 1995; 70(2):89-90.

(107) Godeau B, Lesage S, Divine M, Wirquin V, Farcet JP, Bierling P et al. Treatment of adult chronic autoimmune thrombocytopenic purpura with repeated high-dose intravenous immunoglobulin. Blood 1993; 82(5):1415-1421.

(108) George JN, Raskob GE, Vesely SK, Moore D, Jr., Lyons RM, Cobos E et al. Initial management of immune thrombocytopenic purpura in adults: a randomized controlled trial comparing intermittent anti-D with routine care. American Journal of Hematology 2003; 74(3):161-169.

(109) Unsal CG. Anti-D and intravenous immunoglobulin treatments in chronic idiopathic thrombocytopenic purpura. Turkish Journal of Haematology 2004; 21(1):27-32.

(110) Newman GC, Novoa MV, Fodero EM, Lesser ML, Woloski BM, Bussel JB. A dose of 75 microg/kg/d of i.v. anti-D increases the platelet count more rapidly and for a longer period of time than 50 microg/kg/d in adults with immune thrombocytopenic purpura. British Journal of Haematology 2001; 112(4):1076-1078.

(111) Zaja F, Battista ML, Pirrotta MT, Palmieri S, Montagna M, Vianelli N et al. Lower dose rituximab is active in adults patients with idiopathic thrombocytopenic purpura. Haematologica 2008; 93(6):930-933.

(112) Medeot M, Zaja F, Vianelli N, Battista M, Baccarani M, Patriarca F et al. Rituximab therapy in adult patients with relapsed or refractory immune thrombocytopenic purpura: Long-term follow-up results. European Journal of Haematology 2008; 81(3):165-169.

(113) Ahn YS, Rocha R, Mylvaganam R, Garcia R, Duncan R, Harrington WJ et al. Long-term danazol therapy in autoimmune thrombocytopenia: unmaintained remission and age-dependent response in women.[see comment]. ANN INTERN MED 1989; 111(9):723-729.

(114) Hernandez F, Linares M, Colomina P, Pastor E, Cervero A, Perez A et al. Dapsone for refractory chronic idiopathic thrombocytopenic purpura. Br J Haematol 1995; 90(2):473-475.

(115) Vianelli N, Valdre L, Fiacchini M, de VA, Gugliotta L, Catani L et al. Long-term follow-up of idiopathic thrombocytopenic purpura in 310 patients. Haematologica 2001; 86(5):504-509.

(116) Quiquandon I, Fenaux P, Caulier MT, Pagniez D, Huart JJ, Bauters F et al. Re-evaluation of the role of azathioprine in the treatment of adult chronic idiopathic thrombocytopenic purpura: a report on 53 cases. British Journal of Haematology 1990; 74(2):223-228.

(117) Bouroncle BA, Doan CA. Treatment of refractory idiopathic thrombocytopenic purpura. JAMA 1969; 207(11):2049-2052.

(118) Kotb R, Pinganaud C, Trichet C. Efficacy of mycophenolate mofetil in adult refractory auto-immune cytopenias: A single center preliminary study. European Journal of Haematology 2005; 75(1):60-64.

(119) Peng J, Liu C, Liu D, Ren C, Li W, Wang Z et al. Effects of B7-blocking agent and/or CsA on induction of platelet-specific T-cell anergy in chronic autoimmune thrombocytopenic purpura. Blood 2003; 101(7):2721-2726.

(120) Zver S, Zupan IP, Cernelc P. Cyclosporin A as an immunosuppressive treatment modality for patients with refractory autoimmune thrombocytopenic purpura after splenectomy failure. Int J Hematol 2006; 83(3):238-242.

(121) Emilia G, Messora C, Longo G, Bertesi M. Long-term salvage treatment by cyclosporin in refractory autoimmune haematological disorders. British Journal of Haematology 1996; 93(2):341-344.

(122) Schiavotto C, Castaman G, Rodeghiero F. Treatment of idiopathic thrombocytopenic purpura (ITP) in patients with refractoriness to or with contraindication for corticosteroids and/or splenectomy with immunosuppressive therapy and danazol. Haematologica 1993; 78(6 Suppl 2):29-34.

(123) Facon T, Caulier MT. A randomized trial comparing vinblastine in slow infusion and by bolus i.v. injection in idiopathic thrombocytopenic purpura: A report on 42 patients. British Journal of Haematology 1994; 86(3):678-680.

(124) Robak T, Salama A, Kovaleva L, Vyhovska YI, Davies S, Mazzucconi MG et al. Efficacy and safety of a new intravenous immunoglobulin product in patients with chronic immune thrombocytopenic purpura. Blood 2007; 110(11):393A-394A.

(125) Julia A, Kovaleva L, Alberca I, Hernandez F, Loria S, Sandoval V et al. Study on the efficacy and safety of IGIV3I grifols (human intravenous immunoglobulin) in patients diagnosed with chronic immune thrombocytopenic purpura. Blood 2006; 108(11):66B.

(126) Leibl H, Varga G, Volkova Z, Gasztonyi Z, Hlusi A, Mayer J et al. Efficacy and safety of a new intravenous immunoglobulin in adult subjects with chronic idiopathic thrombocytopenic purpura. Blood 2005; 106(11):76B.

(127) Milligan D, Eden A, Sklenar I, Adams C, Andresen I, Bender K. Therapy of patients with chronic immune thrombocytopenic purpura (ITP): efficacy, tolerability, and safety of a new liquid intravenous immunoglobulin. European Hematology Association Website http://www ehaweb org 2004.

(128) Bussel JB, Eldor A, Kelton JG, Varon D, Brenner B, Gillis S et al. IGIV-C, a novel intravenous immunoglobulin: evaluation of safety, efficacy, mechanisms of action, and impact on quality of life. Thrombosis & Haemostasis 2004; 91(4):771-778.

(129) Wolf HH, Davies SV, Borte M, Caulier MT, Williams PE, Bernuth HV et al. Efficacy, tolerability, safety and pharmacokinetics of a nanofiltered intravenous immunoglobulin: studies in patients with immune thrombocytopenic purpura and primary immunodeficiencies. Vox Sanguinis 2003; 84(1):45-53.

(130) Colovic M, Dimitrijevic M, Sonnenburg C, Suvajdzic N, Donfrid M, Bogdanovic A et al. Clinical efficacy and safety of a novel intravenous immunoglobulin preparation in adult chronic ITP. Hematology Journal 2003; 4(5):358-362.

(131) Pugina SA, Evdokimova NM, Rastorguev GG, Samoilova OS, Sorokina IV, Sidnev GV et al. [Treatment of idiopathic thrombocytopenic purpura in adults: efficacy of domestic intravenous immunoglobulin in immune thrombocytopenia]. [Russian]. Terapevticheskii Arkhiv 1999; 71(8):50-54.

(132) Altintop L, Albayrak D. Oral high-dose methylprednisolone and intravenous immunoglobulin treatments in adult chronic idiopathic thrombocytopenic purpura. American Journal of Hematology 1997; 56(3):191-192.

(133) Newland AC, Burton I, Cavenagh JD, Copplestone A, Dolan G, Houghton J et al. Vigam-S, a solvent/detergent-treated intravenous immunoglobulin, in idiopathic thrombocytopenic purpura. Transfusion Medicine 2001; 11(1):37-44.

(134) Cooper N, Stasi R, Cunningham-Rundles S, Feuerstein MA, Leonard JP, Amadori S et al. The efficacy and safety of B-cell depletion with anti-CD20 monoclonal antibody in adults with chronic immune thrombocytopenic purpura. British Journal of Haematology 2004; 125(2):232-239.

(135) Fenaux P, Quiquandon I, Huart JJ, Caulier MT, Bauters F, Fenaux P et al. The role of danazol in the treatment of refractory idiopathic thrombocytopenic purpura. A report of 22 cases. Nouvelle Revue Francaise d Hematologie 1990; 32(2):143-146.

(136) Majer RVG. Danazol is effective in refractory adult immune thrombocytopenia. Hematology Reviews and Communications 1990; 4(2-3):125-131.

(137) Nozaki H, Tanaka K, Yonekura S, Shimizu M, Komatsuda M, Nagao T et al. [Low-dose danazol therapy in idiopathic thrombocytopenic purpura]. [Japanese]. Rinsho Ketsueki - Japanese Journal of Clinical Hematology 1990; 31(10):1750-1751.

(138) Mylvaganam R, Ahn YS, Garcia RO, Kim C, I, Harrington WJ. Very Low Dose Danazol in Idiopathic Thrombocytopenic Purpura and Its Role As An Immune Modulator. American Journal of the Medical Sciences 1989; 298(4):215-220.

(139) Mazzucconi MG, Francesconi M, Falcione E, Ferrari A, Gandolfo GM, Ghirardini A et al. Danazol therapy in refractory chronic immune thrombocytopenic purpura. Acta Haematologica 1987; 77(1):45-47.

(140) Buelli M, Cortelazzo S, Viero P, Minetti B, Comotti B, Bassan R et al. Danazol for the treatment of idiopathic thrombocytopenic purpura. Acta Haematologica 1985; 74(2):97-98.

(141) Mcverry BA, Auger M, Bellingham AJ, Mcverry BA, Auger M, Bellingham AJ. The use of danazol in the management of chronic immune thrombocytopenic purpura. British Journal of Haematology 1985; 61(1):145-148.

(142) Manoharan A. Targeted-immunosuppression with vincristine infusion in the treatment of immune thrombocytopenia. Aust N Z J Med 1991; 21(4):405-407.

(143) British National Formulary (BNF): /www.bnf.org/bnf. 2008.
Ref Type: Report

(144) Mathias SDG. Impact of chronic Immune Thrombocytopenic Purpura (ITP) on health-related quality of life: A conceptual model starting with the patient perspective. Health and Quality of Life Outcomes 2008; 6, 2008. Article Number: 13. Date of Publication: 08 Feb 2008.

10 Appendices

10.1 Appendix 1

Please see attached the Summary of Product Characteristics for Romiplostim

10.2 Appendix 2: search strategy for section 6

As *described in section 6.8.1, a pragmatic approach was taken in order to identify key studies for each treatment. The following ITP clinical guidelines and recent reviews were used to obtain estimates of efficacy and safety and/or to identify studies:*

Guidelines:

- British Committee for Standards in Haematology (BCSH) Guideline for Management of ITP (Provan et al 2003)
- American Society of Hematology (ASH) Practice Guideline for ITP (George et al 1996)

Reviews:

- Vesely 2004 systematic review of treatments post-splenectomy
- Godeau 2007 literature review of ITP treatments
- Cines & Bussel 2005 review of ITP treatments
- Cines & Blanchette 2002 review of ITP treatments
- Arnold 2007 systematic review of rituximab for ITP
- Zhou 2008 systematic review of rituximab for ITP
- Maloisel 2004 literature review of danazol for ITP
- Bierling & Godeau 2004 & 2005 reviews of IVIg safety

In addition, a literature search has been undertaken to identify any key clinical studies in the relevant comparators published since the review by Godeau et al 2007 (or since the most relevant review for each individual treatment; see Section 6.8.1 for details).

The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline ® In-Process
- The Cochrane Library.

The following databases were searched:

- Medline
- Medline in Process
- Embase
- CINAHL
- The Cochrane library (includes CENTRAL and DARE/NHSEED)
- Science Citation Index (via Web of Science)
- BIOSIS Previews (via Web of Science)

10.2.2 *The date on which the search was conducted*

The search was conducted on 19 May 2008.

10.2.3 *The date span of the search.*

The date span of the search was different for different comparator treatments, according to when existing systematic reviews of that treatment

were published (as described in Section 6.8.1). All searches covered as a minumum the period from 2006-2008 (to identify papers published since the review by Godeau et al 2007). In addition, searches were conducted from 1994 to present for IVIg, from 2006 to present for rituximab (since the Arnold et al 2007 review), for all dates for danazol, and for all dates for azathioprine.

10.2.4 *The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).*

The search terms used were as follows:

Search terms for the condition (ITP):

Purpura, Thrombocytopenic, Idiopathic/ (MeSH term)
ITP
Idiopathic thrombocytopenic purpura
Immune thrombocytopenic purpura
Idiopathic thrombocytopenia
Immune thrombocytopenia
AITP
Autoimmune thrombocytopenic purpura
Autoimmune thrombocytopenia
Idiopathic thrombocytopaenic purpura
Immune thrombocytopaenic purpura
Idiopathic thrombocytopaenia
Immune thrombocytopaenia
Autoimmune thrombocytopaenic purpura
Autoimmune thrombocytopaenia

Search terms for the interventions:

Romiplostim
Romiplostim
AMG 531
AMG531
Romiplostim
Remiplistim

IVIg
Immunoglobulins, Intravenous/ (MeSH term)
IVIg
IgIV
IVIgG
Intravenous immunoglobulin
Intravenous immune globulin
Immune globulin intravenous
Intravenous gammaglobulin
Intravenous gamma globulin

Anti-D
"Rho(D) Immune Globulin"/ (MeSH term)
"Rho(D) Immune Globulin".tw
Anti-D
Rh immune globulin
Rh immunoglobulin
RhD immune globulin

RhD immunoglobulin
Rh D immune globulin
Rh D immunoglobulin
RhoD immune globulin
RhoD immunoglobulin
Rho D immune globulin
Rho D immunoglobulin
RhIG
Anti-RhD
Anti-Rh D
Anti-RhoD
Anti-Rho D
Rhophylac
Partobulin
WinRho
RhoGAM
MICRhoGam
BayRHo-D
Gamulin Rh
HypRho-D
Mini-Gamulin Rh
Rhesonativ

Rituximab
Rituximab/ (MeSH term)
Rituximab
Rituxan
Mabthera

Danazol
Danazol/ (MeSH term)
Danazol

Dapsone
Dapsone/ (MeSH term)
Dapsone

Azathioprine
Azathioprine/ (MeSH term)
Azathioprine
Imuran
Azasan
Azamun
Imurel

Mycophenolate mofetil
Mycophenolic (MeSH term)
Mycophenolate
Mycophenolic
CellCept
Myfortic

Ciclosporin
Cyclosporine/ (MeSH term)
Ciclosporin

Ciclosporine
Cyclosporin
Cyclosporine

Cyclophosphamide
Cyclophosphamide/ (MeSH term)
Cyclophosphamide

Vinca alkaloids
Vincristine/ (MeSH term)
Vincristine
Vinblastine/ (MeSH term)
Vinblastine

Combining search terms:

For each intervention, the search terms were combined as follows:

1) Combine ITP terms with OR
2) Combine intervention terms with OR
3) #1 AND #2

10.2.5 *Details of any additional searches, for example searches of company databases (include a description of each database).*

The following Amgen databases were searched:

(1) Amgen Clinical Trial Database: Database housing safety and efficacy data collected during the conduct of clinical trials.
(2) ARISg (Adverse Reaction Information Systems - global): In the pre-marketing setting, functions as a safety database housing serious adverse events reported during clinical trials. In the post-marketing, houses all reported adverse events regardless of designation of seriousness.

10.2.6 *The inclusion and exclusion criteria.*
Studies were excluded if they related to secondary thrombocytopenia associated with other conditions, ITP in childhood or pregnancy, or if they included less than 5 patients.

10.2.7 *The data abstraction strategy.*

Data was abstracted by a single reviewer. In addition, many included papers were described in the reviews and guidelines listed above, which allowed us to check the accurary of the data abstracted.

10.3 Appendix 3: search strategy for section 7

The following information should be provided.

10.3.1 *The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:*

- *Medline*
- *Embase*
- *Medline ® In-Process*
- *Health Economic Evaluation Database*
- *NHS Economic Evaluation Database (NHS EED).*

The following databases were searched:

- Medline
- Medline in Process
- Embase
- CINAHL
- The Cochrane library (includes CENTRAL and DARE/NHSEED)
- Science Citation Index (via Web of Science)
- BIOSIS Previews (via Web of Science)

10.3.2 *The date on which the search was conducted*.

The search was conducted on 19 May 2008.

10.3.3 *The date span of the search*.

No limits on dates were imposed on the search.

10.3.4 *The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the elationship between the search terms (for example, Boolean).*

The following search terms were used in order to identify all published studies of romiplostim:

Romiplostim
AMG 531
AMG531
Romiplostim
Remiplistim

10.3.5 *Details of any additional searches, for example searches of company databases (include a description of each database).*

No further searches were undertaken.

10.4 Appendix 4: Development of the ITP-Patient Assessment Questionnaire (ITP-PAQ)

ITP-PAQ is a disease-specific instrument to assess HRQoL in ITP patients. The development, validity and reliability of the ITP-PAQ is described in more detail here.

ITP-PAQ Conceptual Model

The development of the ITP-PAQ began by conducting an extensive literature review followed by a systematic focus group study to identify areas of HRQoL affected by ITP. Published literature was reviewed to identify key HRQoL issues and existing questionnaires used to assess HRQoL. A focus group study was conducted and transcripts of ITP patients reviewed, and common themes were extracted by grouping conceptual categories that described the impact on their HRQoL. The literature synthesis and themes from the patient focus group data suggest that decreased platelet counts, disease symptoms, and treatment side effects influence multiple domains of HRQoL for ITP patients. This research provided evidence that the key areas affected by ITP and its treatments include emotional and functional health, work life, social and leisure activities, and reproductive health (Mathias et al, 2008).[144]

ITP-PAQ Development

Subjects with ITP participated in three focus groups conducted in geographically diverse locations (San Diego, CA, New York, NY, and Oklahoma City, OK).The development of the ITP-PAQ included data from the literature, existing questionnaires, expert clinical opinion, and input from subjects with ITP (Mathias et al, 2007).[63] The initial draft of the questionnaire contained 50 items, however, after multivariate analyses and testing, 6 unique domains emerged with 10 scales composed of 44 items:

ITP-PAQ Scale	Number of Items
Symptoms	6
Bother	3
Fatigue	4
Activity	2
Fear	5
Psychological	5
Work	4
Social Activity	4
Women's Reproductive Health	6
Overall Quality of Life	5
Total	44

Validity and Reliability of the ITP-PAQ

The ITP-PAQ was evaluated for validity and reliability in the romiplostim open-label study (protocol 20030213) that enroled subjects from several ITP clinical trials including the 2 pivotal phase III trials assessing the tolerability and durability of platelet count with romiplostim.

Responsiveness or Sensitivity to Change

Responsiveness or sensitivity to change is the measure of an instrument's ability to detect a clinically important treatment effect, however small. Responsiveness was assessed in patients who obtained clinical improvement vs. those who did not. Clinical improvement in patients was defined as (1) platelet responders (those with a platelet count ≥50x10 ^{9} cells/L) and (2) patients with a doubling of platelet count since baseline ≥50x10 ^{9} cells/L and also ≥6 times during weeks 17-24. Five scales were found to be responsive based on effect size and 1 based on sample t-test values ($p<0.05$ for Symptoms, Fatigue/Sleep, Bother, Fear, and Overall Quality of Life). Nine of the 10 scales were found to be responsive based on Guyatt's statistic, i.e. had a Guyatt's statistic ≥0.20. The fertility subscale of the Women's Reproductive Health scale was the only measure to be found non-responsive.

Test re-test Reliability

Test re-test reliability was evaluated in terms of the intraclass correlation coefficient (ICC) and Pearson's correlation coefficient from a cohort of patients who remained stable between baseline and week 4 (correlation coefficients ≥ 0.70 were considered to indicate reliability). ICC values were acceptable for all ITP-PAQ scales (range 0.725 to 0.867) with the exception of Symptoms (0.677) and Women's Reproductive Health (0.592). Pearson's values were acceptable for all values (range 0.771 to 0.874) except for Symptoms (0.698), Women's Reproductive Health (0.380), and Work (0.626).

Internal Consistency Reliability

Cronbach's alpha was utilized to assess internal consistency reliability at baseline and weeks 4, 12, and 24. Cronbach's alpha coefficients were high for all ITP-PAQ scales (range 0.715 to 0.988), except for work (0.691).

Construct Validity

Convergence of ITP-PAQ scales with SF-36 scales was performed with Pearson's correlation coefficients. Strong convergence was demonstrated for the ITP-PAQ bother, fatigue/sleep, activity, psychological, and social activity scales (range 0.46 to 0.86). The ITP-PAQ social functioning scale had the highest convergence at baseline (0.85) and week 4 (0.80).

Complete validation results can be found in Mathias et al., 2007.[63]

Therefore, the ITP-PAQ was demonstrated to be a valid and reliable measure.