NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Avatrombopag in combination for treating chronic immune thrombocytopenia [ID3838]

Committee Papers

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SINGLE TECHNOLOGY APPRAISAL

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The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from Swedish orphan biovitrum
2. **Clarification questions and company responses**
3. **Patient group, professional group and NHS organisation submissions** from:
   a. ITP Support Association
   b. UK ITP Forum
   c. Patient expert statement from Dianne White, nominated by the ITP Support Association
4. **Evidence Review Group report prepared by University of York**
5. **Evidence Review Group report – factual accuracy check**
6. **Technical engagement response from company**
   a. Company response
   b. Appendix 1 - NMA with inclusion of previous excluded studies
   c. Appendix 2 - Clinician survey on real-world treatment patterns and utilisation in chronic ITP
7. **Technical engagement responses and statements from experts:**
   a. Dr Quentin A Hill, Consultant Haematologist – clinical expert, nominated by UK ITP Forum
   b. Dianne White – patient expert, nominated by the ITP Support Association
8. **Technical engagement responses from consultees and commentators:**
   UK ITP Forum
9. **Evidence Review Group critique of company response to technical engagement** prepared by University of York

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Avatrombopag in combination for treating chronic immune thrombocytopenia ID3838

Document B

Company evidence submission

September 2021

File name	Version	Contains confidential information	Date
NICE_STA_ Avatrombopag_ Full_Submission	V1.0	Yes	10/09/2021

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Table of abbreviations

Abbreviation	Definition
AE	Adverse event
Anti-D	Anti-D immune globin therapy
ASH	American Society of Hematology
AVA	Avatrombopag
BMI	Body mass index
BNF	British National Formulary
CE	Cost-effective
CEA	Cost-effectiveness analysis
CENTRAL	Cochrane Central Register of Controlled Trials
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
COMP	Comparator
CRD	Centre for Review and Dissemination
CrI	Credible interval
CsA	Cyclosporin A
CSR	Clinical study report
CT	Computed tomography
CUA	Cost-utility analysis
DIC	Deviance information criterion
DSA	Deterministic sensitivity analysis

ELT	Eltrombopag
EMA	European Medicines Agency
EQ-5D	Euroqol 5-dimension
EQ-VAS	Euroqol - visual analogue scale
ER	Emergency room
FAS	Final analysis set
FDA	Food and Drug Administration
FE	Fixed effects
FOS	Fostamatinib
GBP	Great British Pound
HRQoL	Health-related quality of life
HSUV	Health state utility values
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IRR	Incidence rate ratio
ITP	Immune thrombocytopenia
IV	Intravenous
IVIG	Intravenous immunoglobulin
LUSU	Lusutrombopag
M	Month
MCMC	Markov chain monte carlo
MCS	Mental component summary
mg	Milligram
MMF	Mycophenolate mofetil
MRI	Magnetic resonance imaging
N/A	Not applicable
N/A	Not applicable
NCT	National Clinical Trial number
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Non-responder
OR	Odds ratio
PAS	Patient access scheme
PC	Platelet count
PCS	Physical component summary
PICOS	Population intervention comparator outcomes subgroups
PROB	Probability
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
QD	daily
RAND	Randomised
RCT	Randomised controlled trial
RE	Random effects
ROM	Romiplostim
RTX	Rituximab
SAE	Serious adverse event
SAS	Safety analysis set
SD	Standard deviation
SF-36	Short-form 36
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SoC	Standard of care
SUCRA	Surface under the cumulative ranking curve
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TPO-RA	Thrombopoietin receptor agonist
URTI	Upper respiratory tract infection
VAS	Visual analogue scale
WHO	World Health Organisation
µg	Microgram

B.1 Decision problem, description of the technology and clinical care pathway

Decision problem

- The decision problem concerns an evaluation of the clinical and cost-effectiveness of avatrombopag (Doptelet®) for the treatment of primary chronic immune thrombocytopenia (ITP) which is refractory to other treatments (e.g. corticosteroids or immunoglobins).
- ITP is a rare autoimmune disorder characterised by abnormally high platelet destruction and impaired platelet production; it evolves into a chronic disorder in 80% of affected adults.
- ITP patients experience purpura, bruising and regular bleeding episodes, ranging from minor bleeds to severe life-threatening haemorrhages.
- ITP also has a substantial impact on patient quality of life due to disease symptoms, bleeding episodes as well as fear and anxiety about platelet levels.

Description of the technology

- Avatrombopag is a thrombopoietin receptor-agonist (TPO-RA) that mimics the biological effect of endogenous thrombopoietin to stimulate platelet production.
- Avatrombopag is administered as a once-daily oral tablet that is taken with food – the avatrombopag dosing regimen is easy to follow, and unlike other TPO-RAs there is no need to fast and a lack of dietary restrictions supports patient adherence.
- Avatrombopag provides a flexible dosing regimen which supports predictable and reliable platelet control for ITP patients who are refractory to other treatments including immunosuppressive therapy, splenectomy and other TPO-RAs.

Clinical care pathway

- Current management of primary ITP is aimed at elevating and maintaining the patient's platelet count to $\geq 50 \times 10^9$/L, the level at which the risk of bleeds is generally considered to be minimised.
- Following diagnosis, ITP guidelines recommend initial treatment of either corticosteroid and/or intravenous immunoglobulin therapy. Owing to the risk of adverse events and reduced long-term efficacy, corticosteroid therapy is transient, and most patients progress to receive subsequent lines of therapy.
- TPO-RAs, rituximab and splenectomy are all treatment options in the refractory setting. However, TPO-RAs are considered the well-established standard of care – eltrombopag and romiplostim are the currently NICE approved TPO-RAs (TA293 and TA221) – while splenectomy is becoming increasingly rare.
- TPO-RAs have been shown to be effective at rapidly improving and durably maintaining platelet levels in ITP, however, existing options may present dosing challenges, safety concerns, as well as not meeting many remaining unmet needs. The effectiveness of TPO-RA treatment switching is also limited by the small number of existing therapies and in turn the resultant data paucity.
- If approved, avatrombopag will be available as an additional TPO-RA option for patients with chronic ITP, where either eltrombopag or romiplostim are the current standard of care.

B.1.1 Decision problem

The submission covers the technology's full EMA marketing authorisation of avatrombopag, a thrombopoietin receptor agonist (TPO-RA), for the treatment of primary chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g. corticosteroids or immunoglobulins).

The decision problem addressed within this submission is consistent with the NICE final scope for this appraisal with respect to the population, intervention and outcomes.

This decision problem is different to the NICE draft scope in respect of comparators and subgroups. In respect of comparators, it is anticipated that the population eligible for avatrombopag will be identical to those who currently receive a TPO-RA, NICE-approved TPO-RAs eltrombopag and romiplostim are the only treatments that represent established clinical management with TPO-RAs and are therefore the only relevant comparators. Subgroup analyses of patients with prior rituximab and splenectomy treatment were not appropriate for this appraisal owing to highly varied use of rituximab by treatment centre and clinical opinion increasingly positioning splenectomy as a later-line treatment once medical interventions are exhausted, respectively.

The full decision problem addressed within this submission and the NICE final scope is presented in Table 1.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with chronic immune thrombocytopenia that is refractory to other treatments.	Adults with chronic immune thrombocytopenia that is refractory to other treatments.	
Intervention	Avatrombopag	Avatrombopag in addition to current clinical management.	
Comparator(s)	Established clinical management without avatrombopag, which may include: • Thrombopoietin receptor agonists (romiplostim and eltrombopag) • Immunosuppressive agents (rituximab, mycophenolate mofetil, azathioprine, dapsone, danazol and cyclosporin A [currently none have a marketing authorisation in the UK for this indication]) • watch and rescue • splenectomy	Eltrombopag and romiplostim	TPO-RAs are considered the well-established standard of care for ITP. It would be inappropriate to include either splenectomy or rituximab given there are multiple TPO-RA alternatives available. In the former case, clinical opinion now positions splenectomy as a later-line treatment procedure once all medical treatment options have been exhausted owing to risk of relapse and mortality(1, 2). For rituximab, its use is highly varied across treatment centres and lines of therapy. Therefore, it does not represent established clinical practice for the population under consideration in this appraisal. It is anticipated that the population eligible for avatrombopag will be exactly the same as those who currently receive a TPO-RA.
Outcomes	The outcome measures to be considered include: • platelet count • response rate and duration • use of concurrent treatments and rescue treatments • reduction in symptoms • mortality • adverse effects of treatment	The outcome measures to be considered include: • platelet count • response rate and duration • use of concurrent treatments and rescue treatments • reduction in symptoms • mortality • adverse effects of treatment	

	• HRQoL	• HRQoL	
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. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account	Sobi believes that avatrombopag is suitable for a fast-track appraisal because it is anticipated to be a highly cost-effective use of NHS resources, with an ICER <£10,000.	
Subgroups to be considered	If the evidence allows the following subgroups will be considered: • prior rituximab	N/A	Subgroup analyses of patients with prior rituximab treatment were not appropriate for this appraisal owing to limited clinical data.
Special considerations including issues related to equity or equality		It is not anticipated that this appraisal will exclude from consideration any people protected by the equality legislation, lead to a recommendation that has a different impact on people protected by equality legislation than on the wider population, or lead to recommendations that have any adverse impact on people with a particular disability or disabilities.	

Abbreviations: ITP, immune thrombocytopenia; ICER, incremental cost-effectiveness ratio; HRQoL, health-related quality of life; TPO-RA, thrombopoietin receptor agonist

B.1.2 Description of the technology being appraised

The Summary of Product Characteristics (SmPC) and the European Public Assessment (EPAR) are presented in Appendix C. Table 2 provides a description of the technology being appraised.

Table 2. Technology being appraised

UK approved name and brand name	**Avatrombopag (approved name)** **Doptelet® (brand name)**
Mechanism of action	Avatrombopag is a TPO-RA (ATC code: B02BX) that stimulates proliferation and differentiation of megakaryocytes from haematopoietic stem and progenitor cells via the TPO receptor, resulting in increased platelet production. Avatrombopag binds non-competitively to the TPO receptor at a distinct site to endogenous TPO, exerting a potentially additive effect on platelet production to endogenous TPO alone.
Marketing authorisation/CE mark status	Avatrombopag is European Medicines Agency (EMA) approved for the indication "treatment of primary chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g. corticosteroids or immunoglobulins)". Filing was submitted in February 2020, positive Committee for Medicinal Products for Human Use (CHMP) was received on 10th December 2020 and marketing authorisation approval was granted in January 2021.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Avatrombopag has marketing authorisation from the EMA for the following indications: • Doptelet is indicated for the treatment of severe thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo an invasive procedure. • Doptelet is indicated for the treatment of primary chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). No restrictions are described in the SmPC
Method of administration and dosage	Avatrombopag is presented as a 20 mg yellow film-coated tablet to be taken orally before, during or after food at a variable dose depending on individual patient platelet count. The maintenance dose is variable between 20 mg weekly and 40 mg daily: • Dose level 1 = 20 mg once weekly • Dose level 2 = 20 mg twice a week OR 40 mg once weekly • Dose level 3 = 20 mg thrice weekly • **Dose level 4 (initial dose) = 20 mg once daily** • Dose level 5 = 40 mg thrice weekly, 20 mg on the remaining 4 days • Dose level 6 = 40 mg once daily
Additional tests or investigations	Not applicable
List price and average cost of a course of treatment	The anticipated list prices are as follows: • 10×20mg tablets, price £640 • 15×20mg tablets, price £960 • 30×20mg tablets, anticipated price £1,920 Assuming 20mg daily, the annual cost of treatment is £21,983
Patient access scheme (if applicable)	[redacted]

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

Primary ITP is a rare autoimmune disorder characterised by the destruction and impaired production of platelets(3), and defined by an abnormal platelet count of $<100\times10^9$/L(4) (normal adult platelet count range is $150–450\times10^9$/L). Patients with ITP experience purpura, bruising and regular bleeding episodes which may impair health-related quality of life (HRQoL) (4, 5). A platelet count of $<30\times10^9$/L may cause regular bruising or can lead to severe life-threatening haemorrhage and significantly impaired HRQoL (6-8). ITP develops into a chronic disorder in 80% of adult patients (9, 10).

Data indicate that the impact of ITP is greatest when platelet counts are $<30\times10^9$/L, however a risk of bleeding is still observed when platelet counts are between $30–50\times10^9$/L (11). More generally in thrombocytopenia, 50×10^9/L delineates the clinical boundary between moderate ($\geq50\times10^9$/L) and severe ($<50\times10^9$/L) thrombocytopenia (12). In the refractory ITP setting, maintaining a platelet counts of at least $50–70\times10^9$/L is recommended to prevent clinically significant bleeding (13). As a result, the platelet response threshold of 50×10^9/L is an accepted measure for treatment response in both ITP clinical studies and clinical practice. While data indicate that the impact of ITP is greatest when platelet counts are $<30\times10^9$/L, a risk of bleeding is still observed when platelet counts are between $30–50\times10^9$/L

B.1.3.2 Epidemiology

The EMA recognises ITP as a rare condition owing to a prevalence of less than 50/100,000 people across the EU (14-16). Prevalence is higher in females and in patients over age 50 (14, 17), and the majority of diagnosed cases in adults progress to chronic disease (2). The incidence of ITP in Northern Europe is around 2.4/100,000 person-years (15, 18). In the UK, the assumed prevalence rate based on the majority of published studies is 10/100,000 people and incidence is reported as 3.9/100,000 person-years, whilst 3,000-4,000 UK adults are estimated to have ITP at any one time (14, 15, 17-20).

B.1.3.3 Standard clinical practice

Current management of ITP in adults emphasises elevating platelet count to >30×10^9/L to minimise the risk of bleeds, thereby lowering hospitalisations and use of concomitant medications for patients (2, 8, 21). Initial treatment of ITP following diagnosis consists of corticosteroid therapy or intravenous immunoglobulin. Owing to the risk of adverse events (AEs) and reduced long-term efficacy, corticosteroid therapy is transient and while some patients may achieve a durable remission following initial treatment, most progress to subsequent lines of therapy. TPO-RAs, short-course rituximab, fostamatinib, or splenectomy are treatment options for patients with chronic refractory ITP. The latter 3 therapies are not consistently used in standard practice. For chronic refractory ITP, splenectomy carries long term infectious and cardiovascular safety risks and is increasingly avoided by UK clinicians if treatment with TPO-RAs is effective (22). Furthermore, a third of patients who do undergo splenectomy may experience post-surgical relapse of ITP (13). Fostamatinib was recently EMA-approved for use in ITP. UK clinicians suggested this agent would be considered after TPO-RAs (23) and the manufacturers have recently applied for reimbursement post-TPO-RAs (24). Rituximab use is highly varied across treatment centres and lines of therapy. TPO-RAs are considered standard care following initial treatment with corticosteroids, and effectively raise platelet count (25, 26). As such, the current TPO-RAs approved by NICE — eltrombopag and romiplostim — represent the only relevant comparators in clinical practice for consideration in this submission. An additional TPO-RA is required in UK clinical practice due to the chronic nature of ITP requiring long-term treatment and because patients with chronic ITP may experience loss of response or AEs on a given TPO-RA (2, 21, 23, 27). In addition current TPO-RAs may require hepatoxicity monitoring and/or have dietary restrictions; there are no requirements for liver monitoring or food-type restrictions associated with avatrombopag which may support patient adherence.

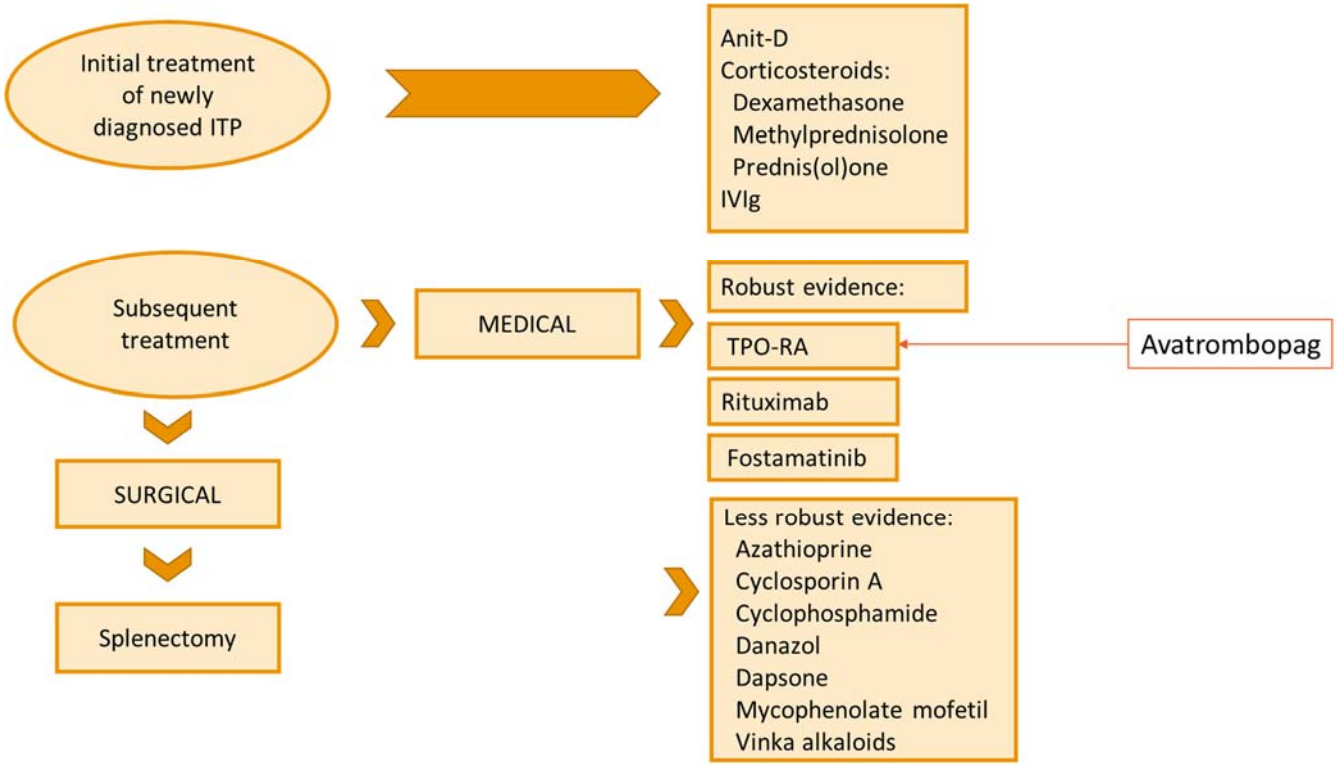
B.1.3.4 Mechanism of action

Avatrombopag is a TPO-RA (ATC code: B02BX) that stimulates proliferation and differentiation of megakaryocytes from haematopoietic stem and progenitor cells via the TPO receptor, resulting in increased platelet production. Pre-clinical evidence demonstrates that avatrombopag binds non-competitively to the TPO receptor at a distinct site to endogenous TPO, exerting an additive effect on platelet production (28).

B.1.3.5 Place in therapy

Avatrombopag will be available as an additional TPO-RA treatment option for patients with chronic ITP in the UK to currently available treatments eltrombopag and romiplostim (29, 30). Availability of an additional TPO-RA option should decrease the need for splenectomy, as well as steroid use with associated patient and budgetary benefits. The current clinical pathway of care and proposed positioning of avatrombopag is aligned with other TPO-RAs prior to rituximab and fostamatinib and is summarised in Figure 1.

Figure 1. Clinical care pathway of ITP and avatrombopag positioning



(Adapted from: (21))

Abbreviations: IVIg, intravenous immunoglobulin g; TPO-RA, thrombopoietin receptor agonist

B.1.4 Equality considerations

It is not anticipated that this appraisal will exclude from consideration any people protected by the equality legislation, lead to a recommendation that has a different impact on people protected by equality legislation than on the wider population, or lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

B.2 Clinical effectiveness

Evidence for avatrombopag in ITP

- The clinical trial programme for avatrombopag in the adult ITP indication includes 3 controlled trials: one study in Phase II with an extension phase (CL003 and CL004) and two further phase III trials (Study 302 and 305)
- Both phase III trials included open-label extension arms, which sought to provide long-term follow-up data on avatrombopag beyond the core study – however, [redacted]
- The pivotal study for avatrombopag in ITP is the phase III trial 'Study 302' (NCT01438840)

Efficacy

- Avatrombopag delivers rapid and sustained improvements in platelet count to the $\geq 50 \times 10^9$/L threshold, thereby lowering the risk of bleeding, reducing need for concomitant medication, and improving HRQoL for patients compared with placebo:
  - Avatrombopag treatment improved platelet count, providing reliable, predictable platelet control for patients with ITP compared with placebo
  - Platelet response with avatrombopag lowered the need for concomitant medication use vs. placebo and the risk of incidence of bleeding events was lower when adjusted for the 2.6-fold longer mean exposure time for avatrombopag-treated patients vs. placebo
  - Avatrombopag treatment did not negatively impact HRQoL relative to placebo

Safety

- Avatrombopag is well tolerated and has a predictable safety profile:
  - Avatrombopag has a low incidence of treatment-related and serious AEs — there was a comparable number of AEs between avatrombopag and placebo when adjusted for treatment-exposure
  - Patients treated with avatrombopag reported no significant events of hepatotoxicity and a low incidence of thromboembolic events in a pooled analysis of clinical studies in ITP

Indirect treatment comparison / network meta-analysis

- In the absence of head-to-head clinical trial evidence for avatrombopag vs eltrombopag or romiplostim, a network meta-analysis (NMA) was performed
  - Numerical trends were observed in favour of avatrombopag for durable platelet response as well as significantly lower incidence of any bleed events with avatrombopag vs. eltrombopag and romiplostim. While some trends for improvement were observed, including statistically significantly lower incidence of bleed events, the NMA indicates at least similarity in the efficacy points examined
  - The rates of safety outcomes were comparable between treatments
- Overall, the NMA demonstrated at least similarity between avatrombopag, eltrombopag and romiplostim for efficacy and safety, with numerical trends observed in favour of avatrombopag for durable platelet response as well as

significantly lower incidence of any bleed events with avatrombopag vs. eltrombopag and romiplostim, which were key indicators of efficacy and safety, respectively.
- The findings and study limitations from the NMA are consistent with previous NMAs and clinical opinion

Innovation

- In current clinical practice, TPO-RA treatment selection is often based on patient choice — unlike other TPO-RAs, avatrombopag is the only TPO-RA available orally without dietary restrictions, the need for fasting or hepatoxicity monitoring, which should reduce the healthcare resource burden and increase likelihood of adherence compared with existing TPO-RA options
- Avatrombopag provides an additional treatment option for patients who may experience an AE or loss of response on a given TPO-RA, especially those patients unable to undergo hepatoxicity monitoring who may be currently limited to receive romiplostim only
- Avatrombopag has a flexible dosing regimen which allows for more accurate dose titration to maintain platelet counts within the target range as compared to the existing oral TPO-RA option, a valuable treatment strategy in certain circumstances, such as patients who are at an increased risk of thromboembolism

Conclusion

- Avatrombopag offers patients with chronic ITP an additional well-tolerated TPO-RA therapy with rapid and predictable efficacy. It is the only oral TPO-RA without burdensome food-type restrictions, as well as a TPO-RA that does not need extra monitoring for hepatoxicity.

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was performed to identify all relevant clinical data from published literature regarding the clinical efficacy and safety of licensed pharmacological treatments for ITP. Full details of the methodology used to identify all evidence relevant to the technology and results are provided in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

The clinical trial programme for avatrombopag in the adult ITP indication investigated the safety and efficacy of the investigational product as a TPO-RA therapy for adults with ITP. Two double-blind, randomised phase III trials with open-label extensions (Study 302 and 305) and one Phase II trial with an open-label (Study CL-003/04) are provided as evidence for the technology being appraised and are listed in Table 3.

Study	Study 302 (NCT01438840) (31, 32)	Study 305 (NCT01433978) (33)	CL-003 and CL-004 (NCT00441090) (34) and (NCT00625443) (31)
Study design	Phase III, multicentre, randomised, double-blind, parallel-group study with an open-label extension phase	[redacted]	[redacted]
Population	Adults ≥18 years of age with ITP ≥12 months in duration, and an average of two platelet counts <30×10^9/L as well as previous treatment with one or more therapies for ITP	[redacted]	[redacted]
Intervention/comparator	Avatrombopag/Placebo	[redacted]	[redacted]
Supports marketing authorisation	Yes	[redacted]	[redacted]
Used in economic model	Yes	[redacted]	[redacted]
Rationale for use/non-use in the model	This trial supports the economic analysis because it is a pivotal phase III trial in adults with ITP treated with the investigational product	[redacted]	[redacted]
Reported outcomes specified in the decision problem **(bold = outcomes incorporated in the economic model)**	• **Durable platelet response, time to response (Cumulative number of weeks of platelet response ≥50×10^9/L over 26 weeks)** • **Bleeding events (all grades)** • **Concomitant ITP medication** • **Rescue therapy** • **HRQoL** • Reduction in symptoms • Adverse effects of treatment • Mortality	[redacted]	[redacted]
All other reported outcomes **(bold = outcomes incorporated in the economic model**	N/A	[redacted]	[redacted]

[redacted]

Abbreviations: HRQoL, health-related quality of life; ITP; immune thrombocytopenia TPO-RA, thrombopoietin receptor agonist

[redacted]

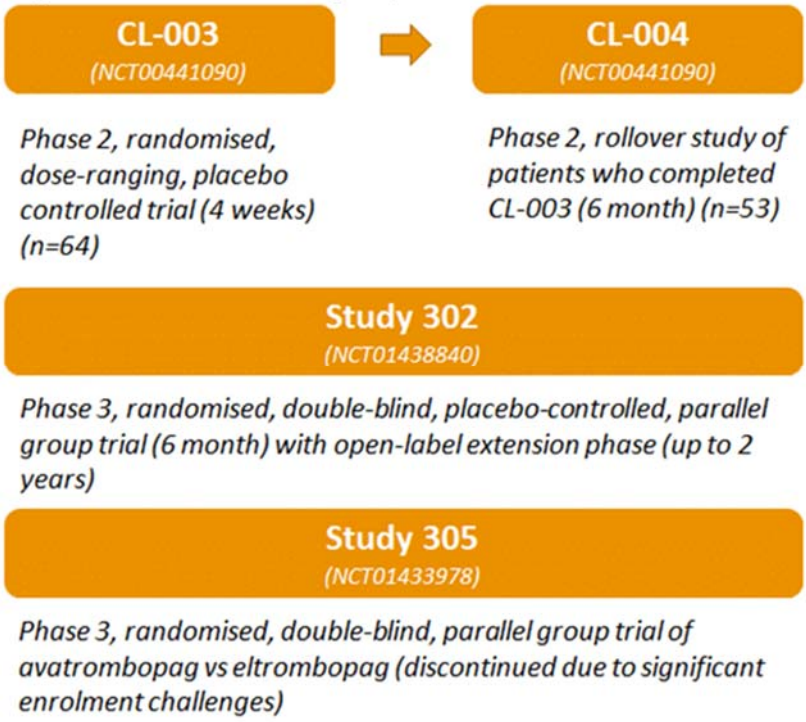
Study 302 was a pivotal placebo-controlled phase III trial of avatrombopag and is the only avatrombopag study with data appropriate to populate the economic model as it contains robust comparative data on key efficacy and safety outcomes.

Studies 305, CL-003 and 004 were not used to populate the economic model but are included in sections 2.2 to 2.6. The results of these studies support the safety and efficacy profile of avatrombopag; however, they are not appropriate for inclusion in the economic model [redacted] Safety data from this study was collected and is presented in the adverse reactions section B.2.10.2. CL-003 and 004 are phase II studies and therefore do not provide the appropriate data for inclusion in the economic model but are presented in the clinical section for supporting efficacy and safety data of avatrombopag.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

The clinical trial programme for avatrombopag in the adult ITP indication includes 3 controlled trials: one study in Phase II with an extension phase (CL-003 and CL-004) and two further phase III trials (Study 302 and 305) (Figure 2). Both phase III trials included open-label extension arms, which sought to provide long-term follow-up data on avatrombopag beyond the core study. The pivotal study for avatrombopag in ITP is the phase III trial 'Study 302' (NCT01438840). A comparative methodology summary of the included studies is provided in Table 4.

Figure 2. Clinical trial programme



Trial name	Study 302	Study 305	CL-003/004
Location	27 sites in Australia, Belgium, Bulgaria, Czech Republic, Netherlands, New Zealand, Poland, Singapore, Slovakia, South Africa, and Ukraine	[redacted]	[redacted]
Trial design	Phase III, multicentre, randomised, double-blind, parallel-group study with an open-label extension phase	[redacted]	[redacted]
Patient population	Adults ≥18 years of age with ITP ≥12 months in duration, and an average of 2 platelet counts <30×10^9/L as well as previous treatment with one or more therapies for ITP	[redacted]	[redacted]
Key inclusion/exclusion criteria	**Key inclusion criteria (core phase)** 1. Male or female, ≥18 years of age 2. Diagnosed with chronic ITP (≥12 months duration) according to the American Society for Hematology/British Committee for Standards in Hematology guidelines, and an average of 2 platelet counts <30×10^9/L (no single count should have been >35×10^9/L). In addition, a peripheral blood smear should have supported the diagnosis of ITP with no evidence of other causes of thrombocytopenia (e.g. pseudo thrombocytopenia, myelofibrosis). The physical examination was not to have suggested any disease that might have caused thrombocytopenia other than ITP. 3. Previously received 1 or more ITP therapies (including, but not limited to corticosteroids, immunoglobulins, azathioprine, danazol, cyclophosphamide and/or rituximab). 4. Must have had either initially responded (platelet count >50×10^9/L) to a previous ITP therapy or have had a bone marrow examination consistent with ITP within 3 years to rule out myelodysplastic syndrome or other causes of thrombocytopenia. 5. Prothrombin time/International Normalized Ratio and activated partial thromboplastin time	[redacted]	[redacted]

must have been within 80% to 120% of the normal range with no history of hypercoagulable state.
6. Had a complete blood count (excluding platelet count), within the reference range (with white blood cell) differential not indicative of any significant haematological disorder), with the following exceptions:
• Haemoglobin: Subjects with haemoglobin levels between 10 g/dL (100 g/L) and the lower limit of
normal were eligible for inclusion, if anaemia was clearly attributable to ITP (excessive blood loss)
• Absolute neutrophil count ≥1500/μL (1.5×10^9/L)
• Elevated WBC or ANC (e.g., due to corticosteroid treatment) provided this was discussed with the medical monitor

Extension phase
1. Completed 6 months of study treatment in the Randomization Phase provided the open-label Extension Phase was still ongoing
2. Discontinued from the Core Study early due to lack of treatment effects provided the open-label Extension Phase was still ongoing
3. No significant safety or tolerability concerns with the subject's participation of Randomization Phase as determined by the investigator

Key exclusion criteria (core study)
1. Known secondary immune thrombocytopenia (e.g. with known Helicobacter pylori-induced ITP subjects infected with known human immunodeficiency virus or hepatitis C virus or subjects with known systemic lupus erythematosus).
2. Significant medical conditions that may have impacted on the safety of the subject or interpretation of the study results (e.g. acute

	hepatitis, active chronic hepatitis; lymphoproliferative disease; myeloproliferative disorders, leukaemia). 3. History of myelodysplastic syndrome 4. History of gastric atrophy 5. History of pernicious anaemia or subjects with vitamin B12 deficiency (defined as <lower limit of normal) who had not had pernicious anaemia excluded as a cause 6. Any prior history of arterial or venous thrombosis (stroke, transient ischemic attack, myocardial infarction, deep vein thrombosis or pulmonary embolism), and more than 2 of the following risk factors: oestrogen-containing hormone replacement or contraceptive therapies, smoking, diabetes, hypercholesterolemia, medication for hypertension, cancer, hereditary thrombophilia disorders (e.g., Factor V Leiden, antithrombin III deficiency, etc.), or any other family history of arterial or venous thrombosis. 7. A history of significant cardiovascular disease (e.g. congestive heart failure New York Heart Association Grade III/IV, arrhythmia known to increase the risk of thromboembolic events [e.g. atrial fibrillation], subjects with a QT interval corrected for heart rate of >450 milliseconds, angina, coronary artery stent placement, angioplasty, coronary artery bypass grafting) 8. History of cirrhosis, portal hypertension, and chronic active hepatitis 9. Concurrent malignant disease 10. Use of immunoglobulins (intravenous gamma globulin and anti-D) within 1 week of randomization 11. Splenectomy or use of rituximab within 12 weeks of randomization 12. Use of romiplostim or eltrombopag within 4 weeks of randomization 13. Treated with corticosteroids or azathioprine but had not received a stable dose for at least	[redacted]		[redacted]

	4 weeks prior to randomization or had not completed these therapies more than 4 weeks prior to randomization 14. Were currently being treated with mycophenolate mofetil, Cyclosporine A, or danazol but had not received a stable dose for at least 12 weeks prior to randomization or have not completed these therapies more than 4 weeks prior to randomization 15. Use of cyclophosphamide or vinca alkaloid regimens within 4 weeks of randomization 16. Were currently being treated with proton pump inhibitor or H2 antagonist therapy but had not received a stable dose for at least 6 weeks prior to randomization or had not completed these therapies more than 2 weeks prior to randomization 17. Fasting gastrin-17 blood levels exceeding the upper limit of normal at Screening for subjects not on proton pump inhibitors or H2 antagonists 18. Fasting gastrin-17 blood levels exceeded 1.5 times the upper limit of normal at Screening for subjects on proton pump inhibitors or H2 antagonists 19. Blood creatinine exceeding upper limit of normal by more than 20% OR total albumin below the lower limit by 10% 20. Alanine aminotransferase OR aspartate aminotransferase levels exceeding 3 times the upper limit OR total bilirubin exceeding 2 times the upper limit 21. History of cancer treatment with cytotoxic chemotherapy and/or radiotherapy. Subjects with a history of ITP treatment with cytotoxic chemotherapy remained eligible for enrolment. 22. Females who were pregnant (positive beta-human chorionic gonadotropin positive test) or breastfeeding 23. Known allergy to avatrombopag and any of its excipients	[redacted]	[redacted]	

	Extension phase 1. Participation in the Extension Phase was considered unsafe, based on the investigator's judgment 2. Considered unable, or unwilling to comply with the study protocol requirements or to give informed consent, as determined by the investigator 3. Required the following drugs or treatments at the time of enrolment in the Extension Phase: o Rituximab o Splenectomy o Other thrombopoietin agonists			
Trial drugs administration, dosing and schedule	Avatrombopag was administered orally as 5, 10, 20, 30, or 40mg in a flexible dose design. Avatrombopag was started at a dose of 20 mg, with dose titration down to 5 mg or up to 40 mg as per specified guidelines. Matching placebo were tablets administered orally.	[redacted]		[redacted]

Permitted and disallowed concomitant medication	**Permitted ITP concomitant background therapies were as follows:** • Corticosteroids and/or azathioprine taken at a stable dose for 4 weeks before randomization • mycophenolate mofetil or danazol taken at a stable dose for at least 12 weeks before randomization • Cyclosporine A (due to the fact it is a P-glycoprotein–mediated transport inhibitor) was to be avoided unless deemed medically necessary; taken at a stable dose for at least 12 weeks before randomization. At the discretion of the investigator, subjects were allowed to use aspirin, other salicylates, or approved adenosine diphosphate receptor antagonists, (e.g. clopidogrel, prasugrel) during the study once their platelet count had risen. Subjects treated with proton pump inhibitors and H2 antagonist therapy received a stable dose for at least 6 weeks prior to randomization. Treatment with these therapies must have been completed at least 2 weeks prior to randomization.	[redacted]	[redacted]
	Prohibited concomitant therapy: • Platelet transfusion within 7 days before the first dose of study drug • Antifibrinolytic agents (aprotinin, tranexamic acid, and aminocaproic acid) and recombinant activated factor VII during the treatment phase of the study • Heparin, warfarin, factor Xa inhibitors, direct thrombin inhibitors, fresh frozen plasma and cryoprecipitate. • Chronic antiplatelet therapy (>4 weeks) with aspirin, clopidogrel, prasugrel, ticlopidine, or glycoprotein Ib/IIIa antagonists (e.g. tirofiban) during the treatment phase of the study.	[redacted]	[redacted]

	• The use of nonsteroidal anti-inflammatory drugs other than aspirin for more than 7 days per month. • Some ITP therapies/procedures, such as vinca alkaloids, cyclophosphamide, rituximab, splenectomy, and other TPO receptor agonists (eltrombopag, romiplostim) during the treatment phase.	[redacted]
Primary outcomes (**bold=outcomes incorporated in the economic model**)	• **Durable platelet response, time to response (cumulative number of weeks of platelet response ≥50×10^9/L over 26 weeks)**	[redacted]
Other outcomes[b] used in the economic model/specified in the scope (**bold=outcomes incorporated in the economic model**)	• **Bleeding events (all grades)** • **Concomitant ITP medication** • **Rescue therapy** • **Health-related quality of life** • Reduction in symptoms • Adverse effects of treatment • Mortality	[redacted]
Pre-planned subgroups	N/A	[redacted]

B.2.3.1 Trial designs

B.2.3.1.1 Study 302

The design of Study 302 is shown in Figure 3. Eligible patients ≥18 years of age with chronic ITP and an average of 2 platelet counts <30×10^9/L were enrolled in the trial and stratified based on splenectomy status, baseline platelet count, and use of concomitant ITP treatments (n=49). Patients were randomised to receive either placebo (n=17) or avatrombopag (n=32) for 26 weeks, at a starting dose of 20 mg per day in a double-blind fashion. Treatment doses were adjusted according to individual responses to treatment as shown in Table 5. Platelet count was performed every 2 weeks and dose targeted to maintain a platelet count between ≥50×10^9/L and ≤150×10^9/L.

Table 5. Dose adjustment based on platelet count during the core and extension phases of Study 302

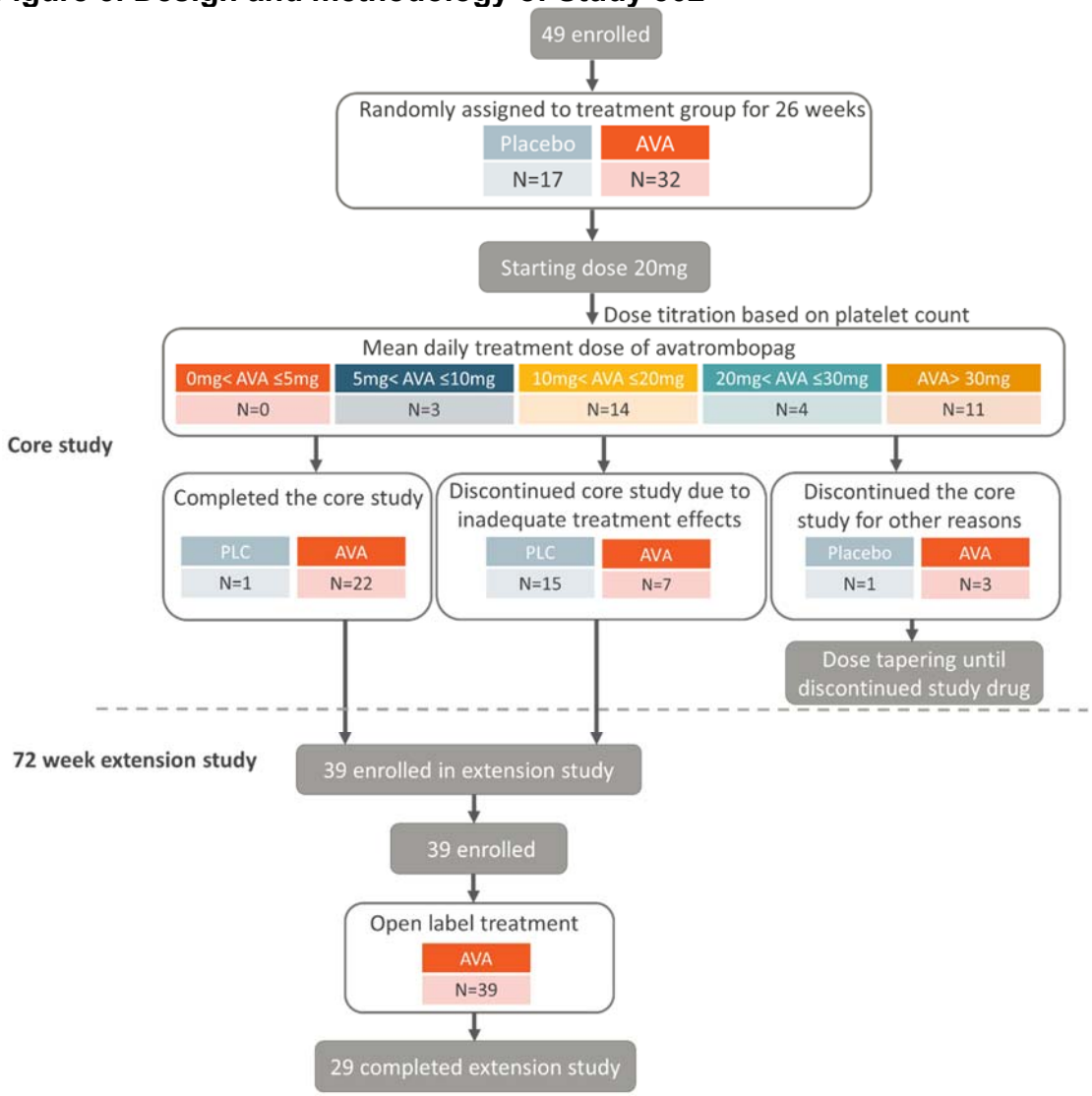
Platelet count	Dose adjustment
<50×10^9/L	Up titrate 1 dose level
≥50×10^9/L to ≤150×10^9/L	Keep on the current dose
>150×10^9/L to ≤250×10^9/L	Down titrate 1 dose level
>250×10^9/L	Stop dose, return for twice weekly platelet counts, then down titrate study drug 1 dose level when platelet count is ≤150×10^9/L

Source: (31)

Doses ranged from 5 mg to >30 mg daily, the most common dosage was between 10 mg and 20 mg (Figure 3) and the most frequently received dose was 20 mg (31). Dose-tapering was carried out for patients who did not proceed to the extension phase of the trial and were followed up for a period of 30 days. This involved weekly visits and the study drug down-titrated 1 dose level per week until the study drug was discontinued.

Patients who entered the extension phase received open-label avatrombopag for a further 72 weeks at starting dose of 20 mg per day, with further dose adjustment based on platelet response.

Figure 3. Design and methodology of Study 302



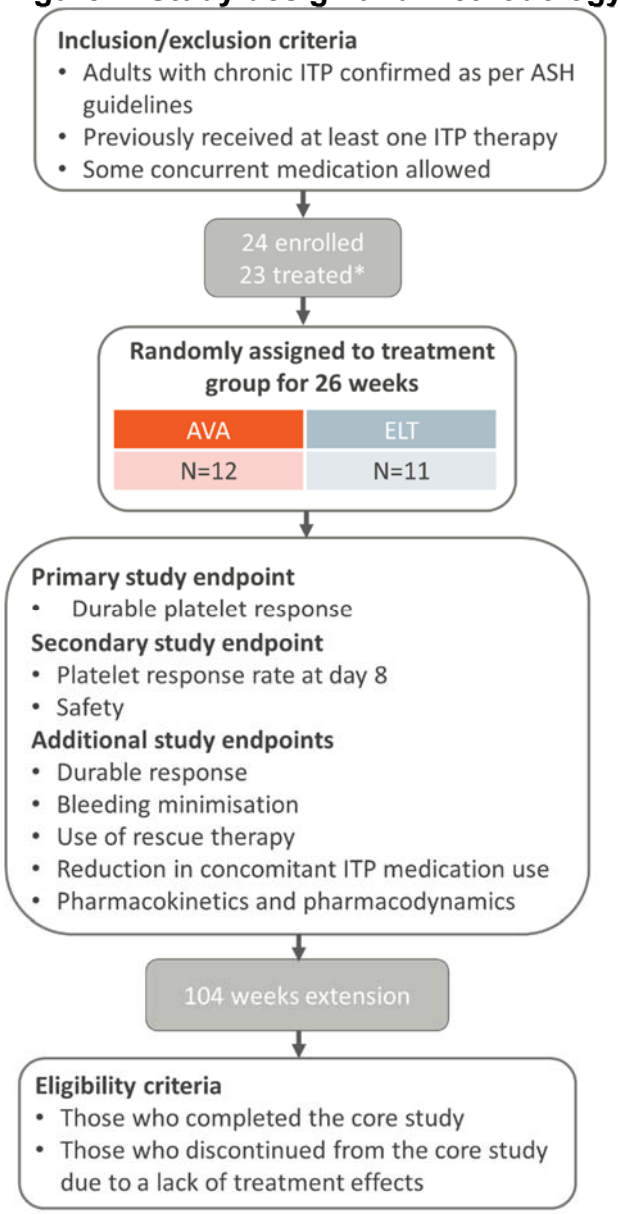
Abbreviations: AVA, avatrombopag, PLC, placebo. Source: (31)

B.2.3.1.2 Study 305

Study 305 (NCT01433978) was a phase III, randomised, double-blind clinical trial designed to compare the efficacy and safety of avatrombopag vs. eltrombopag in adult patients with chronic ITP. The study design and methodology of this study is shown in Figure 4. The study was discontinued due to significant enrolment challenges[2] (33). Some safety data were still collected which is the reason for inclusion in this submission.

[redacted]

Figure 4. Study design and methodology of Study 305



*One screen-failed subject was randomised into the study in error, but not dosed, and is counted as both a screen failure and as continuing into the study.

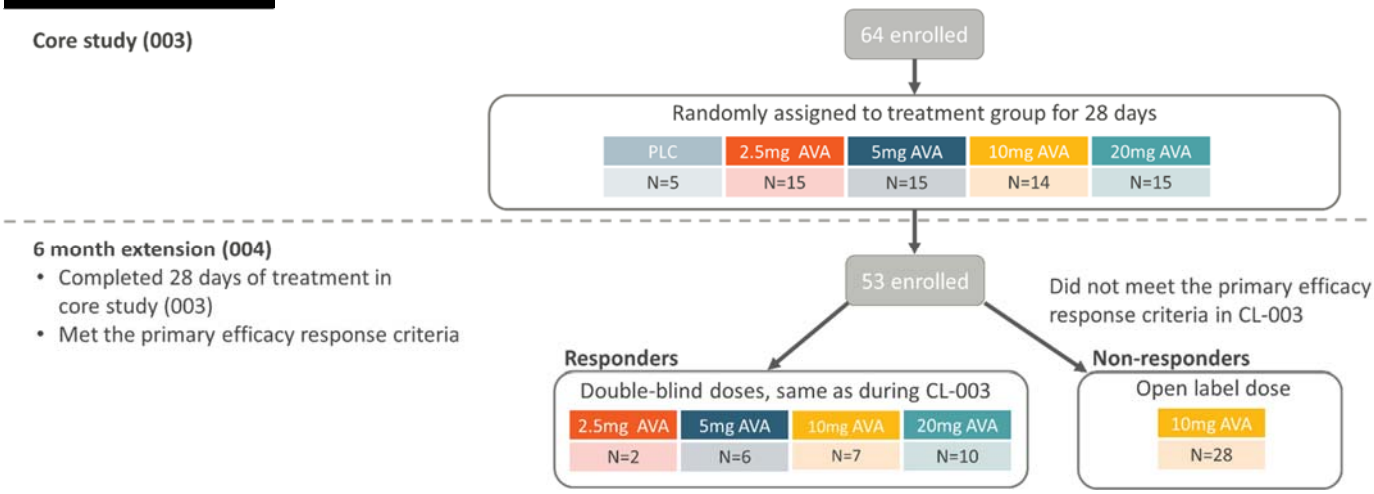
Abbreviations: ASH, American Society of Hematology; AVA, avatrombopag; ELT, eltrombopag; ITP, immune thrombocytopenia. Source: (33)

B.2.3.1.3 CL-003/004

CL-003 was a phase II, double-blind, randomised controlled trial of avatrombopag treatment vs. placebo in adult patients with chronic ITP across 28 days (34), and extension 004 was the 6-month extension of this study (31). The study design and

methodology of CL-003 and extension 004 are shown in Figure 5.

[redacted]



Abbreviations: AVA, avatrombopag; PLC, placebo. Source: (31, 34)

B.2.3.2 Eligibility criteria

B.2.3.2.1 Study 302

The eligibility criteria of Study 302 are detailed in Table 4. Study 302 did not include any treatment centres in the UK; however international consensus guidelines report similarity in care across countries represented in the trial (21). Additionally, UK clinicians consulted during the development of this submission indicated that there were no issues of applicability of Study 302 results to the UK population (23).

[redacted]

B.2.3.3 Endpoints

B.2.3.3.1 Study 302

The primary endpoint of the core 302 Study was the cumulative number of weeks of platelet response, measured across 26 weeks (Table 6). Platelet response was defined as a platelet count of ≥50×10^9/L. Secondary study endpoints included proportion of patients with platelet response at Day 8, proportion of patients with reduction in concomitant ITP medication use, and safety. Additional exploratory

endpoints included durable platelet response, bleeding minimisation, use of rescue therapy, pharmacokinetics and pharmacodynamics, and HRQoL (assessed by 36-item Short Form Survey (SF-36) and EuroQol-Visual Analogue Scale). In the extension phase, the primary endpoint was the long-term safety and tolerability of avatrombopag treatment. The secondary study endpoints were platelet response, bleeding, and use of rescue medication.

Table 6. Overview of the study endpoints from the core study and extension of Study 302

Core phase endpoints		
Primary study endpoint	**Secondary study endpoints**	**Exploratory study endpoints**
• Cumulative number of weeks of platelet response ≥50×10^9/L over 26 weeks	• Proportion of patients with platelet response (platelet count ≥50×10^9/L without rescue therapy*) at Day 8 • Proportion of subjects with reduction in concomitant ITP medication use • Safety	• Durable platelet response rate (proportion of patients who had a platelet response for ≥6 of the last 8 weeks of treatment) • Bleeding minimisation and use of rescue therapy • Pharmacokinetics and pharmacodynamics • HRQoL
Extension phase endpoints		
Primary study endpoint	**Secondary study endpoints**	
• Safety and tolerability of long-term treatment	• Platelet response • Bleeding • Use of rescue medication	

* Rescue therapy was defined as: The addition of any new ITP medication or medication to treat thrombocytopenia" , for example: Corticosteroids, IVIg therapy, Anti-D therapy, MMF, Azathioprine, Danazol, Dapsone, CsA (avoided unless deemed medically necessary), Platelet transfusion and any increase in a baseline dose of a concomitant ITP medication
Abbreviations: HRQoL, health-related quality of life; CsA, cyclosporin A; MMF, mycophenolate mofetil
Source: (31, 32)

B.2.3.3.2 Study 305

See Table 4. [redacted]

B.2.3.3.3 CL-003/004

Study endpoints of CL-003/004 are summarised in Table 7.

Table 7. Overview of the study endpoints from the CL-003 and extension 004

Core study endpoints	
Primary study endpoint	**Secondary study endpoints**
• Responder rate* (increased platelet count) on Day 28 of treatment	• Pharmacokinetics and pharmacodynamics • Additional efficacy markers, e.g. peripheral blood platelet count • Safety/tolerability
Extension study endpoints	
Primary study endpoint	**Secondary study endpoints**
• Safety and tolerability over 6 months	• Markers of effectiveness including changes in/maintenance of peripheral blood platelet count, and decreasing need for ITP-directed concomitant medications

*Defined as the proportion of patients with Day 1 platelet count of <30×10^9/L who achieved a platelet count of ≥50×10^9/L on Day 28 plus the proportion of patients using steroids who had a Day 1 platelet count ≥ 30×10^9/L but <50×10^9/L who achieved a platelet count ≥20×10^9/L above their Day 1 platelet count on Day 28. Abbreviations: ITP, immune thrombocytopenia. Source: (31, 34)

B.2.3.4 Baseline demographics and patient characteristics

B.2.3.4.1 Study 302

Baseline demographics for Study 302 are shown in Table 8. Study participants were balanced across the treatment groups, except gender (63.3% overall were female, whilst 71.9% of the avatrombopag treatment group vs. 47.1% of the placebo group were female). Most participants were Caucasian (93.9%) and aged <65 years (91.8%), with a mean age of 44.6 years. Two-thirds (67.3%) were non-splenectomised, around half (55.1%) had no concomitant ITP treatment at baseline, and more than one third in both the avatrombopag (37.5%) and placebo group (35.3%) had previously received a TPO-RA. The mean (±SD) baseline platelet count of participants was 13.59±8.312, range; 1–31.5×10^9/L. Only 2% (n=1) of participants had a platelet count >30×10^9/L.

Table 8. Baseline demographics and characteristics of patients in Study 302

Characteristic	PLC (n=17) (%)	AVA (n=32) (%)	Total (n=49) (%)
Age (years), mean (SD)	41.2 (14.7)	46.4 (14.2)	44.6 (14.4)
<65 years, N (%)	16 (94.1)	29 (90.6)	45 (91.9)
Female	8 (47.1)	23 (71.9)	31 (63.3)
Ethnicity, N (%)			
Caucasian	15 (88.2)	31 (96.9)	46 (93.9)
Black or African American	1 (5.9)	0	1 (2.0)
Asian	1 (5.9)	1 (3.1)	2 (4.1)
Weight (kg), mean (SD)	84.97 (20.48)	81.9 (22.71)	82.97 (21.79)
Height (cm), mean (SD)	170.53 (7.46)	167.89 (8.00)	168.81 (7.84)
BMI (kg/m2), mean (SD)	29.24 (6.64)	28.99 (7.32)	29.08 (7.02)
Baseline platelet count, N (%)			
≤15 x 109/L	10 (58.8)	18 (56.3)	28 (57.1)
15–30 x 109/L	7 (41.2)	13 (40.6)	20 (40.8)
≥30 x 109/L	0	1 (3.1)	1 (2.0)
Prior TPO-RA, N (%)	6 (35.3)	12 (37.5)	18 (36.7)
Prior splenectomy, N (%)	5 (29.4)	11 (34.4)	16 (32.7)
Use of concomitant ITP medication at baseline, N (%)	7 (41.2)	15 (46.9)	22 (44.9)

Abbreviations: AVA, avatrombopag; BMI, body mass index; PLC, placebo

B.2.3.4.2 Study 305

Baseline demographics for Study 305 are shown in Table 9.

[redacted]

Characteristic	ELT (n=11) (%)	AVA (n=12) (%)	Total (n=23) (%)
Age (years), mean (SD)	[redacted]	[redacted]	[redacted]
<65 years, N (%)			
Female			
Ethnicity, N (%)			
Caucasian			
Black or African American			
Asian			
Other			
Weight (kg), mean (SD)			
Height (cm), mean (SD)			
BMI (kg/m^2), mean (SD)			
Baseline platelet count, N (%)			
≤15 x 10^9/L			
15–30 x 10^9/L			
Splenectomy, N (%)			
Use of concomitant ITP medication at baseline, N (%)			

Abbreviations: AVA, avatrombopag; BMI, body mass index; ELT, eltrombopag

B.2.3.4.3 CL-003/004

Baseline demographics for CL-003/004 are shown in Table 10.

[redacted]

Characteristic	PLC (n=5) (%)	AVA (n=59) (%)
Age (years), mean (SD)	[redacted]	[redacted]
Min, Max		
Female		
Ethnicity, N (%)		
Caucasian		
Black or African American		
Hispanic		
Asian		
Other		
Child-bearing potential, N (%)		
Weight (kg), mean (SD)		
Height (cm), mean (SD)		
Baseline platelet count, N (%)		
≤15 x 10^9/L		
>15 x 10^9/L		
Splenectomy, N (%)		
Baseline steroid usage, N (%)		
No. of lines of prior therapies (%)		
1		
2		
3		
4		
5		
6		
7		
8		
9		

Abbreviations: AVA, avatrombopag; BMI, body mass index; PLC, placebo

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Definitions of study populations

Study populations in Study 302, 305 and CL-003/004 are defined in Table 11. All presented efficacy and safety data are from the full-analysis and safety analysis sets, respectively.

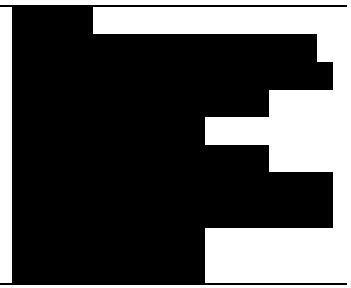
[redacted]

Study	Population	Definition
302 and 305	Full-analysis Set	[redacted]
	Safety Analysis Set	
	Modified Full Analysis Set	
CL-003/004	Full-analysis Set	
	Safety Analysis Set	
	Per protocol population	
	Pharmacokinetics population	

B.2.4.2 Statistical analysis

Efficacy and safety analyses were performed in accordance with a comprehensive statistical analysis plan, these are detailed in the clinical study reports (CSRs) for Study 302, 305 and CL-003/004 and are summarised in Table 12.

Table 12. Summary of statistical analyses in Study 302, 305 and CL-003/004

Trial	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Study 302	The primary efficacy analysis was to compare the cumulative number of weeks of platelet response for avatrombopag vs. placebo. The secondary efficacy analyses were performed to compare: • the platelet response rate at day 8 of avatrombopag vs. placebo • the proportion of subjects with a reduction in use of concomitant ITP medications from baseline of avatrombopag vs. placebo	Descriptive analyses (mean, median, frequency distribution, etc) were used to summaries the platelet counts and change from baseline by visit as well as platelet counts by the category by visit in the open label avatrombopag extension phase. Safety data were summarised descriptively. The Wilcoxon rank sum test was adopted to test the null hypothesis at the 5% (2-sided) level of significance for the primary efficacy endpoint. The CMH test was used to analyse the secondary endpoints at the 5% (2-sided) significant level, adjusting for splenectomy status and baseline platelet count. The Fisher's exact test was used where assumptions for a CMH test were not met.	All subjects who were randomised into the study were included as the primary population for all efficacy analyses. The per protocol dataset was aligned to support the analysis of the primary efficacy endpoint. Subjects who received study medication and who provided at least one platelet count to derive at least one effectiveness assessment were evaluated for the open label avatrombopag extension phase in order to assess the long-term safety, tolerability and effectiveness of avatrombopag Based on the CL-003 results, a total of 45 subjects (15 placebo and 30 avatrombopag) were required to provide ≥95% power to detect a treatment difference between avatrombopag and placebo regarding the cumulative number of weeks of platelet response during 4-week treatment and 6-month treatment respectively at a 5% (2-sided) significant level. This sample size also provided ≥99% power to detect the difference in platelet response rate at day 8 at the 5% (2- sided) level of significance.	Missing platelet assessments at a specific visit was classified as a nonresponse. If subjects discontinued the treatment or lost to follow-up before the 6-month treatment period, their subsequent platelet assessments at the scheduled visits were regarded as missing platelet values. A platelet count that occurred within 8 weeks after rescue therapies was considered as a nonresponse in any analysis of platelet response.
Study 305				
CL-003/004				

[redacted]

Abbreviations: CMH, Cochran–Mantel–Haenszel; WHO, World Health Organization; LOCF, last observation carried forward

B.2.4.3 Participant flows

Details of patient disposition in Study 302, 305 and CL-003/004 are presented in Table 13. CONSORT diagrams documenting the participant flows for each study are available in Appendix D.

[redacted]

Participant flow	Study 302		Study 305		CL-003/004	
	PLC	AVA	ELT	AVA	PLC	AVA
Total patients randomised	17	32	[redacted]			
Patients completing trial	1	22	[redacted]			
Total discontinuations	16	10	[redacted]			
Inadequate treatment effects	15	7	[redacted]			
Adverse event	0	0	[redacted]			
Other	1	3	[redacted]			

Abbreviations: N/A: not applicable

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Quality assessment of Studies 302 and 305 are presented in Table 14. CL-003/004 is a phase II study and was not quality assessed. Each study was completed to the highest standard, with adequate randomisation and blinding procedures.

Table 14. Quality assessment of Study 302 and 305

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data	Selective reporting (reporting bias)	Other bias
Study 302 **(32)**	LR	LR	LR	LR	UC	LR	LR
Study 305 **(33)**	LR	UC	LR	UC	UC	LR	UC

Abbreviations: LR, low risk; UC, unclear

Full quality assessment details are presented in Appendix D.

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 Study 302

Key results of Study 302 are summarised in Table 15.

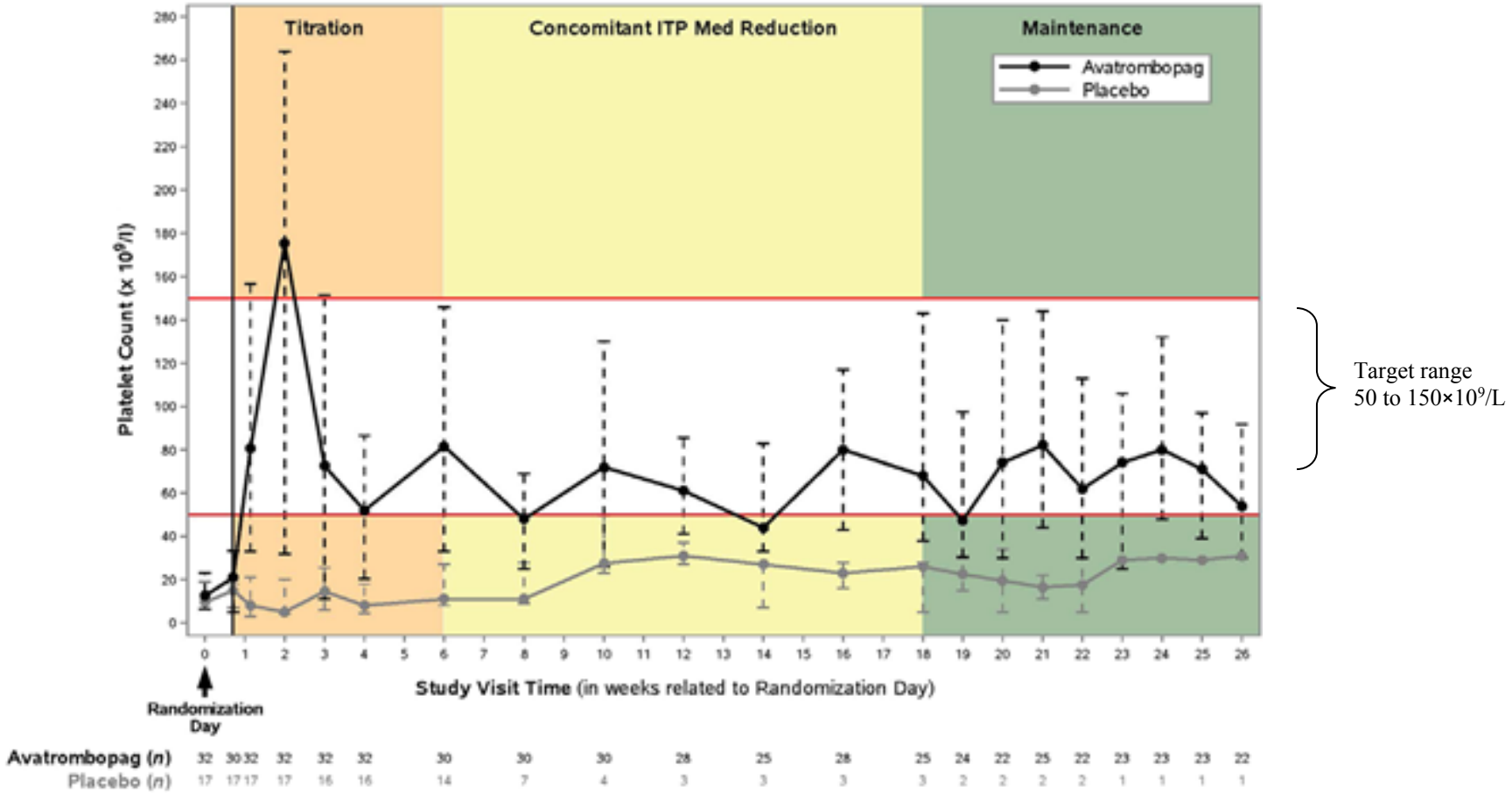
Table 15. Key efficacy results of Study 302

Endpoint	Result	
	PLC	AVA
Median cumulative number of weeks of platelet response ≥50×10^9/L over 26 weeks	0.0	12.4*
% of patients with platelet response (platelet count ≥50×10^9/L without rescue therapy) at Day 8	0.0	65.6*
% of subjects with reduction in concomitant ITP medication use	0.0	33.3
Durable platelet response rate (% of patients who had a platelet response for ≥6 of the last 8 weeks of treatment)	0.0	34.4*
% Incidence of bleeding events	52.9	43.8
% Use of rescue therapy	11.8	21.9

* = Statistical significance
Abbreviations: PLC, placebo; AVA, avatrombopag.

The median platelet count by visit in avatrombopag-treated patients was consistently higher than that of the placebo treatment group starting at Day 8 (80.5×10^9/L vs. 8×10^9/L, respectively) during the core study (Figure 6). Platelet count increased rapidly and remained within the target platelet count range (50–150×10^9/L) over 26 weeks. Onset of platelet count increase was observed within 3 to 5 days of avatrombopag treatment and peak effect was observed after 10 to 13 days (Figure 6).

Figure 6. Median platelet count during the core phase of Study 302



Abbreviations: ITP, immune thrombocytopenia. Source: (31, 32)

B.2.6.1.1 Primary endpoint

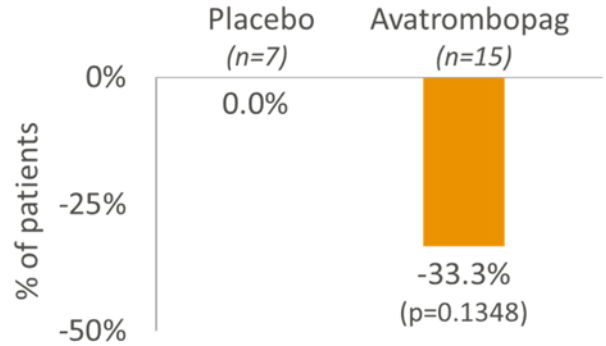
Patients receiving avatrombopag (n=32) experienced a significantly higher median cumulative number of weeks with platelet response of ≥ 50 $\times 10^9$/L compared to those receiving placebo (n=17) (12.4 vs. 0.0 weeks, respectively; p<0.0001) during the 26-week core treatment phase (Figure 6).

B.2.6.1.2 Secondary endpoints

At Day 8, a greater platelet response rates were observed for patients treated with avatrombopag compared with placebo (65.6 vs. 0.0%; p< 0.0001).

Use of concomitant ITP medications was reduced amongst patients receiving avatrombopag compared with placebo (33.3 vs. 0% reductions, respectively; p=0.1348). This was not significant due to the small number of patients (n=22) receiving concomitant ITP medications at baseline (Figure 7).

Figure 7. Reduction in concomitant ITP medication usage from baseline during Study 302

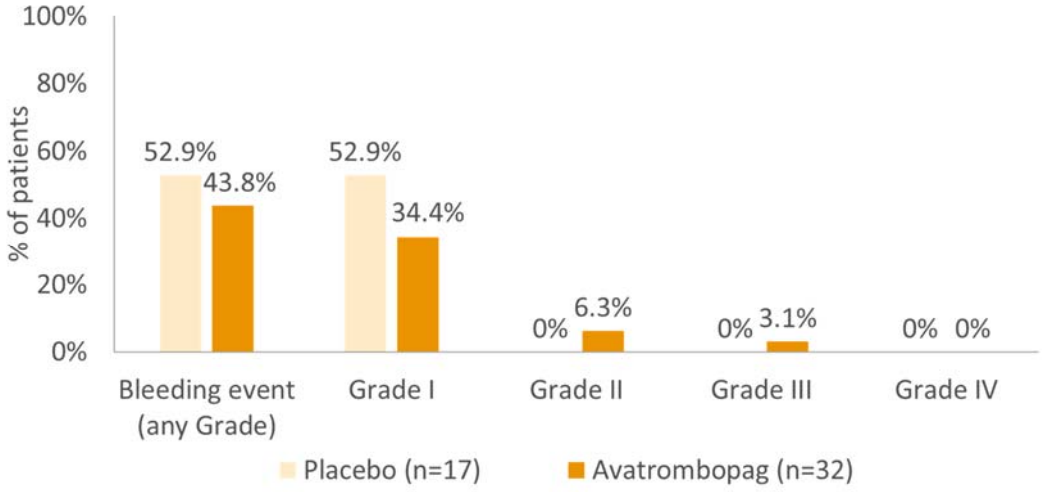


B.2.6.1.3 Exploratory endpoints

The durable platelet response rate, defined as the proportion of patients who had a platelet response for ≥6 of the last 8 weeks of treatment, was significantly greater in avatrombopag-treated patients compared with those receiving placebo (34.4 vs. 0.0%; p=0.009), with a treatment difference of 34.4% (95% confidence interval [CI]; 17.92, 50.83).

The incidence of bleeding events during the core study was not statistically different between the avatrombopag and placebo treatment groups (43.8 vs. 52.9%, respectively; p=0.5394) (Figure 8), and was lower for avatrombopag when adjusted for the 2.6-fold longer mean exposure time for avatrombopag-treated patients. All bleeding events were World Health Organization (WHO) Grade 1, except for 3 patients in the avatrombopag treatment group who experienced Grade 2 (n=2) or Grade 3 (n=1) bleeding events. The WHO Grade 3 bleeding event (epistaxis) was also reported as an AE of special interest (AESI).

Figure 8. Incidence of bleeding events during Study 302



Rescue therapy was required by 21.9% of avatrombopag-treated patients and 11.8% of those who received placebo, however there was no statistically significant difference in the use of rescue therapy between these groups (p=0.4668 using Fisher's exact test). The lower use of rescue therapy by patients in the placebo treatment group is likely artefactual due to the 2.6-fold shorter period of exposure in placebo-treated individuals, resulting from the high rate of early discontinuations due to lack of treatment effect.

B.2.6.1.4 Extension phase endpoints

During the extension phase of Study 302, platelet counts above 50×10^9/L with avatrombopag were maintained up to week 38 (9 months). Beyond week 38, platelet response was lower and more variable, but the small number of patients (n<15) at these time points limits further interpretation.

B.2.6.2 Study 305

Study 305 was discontinued due to significant enrolment challenges[3]. Only safety data are presented for this study.

B.2.6.3 CL-003/004

During Study CL-003/004 the responder rate was greater with avatrombopag at all doses than placebo on Day 28. The response rate was 49.2% amongst all patients who received avatrombopag vs. 0% for patients who received placebo (31, 34). Platelet count was increased by Day 7 and peaked on Day 14 in the 10 mg and 20 mg avatrombopag treatment groups. In the 20 mg avatrombopag treatment group, 80% of patients achieved a platelet count of ≥50×10^9/L on Day 28 compared with 0% of the placebo group (p=0.0036).

B.2.7 Subgroup analysis

B.2.7.1 Study 302 subgroup analyses

A summary of subgroup analyses from Study 302 is provided in Appendix E.

B.2.3.7.1 Study 302 pre-planned subgroup analyses

Study 302 included pre-planned subgroup analyses based on splenectomy status, baseline platelet count (≤15 x 10^9/L vs. >15 to <30 x 10^9/L) and concomitant ITP medication. See Appendix E for details.

B.2.3.7.1 Study 302 post-hoc subgroup analyses

A post-hoc sub-group analysis of Study 302 (n=32) based on prior TPO-RA use found that avatrombopag was equally effective for patients who had vs. had not received a prior TPO-RA (35) (Table 16).

Another post-hoc analysis of Study 302 demonstrated consistent efficacy of avatrombopag regardless of number of lines of prior treatment (<3 prior ITP treatments vs. >3 prior ITP treatments) (36).

[redacted]

Table 16. Study 302 avatrombopag responders by prior TPO-RA administration

Cumulative number of weeks of platelet response ≥50×109/L	Avatrombopag patients (n=32)	
	Prior TPO-RA (n=12)	No prior TPO-RA (n=20)
Median	12.7	12.4
Mean (SD)	11.8 (9.1)	12.0 (8.77)

Abbreviations: SD, standard deviation

B.2.8 Meta-analysis

Evidence comparing avatrombopag with all relevant comparators is not available. Study 305 was planned as a head-to-head phase III study of avatrombopag vs. eltrombopag but was discontinued early (see section 2.3.), therefore efficacy data are not available for an appropriate pooled analysis of the avatrombopag studies.

A NMA was conducted to inform the relative efficacy of avatrombopag versus all relevant comparators (see section 2.9).

B.2.9 Indirect and mixed treatment comparisons

A NMA was conducted to indirectly compare avatrombopag to relevant comparators. Fostamatinib was included as part of the NMA because it falls within the same Population, Intervention, Comparator, Outcomes and Subgroups (PICOS) for evidence search, and because it broadens the NMA network, which may enhance robustness. However, it is not considered relevant because it falls outside the specified population (i.e. patients who currently receive a TPO-RA). Therefore, this submission will not discuss the fostamatinib results of the NMA. A summary of methods and results are provided below with further details provided in Appendix D.

B.2.9.1 Overview

The evidence for this NMA was identified through a SLR aiming to identify clinical trials and observational studies for avatrombopag, eltrombopag, fostamatinib, lusutrombopag, rituximab and romiplostim used for the treatment of adult patients with chronic ITP, who have had an insufficient response to a previous treatment. No studies were identified for lusutrombopag and therefore it was not included in the NMA.

The search was conducted on in Embase, Medline, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews and on the

clinicaltrials.gov website on the 14th March and 20th May 2020, and was updated on 23rd November 2020, 8th December 2020, 12th July 2021 and 13th July 2021 (37).

Evidence was initially screened using the definition of chronic ITP of at least 12 months duration, which was consistent with:

- the definition developed by the International Working Group in 2009 (13)
- the inclusion criteria for the pivotal phase III trial assessing avatrombopag (32)

However, with this definition the indirect comparison between avatrombopag and comparators was considered unfeasible due to lack of studies for comparators meeting the eligibility criteria. This is because the trials assessing eltrombopag and romiplostim were designed and conducted before the current definition of chronic ITP was developed and allowed the inclusion of patients with the disease lasting ≥6-months.

For this reason, the inclusion criteria regarding the duration of the disease were relaxed for comparator trials in order to include studies enrolling patients with shorter disease duration, provided that the study met all other inclusion criteria for the NMA and the average duration of the disease is at least 12 months. The SLR identified 14 RCTs, of which 7 met this NMA's inclusion criteria:

- 1 RCT comparing avatrombopag vs. placebo (32)
- 1 RCT comparing avatrombopag vs. eltrombopag (the study was prematurely discontinued) (33)
- 1 RCT comparing eltrombopag vs. placebo (38)
- 2 RCTs comparing romiplostim vs. placebo (39)
- 2 RCTs comparing fostamatinib vs. placebo (40)

The NMA was carried out in a Bayesian framework, using a Markov Chain Monte Carlo (MCMC) method as implemented in the WinBUGS software package with vague prior distributions used for the model parameters. The outcomes were represented either as odds ratios (ORs) or incidence rate ratios (IRR), with corresponding 95% credible intervals (95% CrI). IRR for the comparison between groups within each study were calculated by dividing incidence rates estimated for the treatment and control groups, respectively. The 95% CrI s around IRR were calculated as follows:

$$CI_{95\%}(IRR) = \mathrm{e}^{ln\,IRR \pm z_{2.5\%}\sqrt{var(ln(IR_{active})) + var(ln(IR_{control}))}},$$

Where, $z_{97.5\%}$– the inverse of the standard normal distribution at 97.5%

Fixed-effect (FE) and random-effect (RE) models were fitted. The model fit was assessed based on deviance information criterion (DIC). The FE model was chosen for all outcomes because it was the simpler one with a lower number of estimable parameters and the lower DIC values (41). For some outcomes the RE model had a lower DIC value, however the difference vs. FE was <5 points and therefore the choice of FE model was still appropriate as it contains a lower number of parameters for clinical interpretation and an improvement of DIC value <5 does not justify the additional complexity of the RE model (42).

Overall, the NMA demonstrated at least similarity between avatrombopag, eltrombopag and romiplostim regarding durable platelet response, need for rescue treatments, reduction in the use of concomitant ITP therapies and incidence of higher-grade bleeding events. These results are consistent with previous NMAs and clinical opinion (23, 43). Numerical trends were observed in favour of avatrombopag for durable platelet response as well as significantly lower incidence of any bleed events with avatrombopag vs. eltrombopag and romiplostim. The rates of safety outcomes were comparable between treatments. There is no indication that extrapolation of these results to the UK population is inappropriate, and clinician feedback indicates good comparability in patterns of treatment and effect across countries (23).

B.2.9.2 Study selection

B.2.9.2.1 SLR framework

The SLR was performed according to the PICOS framework shown in Table 17.

Table 17. PICOS framework of the SLR

PICOS	Inclusion criteria
Population	Participants ≥18 years of age at screening with chronic ITP
Intervention	• AVA • ELT • ROM • FOS • LUSU

	• RTX	
Comparator	Any comparator or none	
Outcomes	• Platelet count and duration of platelet count • Response rate and duration of response rate • Need for rescue treatments for bleeding (referred to as 'rescue therapy') • Reduction in use of concomitant ITP treatments • Bleeding events • Mortality	AEs: Total number of AEs Total number of TEAEs Total number of SAEs Hepatoxicity Food interactions Injection interactions Drop-outs due to AEs
Study design	• RCTs • Observational studies (cohort or case series) of at least 20 participants	

Abbreviations: AE, adverse event; AVA, avatrombopag; ELT, eltrombopag; FOS, fostamatinib; ITP, immune thrombocytopenia; LUSU; lusutrombopag; RTX, rituximab; RCT, randomised clinical trial; ROM, romiplostim; SAE, serious adverse event; SLR, systematic literature review; TEAE, treatment-emergent adverse event

Overall, 116 records were included in the SLR. There were 14 RCTs identified by the SLR for inclusion in the NMA which are listed in Table 18. All studies were placebo controlled except Study 305 which compared avatrombopag vs. eltrombopag. Excluded studies are listed in Appendix D.

Table 18. RCTs identified in the SLR for inclusion in the NMA

Intervention	Study name/ID	References
AVA	Study 302/NCT01438840	(32)
ELT	TRA100773A/NCT00102739	(44)
	TRA100773B/NCT00102739	(45)
	RAISE Study/NCT00370331	(38)
	NCT00540423 NCT01762761 TRA113765	(46) (47) (48)
AVA/ELT	Study 305/NCT01433978	(33)
ROM	NCT00102323 NCT00102336 NCT00415532 NCT00603642	(39) (39) (49) (50)
FOS	FIT 1/NCT02076399 FIT 2/NCT02076412	(40) (40)

Abbreviations: AVA, avatrombopag; ELT, eltrombopag; FOS, fostamatinib; ROM, romiplostim; N/A, not applicable

B.2.9.2.2 Criteria for inclusion in NMA

To meet the NMA inclusion criteria, studies identified in the SLR were subjected to an additional round of selection because the objective of the NMA was to inform estimates of relative efficacy and safety between avatrombopag and other treatments used in patients with chronic ITP that were representative of the target population. The following restrictions were adopted:

- **Population**

Studies conducted exclusively on Asian patients were excluded to minimise the potential bias caused by ethnic differences. This approach is justified in the light of the differences in recommended posology of eltrombopag between patients with Asian and non-Asian ethnicity.

- **Dose regimens relevant for European population**

Studies assessing dose regimens approved by the EMA only were included. Studies or study arms assessing treatment schemes exclusively used in other ethnicities were excluded. The relevant treatment regimens include:

  - Avatrombopag: initial dose of 20 mg once daily
  - Eltrombopag: initial dose of 50 mg once daily
  - Romiplostim: initial dose of 1 µg/kg once weekly

- **Design**

The NMA was conducted based on clinical evidence from RCTs only.

- **Short treatment period – excluded as not compatible with other trials**

Study 302 was designed to compare avatrombopag vs. placebo over a 26 week treatment period although, due to noticeable differences in discontinuation, the mean treatment durations were 22.8 and 8.9 weeks in the avatrombopag and placebo groups, respectively. To minimise the bias associated with a wide range of treatment durations, all studies in which patients received the investigated treatment for a period shorter than 9 weeks (corresponding to the mean duration of treatment in the placebo group in Study 302), were excluded from the NMA. Five studies were excluded partially for this reason as well as for meeting other exclusion criteria.

In accordance with these criteria, 7 RCTs (5 comparing eltrombopag and 2 comparing romiplostim vs. placebo, respectively) identified by the SLR were excluded from the NMA due to inadequate population, dosing or duration of treatment. Characteristics and full explanations for excluded RCTs according to these criteria are provided in Appendix D.

B.2.9.3 Studies included in the NMA

The designs of the 7 studies which met the inclusion criteria and were included in the NMA are shown in Table 19. A diagram of the network between the studies is shown

in Figure 9.

Avatrombopag Study 302 (32) and Study 305 (31) are the only trials which enrolled patients with the disease lasting ≥12 months, which is consistent with the definition developed by the International Working Group in 2009 (13). The avatrombopag Study 305 was prematurely discontinued due to enrolment challenges[4], hence patient numbers were low. The studies assessing comparators included patients with shorter duration of ITP. The RAISE trial included patients with ITP duration of at least 6 months (38). Kuter et al. report on 2 studies recruiting patients with or without previous splenectomy (39). The studies' inclusion criteria required that splenectomy was conducted at least 24 weeks before enrolment, while there were no restrictions regarding duration of thrombocytopenia in non-splenectomised individuals (39). The median duration of the disease was 7.8–8.5 and 1.6–2.2 years, respectively, in studies enrolling splenectomised and non- splenectomised patients (39). Bussel et al. describe 2 randomised, double-blind, placebo-controlled trials (FIT1 and FIT2) enrolling patients with persistent or chronic primary ITP of at least 3 months. Chronic patients contributed to 92% and 94% of placebo and fostamatinib groups and median duration of the disease was 7.8 and 8.7 years, respectively (40).

Table 19. RCTs included in the NMA

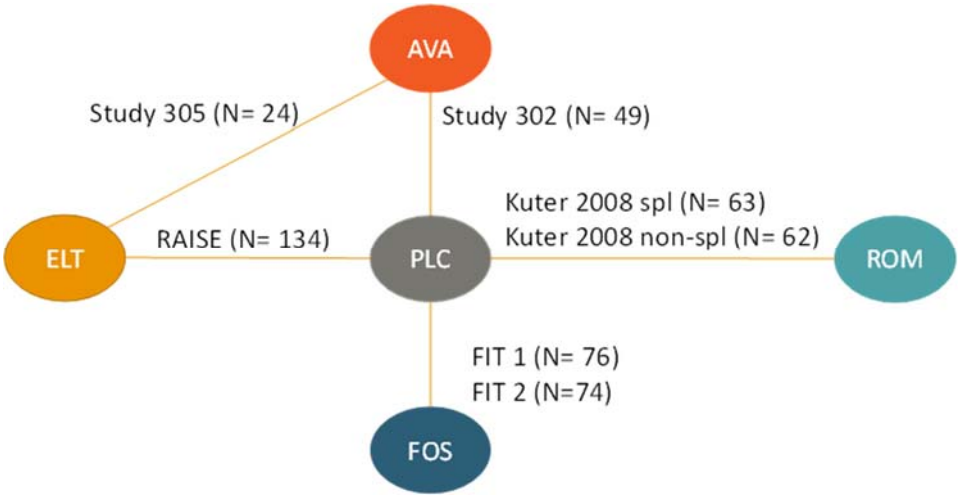
Study ID	Study design	Intervention vs. comparison	Dose regimen	N	Follow-up (weeks)	Duration of ITP	Primary outcome
NCT01438840 (Study 302) **(32)**	Phase III, MC, RAND, DB	AVA vs. PLC	20 mg QD	32 vs. 17	26	≥12M	No. of weeks with PC ≥ 50×109/L during 6M treatment period
NCT01433978* (Study 305) **(33)**	Phase III, MC, RAND, DB	AVA vs. ELT	20 mg vs. 50 mg QD	12 vs. 11	N/A*	≥12M	Change from baseline in local PC for the 6 M treatment period
NCT00370331 (RAISE Study) **(38)**	Phase III, MC, RCT, DB	ELT vs. PLC	50 mg QD	135 vs. 62	30	≥6M	Percentage of responders
NCT00102323 (Splenectomised) **(39)**	Phase III, MC, RCT, DB	ROM vs. PLC	1 µg/kg	42 vs. 21	36	≥6M	Durable platelet response during the

[redacted]

NCT00102336 (Non-splenectomised) **(39)**				41 vs. 21		Unrestricted	last 8 W of treatment and other platelet response parameters
NCT02076399 (FIT 1) **(40)** NCT02076412 (FIT 2) **(40)**	Phase III, MC, RCT, DB	FOS vs. PLC	100 mg BID	101 vs. 49	24	≥3M	Stable response (response on at least 4 of the last 6 visits between 14W - 24W)

*Terminated early
Abbreviations: AVA, avatrombopag, BID, twice-daily; DB, double blind; ELT, eltrombopag; FOS, fostamatinib; ITP, immune thrombocytopenia; M, months; MC, multicentre; NMA, network meta-analysis; PC, platelet count; PLC, placebo; QD, daily; RAND, randomised; RCT, randomised clinical trial; ROM, romiplostim; W, weeks; mg, milligrams; µg, micrograms

Figure 9. Network between RCTs included in the NMA



Abbreviations: AVA, avatrombopag; ELT, eltrombopag; FOS, fostamatinib; NMA, network meta-analysis; PLC, placebo; ROM, romiplostim

B.2.9.3.1 Baseline characteristics of included studies

Patient characteristics of included studies are shown in Table 20. Mean age was reported in 5 trials and ranged from 45 to 56 years. Two trials reported by Kuter et al 2008 presented median age which ranged from 46 to 56. The proportion of patients who were female across included studies ranged from 61 to 69% with no evidence for significant differences between treatment groups. The ethnic distributions of study populations were reported in all trials. The pivotal phase III trial Study 302 comprised predominantly Caucasian patients (94%) with a relatively small contribution of participants of Asian or African origin. Similarly, the populations of the remaining studies consisted predominantly of Caucasian (74–100%), followed by Asian (0–17%), Black or African American (0–9%) and other ethnicities (0–11%). Mean body weights

at baseline in Study 302 and 305 were 83 and 79 kg, respectively, and median body weights in trials reported by Kuter et al 2008 ranged from 71 to 89 kg (32) (33) (39). The other studies did not report baseline body weight. Information on the number of previous treatments for ITP was reported in all trials. All patients had at least 1 previous treatment, and the distribution of patients by previous treatment was similar across trials.

In general, the splenectomised population was similar across studies assessing avatrombopag and eltrombopag, ranging from 31.2–36%. Romiplostim was assessed in 2 RCTs, of which one recruited patient following splenectomy and the other enrolled only non-splenectomised individuals (Table 20). Information regarding concomitant treatment for ITP was reported in all studies. Between 13 and 48% of patients were receiving concomitant ITP medications at baseline across the studies (Table 20).

[redacted]

	Study						
Characteristic	NCT01438840 (Study 302)	NCT01433978 (Study 305)	Cheng 2011 NCT00370331 (RAISE Study)	Kuter et al 2008 NCT00102323 (Splenectomised)	Kuter et al 2008 NCT00102336 (Non-splenectomised)	Bussel et al 2018 NCT02076399 (FIT 1)	Bussel et al 2018 NCT02076412 (FIT 2)
Intervention	AVA/PLC	[redacted]	ELT/PLC	ROM/PLC	ROM/PLC	FOS/PLC	FOS/PLC
Sample size (n)	32/17	[redacted]	135/62	42/21	41/21	51/25	50/24
Age, mean (years)	44.6	[redacted]	47.9	median 51/56	median 52/46	56	49.2
Female (%)	63.3	[redacted]	69	60	69.4	61.8	59.5
Ethnicity (%)							
Caucasian	94	[redacted]	74	84.3	79.4	85.5	100
Black or African American	2	[redacted]	N/A	8	6.3	5.3	0
Asian	4	[redacted]	17	N/A	N/A	6.6	0
Other	N/A	[redacted]	9	N/A	N/A	2.6	0
Body weight, mean (kilograms)	83	[redacted]	N/A	median 77/89	median 78/71	N/A	N/A
No. of previous treatments (%)							
≥ 1	100	[redacted]	100	100	100	100	100
≥ 2	71	[redacted]	79	N/A	N/A	N/A	N/A
≥ 3	57	[redacted]	54	93	32.6	N/A	N/A
≥ 4	35	[redacted]	36	N/A	N/A	N/A	N/A
≥ 5	31	[redacted]	23	N/A	N/A	N/A	N/A
Splenectomy, (%)	32	[redacted]	36	100	0	39.3	31.2

Use of concomitant ITP medication at baseline (%)	45	[redacted]	48	29	34.1	N/A	N/A

Abbreviations: AVA, avatrombopag; ELT, eltrombopag; FOS, fostamatinib; ROM, romiplostim; N/A, not applicable

B.2.9.3.2 Quality assessment of included studies

A quality assessment of the 7 included studies was performed. The methodological quality of the RCTs that were included in the NMA were assessed using criteria based upon 'Systematic reviews: CRD's guidance for undertaking reviews in health care, (University of York Centre for Reviews and Dissemination) (51). All items had 3 possible responses: "yes", "no", and "unclear" to assess the risk of bias in analysed RCTs (Table 21).

Table 21. Risk of bias assessment

Criterion	Answer
Was randomisation carried out appropriately?	Yes/No/Unclear
Was the concealment of treatment allocation adequate?	Yes/No/Unclear
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes/No/Unclear
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes/No/Unclear
Were there any unexpected imbalances in drop-outs between groups?	Yes/No/Unclear
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes/No/Unclear
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes/No/Unclear
Was randomisation carried out appropriately?	Yes/No/Unclear

The quality assessment of the 7 studies included in the NMA is as follows. The methods of treatment randomisation were fully described and assessed to be associated with a low risk of bias in all of the included RCTs. Treatment allocation was adequately concealed in 70% of studies. In other studies, there was insufficient information to make a judgement. Regarding the risk of performance bias, all studies were assessed to have low risk, whereas the risk of detection bias was assessed as high, unclear, and low in 29%, 14% and 57% of studies, respectively. An unclear risk of detection bias was due to lack of sufficient information to make a judgement. For 43% of the included studies, the outcome data was complete, and the risk of reporting bias was low in 57%.

B.2.9.3.3 Adjustment for premature discontinuation

The significant and imbalanced discontinuation in the placebo group of Study 302 reduced the effective treatment period leading to a likely underestimation of the true

event risks. Since the majority of early dropouts (88%, n=15) occurred due to inadequate efficacy, it is highly unlikely that early discontinuation would affect durable platelet response and the reduction in the use of concomitant ITP medication. Adjustments to avoid bias associated with premature discontinuation are discussed in Table 22.

Table 22. Impact of premature discontinuation on outcomes

Outcome	Impact of discontinuation due to suboptimal efficacy	Comment on the impact of premature discontinuation	Analysed effect measure
Durable response	Low	The impact is considered limited since the likelihood for achieving durable platelet response in patients who discontinue due to insufficient response is marginal	Analysis based on observed events with OR
Need for rescue treatment	High	The impact is considered high since the alternative treatments and rescue therapies were likely administered patients after decision to discontinue. Therefore, reduced exposure may noticeably reduce the true risk of rescue treatment.	Analysis based on estimated incidence with IRR
Reduction in the use of concomitant ITP medication	Low	The impact is considered limited since the likelihood for the reduction of the intensity of treatment in patients who discontinue due to insufficient response is marginal	Analysis based on observed events with OR
Bleeding events	High	The impact is considered high since reduced effective exposure is highly likely to lead to underestimation of the true event risk	Analysis based on estimated incidence with IRR
Safety outcomes	High	The impact is considered high since reduced effective exposure is highly likely to lead to underestimation of the true risk of events	Analysis based on estimated incidence with IRR

Abbreviations: OR, odds ratio; IRR, incidence rate ratio

To avoid bias associated with imbalanced premature discontinuation we conducted the NMA based on estimated IRR, thus accounting for the differences in the effective treatment duration across groups.

The time on treatment in all arms of the respective studies was estimated assuming an exponential survival curve for time to discontinuation:

$$c(t) = e^{-\lambda t}$$

Where,

c(t) – proportion of patients, who remained on treatment

λ - rate of discontinuation

t – time

The mean exposure was estimated by calculating the surface below the survival curve for time to discontinuation:

$$\text{mean exposure time} = \int_0^{observation\ time} c(t)dt = -\frac{1}{\lambda}\left(e^{\left(\frac{observation\ time}{\lambda}\right)} - 1\right)$$

Estimated exposure durations are shown in Table 23. Mean exposure duration in Study 302 was reported by the authors as 22.8 weeks and 8.9 weeks in the avatrombopag and placebo groups, respectively.

[redacted]

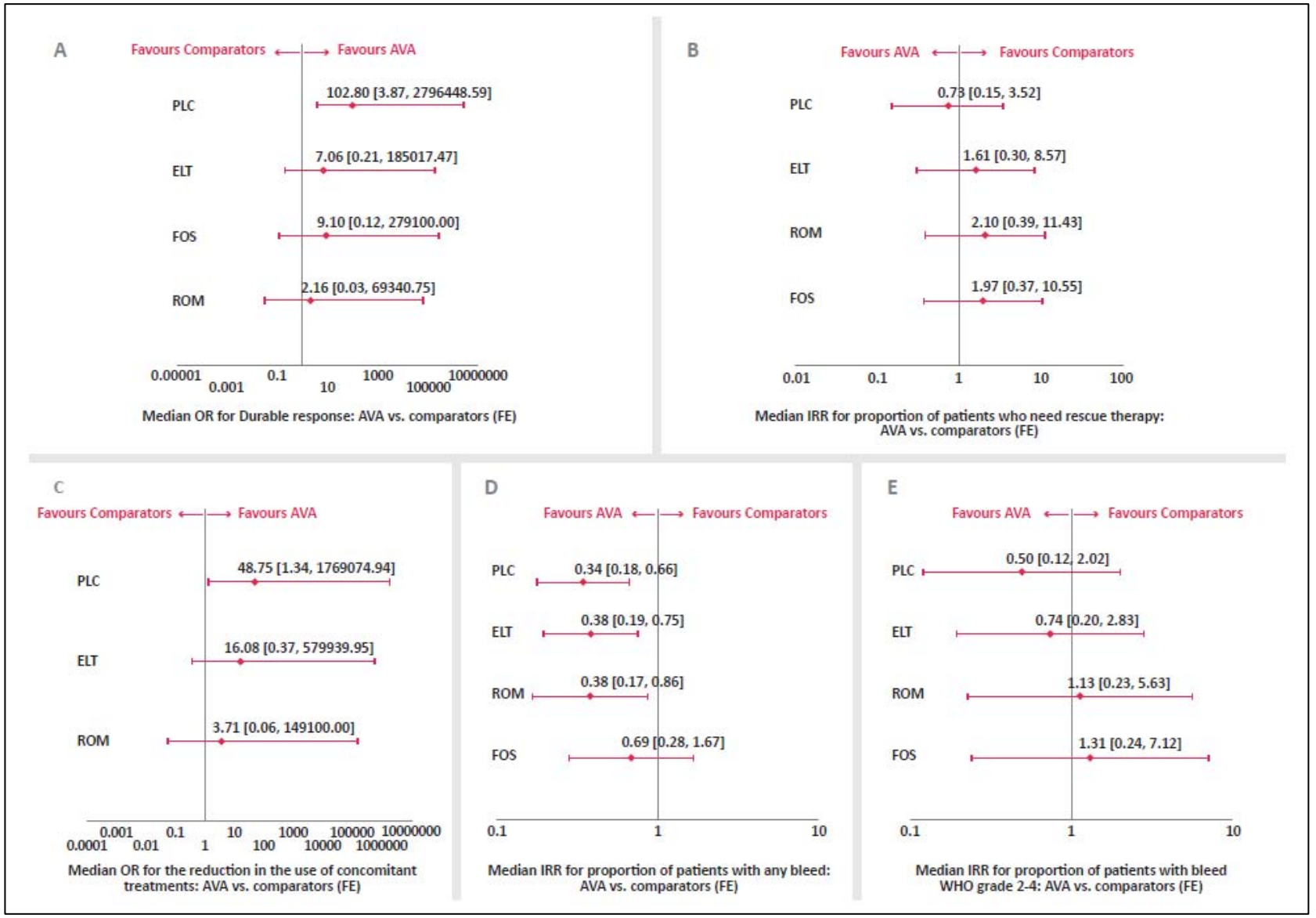
Study	Treatment	Percentage of non-completers	Mean exposure (years)	Total exposure (years)
NCT01438840 (Study 302) **(32)**	AVA	10/32 (31%)	0.44*	14.02
	PLC	16/17 (94%)	0.17*	2.92
NCT01433978* (Study 305) **(33)**	AVA	[redacted]	[redacted]	[redacted]
	ELT	[redacted]	[redacted]	[redacted]
NCT00370331 (RAISE Study) **(38)**	ELT	23/135 (17%)	0.46	43.33
	PLC	7/62 (11%)	0.47	18.38
NCT00102323 (Splenectomised) **(39)**	ROM	2/42 (5%)	0.45	19.07
	PLC	2/21 (10%)	0.45	9.38
NCT00102336 (Non-splenectomised) **(39)**	ROM	2/41 (5%)	0.45	18.61
	PLC	4/21 (19%)	0.43	9.04
NCT02076399 (FIT 1)**(40)**	FOS	39/51 (76%)	0.24	12.44
	PLC	24/25 (96%)	0.14	3.44
NCT02076412 (FIT 2) **(40)**	FOS	37/50 (74%)	0.25	12.68
	PLC	22/24 (92%)	0.17	4.09

*True exposure reported in trial
Abbreviations: AVA, avatrombopag; ELT, eltrombopag; FOS, fostamatinib; PLC, placebo; ROM, romiplostim

B.2.9.4 Efficacy outcomes

Detailed input data for efficacy outcomes are outlined in Appendix D. Forest plots for the efficacy outcomes of durable response, need for rescue therapy, reduction in use of concomitant ITP medication, any bleeding event and WHO grade 2–4 bleeding events are shown in Figure 10.

Figure 10. Forest plots for the IRR/OR for comparison of avatrombopag vs. comparators for A. Durable response B. Need for rescue therapy C. Reduction in use of concomitant ITP medication D. Any bleeding events and E. Bleeding events WHO grade 2–4 – fixed effect model



Abbreviations: AVA, avatrombopag; ELT, eltrombopag; FE, fixed-effects; FOS, fostamatinib; IRR, incidence rate ratio; OR, odds ratio; PLC, placebo; ROM, romiplostim; WHO, World Health Organisation

B.2.9.4.1 Durable response (binary data)

Results of the NMA regarding the proportion of patients with durable response are depicted in Figure 10, panel A and summarised in Table 24. The NMA showed that all treatments were associated with significantly higher odds of durable response compared with placebo. No significant differences regarding the proportion of patients with durable response were observed between avatrombopag and active comparators but odds were numerically in favour of avatrombopag. The treatment with the highest probability for achieving the highest proportion of patients with durable response was avatrombopag (58%). The probabilities of avatrombopag achieving the highest proportion of patients with durable response vs. eltrombopag, romiplostim and placebo were 82, 62, and 100%, respectively.

Table 24. OR and rankings for durable response – fixed effect model

	OR for all comparisons [95% CrI] (FE model)					Prob of being best (%)	SUCRA (%)	Prob of AVA being better than comp (%)
	vs. PLC	vs. AVA	vs. ELT	vs. FOS	vs. ROM			
PLC	PLC	**0.01 [0.00, 0.26]**	**0.07 [0.02, 0.19]**	**0.09 [0.01, 0.47]**	**0.02 [0.00, 0.11]**	0	0	100
AVA	**102.80 [3.87, 2796448.5]**	AVA	7.06 [0.21, 185017.47]	9.10 [0.12, 279100.00]	2.16 [0.03, 69340.75]	58	82	-
ELT	**14.27 [5.14, 53.73]**	0.14 [0.00, 4.78]	ELT	1.30 [0.07, 10.73]	0.31 [0.02, 2.53]	3	48	82
FOS	**10.94 [2.13, 181.70]**	0.11 [0.00, 8.04]	0.77 [0.09, 14.59]	FOS	0.24 [0.01, 5.58]	6	44	83
ROM	**46.49 [9.12, 670.61]**	0.46 [0.00, 30.02]	3.26 [0.40, 54.38]	4.13 [0.18, 97.06]	ROM	32	77	62

Abbreviations: AVA, avatrombopag; CrI, credible interval; comp, comparator; ELT, eltrombopag; FE, fixed effect; FOS, fostamatinib; OR, odds ratio; PLC, placebo; prob, probability; ROM, romiplostim; SUCRA, surface under the cumulative ranking curve. Statistically significant values shown in bold

B.2.9.4.2 Need for rescue therapy (estimated incidence)

Results of the NMA regarding the estimated incidence of the need for the rescue therapy are depicted in Figure 10, panel B and summarised in Table 25. No significant differences regarding the estimated incidence of the need for rescue therapy were observed between avatrombopag and comparators. The treatment with the highest probability for achieving the lowest proportion of patients who need rescue therapy was romiplostim (42%). The probability of avatrombopag achieving a lower proportion of patients who need rescue therapy vs. placebo was 65%.

Table 25. IRR and rankings for proportion of patients who need rescue therapy – fixed effect model

IRR for all comparisons [95% CrI] (FE model)						Prob of being best (%)	SUCRA (%)	Prob of AVA being better than comp (%)
	vs. PLC	vs. AVA	vs. ELT	vs. ROM	vs. FOS			
PLC	PLC	1.36 [0.28, 6.60]	**2.19 [1.26, 3.84]**	**2.87 [1.56, 5.28]**	**2.69 [1.53, 4.72]**	0	9	65
AVA	0.73 [0.15, 3.52]	AVA	1.61 [0.30, 8.57]	2.10 [0.39, 11.43]	1.97 [0.37, 10.55]	14	34	-
ELT	**0.46 [0.26, 0.79]**	0.62 [0.12, 3.32]	ELT	1.31 [0.57, 3.01]	1.23 [0.56, 2.72]	12	57	29
ROM	**0.35 [0.19, 0.64]**	0.48 [0.09, 2.59]	0.76 [0.33, 1.75]	ROM	0.94 [0.41, 2.15]	42	78	20
FOS	**0.37 [0.21, 0.65]**	0.51 [0.09, 2.72]	0.81 [0.37, 1.80]	1.07 [0.47, 2.44]	FOS	32	73	21

Abbreviations: AVA, avatrombopag; CrI, credible interval; comp, comparator; ELT, eltrombopag; FE, fixed effect; FOS, fostamatinib; IRR, incidence rate ratio; PLC, placebo; prob, probability; ROM, romiplostim; SUCRA, surface under the cumulative ranking curve. Statistically significant values shown in bold

B.2.9.4.3 Reduction in the use of concomitant ITP medication (binary data)

Results of the NMA regarding the proportion of patients with reduced use of concomitant ITP medications are depicted in Figure 10, panel C and summarised in Table 26. Although the estimates from this analysis were imprecise due to the low number of events, this NMA showed that all treatments were associated with significantly higher odds of a reduction in concomitant ITP therapy compared with placebo. No significant differences regarding the proportion of patients with a reduction in the use of concomitant ITP medications were observed between avatrombopag and comparators. The treatment with the highest probability for the highest proportion of patients with a reduction in concomitant ITP medication was avatrombopag (71%). The probability of avatrombopag achieving a higher proportion of patients with reduced use of concomitant ITP medications vs. eltrombopag, romiplostim and placebo was 91, 70 and 99%, respectively.

Table 26. OR and rankings for proportion of patients with reduction in use of concomitant ITP medications – fixed effect model

OR for all comparisons [95% CrI] (FE model)					Prob of being best (%)	SUCRA (%)	Prob of AVA being better than comp (%)
	vs. PLC	vs. AVA	vs. ELT	vs. ROM			
PLC	PLC	**0.02 [0.00, 0.74]**	**0.33 [0.13, 0.80]**	**0.07 [0.01, 0.35]**	0	1	99
AVA	**48.75 [1.34, 1769074.94]**	AVA	16.08 [0.37, 579939.95]	3.71 [0.06, 149100.00]	69	86	-
ELT	**3.08 [1.25, 7.98]**	0.06 [0.00, 2.69]	ELT	0.22 [0.03, 1.44]	1	38	91
ROM	**13.72 [2.84, 88.83]**	0.27 [0.00, 17.39]	4.46 [0.69, 35.30]	ROM	30	75	70

Abbreviations: AVA, avatrombopag; CrI, credible interval; comp, comparator; ELT, eltrombopag; FE, fixed effect; OR, odds ratio; PLC, placebo; prob, probability; ROM, romiplostim; SUCRA, surface under the cumulative ranking curve. Statistically significant values shown in bold

B.2.9.4.4 Any bleeding events (estimated incidence)

Results of the NMA regarding the proportion of patients with any bleed are depicted in Figure 10, panel D and summarised in Table 27. Avatrombopag was associated with a significantly lower estimated incidence of any bleeding compared with placebo. Additionally, avatrombopag was associated with a significantly lower incidence rate of any bleeding compared with eltrombopag and romiplostim (IRR = 0.38 [0.19, 0.75], 0.38 [0.17, 0.86], respectively). The treatment with the highest probability for the lowest proportion of patients with any bleed was avatrombopag (79%). The probability of avatrombopag achieving a lower proportion of patients with any bleed vs. romiplostim, eltrombopag and placebo was 99 and 100%, respectively.

Table 27. IRR and rankings for any bleed – fixed effect model

IRR for all comparisons [95% CrI] (FE model)						Prob of being best (%)	SUCRA (%)	Prob of AVA being better than comp (%)
	vs. PLC	vs. AVA	vs. ELT	vs. ROM	vs. FOS			
PLC	PLC	2.94 [1.52, 5.71]	**1.12 [0.82, 1.53]**	1.11 [0.69, 1.80]	**2.00 [1.10, 3.66]**	0	13	100
AVA	**0.34 [0.18, 0.66]**	AVA	**0.38 [0.19, 0.75]**	**0.38 [0.17, 0.86]**	0.68 [0.28, 1.67]	79	95	-
ELT	0.89 [0.65, 1.22]	**2.63 [1.33, 5.17]**	ELT	0.99 [0.56, 1.77]	1.79 [0.91, 3.54]	0	32	100
ROM	0.90 [0.55, 1.46]	**2.64 [1.16, 6.01]**	1.01 [0.57, 1.79]	ROM	1.81 [0.84, 3.93]	0	31	99
FOS	**0.50 [0.27, 0.91]**	1.47 [0.60, 3.57]	0.56 [0.28, 1.10]	0.55 [0.25, 1.20]	FOS	20	79	80

Abbreviations: AVA, avatrombopag; CrI, credible interval; comp, comparator; ELT, eltrombopag; FE, fixed effect; FOS, fostamatinib; IRR, incidence rate ratio; PLC, placebo; prob, probability; ROM, romiplostim; SUCRA, surface under the cumulative ranking curve. Statistically significant values shown in bold

B.2.9.4.5 Bleeding events WHO grade 2–4 (estimated incidence)

Results of the NMA regarding the proportion of patients with WHO grade 2–4 bleed are depicted in Figure 10, panel E and summarised in Table 28. No significant differences regarding the proportion of patients with WHO grade 2–4 bleed were observed between avatrombopag and comparators. The probabilities of avatrombopag achieving a lower proportion of patients with bleed of WHO grade 2–4 vs. eltrombopag and placebo were 67 and 84%, respectively.

Table 28. IRR and rankings for bleeding events WHO grade 2–4 – fixed effect model

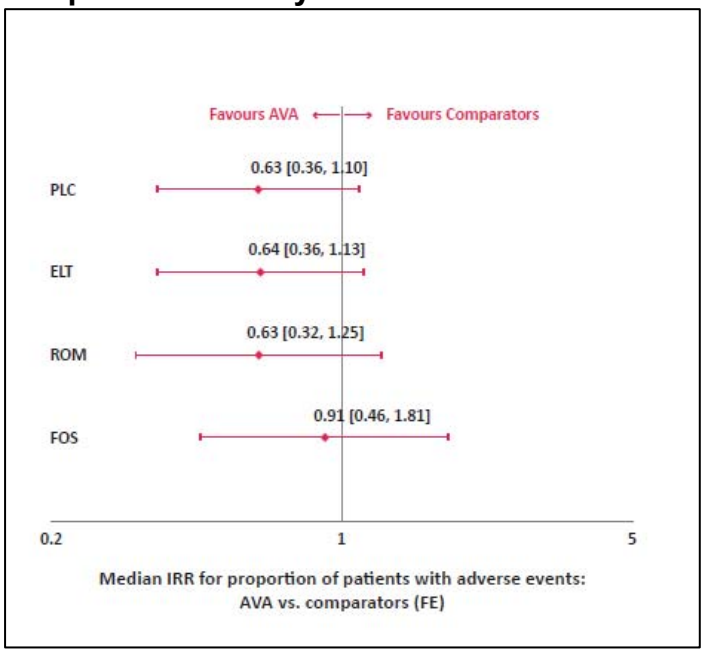
	IRR for all comparisons [95% CrI] (FE model)					Prob of being best (%)	SUCRA (%)	Prob of AVA being better than comp (%)
	vs. PLC	vs. AVA	vs. ELT	vs. ROM	vs. FOS			
PLC	PLC	2.01 [0.50, 8.20]	1.50 [0.95, 2.36]	**2.29 [1.07, 4.89]**	**2.65 [1.04, 6.68]**	0	6	84
AVA	0.50 [0.12, 2.02]	AVA	0.74 [0.20, 2.83]	1.13 [0.23, 5.63]	1.31 [0.24, 7.12]	29	58	-
ELT	0.67 [0.42, 1.05]	1.34 [0.35, 5.10]	ELT	1.53 [0.63, 3.73]	1.77 [0.63, 4.95]	1	40	67
ROM	**0.44 [0.20, 0.93]**	0.88 [0.18, 4.34]	0.65 [0.27, 1.58]	ROM	1.16 [0.35, 3.83]	27	69	44
FOS	**0.38 [0.15, 0.96]**	0.76 [0.14, 4.12]	0.57 [0.20, 1.59]	0.87 [0.26, 2.88]	FOS	43	76	38

Abbreviations: AVA, avatrombopag; CrI, credible interval; comp, comparator; ELT, eltrombopag; FE, fixed effect; FOS, fostamatinib; IRR, incidence rate ratio; PLC, placebo; prob, probability; ROM, romiplostim; SUCRA, surface under the cumulative ranking curve. Statistically significant values shown in bold

B.2.9.5 Safety outcomes

Detailed input data for safety outcomes are outlined in Appendix D. Forest plots for safety outcomes of any AEs are shown in Figure 11.

Figure 11. Forest plots for the IRR for comparison of avatrombopag vs. comparators for any AE – fixed effect model



Abbreviations: AE, adverse event; AVA, avatrombopag; ELT, eltrombopag; FE, fixed-effects; FOS, fostamatinib; IRR, incidence rate ratio; PLC, placebo; ROM, romiplostim; SAE, serious adverse event

B.2.9.5.1 Adverse events

Results of the NMA regarding the estimated incidence of any AE are depicted in Figure 11 and summarised in Table 29. No significant differences regarding the estimated incidence of any AE were observed between avatrombopag and comparators. The treatment with the highest probability for the lowest estimated incidence of any AE was avatrombopag (59%). The probabilities of avatrombopag achieving a lower estimated incidence of any AE vs. eltrombopag, romiplostim and placebo were 94, 91 and 95%, respectively.

Table 29. IRR and rankings for any AE – fixed effect model

IRR for all comparisons [95% CrI] (FE model)						Prob of being best (%)	SUCRA (%)	Prob of AVA being better than comp (%)
	vs. PLC	vs. AVA	vs. ELT	vs. ROM	vs. FOS			
PLC	PLC	1.58 [0.91, 2.77]	1.01 [0.75, 1.37]	1.00 [0.69, 1.47]	1.44 [0.98, 2.13]	0	26	95
AVA	0.63 [0.36, 1.10]	AVA	0.64 [0.36, 1.13]	0.63 [0.32, 1.25]	0.91 [0.46, 1.81]	59	85	-
ELT	0.99 [0.73, 1.34]	1.57 [0.88, 2.77]	ELT	0.99 [0.61, 1.62]	1.43 [0.87, 2.34]	1	30	94
ROM	1.00 [0.68, 1.46]	1.58 [0.80, 3.11]	1.01 [0.62, 1.64]	ROM	1.44 [0.84, 2.48]	2	29	91
FOS	0.69 [0.47, 1.02]	1.10 [0.55, 2.17]	0.70 [0.43, 1.15]	0.69 [0.40, 1.20]	FOS	38	80	61

Abbreviations: AVA, avatrombopag; CrI, credible interval; comp, comparator; ELT, eltrombopag; FE, fixed effect; FOS, fostamatinib; IRR, incidence rate ratio; PLC, placebo; prob, probability; ROM, romiplostim; SUCRA, surface under the cumulative ranking curve. Statistically significant values shown in bold

B.2.9.6 Uncertainties in the indirect and mixed treatment comparisons

The NMA is associated with a range of limitations due to the nature of the dataset available – these lead to uncertainty and restrict definitive conclusions. In summary, the following limitations of the indirect treatment comparison were identified:

- **The inclusion criteria regarding disease duration had to be relaxed for comparator trials to allow for indirect comparisons.**
  - The median duration of the disease at baseline was above 12 months in all studies indicating that most patients met the definition of chronic ITP
- **The number of included patients was small across all the included studies**
  - Low sample sizes limit the confidence of estimates
- **Each treatment was only assessed by a maximum of 2 studies**
  - The low sample size in Study 302 and enrolment challenges of Study 305 reflect the rarity of the disease and availability of other treatment options that were approved before the avatrombopag clinical programme was initiated.
  - The number of studies included in the NMA for eltrombopag and romiplostim was also limited to 1 and 2 studies, respectively.
- **High discontinuation from the placebo arm of Study 302**
  - To avoid bias associated with imbalanced discontinuation the NMA was conducted based on the estimated incidence rate ratio, thus accounting for the differences in the treatment duration.
- **Inconsistent definitions of outcomes**
  - Included studies were conducted according to different protocols, had different objectives and analysed different outcomes, which limited the feasibility for the comparative analysis
  - There were similar definitions of several outcomes' representative of clinical efficacy and safety, thus allowing comparisons between drugs to be attempted, however they were not fully uniform which potentially impacts comparative estimates. For example, trials collected multiple outcomes for platelet response, which allowed for comparison of durable response in the NMA only.
- **Post-hoc assessment of clinical efficacy**

- Key outcomes for the analysis were not pre-specified in all studies and sometimes were assessed retrospectively based on available data only (e.g. durable response in the RAISE trial)

- **Assumptions related to estimates of incidence rates**
  - Incidence rates were estimated based on data regarding the number of patients with at least 1 event. For this estimation the assumption was made that 1 patient could have only 1 event, which may not be true, especially for outcomes related to clinical safety. Thus, this analysis does not take into account the possibility that 1 patient could potentially experience several events of the same kind, and therefore the outcomes should be interpreted with appropriate caution. However, the same approach was adopted for all studies, therefore this approach should not favour any one intervention over another.

B.2.10 Adverse reactions

B.2.10.1 Study 302

As shown in Table 30, treatment-emergent adverse events (TEAEs) adjusted by exposure were lower overall in the avatrombopag treated group compared to placebo in Study 302 (31). In the avatrombopag group, the most common AEs were headache and contusion. TEAEs are presented as adjusted by exposure owing to the high drop-out rate in the placebo group (the avatrombopag-treated group had a 2.6-fold greater exposure than the placebo group).

Table 30. Most frequent TEAEs and SAEs during the 302-core study and extension phase adjusted by treatment exposure*– NCT01438840 (24)

	Core study exposure-adjusted incidence rate*		Core study + extension phase exposure-adjusted incidence rate*
	PLC (n=17) %	AVA (n=32) (%)	AVA (n=47) (%)
Any TEAE	**6.6**	**4.3**	**2.2**
Headache	1.3	1.6	0.7
Contusion	2.6	1.4	0.9
URTI	0.7	0.8	0.5
Arthralgia	0	0.5	0.2
Epistaxis	2.0	0.5	0.4
Fatigue	0.7	0.5	0.3
Gingival bleeding	0	0.5	0.4
Petechiae	0.7	0.5	0.3
Thrombocytopenia	0	0.3	0.4
Pharyngitis	0.7	0	0.3
Hypertension	0.7	0.3	0.2
Nasopharyngitis	0	0.4	0.2
Any SAE	**0.7**	**1.2**	**0.7**
Headache	0	0.3	0.1

Vomiting	0	0.3	0.1
Platelet count decreased	0	0.1	0.1

*Rate is calculated as 100 × (the number of subjects with events/ total exposure in subject-weeks) within each category. Abbreviations: AVA, avatrombopag; PLC, placebo; SAE, serious adverse event; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection

B.2.10.2 Study 305

TEAEs were similar between avatrombopag and eltrombopag treated groups during Study 305 as shown in Table 31. In the avatrombopag group, the most common AEs were dizziness, headache, insomnia, musculoskeletal pain and nausea (Table 31).

[redacted]

	Core study		Core study + extension phase
	ELT (n=11) n (%)	AVA (n=12) n (%)	AVA (n=17) n (%)
Any TEAE	[redacted]	[redacted]	[redacted]
Dizziness			
Headache			
Insomnia			
Musculoskeletal pain			
Nausea			
Diarrhoea			
Nasopharyngitis			
Fatigue			

Abbreviations: AVA, avatrombopag; CI, confidence interval; ELT, eltrombopag N/A, not applicable; TEAE, treatment-emergent adverse event.

B.2.10.3 CL-003/004

As shown in Table 32, fatigue and headache were the most common AEs experienced by patients receiving either avatrombopag or placebo.

[redacted]

	Core study		Core study + extension phase
	PLC (n=5) n (%)	**AVA (n=59) n (%)**	**AVA (n=64) n (%)**
Any TEAE	[redacted]	[redacted]	[redacted]
Fatigue			
Headache			
Epistaxis			
Diarrhoea			
Contusion			
Platelet count increased			
Vomiting			
Ecchymosis			
Nausea			
Pain in extremity			
URTI			
Arthralgia			
Thrombocytopenia			
Gingival bleeding			
Back pain			
Oedema peripheral			
Petechiae			
Dyspnoea			
Cough			

Dizziness	[redacted]		[redacted]		[redacted]		
Insomnia							

Abbreviations: AVA, avatrombopag; CI, confidence interval; PLC, placebo; N/A, not applicable; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection

B.2.11 Ongoing studies

Not applicable, there are no ongoing trials assessing the safety and/or efficacy of avatrombopag according to the indication being appraised in this submission.

B.2.12 Innovation

An additional, effective, well-tolerated and oral treatment choice will support effective TPO-RA therapy in this patient group, controlling disease symptoms and facilitating disease control for longer. Increased treatment options are a necessary innovation in ITP where patients may experience loss of response or an AE on a given TPO-RA and switching is used as a treatment strategy (22) and there are many unmet needs with the available TPO-RAs which avatrombopag may alleviate.

Eltrombopag is associated with food and drug restrictions which are likely to influence treatment choice and may potentially affect patient adherence. American Society of Hematology (ASH) guidelines for the treatment of ITP suggest that there may be adherence challenges with eltrombopag due to these dietary restrictions (2). Furthermore, eltrombopag is also associated with hepatoxicity risk which requires specific, additional patient monitoring (52). Romiplostim is administered via subcutaneous injection by a health care professional or may be self-administered after completing injection training (53). ASH guidelines for the treatment of ITP have previously suggested adherence challenges owing to this which is also a well-documented phenomenon in other chronic conditions, such as diabetes (2, 54).

Unlike other TPO-RAs, avatrombopag is the only orally available TPO-RA without the need for fasting, dietary restrictions or hepatoxicity monitoring which should reduce healthcare resource burden and increase likelihood of adherence, potentially resulting in fewer inpatient hospitalisations due to bleeding compared with existing TPO-RA options (eltrombopag and romiplostim). In current clinical practice, TPO-RA treatment selection can be based on patient choice (22) and a recent study on ITP patient preferences of TPO-RAs in the UK found that route of administration and dietary restrictions are significant drivers of patient preference towards TPO-RA choice (55).

Avatrombopag also has a flexible dosing regimen which allows for more accurate dose titration to maintain platelet counts within the target range as compared to the existing oral TPO-RA option, a valuable treatment strategy in certain circumstances, such as patients who are at an increased risk of thromboembolism. Furthermore, avatrombopag will be a relevant option for patients who cannot undergo hepatotoxicity monitoring or be exposed to a hepatotoxic risk and subsequently may currently be limited to only receive romiplostim and therefore are currently unable to easily implement treatment switching. This is particularly relevant since ITP often occurs in the more elderly population (14) who may have a degree of organ impairment including the kidneys and liver, allowing avatrombopag to be used in patients with liver disease. Finally, an additional TPO-RA option to manage bleeding risk in ITP may result in carers and families attending fewer planned and emergency hospital visits.

B.2.13 Interpretation of clinical effectiveness and safety evidence

The placebo-controlled design of Study 302 does not directly compare avatrombopag with other approved TPO-RAs; however, it is aligned with contemporary clinical studies of other TPO-RAs, and the robustness of the treatment effect with avatrombopag is supported by the high statistical significance of the primary endpoint ($p<0.0001$). Furthermore, all endpoints which related to improved platelet count were significant (section 2.6.1). A head-to-head comparison of avatrombopag vs. eltrombopag, Study 305, was initiated but was subsequently discontinued owing to significant enrolment challenges[5] (33). Therefore, an NMA has been performed to explore comparative efficacy and safety versus existing TPO-RAs. This NMA estimates that, based on the available evidence, efficacy can be considered at least similar across the TPO-RA comparators with numerical trends in favour of avatrombopag for durable platelet response as well as significantly lower incidence of any bleed events with avatrombopag vs. eltrombopag and romiplostim. These results are consistent with previous NMAs and clinical opinion (23, 43).

[redacted]

Some of the secondary endpoints of Study 302 did not reach statistical significance. However, this can be explained by limited population size and drop-out rate in the placebo arm: for example, more patients treated with avatrombopag were able to reduce concomitant ITP medication than with placebo (33 vs. 0%, p=0.1348), but as few patients across both arms were receiving concomitant ITP medication at baseline (n=22), statistical significance was not reached. This also may not reflect clinical practice. Furthermore, the study was not powered to show differences in bleeding or concomitant ITP medication use and the high drop-out rate in the placebo group (the avatrombopag-treated group had a 2.6-fold greater exposure than placebo) may have confounded analyses.

Approximately one-third of patients in Study 302 had received a splenectomy, however as treatment has since evolved in clinical practice, this is likely to be higher than the proportion of splenectomised ITP patients in the UK. The implication of this finding is that avatrombopag has demonstrable efficacy in a population of patients who may have been at a more severe stage of chronic disease than ITP patients in current clinical practice, which is viewed favourably by clinicians (23).

A safety analysis of TEAEs in Study 302 adjusted by treatment exposure showed that TEAEs were lower overall in the avatrombopag treated group compared to placebo (32). The NMA also demonstrates safety outcomes are comparable between treatments.

Patients with ITP have significant concerns affecting their day-to-day functioning and HRQoL, including bleeding, lifestyle restrictions, corticosteroid side effects and fear of undergoing splenectomy (5, 56). An international survey of over 1500 patients with ITP reported that fatigue, anxiety (of unstable platelet count) and bruising were the top 3 symptoms patients would most like to be resolved (57).

An SLR of 4 real-world studies described a strong correlation between low platelet counts ($<30\times10^9$/L) and an increased risk of bleeding in patients with ITP (58), and the risk of bleeding event was reported as 4.1 times greater for patients with a platelet count $<20\times10^9$/L than for patients with a count $>20\times10^9$/L (59). Increased rates of bleeds and infections in patients with ITP are associated with mortality (6) and an increased risk of death was reported for ITP patients with a platelet count $<30\times10^9$/L

compared with the overall ITP population (7). ITP related and non-related clinical resource use is also higher for ITP patients without platelet response following treatment vs. patients with a platelet response (6). Furthermore, a study of 73 patients with ITP reported that patients receiving treatment for low platelet count had significantly better scores in the Role Physical, Bodily Pain, General Health, Social Function, Role Emotional and Mental Health domains of the SF-36 compared to patients who weren't receiving treatment (60). An analysis of US open-label trial data in ITP also found that patients with platelet count response due to treatment had a higher HRQoL score than patients who did not response to treatment (61).

Platelet count is a widely accepted endpoint for monitoring patient response to treatment in ITP, used in both clinical studies and clinical practice (23). As per international guidelines on the standardisation of terminology and outcome criteria in ITP, a key treatment goal is to maintain to a platelet count of >20–30×10^9/L (2, 21). Across the pivotal phase III clinical studies of TPO-RAs in ITP, the primary endpoint was based on a patient's platelet count whilst on therapy, where platelet response was defined as a count of ≥50×10^9/L (32, 38, 39).

In clinical practice, patients with ITP may experience loss of response or AEs on their prescribed TPO-RA. In the case of ineffective treatment with a TPO-RA, the consensus of the Spanish ITP group (GEPTI) was to prescribe an alternative TPO-RA treatment (62) and another study reported that this can be an effective treatment strategy in cases of loss of efficacy, platelet count fluctuation, side effects and patient preference (27). International consensus guidelines also recommend this strategy in patients with refractory ITP for whom treatment with the initially-chosen TPO-RA lacks efficacy (21). All 13 respondents of a UK survey of clinicians treating ITP who used both existing TPO-RAs in clinical practice reported that they consider alternative agents in cases of lack of response, platelet fluctuation or AEs (22). This approach to treatment was also validated by UK clinical experts during the development of this submission (23). Therefore, avatrombopag will be beneficial in this context as an additional TPO-RA treatment option.

In Study 302, a relatively low number of patients who received avatrombopag had received a prior TPO-RA (12/32), however, treatment switching between TPO-RAs is common clinical practice (22). Despite low cohort numbers which may limit the interpretation of subgroup analyses, a post-hoc analysis of Study 302 found that avatrombopag was equally effective for patients who had vs. had not received a prior TPO-RA (35).

In the clinical study of avatrombopag, platelet count was significantly improved compared to placebo across a range of measures including median count, cumulative weeks of response and response at Day 8. The platelet increase was rapid and reliable (Section 2.6.1). These results are comparable to existing TPO-RAs (Section 2.9) Therefore, the available clinical evidence support the value of avatrombopag availability in clinical practice as an additional TPO-RA option for those patients in whom current TPO-RA options are currently considered.

B.3 Cost effectiveness

Model structure

- A de novo Markov cohort model was developed to establish the cost-effectiveness of avatrombopag vs eltrombopag and romiplostim; the model was designed to reflect clinical practice for ITP and the requirements of the NICE reference case
- The model considers platelet response (platelet count ≥50x10^9/L) as the basis for defining health states
- Model health states influence the likelihood of ITP related events including patient bleeds, use of rescue therapy and concomitant ITP medication

Clinical parameters

- Comparative effectiveness estimates for avatrombopag and comparators were obtained from the NMA. The model base case assumed a mean OR, whilst sensitivity analyses explored the impact of uncertainty and an assumption of TPO-RA similarity in terms of efficacy
- A combination of clinical data from Study 302, previous NICE appraisals (TA293 and TA221) and published literature was used to estimate other key clinical parameters. Study 302 data was used were possible, with other sources of information incorporated into the model when a paucity of data prevented the use of Study 302

Health-related quality of life

- The model included utility values for health states, bleeding events and AEs based upon a combination of data from Study 302 and TA293

Costs and medical resource use

- Costs and resource use estimates were taken from a combination of published literature, national reference cost databases and practising UK clinical experts through a market research survey
- Lower platelet counts (i.e. <50x10^9/L) are associated with increased disease management costs due to bleeding events and a greater utilisation of rescue therapies and concomitant ITP medications

Results

- The base-case analysis indicates that avatrombopag is dominant vs. both eltrombopag and romiplostim
- Despite uncertainty in the estimates of response rate from the NMA, the sensitivity analyses demonstrated the following:
  - In the probabilistic sensitivity analysis, avatrombopag was cost-effective at a willingness to pay threshold of £10,000 per QALY in [redacted] and [redacted] of simulations vs eltrombopag and romiplostim, respectively
  - Avatrombopag was still cost effective at the £10,000 cost per QALY threshold when a true assumption of similarity was adopted (i.e. the same OR used for all comparators)

Conclusion

- Avatrombopag is expected to be budget saving if introduced as an additional TPO-RA option in the population where TPO-RAs are currently used.
- Avatrombopag delivers at least similar clinical/patient outcomes but with additional benefits addressing the many unmet needs that remain with current therapies.
- Avatrombopag meets the NICE fast track assessment criteria, as the base case ICER is dominant and probabilistic analyses returned a very high probability [redacted] of being below £10,000 per QALY.

B.3.1 Published cost-effectiveness studies

An SLR was conducted to identify any relevant economic evaluations for the treatment of chronic ITP. The SLR was performed in March 2020 and subsequently updated in March 2021. In total, 20 studies (11 conference abstracts; 9 full-text publications) were identified: 19 from the original SLR and a further 1 in the updated SLR.

A summary of the published cost effectiveness studies identified in SLR is presented in Table 33 below. Full details of the SLR search strategy, study selection process and results are reported in Appendix G.

Table 33. Summary list of published cost-effectiveness studies

Author, country	Population	Comparison	Type of model	Incremental QALY/LY	Incremental costs	ICER (costs/LYG)	ICER (costs/QALY)	Sensitivity analyses
Gonzalez-Porras, Parrondo Garcia (63), Spain	Adult patients with chronic-refractory primary immune thrombocytopenia	• Oral TPO-RA (ELT) • RTX	Cost-consequence model was developed using a decision tree approach	NR	RTX vs. ELT: €4,231.5	NR	• CER RTX: €18,964.15 • CER ELT: €14,732.65	• DSA: no • PSA: no • Scenarios: yes
Tremblay, Dolph (64), US	cITP patients who were refractory to at least one other treatment (eg, corticosteroids, immunoglobulins)	• ELT • ROM	Markov model	Incremental QALY: •ELT vs. ROM: 0.01 Incremental LY: •ELT vs. ROM: 0.06	ELT vs. ROM: -$545,562	Cost per LYG: ELT dominant	Cost per QALY: ELT dominant	• DSA: yes • PSA: yes • Scenarios: yes

Fust, Parthan (65), US	Splenectomised (51%) and non-splenectomised (49%) adults with cITP	• ROM • ELT • W&R (monitoring until rescue therapies are required)	Decision tree	NR	• Incremental Cost Per Additional Responder ELT vs. ROM: $31,922 ROM vs. W&R: $33,815 • Alternative analysis 1 ELT vs. ROM: $32,350 ROM vs. W&R: $33,500 • Alternative analysis 2 ELT vs. ROM: $28,540 ROM vs. W&R: $33,815 • Alternative analysis 3 ELT vs. ROM: $31,756 ROM vs. W&R: $34,607 • Alternative analysis 4 ELT vs. ROM: $31,922 ROM vs. W&R: $33,815 • Alternative analysis 5 ELT vs. ROM: $32,637 ROM vs. W&R: $34,530 • Alternative analysis 6 ELT vs. ROM: $29,401 ROM vs. W&R: $33,815 • Incremental Cost Per BRE Avoided	NR	ICER (Per Additional Responder) • ELT vs. ROM: Weakly dominated • ROM vs. W&R: $45,973	• DSA: yes • PSA: no • Scenarios: yes

					ELT vs. ROM: $31,922 ROM vs. W&R: $33,815			
Tremblay, Dolph (66), US	Previously treated adult patients with cITP	• ELT • ROM • W&R	Cost-consequence model was developed using a decision tree approach	NR	NR	NR	ROM vs. ELT: $113,055	NR

Tremblay, Dolph (66), US	Adults with cITP who had an insufficient response to corticosteroids, immunoglobulins, or splenectomy	• ELT • ROM • W&R	Cost-consequence model	NR	Total costs: • EPAG-ROM: -$24,480 • EPAG-W&R: $36,460	NR	Splenectomised patients: • EPAG-ROM: -$25,487 • EPAG-W&R: $34,436 Non-splenectomised patients: • EPAG-ROM: -$24,303 • EPAG-W&R: $37,801 ICERs for severe bleeding events avoided: ITT population: • EPAG/ROM: Dominant • EPAG/W&R: $862,071 • ROM/EPAG: Dominated • ROM/W&R: $2,197,935 Splenectomised patients: • EPAG/ROMI: Dominant • EPAG/W&R: $403,994 • ROMI/EPAG: Dominated • ROMI/W&R: $1,192,142 Non-splenectomised patients: • EPAG/ROMI: Dominant • EPAG/W&R: $2,802,913 • ROMI/EPAG: Dominated • ROMI/W&R: $26,696,956	• DSA: yes • PSA: yes • Scenarios: no

Churn-Shiouh and Ying (67), Taiwan	cITP patients	•TPO-RA (ROM, ELT) group • Control group (placebo)	Markov model	Incremental QALY: •TPO-RAs vs Current clinical practice: 1.44 Incremental LY: •TPO receptor agonists vs Current clinical practice: 1.52	NR	NR	NR	• DSA: no • PSA: no • Scenarios: no
Krysanova, Krysanov (68), Russia	Medical care patients with cITP	• ELT • ROM	MS Excel based model	NR	NR	NR	ROM vs. ELT: $29,338 in favour of the romiplostim	NR
Naranjo, Alva (69), Mexico	cITP patients	• ELT • ROM	Decision tree	NR	NR	NR	ROM vs. ELT: Dominant	NR
Tremblay, Dolph (70), Canada	Adult cITP	• ELT • ROM	Markov model	Incremental QALY: •EPAG vs ROM: 0.01 Incremental LY •EPAG vs ROM: 0.08	EPAG vs ROMI: $-291,724	ELT dominant	ELT dominant	• DSA: yes • PSA: yes • Scenarios: NR
Allen, Bryden (71), England, Wales	Adult splenectomised and non-splenectomised patients with cITP who are refractory to other treatments (e.g., corticosteroids and IVIg) and who were at high risk of bleeding or who require frequent rescue therapy.	• ELT • ROM	Markov cohort model	Incremental QALY - Base case(probabilistic): • Splenectomised: ELT vs. ROM = -0.02 • Non-splenectomised: ELT vs. ROM = -0.02 Incremental LY • NR	Base case (probabilistic): • Splenectomised: ELT vs. ROM = £88,904 • Non-splenectomised: ELT vs. ROM = £40,261	NR	ROM vs. ELT •Splenectomised: Dominant •Non-splenectomised: Dominant	• DSA: yes • PSA: yes • Scenarios: yes
Dos Santos, Vargas-Valencia (72), Brazil	Adult ITP splenectomised patients with refractory disease or non-splenectomised	• ROM • IVIg rescue therapy	Cost per response model	NR	NR	NR	ROM vs. IVIg: Dominant	NR

	patients with surgery contra-indication							
Kikuchi, Miyakawa (73), Japan	A typical adult patient with intractable ITP for whom the first treatment option of corticosteroids is ineffective was set as a target Japanese woman of 50 years of age, 60 kg in weight, and 160 cm in height, with idiopathic thrombocytopenia purpura	•Splenectomy - ROM (sequence 1), •Splenectomy - ROM-RTX (sequence 2), •Splenectomy -RTX- ROM (sequence 3)	Markov model	NR	NR	NR	ROM + RTX vs. ROM: Dominant	• DSA: no • PSA: no • Scenarios: yes
Augusto, Gouveia (74), Portugal	Splenectomised and non-splenectomised patients	• ROM • ELT • SoC	A lifetime treatment-sequence cost-utility Markov model with an embedded decision tree	Incremental QALY (In the combined population): • ROM vs. ELT: 0,566 • ROM vs. SoC: 0,938 Incremental LY • NR	In the combined population: • ROM vs. ELT: €13.848 • ROM vs.SoC: €18.622	NR	In the combined population: • ROM vs. ELT: €24.451 • ROM vs. SoC: €19.848	• DSA: yes • PSA: yes • Scenarios: no
Brezina, Klimes (75), Czech Republic	Splenectomised and non-splenectomised patients	• ROM vs. SoC with RTX • ROM vs. SoC without RTX • ROM vs. SoC without both RTX and MMF • ROM vs. ELT	A lifetime treatment sequence cost-utility Markov model	Incremental QALY: -Splenectomised patients: • ROM vs. SoC with RTX- QALYs gain = 1.58 • ROM vs. ELT - QALYs gain =1.81 -Combined population: • ROM vs. SoC with RTX - QALYs gain = 1.12 • ROM vs. ELT-	NR	NR	Splenectomised patients and CP: • ROM vs. SoC with RTX: dominant • ROM vs. ELT: dominant • ROM vs. SoC without RTX: dominant • ROM vs. SoC without both rituximab and MMF: dominant	• DSA: no • PSA: no • Scenarios: yes

				QALYs gain = 1.21 Incremental LY • NR				
Lee, Thornton (76), Ireland	Adult ITP patients	• ROM followed by current medical SoC • ELT followed by SoC. • SoC, including RTX.	A lifetime treatment-sequence cost-utility Markov model with embedded decision tree	Incremental QALY: • ROM vs. ELT: 0.76 • ROM vs. SoC: 1.17 Incremental LY: • ROM vs. ELT: 0.73 • ROM vs. SoC: 1.13	• ROM vs. ELT: -€13,258 • ROM vs. SoC: -€13,258	NR	• ROM vs. ELT: Dominant • ROM vs. SoC: Dominant	• DSA: yes • PSA: yes • Scenarios: yes

Vorobyev, Krasnova (77), Russia	Patients with chronic ITP, for whom splenectomy is contradicted	• ELT • ROM	Markov model, developed by GlaxoSmithKline, and adapted to the context of Russian health care system	NR	NR	CER for criterion "additional years of life" after 2 years of onset: •ELT: $27,703 • ROM: $31,988 CER for criterion "additional years of life" after 10 years of onset: •ELT: $21,758 •ROM: $24,700 CER for criterion "additional years of life" after 20 years of onset: •ELT: $17,257 •ROM: $19,577	Cost of QALY after 2 years of onset: • ELT: $39,000 • ROM: $45,530 Cost of QALY after 10 years of onset : • ELT: $35,108 • ROM: $40,218 Cost of QALY after 20 years of onset : • ELT: $32,527 • ROM: $37,204	NR
Dranitsaris and Tsang (78), Canada	Adults with chronic ITP	• ELT • IVIg	NR	NR	NR	NR	Given its oral route of administration and cost-saving potential, eltrombopag would be an economically attractive alternative to IVIg when the intent of therapy is to create a bridge to surgery.	• DSA: yes • PSA: no • Scenarios: no

Hanley, Redmond (79), Ireland	Adult cITP patients, refractory to splenectomy or with splenectomy contraindication	• ELT • ROM or RTX	Markov model		NR	NR	ELT vs. ROM: Dominant	NR
Mowatt, Boachie (80), UK	cITP adult patients	• ROM as first treatment arm • SoC (W&R arm) • RTX (used as comparator by the ERG)	Cohort-type model	NR	NR	NR	• ROM vs. W&R: not cost-effective • ROM vs. RTX: not cost-effective	• DSA: yes • PSA: no • Scenarios: yes
Xie, Blackhouse (81), Canada	Hypothetical group of adults with persistent cITP at age 35 years and a body weight of 70 kg	• IVIg • Prednisone	Markov model	Incremental QALY: •IVIg vs prednisone: 0.0071 Incremental LY • NR	IVIg vs prednisone: $8080	NR	IVIg vs prednisone: Can $1,130,000	• DSA: yes • PSA: yes • Scenarios: yes

*ICER not provided; most of the sensitivity analysis results show that the ICER values were greater than 3GDP per capita in Taiwan

Abbreviations: BRE, Bleeding-related episodes; CER, Cost-effectiveness ratio; cITP , chronic immune thrombocytopenia; DSA, Design sensitivity analysis; ELT, Eltrombopag; EPAG, Eltrombopag; ERG, electroretinogram; GDP, gross domestic product; ICER, Incremental Cost-Effectiveness Ratio; ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin; LY, life years; LYG, life years gained; MMF, mycophenolate mofetil; MS, Microsoft; NR, not reported; PSA, probabilistic sensitivity analysis; ROM, Romiplostim; RTX, rituximab; SoC, Standard of care; TPO-RA, thrombopoietin receptor agonist; UK, United Kingdom; US, United States; W&R, Watch and rescue; QALY, Quality Adjusted Life Years

B.3.2 Economic analysis

As the SLR identified no previous economic evaluations for avatrombopag, a de novo model consistent with the NICE reference case (82) was developed to estimate the cost effectiveness of avatrombopag in ITP. The model was conceptualised to incorporate previous approaches to economic modelling in ITP (as identified in section B.3.1), and the best available data (including comparative effectiveness and key outcomes associated with modelling this patient population). The patient population considered in the model, the model structure and the included intervention and comparators are presented in sections B.3.2.1, B.3.2.2 and B.3.2.3, respectively.

B.3.2.1 Patient population

The cost-effectiveness analysis considers the population defined in the decision problem (see section B.1.1) which is also consistent with the product label for avatrombopag in ITP; treatment of primary chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g. corticosteroids or immunoglobulins).

The patient population included in the model is based on Study 302 (32), the pivotal trial providing efficacy and safety data on avatrombopag which is applicable to the UK ITP population (see section B.2.3.2.1).

The baseline characteristics of patients from Study 302 included in the model are provided in section B.2.3.4.1, Table 8. The population parameters for Study 302 utilised in the model are shown in Table 34.

Table 34. Study 302 population parameters that were used in the cost-effectiveness model

Parameter	Value
Age	44.6
Gender, male (%)	36.7
Weight (kilograms)	82.97
Body area (m^2)	1.94
Splenectomy status	All patients
Proportion of patients post-splenectomy	32.7%

Splenectomy status was included in the model because it was a pre-specified subgroup in Study 302 and efficacy is lower for this population. However, there were no subgroups that were considered relevant for this economic analysis (as per the submitted decision problem in section B.1.1). Furthermore, patient numbers were small in Study 302 and high

discontinuation in the placebo arm meant such analyses were infeasible. Therefore, results are not reported according to splenectomy status.

B.3.2.2 Model structure

A de novo Markov cohort model was developed and executed in Microsoft Excel to assess the cost effectiveness of avatrombopag within its licensed indication for ITP. The model health states were defined depending on the use of active treatment and response was defined as a platelet count ≥50×10^9/L. Model health states are shown in Table 35 and a schematic illustrating the model is provided in Figure 12.

Table 35. Health states included in the model

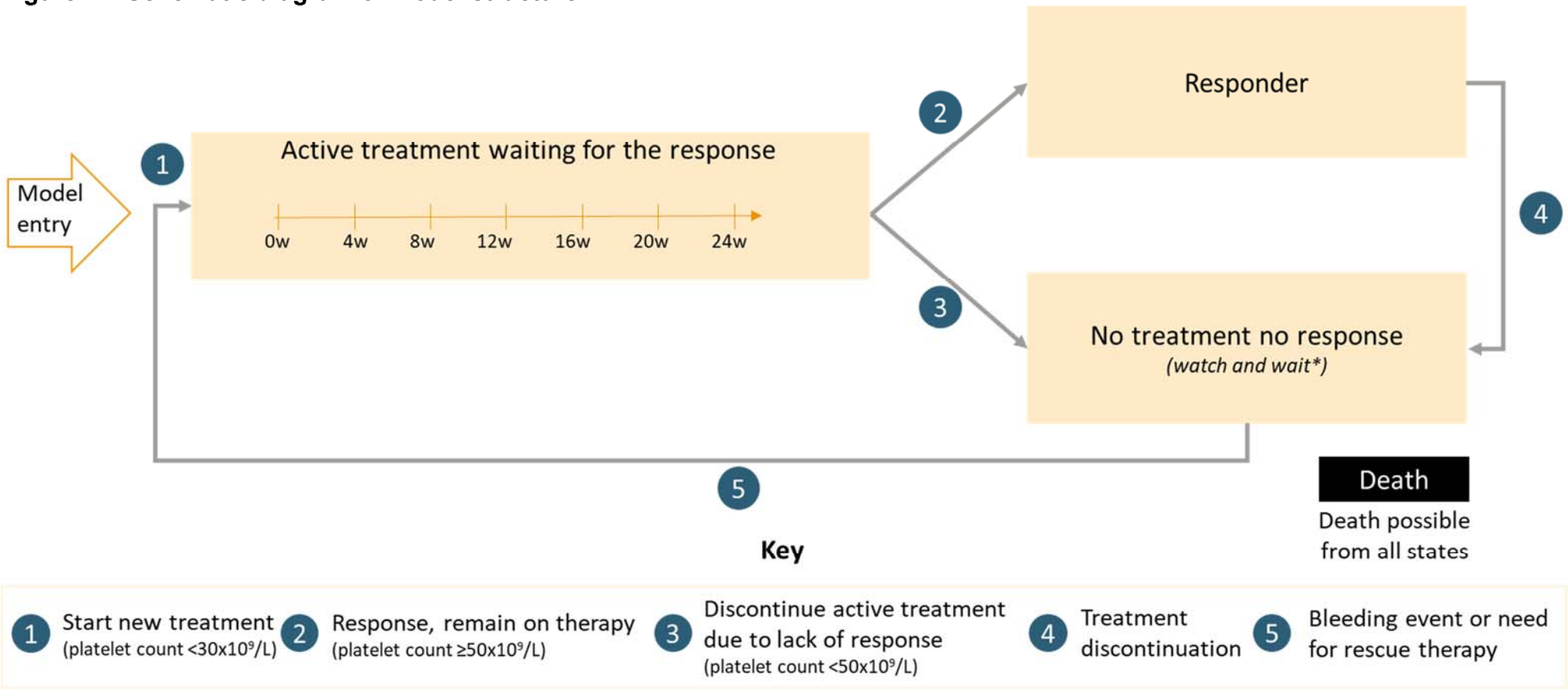
Health state	Description
Treatment, no response* (up to 24 weeks)	Active treatment up to 24 weeks waiting for response (<50×10^9/L platelet count)
Treatment response*	Active treatment with response (≥50×10^9/L platelet count)
No treatment	No active treatment received
Death	Death state

*Response defined as platelet count ≥50×10^9/L

In clinical practice, platelet count is the most significant outcome used to measure disease severity and patient response to treatment and is thought to drive ITP related outcomes including bleeding, use of rescue therapy and concomitant medications (13) (see section B.1.3.1).

The 50×10^9/L threshold is a standard measure used to confirm treatment response in ITP clinical studies which allows for comparative effectiveness estimates between avatrombopag and relevant TPO-RA comparators (see NMA provided in section B.2.9). Across the pivotal phase III clinical studies of TPO-RAs in ITP, the primary endpoint was based on a patient's platelet count whilst on therapy, where platelet response was defined as a count of ≥50×10^9/L (32, 38, 39). This threshold has also previously been used in economic models in the identified literature (Table 33), as well as previous NICE appraisals for ITP (29, 30).

Figure 12. Schematic diagram of model structure



*Patients only receive concomitant ITP medication (for example, corticosteroids)
Abbreviations: NR, non-responder; PLT, platelet; TPO-RA; thrombopoietin receptor agonist; W, weeks

Patients enter the model (step 1, Figure 12) in an uncontrolled disease state, where the platelet count is $<30\times10^9$/L and active treatment is started. Patients remain in this state as non-responders until it is determined whether they are responders or non-responders to treatment. Up to 24 weeks is given for waiting for response/non-response. If patients have responded to treatment during the 24 week treatment phase (platelet count $\geq50\times10^9$/L), they continue on treatment as responders (step 2, Figure 12); if $<50\times10^9$/L they discontinue treatment and move to no active treatment ("watch and wait") and continue receiving concomitant ITP medication (step 3, Figure 12). Patients cannot leave active treatment before 24 weeks regardless of platelet count, response status is only adjudicated at the end of the period. Patients who have responded remain on active treatment with a fixed discontinuation rate (presented in Table 51) applied over time (step 4, Figure 12) and eventually move to no active treatment ("watch and wait"). Patients remain in the no treatment ("watch and wait") health state until they experience a bleeding event or unless they require rescue therapy to re-establish a safe platelet count. If this occurs, they initiate a new active treatment (step 4, Figure 12).

Each model cycle has a duration of 28 days (4 weeks), consistent with the frequency of haematologist consultations to monitor disease which occur monthly during the early stages of disease management. Furthermore, once platelet counts are stable on therapy, blood tests to establish platelet count are performed on a monthly basis (83-85). A half-cycle correction was applied to all cycles.

The base-case analysis assumes a lifetime time horizon, with costs and utilities being estimated from the NHS/PSS and patient perspectives, respectively. In line with the NICE reference case, an annual discount rate of 3.5% was applied to both costs and quality-adjusted life years (QALYs) (82) .

Key features of the economic analysis in comparison to those of previous NICE appraisals for ITP (eltrombopag and romiplostim) are outlined in Table 36.

Table 36. Features of the economic analysis

	Previous NICE appraisals		Current NICE appraisal	
	Eltrombopag (TA293)	**Romiplostim (TA221)**	**Chosen values**	**Justification**
Model mathematical framework	Markov cohort model	Markov model with embedded decision tree	Markov cohort model	Consistent with previous economic models for ITP submitted to NICE and available within the published literature
Perspective	NHS	NHS/PSS	NHS/PSS	Consistent with the NICE reference case
Time horizon (years)	lifetime (53 years – 690 x 4-week cycles)	lifetime	lifetime (56 years)	Consistent with the NICE reference case
Discounting (%)	3.5	3.5	3.5	Consistent with the NICE reference case
Cycle length (weeks)	4	4	4	Haematologist consultations are usually conducted on a monthly basis at the start of treatment. Furthermore, dosing guidance for TPO-RAs suggests monthly platelet count tests for patients who are stable on therapy. Finally, a 4-week cycle is consistent with previous economic models for ITP
Source of utilities	Szende et al. (86) and TA221 (29)	Szende et al. (86) and utility values from Kuter et al. (39)	Tobit model using data from Study 302 (31) and TA293 (30)	As per the NICE reference case, RCT data from Study 302 was used when possible. Additional utility data was sourced from TA293 to address data gaps
Source of resource use and costs	BNF and NHS reference costs	BNF and NHS reference costs	BNF and NHS reference costs	Consistent with the NICE reference case

Abbreviations: BNF, British National Formulary; NHS, National Health Service; PSS, Personal Social Services

B.3.2.3 Intervention and comparators

The model evaluates the cost effectiveness of avatrombopag in addition to standard of care treatment (which includes concomitant ITP medication and rescue therapy as these are defined in Study 302 - see section 2.3, Table 4 and Table 6) compared with the existing NICE-approved TPO-RAs, eltrombopag and romiplostim.

The included doses for the interventions and comparators align with the starting doses specified in the product SmPCs for avatrombopag and eltrombopag, respectively. For romiplostim, dosing is dependent on patient weight and efficacy, ranging from 0.001–0.1 mg/kg; therefore, the mean dose from the pivotal long-term trial of romiplostim by Kuter et al. (87) was assumed (0.004 mg/kg). Dosages for each modelled therapy are shown in Table 37.

Table 37. Base case doses of TPO-RA used in the model

Treatment	Dose (mg)	Source
AVA	20	Avatrombopag SmPC (85)
ELT	50	Eltrombopag SmPC (83)
ROM	0.004 per kg	Kuter et al 2010 (87)

Abbreviations: mg, milligram; kg, kilogram; AVA, avatrombopag; ELT, eltrombopag; ROM, romiplostim; SmPC, summary of product characteristics

For patients who require subsequent therapy after discontinuation of their TPO-RA (i.e. when a bleed has occurred or patients require rescue therapy), the model allows for patients to receive up to 3 subsequent lines of therapy (which include both TPO-RA and non-TPO-RA options (Table 38 and Table 39). In the fourth line of therapy, patients remain in the “watch and wait” state.

The estimated proportion of patients receiving various treatments at each subsequent line of therapy are presented in Table 38. These were obtained from market research which was conducted to inform understanding and provide data on the current treatment of ITP across Europe and the UK. This included a survey as well as structured interviews with 113 physicians across the EU, and included 20 physicians from the UK (88).

The dosing regimens applied for subsequent line therapies (non-TPO-RAs) are provided in Table 39. Information on the use of rescue therapies and concomitant ITP medications is discussed in section B.3.3.

Table 38. The proportion of therapies used in the second, third and fourth lines

Category	Treatment	Second line – eltrombopag comparator	Second line – romiplostim comparator	Third line – eltrombopag comparator	Third line – romiplostim comparator	Fourth line
TPO-RA	ELT	-	13.5%	-	17.6%	-
	ROM	12.5%	-	19.5%	-	-
RTX	RTX	20.5%	20.2%	12.6%	12.9%	-
Splenectomy	Splenectomy	10.2%	10.1%	10.3%	10.6%	-
Wait & see	Watch and rescue	34.1%	33.7%	41.4%	42.4%	100%
Immunotherapy, Chemotherapy, Antibiotics	Azathioprine	2.8%	2.8%	2.0%	2.1%	-
	Mycophenolate mofetil	2.8%	2.8%	2.0%	2.1%	-
	Cyclosporine	2.8%	2.8%	2.0%	2.1%	-
	Danazol	2.8%	2.8%	2.0%	2.1%	-
	Dapsone	2.8%	2.8%	2.0%	2.1%	-
	Cyclophosphamide	2.8%	2.8%	2.0%	2.1%	-
	Vincristine	2.8%	2.8%	2.0%	2.1%	-
	Vinblastine	2.8%	2.8%	2.0%	2.1%	-

Abbreviations: ELT, eltrombopag; ROM, romiplostim; RTX, rituximab; TPO-RA, thrombopoietin receptor agonist

Table 39: Dosage of non-TPO-RA drugs (used as subsequent lines of therapy)

Drug	kg or m^2	Treatment regimen: Dose/kg or m^2 (mg)	Frequency per 4 weeks cycle	Route of administration	Duration (days)	Source
Active treatment						
FOS 1st cycle	–	100	56	Tablet	28	(40) 88% of patients increased their dose to 150 mg BID at or after week 4
FOS subsequent cycles	-	144	56	Tablet	28	
RTX	m^2	375	4	Infusion	28	(89)
Azathioprine	kg	1.5	28	Tablet	28	
Mycophenolate mofetil	-	1000	56	Tablet	24.5	
Cyclosporin	kg	5	28	Tablet	28	
Danazol	-	200	84	Tablet	28	
Dapsone	-	87.5	28	Tablet	28	
Cyclophosphamide	kg	1.5	28	Tablet	28	
Vincristine	-	1.5	4	Injection	28	
Vinblastine	-	10	4	Injection	21	

B.3.3 Clinical parameters and variables

The following sections outline how the clinical data has been incorporated into the model.

B.3.3.1 Treatment effectiveness: platelet response and time to response

Durable platelet response was the only platelet response measure which yielded comparative effectiveness data between avatrombopag and the other TPO-RAs (eltrombopag and romiplostim). This was used to model treatment response and was based on the NMA (section 2.9).

The trials included in the NMA evaluated durable platelet response over a follow-up period of 24-26 weeks. Therefore, time to response for TPO-RA treatments was assumed to be 24 weeks (equivalent to six 4-week model cycles). Non TPO-RA options (i.e. subsequent therapies), which typically have a shorter time to response (especially immunosuppressants and splenectomy) have been adopted from the romiplostim NICE appraisal (30), as reported in Table 40.

The base case of the model adopts the mean OR. The main conclusion from the NMA is that while there were numerical trends in favour of avatrombopag, there is no significant difference in efficacy the TPO-RAs; therefore, model sensitivity analyses will explore the impact of varying response rates for avatrombopag and comparators (to be discussed in section 3.8).

Table 40. Time to response for avatrombopag and comparators

Treatment	Time to respond (no. of 4-week cycles)
TPO-RAs	
AVA	6
ELT	6
ROM	6
Non-TPO-RAs	
FOS	6
RTX	2
Splenectomy	1
Azathioprine	4
Mycophenolate mofetil	4
Cyclosporine	2
Danazol	4
Dapsone	1
Cyclophosphamide	2
Vinca alkaloids	1
Rescue therapy	
IVIg	0
IV steroids	0
Anti-D	0
Dapsone	0
Platelet transfusion	0

Abbreviations: IVIg, intravenous immunoglobulin, IV, intravenous; TPO-RA, thrombopoietin receptor agonist; AVA, avatrombopag; ELT, eltrombopag; ROM, romiplostim; FOS, fostamatinib; RTX, rituximab

Response rates for avatrombopag, eltrombopag and romiplostim sourced from the NMA are summarised in section B.2.9.4, Figure 10. Using these estimates, the probability of achieving a durable platelet response in the placebo group was 2.58%. The response rates for avatrombopag, eltrombopag and romiplostim were calculated, using odds ratios, to be 73, 27 and 55%, respectively (Table 41).

Table 41. NMA results for the probability of achieving durable response for avatrombopag, eltrombopag and romiplostim

Treatment	Probability of durable response	Lower CI	Upper CI
AVA	73.16%	9%	100%
ELT	27.45%	12%	59%
ROM	55.21%	19%	95%

Abbreviations: CI, confidence interval; AVA, avatrombopag; ELT, eltrombopag; ROM, romiplostim

B.3.3.2 Bleeding events

The risk of bleeding is modelled according to platelet count and is thus independent of treatment. Patients with a platelet count ≥50×10^9/L have a lower probability of experiencing bleeding events compared to those with a platelet count <50×10^9/L (13).

The model categorises bleeding events according to: minor, outpatient and inpatient which is consistent with both the eltrombopag NICE appraisal (29) and a previous eltrombopag cost-effectiveness analysis (71). For inpatient bleeds, these are further subdivided into intracranial haemorrhage, gastrointestinal and other serious bleeds requiring an inpatient admission.

Bleeding events at each visit were categorised according to the WHO Bleeding Scale Score. WHO grade 1 bleeds were defined as minor bleeds. WHO grade 2 and 3 bleeds were defined as outpatient bleeds and WHO grade 4 as inpatient bleeds. Patients with multiple bleeds were categorised based on the most severe bleed recorded.

Rate of minor bleed in the core phase of study 302 was equal to 10% in patients with platelet response and 17.1% in patients without platelet response.

For outpatient and inpatient bleeding events, estimating occurrence rates from Study 302 data were not deemed appropriate given the limited number of serious events which were reported during the trial (only 3 >WHO grade 2 bleed events). Therefore, bleeding event rates per cycle (outpatient and inpatient) and inpatient bleed types were sourced from the eltrombopag NICE appraisal (29) as presented in Table 42 and Table 43, respectively.

Table 42. Proportion of patients with bleeding per cycle, by bleeding type and response status

Bleeding type	Platelet count ≥50×10^9/L, % of patients	Platelets <50×10^9/L,% of patients	Source
Minor bleed	10.0	17.1	(31)
Outpatient bleed	7.1	45.5	(29)
Inpatient bleed	0.0	4.3	(29)

Table 43. Frequency of inpatient bleeds requiring hospitalisation, by type

Proportion of inpatient bleeds by bleed type, (%)	Platelet count <50×10^9/L
Intracranial haemorrhage inpatient bleed	19
Gastrointestinal inpatient bleed	19
Other inpatient bleed	63

Source: (29)

The model also assumes that once patients have entered the final no treatment, no response state (i.e. are refractory to all prior therapies), the probability of patients experiencing an inpatient bleed is doubled (8.6%), consistent with the eltrombopag and romiplostim NICE appraisals (29, 30).

B.3.3.3 Concomitant ITP medication usage and rescue therapy

B.3.3.3.1 Concomitant ITP medication usage

Data from Study 302 was used to estimate rates of concomitant ITP medication usage for both platelet responders and non-responders according to the 50×10^9/L platelet count threshold (≥ and <, respectively, see section B.3.2.2).

Subjects receiving concomitant ITP medication at study baseline were able to reduce their dose or discontinue. During the core phase this could only occur between visit 8 and visit 13. Dose reduction of concomitant ITP medication was implemented at the discretion of the investigator and could only be considered if the subject's platelet count remained >150 × 10^9/L. Concomitant ITP medication reduction guidelines in Study 302 are detailed in Table 44.

Table 44. Concomitant ITP medication reduction guidelines in Study 302

Platelet count	ITP Concomitant Dose Adjustment
≤150 × 10^9/L	Keep current dose
>150 × 10^9/L to ≤250 × 10^9/L	Downward titration: ≤ 25% of the original dose for 14 days
>250 × 10^9/L	Downward titration: ≤ 50% of the original dose for 14 days

Based on the concomitant ITP medication use at baseline in Study 302 (see section 2.3.4.1, Table 8), 44.9% was assumed as the proportion of patients in the non-response health state using concomitant ITP medication. For patients with a response to treatment, there was a discontinuation rate of concomitant ITP medication use of 20%; therefore the baseline proportion of 44.9% is reduced by 20% to 35.9% (Table 45).

Furthermore, of the patients with response to treatment who continued receiving concomitant ITP medication, 16.3% received a reduced dose, equivalent to 5.8% of

all responder patients. A summary of concomitant ITP medication usage by model health state is provided in Table 45.

Table 45. Model inputs for proportion of patients using concomitant ITP medication by health states

Health state	Proportion of patients using concomitant ITP medication (%)
Treatment, no response*	44.9
Treatment, response*	
Total	35.9
Without dose reduction	30.1
With dose reduction	5.8

*Response defined as platelet count ≥50×10^9/L

The doses of concomitant ITP medications used in the model are presented in Table 46.

Table 46. Dosage of concomitant ITP medication and rescue therapies

Drug	kg or m^2	Treatment regimen: Dose/kg or m^2 (mg)	Frequency per 4 weeks cycle	Route of administration	Duration (days)	Source
Rescue therapy						
Rescue – IVIg	kg	1000	28	Infusion	1.5	(89)
Rescue – Anti-D	kg	0.0625	28	Infusion	2	
Rescue – IV steroid	-	1.25	28	Injection	3	
Dapsone	-	87.5	28	Tablet	1	
Platelets transfusion	-	2 platelet units	1	Transfusion	1	Assumption
Concomitant ITP medications – without treatment response						
Danazol	-	200	84	Tablet	28	(89)
Azathioprine	kg	1.5	28	Tablet	28	(89)
Cyclosporin	kg	5	28	Tablet	28	(89)
Etamsylate	-	1500	28	Tablet	15	Drug information etamsylate (26)
Dexamethasone	kg	40	4	Tablet	21	(89)
Prednisolone	kg	1.25	21	Tablet	21	(89)
Prednisone	kg	1.25	21	Tablet	21	(89)

RTX, Vincristine, Vinblastine and rescue medications were administered only in 1 cycle
Abbreviations: mg, milligram; Kg, kilogram; IV, intravenous; IVIg; intravenous immunoglobulin; FOS, fostamatinib; RTX, rituximab

B.3.3.3.2 Rescue therapy

A total of 9/49 patients required rescue therapy during Study 302. Therefore, inclusion of this data in the model would be highly uncertain (as health state probabilities would be derived from a low number of events). Thus, the probability of rescue therapy usage by platelet response was sourced from the eltrombopag NICE appraisal (29); rates per cycle of 3% for patients with platelet count ≥50×10^9/L and 22% for patients with a platelet count <50×10^9/L (Table 47).

The model assumes rescue therapy is attributed to either a bleeding or non-bleeding event, such as a low platelet count. For rescue therapy events attributed to bleeds, the costs of these events are captured within bleeding costs (to be discussed further in section B.3.5). For non-bleed related rescue therapy events, costs are captured separately.

The proportions of rescue therapy use attributed to bleeding and non-bleeding events are based on Study 302 data, in which 4/9 rescue therapy events were due to a patient bleed, equivalent to 44.4%.

The doses of rescue therapies used in the model are presented in Table 46.

The response rates of the rescue therapies were based on the chronic liver disease avatrombopag indication submission (90) for platelet use and the eltrombopag NICE appraisal (29) for the other therapies. These are summarised in
Table 48. Sensitivity analyses explore the extent to which different causes of rescue therapy usage influence the results (discussed in section B.3.8).

Table 47. Proportion of patients using rescue therapy

	Platelet count ≥50×10^9/L	Platelet count <50×10^9/L
Patients using rescue therapy (%)	3.0	22.0
Rescue therapy due to reason other than bleed – all patients (%)	44.4	

Table 48. Rescue treatment response rates

Rescue treatment	Response rate (%)
IVIg	80
IV steroids	46
Anti-D	31
Dapsone	49
Platelet transfusion	52

Abbreviations: IVIg, Intravenous immunoglobin

B.3.3.4 Mortality

The model includes 2 separate causes of mortality; all-cause and disease-related/ITP mortality. All-cause mortality was based on life tables from the Office for National Statistics (91), and the average age and sex distribution were based on those observed in Study 302. ITP-related mortality is modelled based on mortality rates associated with ITP-related hospitalisations for severe bleeds. A specific mortality rate is applied to each bleed type which requires hospitalisation, as shown in Table 49. These rates are sourced from Danese et al. (92) and were also used in the

eltrombopag NICE appraisal (29). Treatment impacts mortality through the dependence of the time spent in the non-responder state on treatment which in turn affects bleed rates (as outlined in B.3.3.2).

Table 49. Proportion of deaths among patients with ITP-related hospitalisation for severe bleed

Discharge condition	Mortality rate, % (95% CI)
Other bleed	1.7 (1.4-2.0)
Gastrointestinal haemorrhage	4.6 (2.7-6.4)
Intracranial haemorrhage	13.2 (9.8-16.6)

Abbreviations: CI, confidence interval

B.3.3.5 Adverse events

In the model, adverse events were grouped as either serious adverse events or other adverse events (consistent with the eltrombopag and romiplostim appraisals).

Based on results from the NMA (section 2.9), the respective TPO-RAs as well as fostamatinib are assumed to have comparable safety profiles. Therefore, AE rates for TPO-RAs and non-TPO-RA options were adopted from the romiplostim NICE appraisal (30) and are shown in Table 50.

Table 50. Treatment related AE rates used in model

Drug	Serious AEs	Other AEs
AVA	3%	31%
ELT	3%	31%
ROM	3%	31%
FOS	3%	31%
RTX	3%	0%
Azathioprine	15%	24%
Mycophenolate mofetil	15%	24%
Cyclosporine	15%	24%
Dapsone	11%	24%
Danazol	16%	35%
Cyclophosphamide	21%	30%
Vinca alkaloids (vincristine and vinblastine)	21%	30%
Rescue – IVIg	2%	0%
Rescue – Anti-D	3%	0%
Rescue – IV corticosteroid	3%	70%

Abbreviations: AVA, avatrombopag; ELT, eltrombopag; ROM, romiplostim; FOS, fostamatinib; RTX, rituximab; IVIg, intravenous immunoglobulin; AE, Adverse event

B.3.3.6 Long-term treatment effectiveness

The duration of patients' platelet response whilst on active treatment was based on treatment exposure reported in the avatrombopag, eltrombopag and romiplostim studies (32, 38, 87).

Fitting log-normal curves to eltrombopag and romiplostim data (published in Lee et al. (76)), the mean times on treatment were 109 and 393 cycles for eltrombopag and romiplostim, respectively. However, the model conservatively assumes an identical length of treatment duration and discontinuation rate per cycle between the TPO-RAs of 109 cycles and 0.9%, respectively (Table 51). For all other non-TPO-RA options, time on treatment was based on data from the romiplostim NICE appraisal (30)

Response rates for the non-TPO-RA treatments in subsequent lines of therapy have been adopted from the romiplostim NICE appraisal (30) and are presented in Table 51.

Table 51. Time on treatment, response rates and discontinuation per cycle by treatment

Treatment	Time on treatment (cycles)	Response rate (%)	Discontinuation per cycle (%)
AVA	109	73	0.9
ELT	109	27	0.9
ROM	109	55	0.9
FOS	109	22	0.9
RTX	19	58	5.2
Splenectomy	364	85	0.3
Azathioprine	20	54	4.8
Mycophenolate mofetil	6	53	16.1
Cyclosporine	16	54	6.0
Danazol	147	50	0.7
Dapsone	20	49	4.8
Cyclophosphamide	27	67	3.6
Vinca alkaloids (vincristine and vinblastine)	1	62	51

Abbreviations; AVA, avatrombopag; ELT, eltrombopag; ROM, romiplostim; FOS, fostamatinib; RTX, rituximab; TPO-RA, thrombopoietin receptor agonist

B.3.3.7 Clinical expert assessment

Details of the clinical validation of the model is presented in section B.3.10.

B.3.4 Measurement and valuation of health effects

As per the NICE reference case (82), the economic analysis measures health effects in the form of QALYs.

B.3.4.1 Health-related quality-of-life data from clinical trials

During Study 302 data was collected for the following HRQoL measures:

- **EuroQol 5-Dimension (EQ-5D):** The EQ-5D is a 2-part, multi-attribute, preference-based generic quality of life instrument that classifies health states across 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.
- **EuroQol Visual Analogue Scale (EQ-VAS**): Constitutes the second part of the EQ-5D as a visual analogue scale on which responders were asked to rate their current health from "worst imaginable health state" (0) to "best imaginable health state" (100).
- **36-Item Short-Form Survey (SF-36):** The SF-36 is a 36-item generic health related quality of life instrument covering the following domains: physical functioning, role-physical, bodily pain, general health, social functioning, role-emotional, mental health, and vitality. Higher scores reflect better HRQoL.

A schedule of assessment time points with respect to HRQoL data during Study 302 is presented in Table 52.

Table 52. Schedule of assessments for HRQoL measures in the Study 302

Schedule of assessments		
EQ-5D	**EQ-VAS**	**SF-36**
Baseline; Week 12, Week 26	Baseline; Week 12, Week 26	Baseline; Week 12, Week 26

Abbreviations: EQ-5D, EuroQol 5-Dimenesion; EQ-VAS, EuroQol Visual Analogue Scale; SF-36, 36-Item Short-Form Survey

Improvements in HRQoL across all 3 measures were observed with avatrombopag. An overview of EQ-VAS and SF-36 data from Study 302 is presented in Table 53. For EQ-5D data, see Table 14.2.5.2 of the Study 302 CSR included with this submission.

Table 53. Summary of EQ-VAS and SF-36 data from Study 302

Measure; time point	Mean change from baseline, (n)	
	AVA (n=32)	**PLC (n=17)**
EQ-VAS; week 12	-8.8, (23)	-13.3, (3)
EQ-VAS; week 26	0.6, (19)	-30, (1)
SF-36 MCS, week 12	5.3, (26)	-0.1, (3)

SF-36 MCS, week 26	4.8, (21)	7.8, (1)
SF-36 PCS, week 12	1.6, (26)	-0.2, (3)
SF-36 PCS, week 26	2.3, (21)	2.6, (1)

Abbreviations: EQ-VAS, EuroQol Visual Analogue Scale; SF-36, 36-Item Short-Form Survey; MCS, mental component summary; PCS, physical component summary; AVA, avatrombopag; PLC, placebo

The interpretation of these HRQoL data is limited since the change in baseline is based upon the average of the patients available at each scheduled assessment and therefore is confounded by the high drop-out rate from the placebo arm. Furthermore, the data is not stratified by responder status in the avatrombopag treatment arm.

For the model, EQ-5D data is recalibrated to generate utility estimates stratified by responder status (according to platelet count as outlined in section B.3.2.2) and for bleeding events (to be discussed in section B.3.4.4).

B.3.4.2 Mapping

No mapping methods have been implemented as part of this submission.

B.3.4.3 Health-related quality-of-life studies

An SLR was conducted in March 2020 and updated in March 2021 to identify studies assessing the HRQoL of patients with chronic ITP. The SLR identified 6 studies reporting relevant HRQoL data which are presented in Table 54. Half of studies used health state utility values (HSUVs) as inputs in their cost-effectiveness (CEA) analyses (71, 76, 93). The other 3 publications elicited HSUVs (86, 94, 95). In 2 CEAs (71, 76), utilities used to feed the models were derived from the identified utility elicitation studies (94) (86).

Full details of the methods and results can be found in Appendix H.

Table 54. Overview of studies included in the SLR reporting HRQoL

Author	Country	Population	Type of study	Reported outcome	Sample size	Mean age (SD)	Males (%)	Platelet count, mean (SD)
Allen, Bryden (71)	England and Wales	Splenectomised and non-splenectomised patients with cITP at a high risk of bleeding who required frequent rescue therapy	CEA	Utilities	NR	NR	NR	NR
Lee, Thornton (76)	Ireland	cITP in adult splenectomised patients in Ireland who are refractory to other treatments (e.g. corticosteroids, IVIg)	CUA	Utilities	NR	52 years	35%	NR
Sanz, Aledort (94)	US, UK, France, The Netherlands, and Spain	Adult patients with cITP	Utility elicitation	Utilities	125	•ROM: 52 (15.5) •PLC: 55 (17.8)	•ROM: 31 (34.9) •PLC: 15 (35.7)	•ROM: 16×10^9/L (7.8) •PLC: 17×10^9/L (8.5)
Lee, Kim (95)	Korea	Non-refractory and refractory cITP patients	Utility elicitation	Utilities	11	NR	NR	NR
Szende, Brazier (86)	UK	Adult ITP patients	Utility elicitation	Utilities	359 web survey respondents Male: 165 Female: 194	•Male 20 –<45 years: 66 45 –<65 years: 68 ≥65 years: 38 •Female 20 –<45 years: 101 45 –<65 years: 70 ≥65 years: 23	165 (46)	<50×10^9/L
Cohen, Djuibegovic (93)	International	A hypothetical cohort of patients with thrombocytopenia due to untreated or refractory ITP	CEA	Utilities	1817	NR	0	<30×10^9/L

Abbreviations: HRQoL, health-related quality of life; CEA, cost-effectiveness analysis; cITP, chronic immune thrombocytopenia; CUA, cost-utility analysis; ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin; NR – Not reported; UK – United Kingdom; US, United states; ROM, romiplostim, PLC, placebo

B.3.4.4 Adverse reactions

AEs were grouped into serious AEs and other AEs in the model. Bleeding events were modelled separately as the risk of bleeding events is related to platelet count (and therefore treatment), as outlined in section B.3.3.2.

AEs were associated with a standard disutility value, lasting for 1 model cycle (4 weeks). For both serious and other AEs, a standard disutility value of 0.1 was applied for all TPO-RA therapies, as in the romiplostim NICE appraisal (30).

Other (non-serious) AEs for non-TPO-RA treatments (which are only considered when patients move onto later lines of therapy) were also associated with a disutility value of 0.1, whereas serious AE disutility values were associated with a value of 0.4 as in the romiplostim NICE appraisal (30) (Table 55).

Rescue therapy was associated with a disutility of 0.1 for both other and serious AEs, irrespective of treatment agent used.

Table 55. Utility decrement with serious AEs

Treatment	Utility decrement value applied
AVA	0.10
ELT	0.10
ROM	0.10
FOS	0.10
RTX	0.10
Splenectomy	0.40
Azathioprine	0.40
Mycophenolate mofetil	0.40
Cyclosporin	0.40
Dapsone	0.40
Danazol	0.40
Cyclophosphamide	0.40
Vinca alkaloids (vincristine and vinblastine)	0.40
Rescue – IVIg	0.10
Rescue – Anti-D	0.10
Rescue – IV steroid	0.10
Rescue – dapsone	0.10
Rescue - platelet transfusion	0.10

Abbreviations: AVA, avatrombopag; ELT, eltrombopag; ROM, romiplostim; FOS, fostamatinib, RTX, rituximab; IVIg, intravenous immunoglobulin; IV, intravenous

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

As per the NICE reference case (82), HRQoL values were derived from the pivotal avatrombopag Study 302 wherever possible. A baseline utility value was estimated for

the Study 302 population based upon EQ-5D values from the UK general population (96) as presented in Table 56 (specifically based on the average age of 44.6 years of patients in Study 302).

Using Study 302 data, a TOBIT model (97) was developed to determine how platelet response, bleeding events, splenectomy status and AEs impacted utility values, presented in Table 57. The TOBIT model found that responders with splenectomy had the highest utility value of 0.85. Disutility values were calculated for each parameter (non-response, minor bleed, outpatient bleed and no splenectomy).

Utility values could be generated using the TOBIT model from Study 302 data for minor bleeds and outpatient bleeds, stratified by platelet response. For serious bleeding events (i.e. all inpatient bleeds), the lack of data from Study 302 limited the use of the TOBIT model to generate accurate estimates. Therefore, serious bleed event utility values were sourced from the eltrombopag NICE appraisal (29). Utility values applied in the model and their data sources are presented in Table 58. AE utilities are discussed in section B.3.4.4.

Table 56. Weighted health state index by age and sex of UK general population

Age	Males	Females
Under 25	0.94	0.94
25-34	0.93	0.93
35-44	0.91	0.91
45-54	0.84	0.85
55-64	0.78	0.81
65-74	0.78	0.78
75+	0.75	0.71

Table 57. TOBIT model parameters based on patient-level data of Study 302

Parameter	Estimate	Standard Error	CI	Probability
Intercept	1.0132	0.1779	[0.66; 1.37]	<0.0001
Response status	0.04067	0		<0.0001
Minor bleed	-0.04496	0.0531	[-0.15; 0.06]	0.4013
Outpatient bleed	-0.1758	0.1263	[-0.43; 0.08]	0.1704
Splenectomy	0.06761	0.09603	[-0.13; 0.26]	0.4848
AE Not serious	0.02106	0.1888	[-0.36; 0.40]	0.9116
AE Serious	-0.07893	0.1953	[-0.47; 0.31]	0.6879

Abbreviations: CI, confidence interval; AE, adverse event;

Table 58. Health related quality of life utility values used in the model

State	$<50\times10^9$/L	$\geq 50\times10^9$/L	Source
No bleed	0.760	0.801	Estimations based on utility in general UK population and TOBIT model built based on Study 302 patient data
Minor bleed	0.715	0.756	
Outpatient bleed	0.584	0.625	
Inpatient bleed			(29)

Intracranial haemorrhage	0.038	0.038
Gastrointestinal bleed	0.45	0.45
Other bleed requiring hospitalisation	0.45	0.45

B.3.5 Cost and healthcare resource use identification, measurement and valuation

An SLR was conducted in March 2020 and updated in March 2021 to identify relevant resource use and cost data for of patients with chronic ITP. Three studies were identified and are presented in Table 59. Further details on the search strategy and results from this process are outlined in Appendix I. Unit costs were taken from established UK sources, including the BNF, NHS schedule of reference costs and the PSSRU Unit Costs of Health and Social Care, as per the NICE reference case (82).

Table 59. Overview of studies included in the SLR reporting healthcare resource use

Author	Country	Population	Type of study	Reported outcome	Sample size	Splenectomy (%)	Treatment arms
Allen, Bryden (71)	UK	Splenectomised and non-splenectomised ITP patients	CEA	•Direct costs •Resource use	NR	NR	•ELT •ROM •PLC
Lee, Thornton (76)	UK	cITP in adult patients in Ireland	CEA	•Direct costs •Resource use	NR	50	• ROM followed by current medical SoC • ELT followed by SoC • SoC, including RTX
Boyers, Jia (98)	UK	Splenectomised and non-splenectomised ITP patients	CEA	Resource use	197	36	From the RAISE study* •ELT plus SoC •PLC plus SoC

*Randomized placebo-controlled ITP study with eltrombopag
Abbreviations: ELT, eltrombopag; ROM, romiplostim; PLC, placebo; RTX, rituximab; CEA, Cost Effectiveness Analysis; Citp, Chronic Immune thrombocytopenia; ITP, Immune thrombocytopenia; NR, Not Reported; SoC, Standard of Care; UK – United Kingdom.

B.3.5.1 Intervention and comparators' costs and resource use

The doses of TPO-RAs and non-TPO-RAs used in the model are presented in Table 37 and Table 39, respectively. Drug acquisition costs were sourced from the BNF and are presented in Table 60.

Table 60. Acquisition costs used in economic modelling

Drug	Cost per pack	Total pack size (mg)	Source
[redacted]	[redacted]	[redacted]	(99)
ELT	£1540.00	1400	(100)
ROM	£241.00	0.125	(100)
FOS	£3,090.00	6000	(100)
RTX	£314.43	200	(100)
Azathioprine	£2.57	2800	(100)
Mycophenolate mofetil	£6.16	25000	(100)
Cyclosporin	£18.37	750	(100)
Dapsone	£54.78	2800	(100)
Danazol	£36.32	11200	(100)
Cyclophosphamide	£139.00	5000	(100)
Vincristine	£13.47	1	(100)
Vinblastine	£85.00	50	(100)
IVIg	£50.00	1000	(100)
Anti-D	£46.50	0.30	(100)
IV steroid	£88.81	1200	(100)
Etamsylate	£9.00	500	(100)
Dexamethasone	£49.00	100	(100)
Phrednisolone	£2.41	140	(100)
Prednisone	£2.41	140	(100)

*Fostamatinib price estimated based on currency rate: 1 USD = 0.819616 GBP
Abbreviations: AVA, avatrombopag; ELT, eltrombopag; ROM, romiplostim; FOS, fostamatinib, RTX, rituximab; IVIg, intravenous immunoglobulin; IV, intravenous

For avatrombopag, a simple discount PAS has been agreed with NHS England therefore drug costs for avatrombopag were applied at the discount of [redacted] in the model. Both eltrombopag and romiplostim have been approved by NICE with a PAS. However, as the PAS in both cases is confidential, list prices have been assumed.

Romiplostim can be administered either at home or via a specialist nurse at an outpatient or community clinic. All patients are assumed to receive their first dose at clinic visit. Post the first dose, the proportion of patients requiring administration at clinic was estimated using figures from a congress abstract of phase III data presented at the ASH annual meeting 2010 (101). In that study, 82% of patients had initiated home administration and, of these, 88.3% continued until the end of the study. This equates to 211/292 patients (72.3%) who received home administration. For the 27.7% of romiplostim treated patients whose treatment was administered at the clinic, a per visit unit cost of £241.06 was applied using NHS reference costs (102). This approach is consistent with that adopted in the eltrombopag NICE appraisal (29).

For avatrombopag and eltrombopag, both of which are oral treatments, no administration costs were applied as patients administer treatment independently at

home. For intravenous treatments such as rituximab, vincristine and vinblastine, a standard cost per cycle was assumed based on NHS reference costs (102), which was also used as the source of splenectomy costs, estimated at £2,750 (102). Administration costs are presented in Table 61.

Table 61. Administration costs of treatments

Treatment	Cost (£)	Administration code	Source
Romiplostim	241.06*	SB12Z (simple chemo, first attendance)	(102)
Rituximab	370.68	SB14Z (complex chemo w prolonged infusion, first attendance)	(102)
Splenectomy	2750.00	N/A	(103)
Vincristine	241.06	SB12Z (simple chemo, first attendance)	(102)
Vinblastine	241.06	SB12Z (simple chemo, first attendance)	(102)
Rescue – IVIg	195.66	SA45A (Injection of Rh Immune Globulin or Other Blood Transfusion)	(102)
Rescue – Anti-D	195.66	SA45A (Injection of Rh Immune Globulin or Other Blood Transfusion)	(102)
Rescue – IV steroid	370.68	SB14Z (complex chemo w prolonged infusion, first attendance)	(102)

*From second cycle 72.3% patients assumed to receive administration at home
Abbreviations: IVIg, intravenous immunoglobulin; IV, intravenous; N/A, not applicable

As part of routine monitoring associated with the use of TPO-RAs in ITP, patients were assumed to receive regular haematologist consultations, laboratory tests, full blood count and biochemistry assessments. Unit costs for each were sourced from the NHS schedule of reference costs (2018/19) (Table 62). It was assumed that the additional liver function tests required for patients receiving eltrombopag would be captured through the combined blood (DAPS05) and biochemistry tests (DAPS04).

Table 62. Unit costs of monitoring procedures included in the model

Item	HRG code	NHS reference cost (£)
Haematologist consultation	303 Clinical Haematology, Consultant led	173.39
Blood test*	DAPS05 Haematology	2.79
Biochemistry*	DAPS04 Clinical Biochemistry	1.10

*Assumed to cover liver function tests
Abbreviations: HRG, Health Resource Group; NHS, National Health Service

The model assumes no additional monitoring costs based on treatment between the TPO-RA treatments. Therefore, the model assumes all patients (regardless of TPO-RA received) receive 1 haematologist consultation, 2 laboratory tests, 1 full blood count and 1 biochemistry assessment each month during treatment. This is a conservative assumption considering hepatoxicity monitoring is required with eltrombopag treatment.

B.3.5.2 Health-state unit costs and resource use

As discussed in sections B.3.2 and B.3.3, health states are driven in the model by platelet response which influences costs associated with bleeding events, use of rescue therapy and concomitant ITP medication usage.

Costs associated with bleeding events have been informed by qualitative research (88) which explored the utilisation of different healthcare resource use elements for outpatient and inpatient bleeds, including life threatening (intracranial haemorrhage) bleeds. Minor bleeds were assumed to be self-treated and have no associated costs. How the different healthcare services are utilised for each respective bleeding event is presented in Table 63.

Table 63. Utilisation inputs used in bleed managements by category

Bleed type	Outpatient bleeds		Inpatient bleed; gastrointestinal/other		Inpatient bleed; intracranial haemorrhage	
	utilisation of item per event	utilisation in event %	utilisation of item per event	utilisation in event %	utilisation of item per event	utilisation in event %
ER / Hospital nights						
ER admission	1	100	1	100	1	100
ICU bed					4	100
Ward bed			6	100	7	100
Outpatient care	1	100				
Emergency surgery						
Neurosurgery			1	10	1	30
GI surgery			1	40	1	70
Other						
Ambulance			1	60	1	100
Diagnostic imaging and blood tests						
CT	1	60	1	100	1	100
MRI	1	60	1	100	1	100
Blood work	1	100	1	100	1	100
Follow-ups						
Haematologists follow up	3	100	6	100	12	100
Therapies (total)						
IVIg and corticosteroids						
IVIg (70.8grams, 1grams/kilogram for average adult)	1	40	2	100	2	100
Methylprednisolone (140 mg x 3 days)	3	100	3	100	3	100
Platelets transfusions						
Platelets (price per day)			5	100	15	100
Other						
Factor VIIa, recombinant (5.3 mg, 75µg/kg for average adult)			1	40	1	60

Abbreviations: IVIg, intravenous immunoglobulin; ER, emergency room; ICU, intensive care unit; CT, computed tomography; MRI, magnetic resonance imaging

Each element of resource use is assigned a unit cost from established UK sources, presented in Table 64.

Table 64. Unit costs of resources used in bleeding management

Category	Value (£)	Source
ER / Hospital nights		
ER admission	160	NHS Improvement, Cost of attendance
ICU bed (daily cost)	1,364	Neylon et al. 2003, Clinically significant newly presenting autoimmune ITP in adults: A prospective study of a population-based cohort of 245 patients, Average daily cost of intensive care bed (104)

ICU bed (Level 3 daily cost)	1,932	NHS Wales, Average cost per Level 3 intensive care bed day, NHS Wales (105)
ICU bed	1,648	Average of above
Ward bed (average daily cost)	310	University Hospitals Birmingham, University Hospitals Birmingham (106)
Ward bed (bed day cost)	346	NHS Improvement, NHS Improvement
Ward bed	328	Average of above
Outpatient visit	742	NHS Improvement, NHS Improvement
Emergency surgery		
Neurosurgery	2,383	NHS National Tariff Workbook 2019 / 20, Intermediate intracranial procedures, 19 years and over, with CC score 0-1
GI surgery	2,230	NHS National Tariff Workbook 2019 / 20, Gastrointestinal bleed with a single intervention, with CC score 0-4
Other		
Ambulance		
Incidents attended	1,140,980	London Ambulance Service, London Ambulance Trust (107)
Total operating expenses	378,154,000	London Ambulance Service, London Ambulance Trust (107)
Ambulance (cost per incident)	331	Average of above
Diagnostic imaging and blood tests		
CT	83	NHS National Tariff Workbook 2019 / 20, Tariff includes cost of reporting
MRI	157	NHS National Tariff Workbook 2019 / 20, Tariff includes cost of reporting
Blood work	26	NICE, Full blood count (108)
Follow-ups		
Haematologists follow up (first visit)	275	NHS National Tariff Workbook 2019 / 20, First single professional attendance
Haematologists follow up (every other visit)	125	NHS National Tariff Workbook 2019 / 20, Follow-up attendance, single professional
Therapies		
IVIg and corticosteroids		
IVIG (70.8grams, 1gram/kilogram for average adult)	3823.20	BNF Medicines Complete (100)
Methylprednisolone (140 mg ×3 days)	2.69	BNF Medicines Complete (100)
Platelet transfusions		
Platelets (price per day)	186.86	NHS National Tariff Workbook 2019 / 20
Other		
Factor VIIa, recombinant (5.3 mg, 75µg/kg for average adult)	2783.56	BNF Medicines Complete (100)

Abbreviations: IVIg, intravenous immunoglobulin; ER, emergency room; ICU, intensive care unit; CT, computed tomography; MRI, magnetic resonance imaging

Combining resource utilisation and unit costs provides a cost of management per bleeding event for outpatient bleeds and inpatient bleeds, including life threatening (intracranial haemorrhage) bleeds. The costs per bleeding event used in the model are presented in Table 65.

Table 65. Cost of bleed event management by bleed type used in model (£)

Bleed type	Outpatient bleeds (£)	Inpatient bleed; gastrointestinal/other (£)	Inpatient bleed; intracranial haemorrhage (£)
ER / Hospital nights			
ER admission	160	160	160
ICU bed			6,592
Ward bed		1,968	2,296
Outpatient care	742		
Emergency surgery			
Neurosurgery		238	715

GI surgery		892	1561
Other			
Ambulance		199	331
Diagnostic imaging and blood tests			
CT	50	83	83
MRI	94	157	157
Blood work	26	26	26
Follow-ups			
Haematologists follow up	525	900	1650
Therapies (total)			
IVIg and corticosteroids			
IVIg (70.8gram, 1gram/kilogram for average adult)	1,529	7,646	7,646
Methylprednisolone (140 mg x 3 days)	8	8	8
Platelets transfusions			
Platelets (price per day)		934	2,803
Other			
Factor VIIa, recombinant (5.3 mg, 75ug/kg for average adult)		1,113	1,670
Total	**3,134**	**14,325**	**25,699**

Abbreviations: IVIg, intravenous immunoglobulin; ER, emergency room; ICU, intensive care unit; CT, computed tomography; MRI, magnetic resonance imaging

B.3.5.3 Adverse reaction unit costs and resource use

The costs of bleeding are incorporated into the economic model; the model does not incorporate the costs of treating other adverse events associated with treatment.

B.3.5.4 Miscellaneous unit costs and resource use

There are no further unit costs or resource use included in the model.

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

A summary of the model parameters used in the base case analysis is provided in Table 66.

Table 66. Summary of base-case variables applied in the economic model

Parameter	Base case value	DSA	PSA	Reference to section in submission
General settings				B.3.2
Time horizon (years)	56			
Cohort	1000			
Currency	£			
Discount rate for health outcomes	3.5%	0%-5%	0%-5%	
Discount rate for costs	3.5%	0%-5%	0%-5%	
Half cycle correction	Yes			
Population				
Age	44.6	40.6-48.6	Normal, SD=14.44	B.3.2
Gender, male (%)	37%	±20%	Beta	
Weight (kg)	82.97	±20%	Normal	
Body area (m^2)	1.94	±20%	Normal	
Proportion post-splenectomy	33%			
Treatment				
Treatment arm 1				B.3.2.3 and B.3.3.7
Treatment arm 2				
Dosage				
AVA	20 mg	16.22-23.78		B.3.2.3
ELT	50 mg	45-55		
ROM	0.004	0.0037-0.0043	Normal+, SD=0.0021	
Frequency of dosing (per cycle)				
AVA	28		Normal +	B.3.2.2
ELT	28		Normal +	
ROM	4	±20%	Normal+	
Dosage and frequency of dosing for subsequent lines of therapy				B.3.2.3
Treatments in patients using concomitant ITP medications				
Danazol	5%	±20%	Beta	B.3.3
Azathioprine	9%	±20%	Beta	
Ciclosporin	5%	±20%	Beta	
Etamsilate	5%	±20%	Beta	
Dexamethasone	27%	±20%	Beta	
Phrednisolone	27%	±20%	Beta	
Prednisone	95%	±20%	Beta	
% of patients with bleeding per cycle, by type and response				
Platelet count ≥$50x10^9$/L - Minor bleed	10.0%	±20%	Beta	B.3.3.2
Platelet count ≥$50x10^9$/L - Outpatient bleed	7.1%	±20%	Beta	
Platelet count ≥$50x10^9$/L - Inpatient bleed	0.0%			
Platelet count <$50x10^9$/L - Minor bleed	17.1%	±20%	Beta	

Platelet count <50x10^9/L - Outpatient bleed	45.5%	±20%	Beta	
Platelet count <50x10^9/L - Inpatient bleed	4.3%	±20%	Beta	
Time to response (cycles)				
AVA	6	±1	Normal+	B.3.3.1
ELT	6	±1	Normal+	
ROM	6	±1	Normal+	
FOS	6	±1	Normal+	
RTX	2	±1	Normal+	
Splenectomy	1	±1	Normal+	
Watch and rescue	1	±1	Normal+	
Azathioprine	4	±1	Normal+	
Mycophenolate mofetil	4	±1	Normal+	
Cyclosporine	2	±1	Normal+	
Danazol	4	±1	Normal+	
Dapsone	1	±1	Normal+	
Cyclophosphamide	2	±1	Normal+	
Vincristine	1	±1	Normal+	
Vinblastine	1	±1	Normal+	
Response rate (cycles)				
AVA	73%	±20%	Beta	B.3.3.1
ELT	27%	±20%	Beta	
ROM	55%	±20%	Beta	
FOS	22%	±20%	Beta	
RTX	58%	±20%	Beta	
Splenectomy	85%	±20%	Beta	
Watch and rescue	0%			
Azathioprine	54%	±20%	Beta	
Mycophenolate mofetil	53%	±20%	Beta	
Cyclosporine	54%	±20%	Beta	
Danazol	50%	±20%	Beta	
Dapsone	49%	±20%	Beta	
Cyclophosphamide	67%	±20%	Beta	
Vincristine	62%	±20%	Beta	
Vinblastine	62%	±20%	Beta	
Time on response (cycles)				
AVA	109	±20%	Normal+	B.3.3.6
ELT	109	±20%	Normal+	
ROM	109	±20%	Normal+	
FOS	109	±20%	Normal+	
RTX	19	±20%	Normal+	
Splenectomy	364	±20%	Normal+	

Watch and rescue	-			
Azathioprine	20	±20%	Normal+	
Mycophenolate mofetil	6	±20%	Normal+	
Cyclosporine	16	±20%	Normal+	
Danazol	147	±20%	Normal+	
Dapsone	20	±20%	Normal+	
Cyclophosphamide	27	±20%	Normal+	
Vincristine	1	±20%	Normal+	
Vinblastine	1	±20%	Normal+	
Additional discontinuation per cycle				
AVA	0.9%			B.3.3.6
ELT	0.9%			
ROM	0.9%			
FOS	0.9%			
RTX	5.2%			
Splenectomy	0.3%			
Watch and rescue				
Azathioprine	4.8%			
Mycophenolate mofetil	16.1%			
Cyclosporine	6.0%			
Danazol	0.7%			
Dapsone	4.8%			
Cyclophosphamide	3.6%			
Vincristine	51.0%			
Vinblastine	51.0%			
% of patients using rescue therapy				
Platelet count ≥50x10^{9}/L	3%			B.3.3.3
Platelet count <50x10^{9}/L	22%			
% of patients using concomitant ITP medications in response and no response states				
Among patients without response to active treatment	45%	±20%	Beta	B.3.3.3
Among patients with response to active treatment	36%	±20%	Beta	
Without dose reduction	30%	±20%	Beta	
With dose reduction	6%	±20%	Beta	
Ratio of reduction in dose	5%	±20%	Beta	
Serious AEs				
AVA	3%	±20%	Gamma	B.3.3.5
ELT	3%	±20%	Gamma	
ROM	3%	±20%	Gamma	
FOS	3%	±20%	Gamma	
RTX	3%	±20%	Gamma	

Splenectomy	0%			
Azathioprine	15%	±20%	Beta	
Mycophenolate mofetil	15%	±20%	Beta	
Cyclosporine	15%	±20%	Beta	
Danazol	16%	±20%	Beta	
Dapsone	11%	±20%	Beta	
Cyclophosphamide	21%	±20%	Beta	
Vincristine	21%	±20%	Beta	
Vinblastine	21%	±20%	Beta	
Other AEs				
AVA	31%	±20%	Beta	B.3.3.5
ELT	31%	±20%	Beta	
ROM	31%	±20%	Beta	
FOS	31%	±20%	Beta	
RTX	0%			
Splenectomy	0%			
Azathioprine	24%	±20%	Beta	
Mycophenolate mofetil	24%	±20%	Beta	
Cyclosporine	24%	±20%	Beta	
Danazol	35%	±20%	Beta	
Dapsone	24%	±20%	Beta	
Cyclophosphamide	30%	±20%	Beta	
Vincristine	30%	±20%	Beta	
Vinblastine	30%	±20%	Beta	
Cost per pack				
Active treatment - AVA, 30 x 20 mg	[redacted]	±20%	Gamma	B.3.5.1
Active treatment - ELT, 28 x 50 mg	1540.00	±20%	Gamma	
Active treatment - ROM, 0.125 mg	241.00	±20%	Gamma	
Active treatment - FOS, 60 x 100 mg	9630.75	±20%	Gamma	
Active treatment - RTX	314.43	±20%	Gamma	
Active treatment - Azathioprine	2.57	±20%	Gamma	
Active treatment - Mycophenolate mofetil	6.16	±20%	Gamma	
Active treatment - Ciclosporin	18.37	±20%	Gamma	
Active treatment - Danazol	36.32	±20%	Gamma	
Active treatment - Dapsone	54.78	±20%	Gamma	
Active treatment - Cyclophosphamide	139.00	±20%	Gamma	
Active treatment - Vincristine	13.47	±20%	Gamma	
Active treatment - Vinblastine	85.00	±20%	Gamma	
Concomitant ITP medications - Danazol	36.32	±20%	Gamma	
Concomitant ITP medications - Azathioprine	2.57	±20%	Gamma	
Concomitant ITP medications - Ciclosporin	18.37	±20%	Gamma	

Concomitant ITP medications - Etamsilate	9.00	±20%	Gamma	
Concomitant ITP medications - Dexamethasone	49.00	±20%	Gamma	
Concomitant ITP medications - Phrednisolone	2.41	±20%	Gamma	
Concomitant ITP medications - Prednisone	2.41	±20%	Gamma	
Administration cost (1st cycle)				
Active treatment - AVA, 30 x 20 mg	0.00			B.3.5.4
Active treatment - ELT, 28 x 50 mg	0.00			
Active treatment - ROM, 0.125 mg	241.06	±20%	Gamma	
Active treatment - FOS, 60 x 100 mg	0.00			
Active treatment - RTX	370.68	±20%	Gamma	
Active treatment - Azathioprine	2750.00	±20%	Gamma	
Active treatment - Mycophenolate mofetil	0.00			
Active treatment - Ciclosporin	0.00			
Active treatment - Danazol	0.00			
Active treatment - Dapsone	0.00			
Active treatment - Cyclophosphamide	0.00			
Active treatment - Vincristine	0.00			
Active treatment - Vinblastine	241.06	±20%	Gamma	
Concomitant ITP medications - Danazol	241.06	±20%	Gamma	
Concomitant ITP medications - Azathioprine	0.00			
Concomitant ITP medications - Ciclosporin	0.00			
Concomitant ITP medications - Etamsilate	0.00			
Concomitant ITP medications - Dexamethasone	0.00			
Concomitant ITP medications - Phrednisolone	0.00			
Concomitant ITP medications - Prednisone	0.00			
Administration cost (Subsequent cycles)				
Active treatment - AVA, 30 x 20 mg	0.00			B.3.5.4
Active treatment - ELT, 28 x 50 mg	0.00			
Active treatment - ROM, 0.125 mg	66.77	±20%	Gamma	
Active treatment - FOS, 60 x 100 mg	0.00			
Active treatment - RTX	370.68	±20%	Gamma	
Active treatment - Azathioprine	0.00			
Active treatment - Mycophenolate mofetil	0.00			
Active treatment - Ciclosporin	0.00			
Active treatment - Danazol	0.00			
Active treatment - Dapsone	0.00			
Active treatment - Cyclophosphamide	0.00			
Active treatment - Vincristine	0.00			
Active treatment - Vinblastine	241.06	±20%	Gamma	
Concomitant ITP medications - Danazol	241.06	±20%	Gamma	
Concomitant ITP medications - Azathioprine	0.00			

Concomitant ITP medications - Ciclosporin	0.00			
Concomitant ITP medications - Etamsilate	66.77	±20%	Gamma	
Concomitant ITP medications - Dexamethasone	0.00			
Concomitant ITP medications - Phrednisolone	370.68	±20%	Gamma	
Concomitant ITP medications - Prednisone	0.00			
Cost of follow-up				
Unit cost - Haematologist consultation	173.39	±20%	Gamma	B.3.5.4
Unit cost - Blood test	2.79	±20%	Gamma	
Unit cost - Biochemistry	1.10	±20%	Gamma	
Occurrence/month - Haematologist consultation	1.00	±20%	Gamma	
Occurrence/month - Blood test	1.00	±20%	Gamma	
Occurrence/month - Biochemistry	1.00	±20%	Gamma	
Bleed costs				
Minor bleed	0.00			B.3.5.2
Outpatient bleed	3,134.35	±20%	Gamma	
Intracranial haemorrhage	25,698.84	±20%	Gamma	
Gastrointestinal	14,325.35	±20%	Gamma	
Other bleed	14,325.35	±20%	Gamma	
Death due to bleed	0.00			
Utility (model health states)				
Platelet count ≥50x10^9/L, No bleed	0.801	±20%	Beta	B.3.4.5
Platelet count ≥50x10^9/L, Minor bleed	0.756	±20%	Beta	
Platelet count ≥50x10^9/L, Outpatient bleed	0.625	±20%	Beta	
Platelet count ≥50x10^9/L, Intracranial haemorrhage	0.038	±20%	Beta	
Platelet count ≥50x10^9/L, Gastrointestinal bleed	0.45	±20%	Beta	
Platelet count ≥50x10^9/L, Other bleed requiring inpatient	0.45	±20%	Beta	
Platelet count <50x10^9/L, No bleed	0.760	±20%	Beta	
Platelet count <50x10^9/L, Minor bleed	0.715	±20%	Beta	
Platelet count <50x10^9/L, Outpatient bleed	0.584	±20%	Beta	
Platelet count <50x10^9/L, Intracranial haemorrhage	0.038	±20%	Beta	
Platelet count <50x10^9/L, Gastrointestinal bleed	0.45	±20%	Beta	
Platelet count <50x10^9/L, Other bleed requiring inpatient	0.45	±20%	Beta	
Utility decrement with AEs (serious AEs)				
AVA	0.1	±20%	Beta	B.3.4.4
ELT	0.1	±20%	Beta	
ROM	0.1	±20%	Beta	
FOS	0.1	±20%	Beta	
RTX	0.1	±20%	Beta	
Splenectomy	0.4	±20%	Beta	
Watch and rescue	0			
Azathioprine	0.4	±20%	Beta	

Mycophenolate mofetil	0.4	±20%	Beta	
Cyclosporine	0.4	±20%	Beta	
Danazol	0.4	±20%	Beta	
Dapsone	0.4	±20%	Beta	
Cyclophosphamide	0.4	±20%	Beta	
Vincristine	0.4	±20%	Beta	
Vinblastine	0.4	±20%	Beta	
Utility decrement with AEs (other AEs)				
AVA	0.1	±20%	Beta	B.3.4.4
ELT	0.1	±20%	Beta	
ROM	0.1	±20%	Beta	
FOS	0.1	±20%	Beta	
RTX	0.1	±20%	Beta	
Splenectomy	0.1	±20%	Beta	
Watch and rescue	0			
Azathioprine	0.1	±20%	Beta	
Mycophenolate mofetil	0.1	±20%	Beta	
Cyclosporine	0.1	±20%	Beta	
Danazol	0.1	±20%	Beta	
Dapsone	0.1	±20%	Beta	
Cyclophosphamide	0.1	±20%	Beta	
Vincristine	0.1	±20%	Beta	
Vinblastine	0.1	±20%	Beta	
Mortality rates (Inpatient bleeds)				
Intracranial haemorrhage	13.2%	9.8%-16.6%	Beta	B.3.3.4
Gastrointestinal bleed	4.6%	2.7%-6.4%	Beta	
Other bleed	1.7%	1.4%-2.0%	Beta	
Mortality rates (All cause)				
ONS life tables				B.3.3.4

Abbreviations: DSA, deterministic sensitivity analysis; PSA, probabilistic sensitivity analysis; AVA, avatrombopag; ELT, eltrombopag; ROM, romiplostim; FOS, fostamatinib; RTX, rituximab; AE, adverse events; ITP, immune thrombocytopenia

B.3.6.2 Summary of base-case assumptions

The assumptions applied in the base case of the economic analysis are described in Table 67.

Table 67. Summary of base case assumptions in model

Parameter	Assumption	Justification
Health states	Platelet level is a reasonable surrogate for requiring rescue therapy, concomitant ITP medication and experiencing moderate and major bleeding events	Platelet count is a widely recognised outcome used to measure to treatment response for ITP. Data suggests a strong relationship between platelet level and bleeding and between platelet level and use of concomitant ITP medication and rescue therapy (see section B.1).
	Patients enter the model with a platelet count $<30\times10^9$/L	Across the pivotal studies for avatrombopag, eltrombopag and romiplostim, patients were required to have a platelet count $<30\times10^9$/L at study baseline (32, 38, 39). This is consistent with ITP clinical guidelines which suggest active treatment should be considered when platelet counts fall below 30×10^9/L (2, 21)
	Response to therapy is assumed to be equivalent to achieving a platelet count greater than 50×10^9/L	The 50×10^9/L threshold is the most commonly reported within the literature. A lower threshold may be more relevant to clinical practice but there is a lack of data on the proportion of patients reaching lower thresholds for comparator treatments. Furthermore, 50×10^9/L consistently used to define treatment response in existing economic models for ITP – both across the literature and previous NICE appraisals (TA293 and TA221) (29, 30).
	Response to treatment must be achieved within the first 6 cycles after treatment initiation according to assumed time to response	Time to response was set at 6 cycles for TPO-RA treatments and fostamatinib to allow for the inclusion of comparative effectiveness estimates from the network meta-analysis. For non-TPO-RA options, time to response values were taken from the romiplostim NICE appraisal (TA221) (30)
	Platelet response influences the risk of bleeding events, need for rescue therapy and utilisation of concomitant ITP medication	Existing data shows a direct relationship between platelet response and a lower risk of bleeding events, use of rescue therapy and utilisation of concomitant ITP medication (as discussed in section B.2). Furthermore, this approach remains consistent with previous NICE appraisals for ITP (TA293 and TA221) (29, 30)
Treatment discontinuation	At the end of the defined treatment period, patients with a platelet count of $<50\times10^9$/L discontinue active therapy onto a 'watch and wait' treatment strategy. Patients remain in this health state until they experience a bleeding event or require rescue therapy	Treatment failure does not necessarily result in patients receiving an alternative active treatment. Instead, treatment decisions are based upon the risk and/or ITP symptoms. This approach remains consistent with a previous NICE appraisal for ITP (TA293) (29).
	Following the defined treatment period, a standard discontinuation rate per cycle is applied for treatment responders. Discontinuation rates have been applied for both TPO-RA and non-TPO-RA options	Estimates of long-term treatment effectiveness are based upon best available data
	When moving to a new active treatment, only a proportion of patients will receive each treatment in the pathway. Patients will not receive every available therapy.	Although there is no defined treatment pathway for ITP and practice varies widely in the UK, the treatment pathway presented is thought to reflect clinical practice as closely as possible
	Patients who discontinue the last medication available in the treatment sequence do not use any active treatment until the end of the time horizon (i.e. lifetime). These patients are assumed to receive only the concomitant ITP medication and rescue therapy	This is consistent with clinical feedback and is also consistent with the approach accepted in both TA293 and TA221 (29, 30)

Dosing and posology	Patients receive avatrombopag and eltrombopag at the recommended starting dose (as per products SmPC). For romiplostim, this aligns to the mean dose observed in a pivotal study	Dosing for TPO-RAs is varied and can be adjusted to account for efficacy and fluctuations in platelet count. The model includes the most probable doses for each TPO-RA
Mortality	Patient mortality in the model is caused by either ITP-related or general (all-cause) mortality	In addition to all-cause mortality (i.e., risk of death across the general population), serious bleeding events which result in patient hospitalisation can result in patient death. The inclusion of this assumption is consistent with previous NICE appraisals for ITP (TA293 and TA221) (29, 30)
AEs	AEs have been defined as 'serious' and 'other' in the model	This approach is consistent with eltrombopag NICE appraisal for ITP (TA293) (29) and a similar published economic evaluation for ITP (71)
Resource use and costs	Treatment monitoring	Although treatment monitoring is included in the model, there are assumed to be no additional monitoring costs between the respective treatments.

Abbreviations: ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin; TPO-RA, thrombopoietin receptor agonist; AE, adverse events

B.3.7 Base-case results

The results from the model base-case analysis for avatrombopag compared with eltrombopag or romiplostim are presented in Table 68. A further breakdown of costs and QALYs for each intervention is provided in Table 69.

Over the lifetime time horizon, the total numbers of QALYs accrued per patient were [redacted] for avatrombopag, eltrombopag and romiplostim, respectively. This resulted in incremental QALY gains of [redacted] vs eltrombopag and [redacted] vs romiplostim. In terms of total overall costs, these were estimated at [redacted] for avatrombopag, [redacted] for eltrombopag and [redacted] for romiplostim. Incremental cost savings for avatrombopag were [redacted] vs eltrombopag and [redacted] vs romiplostim.

In the deterministic base case, avatrombopag was therefore dominant when compared with either eltrombopag or romiplostim.

[redacted]

Technologies	Total costs (£)	Total QALYs	Total LY	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental LY
AVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELT							
ROM							

Abbreviations: AVA, avatrombopag; ELT, eltrombopag; ROM, romiplostim; ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years; LY, life years

[redacted]

Costs (£)	AVA	ELT	ROM
Treatment costs	[redacted]	[redacted]	[redacted]
Active treatment			
Treatment I			
Treatment II			
Treatment III			
Treatment IV			
Rescue therapy			
Concomitant ITP medications			
Treatment administration costs			
Active treatment			
Treatment I			
Treatment II			
Treatment III			
Treatment IV			
Rescue therapy			
Concomitant ITP medications			
Monitoring costs			
Treatment I			
Treatment II			
Treatment III			
Treatment IV			
Bleeding costs			
Minor bleeds			
Outpatient bleeds			
Inpatient bleeds			

Intracranial haemorrhage	[redacted]	[redacted]	[redacted]
Gastrointestinal	[redacted]	[redacted]	[redacted]
Other bleed	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Health outcomes			
Number of life years	[redacted]	[redacted]	[redacted]
Health state utility	[redacted]	[redacted]	[redacted]
Disutility due to AEs - active treatment	[redacted]	[redacted]	[redacted]
Disutility to AE – rescue therapy	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse events; AVA, avatrombopag; ELT, eltrombopag; ROM, romiplostim; QALYs, quality adjusted life years

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was undertaken to establish the influence of parameter uncertainty on the cost-effectiveness results. Model parameters subject to uncertainty were randomly sampled within their plausible bounds and the cost-effectiveness results were recorded over a total of 1,000 iterations.

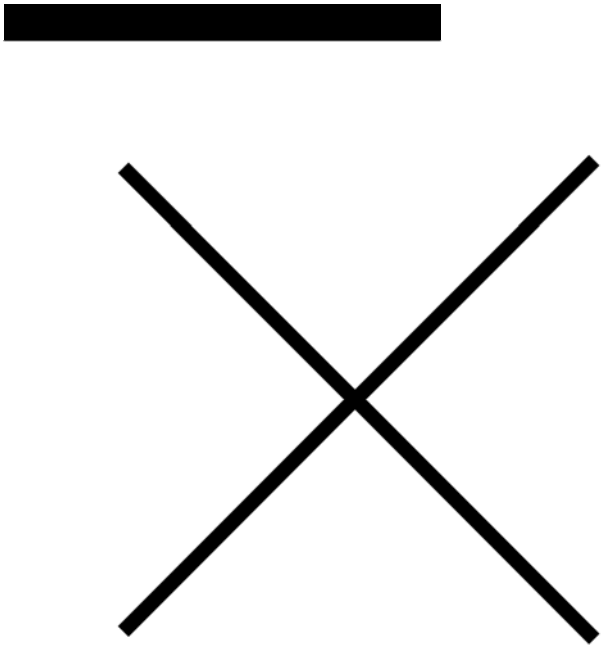
B.3.8.1.1 Avatrombopag vs. eltrombopag

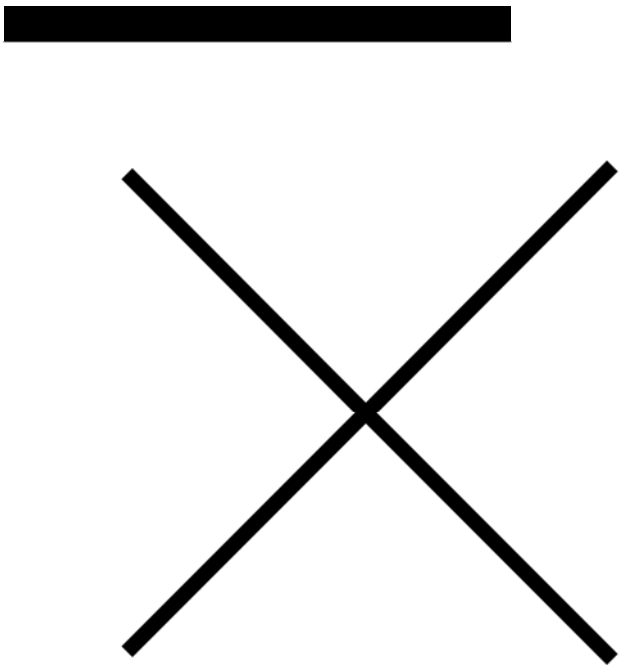
The probabilistic base case results are presented in Table 70 and the cost-effectiveness plane scatterplot and cost-effectiveness acceptability curve are presented in Figure 13 and Figure 14, respectively. The mean results from the probabilistic analysis show that avatrombopag is dominant versus eltrombopag, the same as in the model base case. At the cost-effectiveness thresholds of £30,000, £20,000 and £10,000 per QALY gained, avatrombopag is cost-effective vs. eltrombopag in [redacted] of simulations, respectively.

[redacted]

	Incremental costs	Incremental QALYs	ICER
Mean	[redacted]	[redacted]	[redacted]
Standard deviation			
Median			
Min			
Q 0.025			
Q 0.975			
Max			
[redacted]			
Probability dominant			
Probability dominated			

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years; CE, cost-effectiveness





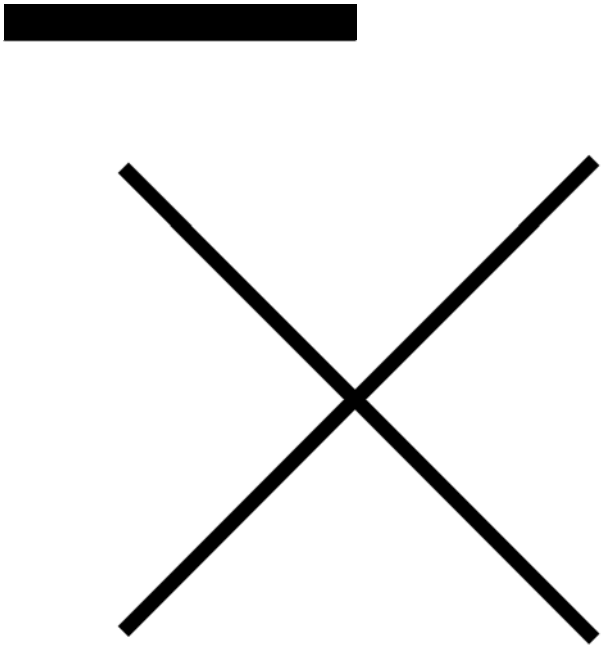
B.3.8.1.2 Avatrombopag vs. romiplostim

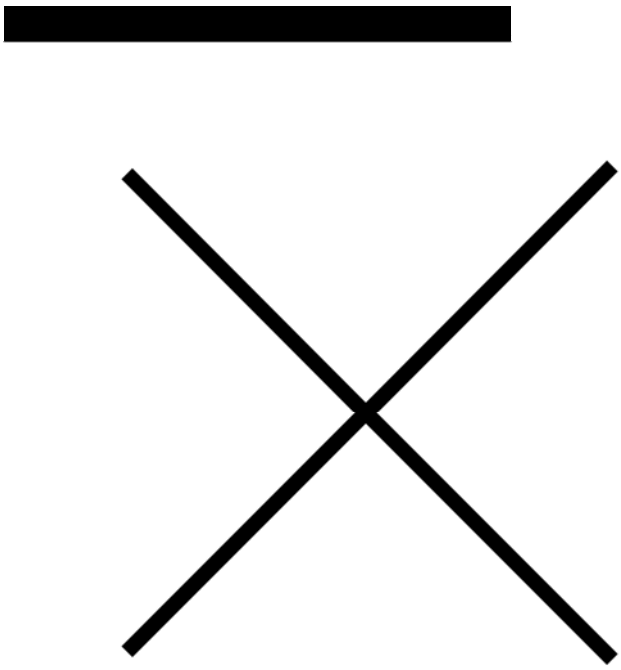
The probabilistic base case results are presented in Table 71 and the cost-effectiveness plane scatterplot and cost-effectiveness acceptability curve are presented in Figure 15 and Figure 16, respectively. The mean results from the probabilistic analysis show that avatrombopag is dominant versus romiplostim, the same as in the model base case. At the cost-effectiveness thresholds of £30,000, £20,000 and £10,000 per QALY gained, avatrombopag is cost-effective vs. romiplostim in [redacted] of simulations, respectively.

[redacted]

	Incremental costs	Incremental QALYs	ICER
Mean	[redacted]	[redacted]	[redacted]
Standard deviation			
Median			
Min			
Q0.025			
Q0.975			
Max			
[redacted]			
Probability dominant			
Probability dominated			

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years; CE, cost-effectiveness





B.3.8.2 Deterministic sensitivity analysis

The robustness of the model was tested by a set of deterministic sensitivity analyses (DSAs). One parameter or model assumption was varied at a time whilst the other

parameters were kept constant at base case values. Table 72 summarises the list of parameters tested in the DSA.

Table 72. Parameters tested in the deterministic sensitivity analysis

Parameters	Base case	DSA input
Discount rates for costs and QALYs	3.5%	0% and 5%
Age	44.6	40.55 and 48.6 years
Weight (kilograms)	82.97	66.38 and 99.56
Dosage	See section B.3.2	All parameters varied +/- 20%
Platelet response rates	See section B.3.3.1	All parameters varied +/- 20%
Time to response	See section B.3.3.1	All parameters varied +/- 1 cycle
Bleeding rates per cycle	See section B.3.3.2	All parameters varied +/- 20%
Mortality (event rates per cycle, inpatient bleeds)	See section B.3.3.4	9.8% and 16.60% (intracranial haemorrhage); 2.7% and 4.6% (gastrointestinal bleed); 1.4% and 2.00% (other bleeds)
AEs (event rates per cycle, serious and other AEs)	See section B.3.3.5	All parameters varied +/- 20%
Rescue therapy and concomitant ITP medication	See section B.3.3.3	All parameters varied +/- 20%
Health state utilities	See section B.3.4.5	All parameters varied +/- 20%
Adverse event utility decrements	See section B.3.4.4	All parameters varied +/- 20%
Drug acquisition costs	See section B.3.5.1	All parameters varied +/- 20%
Bleed costs	See section B.3.5.2	All parameters varied +/- 20%
Administration costs	See section B.3.5.1	All parameters varied +/- 20%
Monitoring costs	See section B.3.5.1	All parameters varied +/- 20%
Rescue therapy and concomitant ITP medication costs	See section B.3.5.1	All parameters varied +/- 20%

Abbreviations: DSA, deterministic sensitivity analysis; AEs, adverse events; ITP, immune thrombocytopenia; QALYs, quality adjusted life years;

In all deterministic analyses, the cost effectiveness of avatrombopag vs. eltrombopag and romiplostim remained consistent with the base case (i.e. dominant).

B.3.8.3 Scenario analysis

A number of scenario analyses were explored in which model assumptions or parameters were altered.

The principal conclusion from the NMA was that avatrombopag was at least similar to the other comparators (i.e. eltrombopag and romiplostim) in terms of efficacy and safety. Therefore, a series of scenarios were performed which explored the impact in terms of costs and QALYs when identical response rates were assumed for avatrombopag and comparators. In addition, analyses were undertaken to explore how different rescue therapy utilisation rates and costs altered the results. A summary of the scenario analyses carried out is provided in Table 73.

[redacted] presents the results from the scenario analyses. Across the parity response scenarios (i.e., 1-3), avatrombopag had an equivalent number of QALYs to the comparators. Avatrombopag vs. eltrombopag and romiplostim had lower total costs, similar to the base case. In the rescue therapy scenarios (i.e. scenarios 4-6), avatrombopag remained dominant relative to comparators.

Table 73: Summary of scenario analyses explored

#	Scenario	Justification	Base case value	Scenario analysis value
	Parity response			
1	Lower bound	Conservative interpretation of the network meta-analysis which assumes similar platelet response rates for avatrombopag and other comparators	Response rate: AVA = 73.2% ELT = 27.5% ROM = 55.2% FOS = 22.5%	Response rate = 27.5% for all TPO-RAs
2	Middle			Response rate = 55.2% for all TPO-RAs
3	Upper bound			Response rate = 73.2% for all TPO-RAs
	Rescue therapy			
4	Rescue therapy rate – Study 302 data	Assume a lower reduction in use of rescue therapy for platelet responders by using trial data from Study 302	Rescue therapy rates (per cycle): >50x10^9/L = 3.0% <50x10^9/L = 22.0%	Rescue therapy rates (per cycle): >50x10^9/L = 4.1% <50x10^9/L = 6.1%
5	Rescue therapy rate – Study 302 + Extension data	Assume a lower reduction in use of rescue therapy for platelet responders by using trial data from Study 302 + extension phase		Rescue therapy rates (per cycle): >50x10^9/L = 3.9% <50x10^9/L = 13.2%
6	Rescue therapy – only used to manage bleeding events	Assumes rescue therapy is not used to cover non-bleeding events, for example, low platelet count. Therefore, cost of rescue therapy is covered under bleeding events	Rescue therapy rates (per cycle) - due to reasons other than bleeding event: >50x10^9/L =1.33% <50x10^9/L = 9.8%	Rescue therapy rates due to reasons other than bleeding event = 0.0% (all states)

Abbreviations, AVA, avatrombopag; ELT, eltrombopag; ROM, Romiplostim; FOS, fostamatinib; TPO-RA, thrombopoietin receptor agonist

[redacted]

	Avatrombopag	Eltrombopag	Romiplostim
Scenario 1			
Total costs	[redacted]	[redacted]	[redacted]
Treatment costs	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]	[redacted]
Bleeding costs	[redacted]	[redacted]	[redacted]
Total QALYS	[redacted]	[redacted]	[redacted]
Incremental costs	[redacted]	[redacted]	[redacted]
Incremental QALYs	[redacted]	[redacted]	[redacted]
ICER	[redacted]	[redacted]	[redacted]
Scenario 2			
Total costs	[redacted]	[redacted]	[redacted]
Treatment costs	[redacted]	[redacted]	[redacted]
Administration costs	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]	[redacted]
Bleeding costs	[redacted]	[redacted]	[redacted]

Total QALYS		[redacted]			[redacted]			[redacted]
Incremental costs								
Incremental QALYs								
ICER								
Scenario 3								
Total costs		[redacted]			[redacted]			[redacted]
Treatment costs								
Administration costs								
Monitoring costs								
Bleeding costs								
Total QALYS								
Incremental costs								
Incremental QALYs								
ICER								
Scenario 4								
Total costs		[redacted]			[redacted]			[redacted]
Treatment costs								
Administration costs								
Monitoring costs								
Bleeding costs								
Total QALYS								
Incremental costs								
Incremental QALYs								
ICER								
Scenario 5								
Total costs		[redacted]			[redacted]			[redacted]
Treatment costs								
Administration costs								
Monitoring costs								
Bleeding costs								
Total QALYS								
Incremental costs								
Incremental QALYs								
ICER								
Scenario 6								
Total costs		[redacted]			[redacted]			[redacted]
Treatment costs								
Administration costs								
Monitoring costs								
Bleeding costs								
Total QALYS								

Incremental costs		[redacted]			[redacted]			[redacted]	
Incremental QALYs		[redacted]			[redacted]			[redacted]	
ICER		[redacted]			[redacted]			[redacted]	

B.3.8.4 Summary of sensitivity analyses results

Sensitivity analyses were conducted to establish the robustness of the model inputs and structural assumptions incorporated into the economic model.

Findings from the DSA were consistent with the model base case for both eltrombopag and romiplostim.

Results from the scenario analyses demonstrated that heterogeneity in response rates (derived from the network meta-analysis) is the most significant cause of uncertainty in the model, as it influences health state costs and QALYs. When an assumption of parallel efficacy is adopted, the associated QALY gain for avatrombopag vs. comparators is mitigated. The cost differences between avatrombopag and eltrombopag are narrowed as bleeding events are reduced and patients also remain on their first-line therapy for a similar duration of time, thus equalising treatment costs. For romiplostim, a cost difference is still observed. This is due to a higher drug acquisition cost with romiplostim. Findings from the scenario analyses are supported by the PSA which shows that avatrombopag remains highly likely ([redacted]) to be dominant or cost-effective at a £10,000 QALY threshold vs. both eltrombopag and romiplostim, respectively.

In conclusion, the results of the sensitivity analyses support the findings from the base case analysis.

B.3.9 Subgroup analysis

No subgroup analyses were considered relevant for this economic analysis (as per the decision problem in section B.1).

B.3.10 Validation

B.3.10.1 Internal validation

An internal validity check was performed by the model developers. This included a quality check of model codes, model inputs including both a comparison to the original source and any intermediate calculations, and a check of model outputs.

B.3.10.2 Cross-validation

Results from the model were compared to selected economic evaluations for TPO-RAs. These were the eltrombopag and romiplostim NICE appraisals (29, 30) as well as the Allen et al. and Lee et al publications (71, 76) which explored cost-effectiveness of TPO-RAs from UK/Irish perspectives. A comparison of results is presented in Table 75 and showed no significant differences between those models and the model presented in this submission. Total QALYs were between 10 and 12, whilst costs were broadly similar when accounting for the different data analyses which were performed. There was 1 notable exception which reported higher QALYs (14.5-15.5) (71). However, this can be attributed to the application of higher base-case utility values for model health states and when bleeding events occurred (0.863-0.841 for states without bleeds and 0.45-0.734 for states with bleeds).

Table 75. Cross validation results: a) avatrombopag base case analysis b) eltrombopag manufacturer submission to NICE (TA293) c) romiplostim manufacturer submission to NICE (TA221) d) Allen et al (2016) e) Lee et al (2013)

a)

Intervention	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	ICER (AVA vs)
Avatrombopag	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eltrombopag					
Romiplostim					

b)

Intervention	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	ICER (ELT vs)
Splenectomised patients					
Eltrombopag	556,089	12.22	-	-	-
Non-TPO-RA pathway	581,073	10.95	-£24,984	1.28	Dominant
Romiplostim	643,598	12.22	£87,508	0.00	N/A
Non-splenectomised patients					
Eltrombopag	297,292	9.55	-	-	-
Non-TPO-RA pathway	332,193	11.86	-£34,900	2.31	£15,105
Romiplostim	372,744	11.86	£40,552	0.00	N/A

c)

Intervention	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	ICER (ROM vs)
Splenectomised patients					
Romiplostim	629,228	12.83	-	-	-
Without romiplostim	611,642	11.70	17,586	1.13	15,595
Non-splenectomised patients					
Romiplostim	432,158	12.40	-	-	-
Without romiplostim	408,203	10.76	23,955	1.64	14,633

d)

Intervention	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	ICER (ELT vs)
Splenectomised patients					
Eltrombopag	322,900	14.83	-	-	-
Romiplostim	411,804	14.81	-88,904	0.02	Dominant
Non-splenectomised patients					
Eltrombopag	236,339	15.33	-	-	-
Romiplostim	279,600	15.31	-40,261	0.02	Dominant

e)

Intervention	Total costs (€)	Total QALYs	Incremental costs	Incremental QALYs	ICER (ROM vs)
Romiplostim	598,704	12.08	-	-	-
Eltrombopag	611,962	11.32	-€13,258	0.76	Dominant
Standard of care	621,376	10.91	-€22,673	1.17	Dominant

B.3.10.3 External validation

The model has been validated by an independent third-party consulting team. The model was checked for errors in model structure, code implementation and model assumptions. Any errors identified by the quality check were addressed ahead of submission.

B.3.10.3 Expert validation

The model structure and the assumptions made within the model were presented at 2 expert advisory panels held virtually by Sobi in November 2020 and March 2021 (23). Attendees at the meeting included UK clinical experts with a background in the management of ITP and health economic experts who provide recommendations on how best to perform an economic analysis for this population. Updates to the model were made based on feedback received at these meetings.

B.3.11 Interpretation and conclusions of economic evidence

The cost-effectiveness analysis compared avatrombopag for the treatment of chronic refractory ITP with other existing TPO-RA treatments, eltrombopag and romiplostim. These treatments are the standard of care in UK clinical practice and are the only NICE-approved products for patients who are refractory to initial ITP therapy.

The analysis utilised a de novo model structure that was consistent with previous economic evaluations for ITP. Fundamental elements of the model design were informed by the eltrombopag NICE appraisal (TA293) (29), most notably the model framework (Markov model) and health state characterisation (health states and how they influence costs and outcomes).

Since the eltrombopag NICE appraisal in 2013 (29), clinical practice and management of ITP have evolved. Therefore, the model in this submission included updated assumptions and inputs to reflect these changes. The most significant included the removal of splenectomised patients as a subgroup (splenectomy is now positioned as a later line “last resort” therapy once medical intervention is exhausted), how resource use and costs are valued for ITP related events (for example bleeding), and the treatment pathway beyond discontinuation with a given TPO-RA.

The base case deterministic analysis showed that avatrombopag was not only cost-effective vs. eltrombopag and romiplostim, but also dominant in both instances. This finding was supported by sensitivity analyses, with deterministic sensitivity analysis were aligned to the base case results. Furthermore, the probabilistic sensitivity analysis showed that avatrombopag was highly likely to be dominant vs. eltrombopag [redacted] and romiplostim [redacted] at a willingness to pay threshold of £10,000 per QALY gained.

The primary limitations of this analysis are centered around the small quantity of data available. The key clinical parameter included in the model was platelet response, defined by the threshold platelet count of 50×10^9/L. There was no direct head-to-head data for avatrombopag vs. comparators regarding platelet response; therefore, data were derived from an NMA. As discussed in section 2.9 and section 2.13, the NMA showed directional improvements in platelet response for avatrombopag vs. comparators. The interpretation of these results was limited owing to considerable heterogeneity; however, they were still consistent with a previous NMA and clinical opinion (23, 43). Thus, a conservative assumption of avatrombopag being “at least as effective” as the other TPO-RAs was adopted for the model.

The model base case assumes mean OR from the NMA as outlined in **Error! Reference source not found.**. To explore the impact of uncertainty and the overall assumption of TPO-RA similarity, scenario analyses were conducted which assumed equivalent response rates for avatrombopag and comparators. These scenario analyses demonstrated that avatrombopag had a similar level of QALYs and health state costs to comparators and that costs remained favourable for avatrombopag vs. both eltrombopag and romiplostim.

A further limitation was the inclusion of clinical data from Study 302 relating to bleeding events, rescue therapy and concomitant ITP medication use. Due to low patient numbers and few reported events (e.g. serious bleeding events), probabilities for these events and utility data could not be calculated. As a result, the model included data from the TA293 eltrombopag NICE appraisal (29) to supplement the clinical data from Study 302. Sensitivity analyses were performed to account for uncertainty in the model, in particular regarding rescue therapy use. A number of additional scenarios

were explored, all of which showed results which were consistent with the model base case of avatrombopag dominance.

In conclusion, there remains a strong unmet need in clinical practice for an effective, tolerable, and easily administrable treatment option for patients with chronic ITP who are currently considered eligible to receive an available TPO-RA. The results from the base case and sensitivity analysis demonstrate that avatrombopag is a cost-effective option that should be approved alongside the existing TPO-RAs. Furthermore, given the probabilistic sensitivity analysis results which show a highly likely cost per QALY of <£10,000, we propose that avatrombopag is a suitable candidate for consideration under the NICE fast-track appraisal programme.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Avatrombopag in combination for treating chronic immune thrombocytopenia [ID3838]

Clarification questions

October 2021

File name	Version	Contains confidential information	Date
		Yes	

Section A: Clarification on effectiveness data

Questions on individual trials

A1. For Figure 3 of the main submission, please describe the reasons that 10 patients dropped out of the extension phase of Study 302.

In total, 9 (23.1%) subjects discontinued from the Extension Phase. The most common reasons for discontinuation from the Extension Phase were adverse event (AE) (3 patients, 7.7%) and subject choice (3 patients, 7.7%) followed by inadequate therapeutic effect (2 patients, 5.1%) and lost to follow-up (1 patient, 2.6%). 1 further subject (Subject 16001001) remained on treatment in the Extension Phase at the time of database lock and has since completed the study on 09 Apr 2015. This subject was not counted in either the completion or discontinuation categories, or in the disposition summary table of the Extension Phase (p 9, Study 302 CSR).

A2. In Table 8 of the main submission please add details regarding which specific concomitant ITP medications were being used at baseline in study 302.

In total, 22 (44.9%) of subjects in Study 302 were using concomitant ITP medications at baseline, the details of which are presented below in Table 1.

Table 1. (Relevant to Table 8 of main submission): concomitant ITP medications taken by subjects in Study 302 at baseline.

Pharmacological Subgroup/ WHO Drug Name (Preferred Term)	Placebo (N=17) n (%)	Avatrombopag (N=32) n (%)
Subjects who took at least one medication	**7 (41.2)**	**15 (46.9)**
Anabolic steroids	**1 (5.9)**	**0**
Danazol	1 (5.9)	0
Immunosuppressants	**2 (11.8)**	**0**
Azathioprine	1 (5.9)	0
Ciclosporin	1 (5.9)	0
Vitamin K and other hemostatics	**3 (17.6)**	**3 (9.4)**
Etamsilate	3 (17.6)	3 (9.4)
Corticosteroids for systemic use, plain	**7 (41.2)**	**14 (43.8)**
Dexamethasone	1 (5.9)	1 (3.1)
Methylprednisolone	1 (5.9)	1 (3.1)
Prednisone	6 (35.3)	11 (34.4)

Data source: Table 14.1.4.5, Study 302 CSR

A3. Please present a table comparing the baseline characteristics of splenectomised patients with those of non-splenectomised patients in Study 302. Please add in a row describing how many patients had taken prior rituximab.

Table 2. Baseline characteristics of splenectomised versus non-splenectomised patients in Study 302

Characteristic	PLC (N=17)	AVA (N=32)	Total (N=49)
Non-splenectomised, n (%)	12 (70.6)	21 (65.6)	33 (67.3)
Age (years), mean (SD)	42.3 (15.2)	43.7 (14.8)	43.2 (15.0)
<65 years, n (%)	11 (92.0)	18 (86.0)	29 (88.0)
Female, n (%)	4 (33.0)	14 (67.0)	18 (55.0)
Ethnicity, n (%)			
Caucasian	11 (92.0)	19 (90.0)	30 (91.0)
Black or African American	0	0	0
Asian	1 (8.0)	1 (5.0)	2 (6.0
Weight (kg), mean (SD)	84.6 (21.4)	79.2 (18.2)	81.1 (19.6)
Height (cm), mean (SD)	170.7 (6.8)	168.3 (8.3)	169.1 (7.9)
BMI (kg/m^2), mean (SD)	29.1 (7.2)	28.0 (6.3)	28.4 (6.7)
Baseline platelet count, n (%)			
≤15 x 10^9/L	6 (50.0)	9 (43.0)	15 (45.0)
15–30 x 10^9/L	6 (50.0)	12 (57.0)	18 (55.0)
≥30 x 10^9/L	0	0	0
Prior TPO-RA, n (%)	3 (25.0)	6 (29.0)	9 (27.0)
Prior rituximab, n (%)	1 (8.0)	1 (5.0)	2 (6.0)
Use of concomitant ITP medication at baseline, n (%)	4 (33.0)	8 (38.0)	12 (36.0)
Splenectomised, n (%)	5 (29.4)	11 (34.4)	16 (32.7)
Age (years), mean (SD)	38.6 (11.1)	51.7 (10.3)	47.6 (12.2)
<65 years, n (%)	5 (100.0)	11 (100.0)	16 (100.0)
Female, n (%)	4 (80.0)	8 (72.7)	12 (75.0)
Ethnicity, n (%)			
Caucasian	4 (80.0)	2 (18.2)	6 (37.5)
Black or African American	1 (20.0)	0	1 (6.3)
Asian	0	0	0
Weight (kg), mean (SD)	85.9 (15.7)	87.1 (27.9)	86.8 (24.7)
Height (cm), mean (SD)	170.2 (8.1)	167.2 (7.0)	168.1 (7.5)
BMI (kg/m^2), mean (SD)	29.5 (4.0)	30.9 (8.3)	30.5 (7.3)
Baseline platelet count, n (%)			
≤15 x 10^9/L	4 (80.0)	9 (81.8)	13 (81.3)
15–30 x 10^9/L	1 (20.0)	1 (9.1)	2 (12.5)
≥30 x 10^9/L	0	1 (9.1)	1 (6.3)
Prior TPO-RA, n (%)	3 (60.0)	6 (54.5)	9 (56.3)
Prior rituximab, n (%)	1 (20.0)	6 (54.5)	7 (43.8)
Use of concomitant ITP medication at baseline, n (%)	3 (60.0)	7 (63.6)	10 (62.5)

AVA, avatrombopag; BMI, body mass index; PLC, placeboTPO-RA, thrombopoietin receptor agonist.

Data sources: Study 302 CSR (Listing 16.2.4.1, Table 14.1.2.2, and Listing 16.2.6.3)

A4. For the CONSORT Figures 8 and 9 in Appendix D:

- Please provide a breakdown of the 42 and 22 patients, respectively, who did not meet the inclusion criteria (i.e. report the most common reasons for exclusion with the associated number of patients). Please report how many were excluded due to lack of response with a previous immune thrombocytopenia therapy (as outlined in Table 4, key inclusion criteria No.4 for study 302).
- Please clarify what the numbers in the 'Analysis' sections signify, given that the submission reports that the full analysis set was used (for most outcomes).

There were 42 patients of Study 302 who failed to meet the inclusion or exclusion criteria and were excluded from the study. No patients were excluded from the study due to a lack of response with a previous ITP therapy (inclusion criteria no. 4). The most common reasons for exclusion are presented in Table 3.

Table 3. Most common reasons for patient exclusion at screening, Study 302.

Failed to meet inclusion / exclusion criteria Common reasons for exclusion (in more than 5% of patients)	**Total (n=42)** **n* (%)**
Did not meet one or more of the study inclusion criteria	**14 (33.3)**
I2: not diagnosed with chronic ITP	12 (28.6)
Met one or more of the study exclusion criteria	**30 (71.4)**
E18: fasting gastrin-17 blood levels >1.5X ULN at screening for subjects on PPIs or H2 antagonists.	8 (19.0)
E16: were currently being treated with proton pump inhibitor (PPIs) or H2 antagonist therapy but had not received a stable dose for at least 6 weeks prior to randomization *or* had not completed these therapies more than 2 weeks prior to randomization.	6 (14.3)
E1: known secondary ITP**.**	5 (11.9)
E15: use of cyclophosphamide or vinca alkaloid regimens within 4 weeks of randomization.	5 (11.9)

***subjects may have had multiple reasons for screening failure and can be counted more than once.**

Data source: Listing 16.2.1.1, Study 302 CSR

There were 22 patients of Study 305 failed to meet the inclusion or exclusion criteria and were excluded from the study. No patients were excluded from the study due to a lack of response with a previous ITP therapy (inclusion criteria no. 4). The most common reasons for exclusion are presented in Table 4.

Table 4. Most common reasons for patient exclusion at screening, Study 305.

Failed to meet inclusion / exclusion criteria Common reasons for discontinuation (in more than 5% of patients)	**Total (n=22)** **n[a] (%)**
Did not meet one or more of the study inclusion criteria	**12 (54.5)**
I2: Subjects considered unable, or unwilling to comply with the study protocol requirements or give informed consent[b]**.**	8 (36.4)

I6: History of pernicious anemia or subjects with vitamin B12 deficiency (defined as <LLN) who have not had pernicious anemia excluded as a cause.	3 (13.6)
Met one or more of the study exclusion criteria	**10 (45.5)**
E18: fasting gastrin-17 blood levels >1.5X ULN at screening (for subjects not on PPIs or H_2 antagonists).	5 (22.7)
E17: Subjects who are currently treated with PPIs or H2 antagonist therapy but have not been receiving a stable dose for at least 6 weeks prior to randomization or have not completed these therapies more than 2 weeks prior to randomization	3 (13.6)

a: subjects may have had multiple reasons for screening failure and can be counted more than once.
b: as determined by the investigator

Data source: Listing 16.2.1.1, Study 305 CSR

The numbers of patients in the 'analysis' boxes at the terminus of the CONSORT flow diagrams (Submission Appendix D Figures 8 and 9) signify the numbers of patients who *completed* the core study of Study 302 (Figure 8) and the core study of Study 305 (Figure 9).

A5. Please elaborate why study 305 was terminated early due to significant enrolment challenges, including why the endoscopy procedure was needed. Please report the mean duration of treatment for each study arm when the study was terminated.

Study 305 was initiated at a time when eltrombopag was approved and became commercially available in the USA [redacted]. Suitable ITP patients were therefore less likely to enter a study where they could be randomised to a non-approved drug (avatrombopag), limiting subject recruitment. [redacted]

An additional challenge to recruitment was presented by the requirements to address a *non-clinical* finding of gastric changes in rodents and cynomologus monkeys, at 3- to 33-fold higher exposure levels than the maximum recommended human dose. These findings led to protocol amendments in Study 305, including criteria mandating that subjects undergo invasive endoscopies, which further impacted recruitment into the study (Clinicaltrials.gov NCT01433978; Sobi data on file). AESIs were prospectively defined and collected, including gastric atrophy events as determined by endoscopy and biopsy assessment. No avatrombopag-treated patients had gastric atrophy events (Table 15, Study 305 CSR). Furthermore, there were no changes of clinical importance in gastric biomarkers over time for all subjects of Study 305, as determined by a gastric biomarker expert review committee (p 14 & p 39, Study 305

CSR). Gastric atrophy was not subsequently identified as an adverse reaction for both licensed indications of avatrombopag (Avatrombopag SmPC); the observed benefit-risk profile to date for the gastrointestinal system remains favourable across the wider evidence base for avatrombopag.

The mean cumulative extent of exposure for the core phase of the study was 10.51 (SD: 10.066) and 15.63 weeks (SD: 11.432) for eltrombopag and avatrombopag-randomized subjects respectively (Table 5). For the 17 subjects continuing into the extension phase, the mean cumulative extent of exposure to avatrombopag was 16.35 weeks (SD: 11.037) across both core and extension phases of the study (Table 6).

Table 5. Cumulative extent of exposure - core study: safety analysis set of core study

	Eltrombopag (N=11)	Avatrombopag (N=12)
Duration of exposure* (weeks)		
n	11	12
Mean (SD)	10.51 (10.066)	15.63 (11.432)

*Duration of exposure = date of last dose of study drug – date of first dose of study drug + 1.

Data source: Table 14.3.1.1, Study 305 CSR

Table 6. Cumulative extent of exposure - core study and extension phase: safety analysis set of extension phase

	Avatrombopag (N=17)
Duration of exposure* (weeks)	
n	17
Mean (SD)	16.35 (11.037)

*Duration of exposure = date of last dose of study drug – date of first dose of study drug + 1.

Data source: Table 14.3.1.3, Study 305 CSR

A6. Please explain why there were so few patients randomised to placebo in trial CL-003? Please provide the allocation ratio.

Subjects were randomly assigned to avatrombopag at 2.5 mg, 5 mg, 10 mg or 20 mg, or placebo in a 3:3:3:3:1 ratio, respectively. That is, 15 subjects were to be treated at each dose level of study drug, while 5 subjects were to receive placebo (Study CL-003 CSR p 22). Fewer subjects were assigned to placebo for ethical reasons - it was assumed that no responses would be observed in these subjects and the sponsor sought to minimize exposure to a nontherapeutic treatment (p 23, Study CL-003 CSR).

Questions on all avatrombopag trials

A7. Priority. The reporting of detailed trial outcomes in the submission is judged to be very limited. Please provide a table of results for each of the avatrombopag trials (study 302, study 305 and study CL003 [only the 20mg vs placebo comparison for study CL003 is required]), and their extension phases, for all outcomes relevant to those listed in the decision problem, including mortality and measures of health-related quality of life (EQ-5D, EQ-VAS, SF-36). Please include platelet response results for each arm of the trials for the following timepoints: Day 8, 6 weeks, 9 weeks and 24 weeks (where available). Please provide detailed numbers (not percentages alone) for the following:

- **The numerators and denominators used for calculating binary outcomes;**
- **The number of patients contributing to each trial arm used for calculating continuous outcomes;**
- **The mean or median with standard deviation or interquartile range for each trial arm for continuous outcomes; and**
- **Outcomes reported for all timepoints (where available). Please state when data is not available for a particular timepoint and report the timepoint for all outcomes.**

Study 302:

- Comprehensive subject, efficacy and safety data relevant to outcomes listed in the decision problem can be found within the Study 302 CSR at **Section 14, pp 133 – 2178**.
- No deaths were reported in this study. The narratives of SAEs and certain other significant AEs are summarised in **Table 14.3.3** (p 709).
- Quality of life data are presented in **Tables 14.2.5.1** to **14.2.5.3** (pp 310 – 325).
- Platelet count responses for both arms of the study are available for all timepoints requested, presented as:
    - Number of subjects in analysis set/population;
    - Number of subjects reported at timepoint (n);
    - Mean platelet count (with standard deviation);
    - Median platelet count;
    - Minimum and maximum recorded values.

- Please find these platelet response data at the following locations:
    - Core study phase: **Table 14.2.3.3** (pp 242 - 244);
    - Extension study phase: **Table 14.2.4.1** (pp 283 - 294).

Relevant to **Table 15** of the main NICE submission, please find full data relevant to key endpoints of Study 302 summarised in the expanded tables below, including numerators and denominators as requested for relevant binary outcomes:

Table 7. Study 302: Primary and secondary efficacy endpoints – FAS of Core Study

Primary endpoint: Cumulative number of weeks of platelet response	**PLC (N=17)**	**AVA (N=32)**
n	17	32
Mean (SD)	0.1 (0.49)	12.0 (8.75)
Median	0.0	12.4
Min, Max	0, 2	0, 25
***P*-value of Wilcoxon rank sum test**		<0.0001

Cumulative number of weeks of platelet response is defined as the total numbers of weeks in which the platelet count is ≥50 x109/L during 6 months of treatment of Core Study in the absence of rescue therapy.

Secondary endpoint: Platelet count ≥50 x 10^9/L at Day 8	**PLC (N=17)** n, percentage (95% CI)	**AVA (N=32)** n, percentage (95% CI)
n[a]	17	32
Yes	0, 0.00 (-,-)	21, 65.63 (49.17, 82.08)
No	17, 100.00	11, 34.38
Missing[b]	0	0
Difference of response rate (95% CI)[c]		65.63 (49.17, 82.08)
***P*-value of Fisher's exact test**		<0.0001
Secondary endpoint: Reduction in use of concomitant ITP medications from baseline	n, percentage (95% CI)	n, percentage (95% CI)
N[d]	**7**	**15**
Yes	0, 0.00 (-,-)	5, 33.33 (9.48, 57.19)
No	7, 100.00	10. 66.67
Difference of response rate (95% CI)[c]		33.33 (9.48, 57.19)
***P*-value of Fisher's exact test**		0.1348

CI, confidence interval
a: Subjects with platelet response at day 8 are defined as those who had a platelet count ≥50 x 109/L at day 8 in the absence of rescue therapy on or before Day 8.
b: Missing values are considered as nonresponse in the P-value calculation.
c: Difference of response rate = platelet response rate at Day 8 of avatrombopag - platelet response rate at Day 8 of placebo, 95% confidence interval (CI) is calculated based on normal approximation.
d: Only subjects with use of concomitant ITP medications at baseline were included in the analysis; this number is used to calculate percentages.
e: Difference of rate of reduction = rate of reduction of in use of concomitant ITP medications from baseline of avatrombopag - rate of reduction of in use of concomitant ITP medications from baseline of placebo, 95% confidence interval is calculated based on normal approximation.

Study 302: Exploratory efficacy endpoint – FAS of Core Study

Durable platelet response	**PLC (N=17)** n, percentage (95% CI)	**AVA (N=32)** n, percentage (95% CI)
Yes	0, 0.00 (-,-)	11, 34.38 (17.92, 50.83)
No	2, 11.76	14, 43.75
Missing	15, 88.24	7, 21.88
Difference of response rate (95% CI)		34.38 (17.92, 50.83)
***P*-value of Fisher's exact test**		0.0090

FAS = full analysis set
1: Subjects with durable platelet response are defined as those who had at least 6 out of 8 weekly platelet responses (≥50 x 10^9/L) during last 8 weeks of treatment over 6-month treatment period in absence of rescue therapy.
2: 95% confidence interval (CI) is calculated based on normal approximation.
3: Missing values are considered as non-responders in the P-value calculation.
4: Difference of response rate = durable platelet response rate of avatrombopag - durable platelet response rate of placebo, 95% CI is calculated based on normal approximation.

Table 8. Study 302: Summary of bleeding events during 6-month treatment – FAS of Core Study

Incidence of bleeding during 6-month treatment[a], n (%)	**PLC (N=17)**	**AVA (N=32)**
Yes	9 (52.9)	14 (43.8)
No	8 (47.1)	18 (56.3)
***P*-value of Chi-square test**		0.5394

FAS = full analysis set
Percentages are based on the total number of subjects in relevant treatment group.
a: Subjects with multiple bleeding events are counted only once.
b: Subjects with multiple bleeding events are counted only once in the highest grade category.
c: P-value is calculated based on Chi-square test.

Table 9. Study 302: Summary of rescue therapy during 6-month treatment – FAS of Core Study

Rescue therapy during 6-month treatment	**PLC (N=19)** n, percentage (95% CI)	**AVA (N=30)** n, percentage (95% CI)
Yes	2, 11.76 (0.00, 27.08)	7, 21.88 (7.55, 36.20)
No	15, 88.24	25, 78.13
Difference of rate of rescue therapy (95% CI[b])		10.11 (-10.86, 31.08)
***P*-value of Fisher's exact test**		0.4668

a: 95% confidence interval (CI) is calculated based on normal approximation.
b: Difference of rate of rescue therapy = durable platelet response rate of avatrombopag - durable response rate of placebo,
95% CI is calculated based on normal approximation.

Study 305:

- The full subject, efficacy and safety data relevant to outcomes listed in the decision problem can be found within the Study 305 CSR at **Section 14, pp 46 – 1296**.
- No deaths were reported in this study. The narratives of SAEs and certain other significant AEs are summarised in **Table 14.3.3** (p 326).
- Quality of life data are not available for this study.
- Platelet response results for both arms of the study are available for all timepoints requested, presented as:
    - Number of subjects in analysis set/population (denominator, printed in column headers);
    - Number of subjects reported at timepoint (numerator, n);
    - Mean platelet count (with standard deviation);
    - Median platelet count;
    - Minimum and maximum recorded values.
- Please find these platelet response data at the following locations:
    - Core study phase: **Table 14.2.1.1** (pp 100 - 109);
    - Extension study phase: **Table 14.2.2.1** (pp 121 - 127).

Study CL-003 (20 mg v placebo comparisons) and extension study CL-004:

- The full subject, efficacy and safety data relevant to outcomes listed in the decision problem can be found within the Study 305 CSR at **Section 14, pp 106 – 1821**.
- No deaths were reported in this study. The narratives of SAEs and certain other significant AEs are summarised in **Section 12.3.2** (p 89).
- Quality of life data were not recorded for this study.
- Platelet response results for both arms of the study are available for all timepoints requested, presented as:
    - Number of subjects in analysis set/population (denominator, printed in column headers);
    - Number of subjects reported at timepoint (numerator, n);
    - Mean platelet count (with standard deviation);
    - Median platelet count;
    - Minimum and maximum recorded values.
- Please find these platelet response data at the following locations:

- Core study phase: **Table 14.2.2.1.1** (pp 188 – 190);
- Extension study CL-004: **Table 14.2.3.1** (pp 389 – 421).

A8. Priority. Please provide Clinical Study Reports for study 302, study 305 and study CL003.

CSRs for studies 302, 305 & CL003 were previously provided to NICE on 16th September, 29th September and 4th October, 2021. Please find these CSRs enclosed again with this response, for the convenience of the ERG.

A9. Please explain why there is such a large difference in the rate of 'Any TEAEs' between Table 30 (of the main submission) and Tables 31-32**.**

Table 30 presents the *exposure-adjusted* rates of TEAEs and SAEs during the Study 302 core study and extension phase (rates calculated as 100 x (number of subjects with events / total exposure in subject-weeks) within each category. By contrast, Tables 31 and 32 present TEAEs without adjustment for duration of exposure.

A10. For Tables 30-32 please present the number of adverse events which were Grade 3 or higher for each treatment arm.

Please find below **Table 10** (**Table 30-amended)** [relevant to Study 302] with the additional requested data **highlighted**:

Table 10. Table 30-amended: Most frequent TEAEs (all grades), CTCAE grade 3 or 4 TEAEs, SAEs and deaths during the 302-core study and extension phase, adjusted by treatment exposure* – NCT01438840 (Study 302 CSR)

	Core study exposure-adjusted incidence rate*		Core study + extension phase exposure-adjusted incidence rate*
	PLC (n=17) %	AVA (n=32) (%)	AVA (n=47) (%)
Any TEAE	**6.6**	**4.3**	**2.2**
Headache	1.3	1.6	0.7
Contusion	2.6	1.4	0.9
URTI	0.7	0.8	0.5
Arthralgia	0	0.5	0.2
Epistaxis	2.0	0.5	0.4
Fatigue	0.7	0.5	0.3
Gingival bleeding	0	0.5	0.4
Petechiae	0.7	0.5	0.3
Thrombocytopenia	0	0.3	0.4
Pharyngitis	0.7	0	0.3
Hypertension	0.7	0.3	0.2
Nasopharyngitis	0	0.4	0.2
Any SAE	**0.7**	**1.2**	**0.7**
Headache	0	0.3	0.1

Vomiting	0	0.3	0.1
Platelet count decreased	0	0.1	0.1
TEAEs (CTCAE grade 3 or 4)	**0**	**0.8**	**0.7**
Deaths	0	0	0

*Rate is calculated as 100 × (number of subjects with events/total exposure in subject-weeks) in each category. Abbreviations: AVA, avatrombopag; CTCAE, common terminology criteria for adverse events; PLC, placebo; SAE, serious adverse event; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection

Relevant also to the Core Submission: Table 30 [Study 302], please find below Table 11, which presents the absolute, *non exposure-adjusted* incidences of CTCAE grade 3 or higher TEAEs for the core and extension phases of Study 302.

Table 11. TEAEs in Study 302 Core and Extension Phase, Safety Analysis Set

	Core study incidence of TEAEs		Core study + extension phase incidence of TEAEs
	PLC (N=17) n (%)	**AVA (N=32) n (%)**	**AVA (N=47) n (%)**
TEAEs	10 (58.8)	31 (96.9)	45 (95.7)
TEAEs with CTCAE grade 3 or 4	0	6 (18.8)	14 (29.8)
Serious TEAEs	1 (5.9)	9 (28.1)	15 (31.9)
Deaths (CTCAE grade 5)	0	0	0

***Rate is calculated as 100 x (the number of subjects with events/total exposure in subject-weeks) within each category. Abbreviations: AVA, avatrombopag; CTCAE, common terminology criteria for adverse events; TEAE, treatment-emergent adverse event; PLC, placebo**

Data source: Table 17 and 18, Study 302 CSR

Please find below **Table 12** (**Table 31-amended)** [relevant to Study 305], with the additional requested data (REDACTED DUE TO AIC)

Table 12. Table 31-amended: TEAEs (all grades) occurring in at least 20% of patients, CTCAE Grade 3 or 4 TEAEs and deaths in all patients during the 305 core study and extension phase (Study 305 CSR)

	Core study		Core study + extension phase
	ELT (n=11) n (%)	**AVA (n=12) n (%)**	**AVA (n=17) n (%)**
[redacted]			

Please find below **Table 13** (**Table 32-amended)** [relevant to study CL-003/004], with the additional requested data (REDACTED DUE TO AIC)

Table 13. Table 32-amended: TEAEs occurring in at least 5% of patients during CL-003 and 004 extension phase – NCT00441090 and NCT00625443 (29, 30)

	Core study		Core study + extension phase
	PLC (n=5) n (%)	AVA (n=59) n (%)	AVA (n=64) n (%)
[redacted]	[redacted]	[redacted]	[redacted]

Network meta-analysis

A11. Priority. Please provide all relevant code and data used to perform the network meta-analyses for both the fixed and random effects models, sufficient to permit the ERG to check and/or reanalyse the NMAs, including:

- **All BUGS model files**
- **All data files (in BUGS format or other reasonable format)**
- **All BUGS "initial value" files**
- **Any other relevant code used (e.g. CODA, R files)**

Please note that this request is in addition to all other requests relating to the NMAs, and should not be a replacement for them.

WinBugs files are embedded below, **please note these files are AIC**

Sent as separate attachment.

A12. For all the NMAs reported in the company submission and additional NMAs requested in this document, please provide the following:

a) the between-study standard deviations and corresponding 95% credible intervals for both the fixed and random effects models;

b) the mean total residual deviances;

c) details on how the assessment of chain convergence was performed.

Table 14. Additional NMA information

Endpoint	Fixed-effect model			Random-effect model			
	$\bar{D}_{res}$	pD	DIC*	$\bar{D}_{res}$	pD	DIC*	SD (95%CrI)
Durable response	46.53	9.46	55.99	46.14	9.92	56.05	0.76 (0.03, 1.91)
Need for rescue therapy	5.29	4.00	9.29	5.38	4.84	10.22	1.19 (0.04, 4.68)
Reduction in concomitant ITP	34.02	6.69	40.71	29.55	7.39	36.94	1.43 (0.13, 1.98)
Any bleeding	1.49	4.00	5.49	2.16	4.71	6.87	1.01 (0.04, 4.27)
Bleeding events WHO 2-4 grade	10.91	4.00	14.91	10.97	5.14	16.11	1.00 (0.04, 4.44)
Any AE	-0.67	4.00	3.33	0.02	4.70	4.73	0.91 (0.03, 4.6)

*Fixed-effect models were preferred as more parsimonious than random-effect models unless a better performance of the latter one was demonstrated with significantly lower DIC value. A difference of ≥5 was assumed significant for DIC.

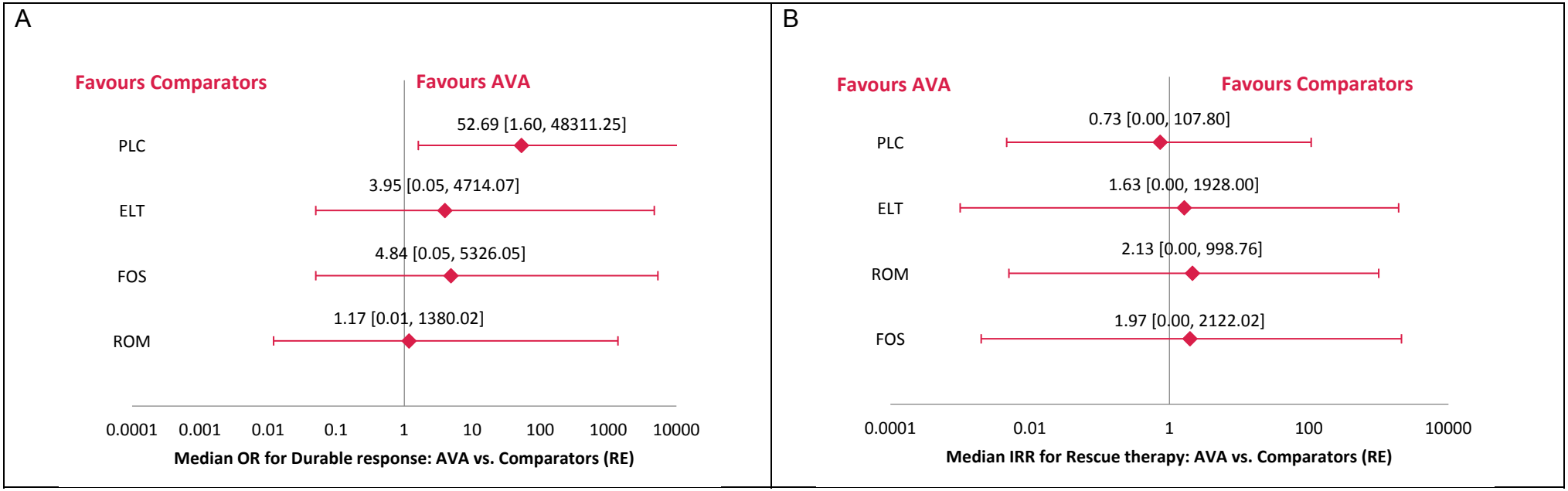
$\bar{D}_{res}$ – posterior mean of residual deviance
pD – effective number of parameters
DIC – deviance information criterion
SD – standard deviation for between-trail differences
95%CrI – 95% credible intervals

Three chains of iterations were run for each analysis. The convergence was assessed by visual inspection of time-series history plots.

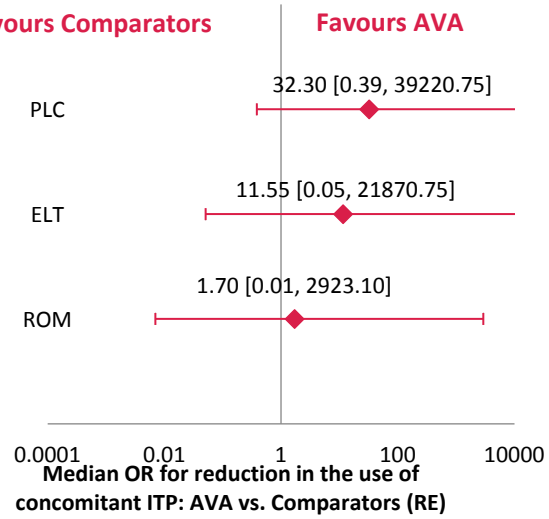
A13. Priority. The company submission only reports the results of the NMAs for fixed effect models. Please provide the corresponding results of the random effects model for all outcomes.

Please see Figure 1, Figure 2 and Table 15-Table 20 below.

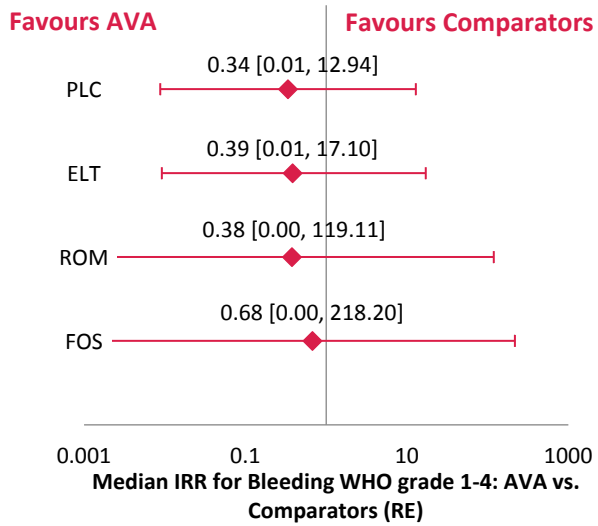
Figure 1. Forest plots for the IRR/OR for comparison of avatrombopag vs . comparators for A. Durable response B. Need for rescue therapy C. Reduction in use of concomitant ITP medication D. Any bleeding events and E. Bleeding events WHO grade 2–4 – random effect model



C


Favours Comparators
Favours AVA
32.30 [0.39, 39220.75]
PLC
11.55 [0.05, 21870.75]
ELT
1.70 [0.01, 2923.10]
ROM
0.0001
0.01
1
100
10000
Median OR for reduction in the use of concomitant ITP: AVA vs. Comparators (RE)

D


Favours AVA
Favours Comparators
0.34 [0.01, 12.94]
PLC
0.39 [0.01, 17.10]
ELT
0.38 [0.00, 119.11]
ROM
0.68 [0.00, 218.20]
FOS
0.001
0.1
10
1000
Median IRR for Bleeding WHO grade 1-4: AVA vs. Comparators (RE)

E

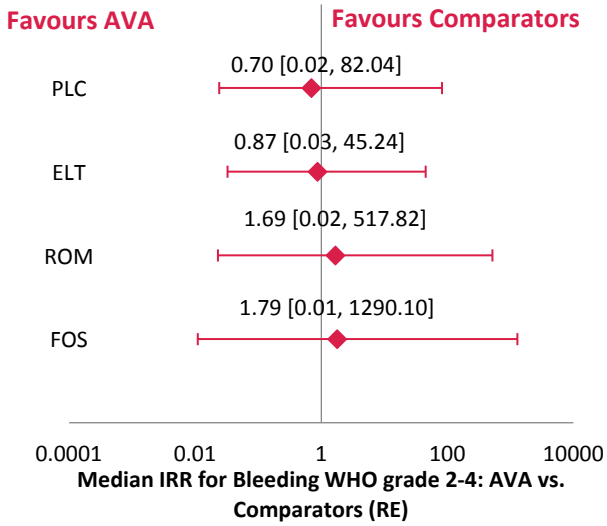

Favours AVA
Favours Comparators
0.70 [0.02, 82.04]
PLC
0.87 [0.03, 45.24]
ELT
1.69 [0.02, 517.82]
ROM
1.79 [0.01, 1290.10]
FOS
0.0001
0.01
1
100
10000
Median IRR for Bleeding WHO grade 2-4: AVA vs. Comparators (RE)

Table 15. OR and rankings for durable response - random effect model

OR for all comparisons (RE model)						Prob of being best (%)	SUCRA (%)	Prob of AVA being better than comp (%)
	vs. PLC	vs. AVA	vs. ELT	vs. FOS	vs. ROM			
PLC	PLC	**0.02 [0.00, 0.62]**	**0.07 [0.01, 0.79]**	**0.09 [0.01, 0.77]**	**0.02 [0.00, 0.19]**	0	1	1
AVA	**52.69 [1.60, 48311.25]**	AVA	3.95 [0.05, 4714.07]	4.84 [0.05, 5326.05]	1.17 [0.01, 1380.02]	47	75	-
ELT	**14.05 [1.27, 158.70]**	0.25 [0.00, 19.86]	ELT	1.29 [0.03, 29.91]	0.31 [0.01, 7.74]	8	51	28
FOS	**10.74 [1.30, 195.50]**	0.21 [0.00, 19.99]	0.77 [0.03, 32.98]	FOS	0.24 [0.01, 8.47]	8	47	25
ROM	**45.02 [5.21, 786.50]**	0.85 [0.00, 81.64]	3.22 [0.13, 133.40]	4.18 [0.12, 142.50]	ROM	37	77	48

Table 16. Incidence risk ratios and rankings for proportion of patients who need rescue therapy - random effect model

IRR for all comparisons (RE model)						Prob of being best (%)	SUCRA (%)	Prob of AVA being better than comp (%)
	vs. PLC	vs. AVA	vs. ELT	vs. ROM	vs. FOS			
PLC	PLC	1.36 [0.01, 212.80]	2.21 [0.02, 314.50]	2.92 [0.09, 91.97]	2.68 [0.02, 312.12]	1	25	58
AVA	0.73 [0.00, 107.80]	AVA	1.63 [0.00, 1928.00]	2.13 [0.00, 998.76]	1.97 [0.00, 2122.02]	17	41	-
ELT	0.45 [0.00, 59.28]	0.61 [0.00, 675.82]	ELT	1.31 [0.00, 514.91]	1.22 [0.00, 1103.00]	22	55	39
ROM	0.34 [0.01, 11.27]	0.47 [0.00, 215.00]	0.76 [0.00, 321.60]	ROM	0.93 [0.00, 335.60]	30	66	32
FOS	0.37 [0.00, 52.26]	0.51 [0.00, 551.01]	0.82 [0.00, 938.60]	1.08 [0.00, 402.72]	FOS	30	62	35

Table 17. Odds ratios and rankings for proportion of patients with reduced use of the concomitant ITP medications - random effect model

OR for all comparisons (RE model)					Prob of being best (%)	SUCRA (%)	Prob of AVA being better than comp (%)
		vs. AVA					
PLC	PLC	0.03 [0.00, 2.60]	0.33 [0.02, 6.91]	0.05 [0.00, 0.65]	0	9	94
AVA	32.30 [0.39, 39220.75]	AVA	11.55 [0.05, 21870.75]	1.70 [0.01, 2923.10]	55	77	-
ELT	3.00 [0.14, 61.38]	0.09 [0.00, 19.60]	ELT	0.16 [0.00, 7.22]	6	38	81
ROM	**19.61 [1.55, 414.00]**	0.59 [0.00, 147.20]	6.40 [0.14, 501.40]	ROM	39	75	57

Table 18. Incidence rate ratios and rankings for any bleed - random effect model

IRR for all comparisons (RE model)						Prob of being best (%)	SUCRA (%)	Prob of AVA being better than comp (%)
	vs. PLC	vs. AVA	vs. ELT	vs. ROM	vs. FOS			
PLC	PLC	2.97 [0.08, 111.50]	1.14 [0.03, 45.23]	1.11 [0.01, 95.54]	2.02 [0.02, 166.10]	2	30	86
AVA	0.34 [0.01, 12.94]	AVA	0.39 [0.01, 17.10]	0.38 [0.00, 119.11]	0.68 [0.00, 218.20]	51	78	-
ELT	0.88 [0.02, 34.56]	2.60 [0.06, 106.90]	ELT	0.98 [0.00, 309.63]	1.76 [0.01, 549.13]	7	39	83
ROM	0.90 [0.01, 80.68]	2.65 [0.01, 816.65]	1.02 [0.00, 358.80]	ROM	1.80 [0.00, 986.43]	12	39	78
FOS	0.50 [0.01, 43.39]	1.48 [0.00, 493.60]	0.57 [0.00, 198.90]	0.56 [0.00, 308.60]	FOS	28	63	64

Table 19 Incidence rate ratios and rankings for bleeding events WHO grade 2-4 - random effect model

	IRR for all comparisons (RE model)					Prob of being best (%)	SUCRA (%)	Prob of AVA being better than comp (%)
	vs. PLC	vs. AVA	vs. ELT	vs. ROM	vs. FOS			
PLC	PLC	1.43 [0.01, 41.58]	1.31 [0.02, 29.68]	2.39 [0.13, 46.10]	2.61 [0.04, 175.70]	2%	28%	60%
AVA	0.70 [0.02, 82.04]	AVA	0.87 [0.03, 45.24]	1.69 [0.02, 517.82]	1.79 [0.01, 1290.10]	20%	47%	-
ELT	0.76 [0.03, 40.77]	1.15 [0.02, 30.34]	ELT	1.85 [0.03, 292.21]	2.03 [0.01, 754.01]	8%	41%	55%
ROM	0.42 [0.02, 7.96]	0.59 [0.00, 44.22]	0.54 [0.00, 34.27]	ROM	1.10 [0.01, 181.00]	31%	66%	37%
FOS	0.38 [0.01, 24.88]	0.56 [0.00, 88.26]	0.49 [0.00, 77.15]	0.91 [0.01, 152.10]	FOS	39%	67%	36%

Figure 2. Forest plot for the IRR for comparison of avatrombopag vs. comparators for any AE – random effect model

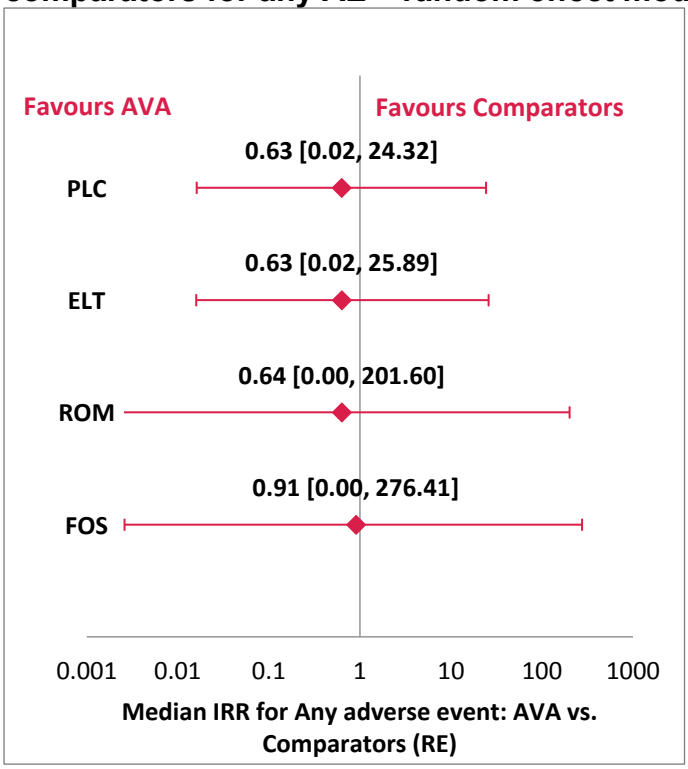


Table 20. Incidence rate ratios and rankings for proportion of patients with any adverse event - random effect model

	IRR for all comparisons (RE model)					Prob of being best (%)	SUCRA (%)	Prob of AVA being better than comp (%)
	vs. PLC	vs. AVA	vs. ELT	vs. ROM	vs. FOS			
PLC	PLC	1.58 [0.04, 62.45]	1.00 [0.03, 40.13]	1.00 [0.01, 85.99]	1.44 [0.02, 128.10]	3%	39%	74%
AVA	0.63 [0.02, 24.32]	AVA	0.63 [0.02, 25.89]	0.64 [0.00, 201.60]	0.91 [0.00, 276.41]	36%	67%	-
ELT	1.00 [0.02, 38.56]	1.58 [0.04, 62.51]	ELT	1.01 [0.00, 317.70]	1.44 [0.00, 445.41]	10%	40%	73%
ROM	1.00 [0.01, 89.15]	1.58 [0.00, 492.92]	0.99 [0.00, 333.30]	ROM	1.44 [0.00, 807.75]	17%	42%	68%
FOS	0.70 [0.01, 61.88]	1.10 [0.00, 373.70]	0.70 [0.00, 235.61]	0.70 [0.00, 436.40]	FOS	34%	62%	54%

A14. Please discuss the extent to which the studies included in the NMAs are generalisable to:

a) the anticipated licensed population;

b) the patient population in UK clinical practice.

As already presented in the core submission document (B.2.9.2.2 Criteria for inclusion in NMA) the criteria for the inclusion of the clinical evidence in the NMA were adequately restricted in order to best reflect the patient population in UK. This restriction was highly justified with different pharmacokinetic profiles of eltrombopag when administered in Asian and Caucasian patients. It was observed that the area under curve was 49% higher among participants of Asian origin compared with their Caucasian counterparts. Therefore, it was recommended that eltrombopag in Asian patients should be initiated from 50% lower daily dose than in Caucasians (25 mg versus 50 mg). Bearing in mind this important racial heterogeneity we decided to implement the following restrictions of the inclusion criteria regarding:

- **Population:**
  - Studies conducted exclusively on Asian patients were excluded in order to minimise the potential bias caused by ethnic differences. This approach is justified

in the light of the differences in recommended posology of ELT between patients with Asian and non-Asian ethnicity.

- **Dose regimens relevant for European population**
  - Studies assessing dose regimens approved by the EMA will only be included. Studies or study arms assessing treatment schemes dedicated for other ethnicities will be excluded. The relevant treatment regimens include:
    - AVA: initial dose of 20 mg once daily
    - ELT: initial dose of 50 mg once daily
    - ROM: initial dose of 1 µg/kg

Therefore, the included clinical trials were adequately representative of the UK population.

A15. Priority. Table 19 of Appendix D provides summary details of the RCTs included in the NMA.

a) Please provide a corresponding table for the (i) seven trials that did not meet the NMA's inclusion criteria, and the (ii) rituximab trials.

Please see Table 21 and

Table 22 below.

Table 21. Studies excluded from the NMA

Study (ID)/ Protocol	Design	Intervention vs. Comparison	Dose Regimens	No of patients	Follow-up (weeks)	Primary outcome	Duration of ITP	Reason for exclusion
Eltrombopag trials excluded from the NMA								
(1)(NCT00540423)	MC, RCT, DB, Japan	ELT vs. PLC	12.5 mg QD for 6 wk	15 vs. 8	DB phase: 6 OL phase: 19	Nb of responders at wk 6	≥6 M	Inadequate population and dose regimen
(2) (NCT01762761)	MC, RCT, DB, China	ELT vs. PLC	25 mg QD	104 vs. 50	32 (8 stage 1 + 26 stage 2)	Nb of pts achieving a PC≥50×10^9/L after the first 6 wk of stage 1	≥12 M	Inadequate population and dose regimen
(3)	SC, RCT, DB, China	ELT vs. PLC	25 mg QD	17 vs. 18	6	Proportion of pts with PC of ≥30×10^9/L in first 2 wk, with PC of ≥30×10^9/L and ≥50×10^9/L in 6 W	NP	Inadequate population and dose regimen
(4) (TRA100773A; NCT00102739)	Phase 2, MC, RCT, DB	ELT vs. PLC	30, 50, 75 mg QD for 6 W	88 (30,30,28) vs. 29	6	PC ≥50×10^9/L on day 43 of the study	≥6 M	Treatment duration
(5) (TRA100773B; NCT00102739)	Phase 3, MC, RCT, DB	ELT vs. PLC	50 mg QD	76 vs. 38	6	proportion of pts with PC ≥50×10^9/L after 6 wk of treatment	≥6 M	Treatment duration
Romiplostim trials excluded due to <u>inadequate dose regimen</u>								
(6) (NCT00415532)	Phase 3b, MC, RCT, open-label	ROM vs. SoC	3µg/kg	157 vs. 77	78 (52 ntervention + 26 follow-up)	Nb of pts during 52-wk treatment period with: 1) splenectomy, 2) treatment failure	NA	Dose, 36% pts had persistent ITP
(7) (NCT00603642)	Phase 3, RCT, DB, Japan	ROM vs. PLC	3µg/kg	22 vs. 12	12	Weeks with weekly platelet response	≥6 M	Dose

Table 22. Rituximab trials

Study (ID)/ Protocol	Design	Intervention vs. Comparison	Dose Regimens	N of patients	Length of Follow-up	Primary outcome	Duration of ITP
(8) (NCT00372892)	RCT, 7 centres in Canada	RTX vs. PLC	375 mg/m^2	32 vs. 26	28 wk (8 + 20)	Treatment failure, defined as the composite of (1) any platelet count below 50 × 109/L; (2) significant bleeding, defined as grade 2 severity from any anatomical site as per the ITP bleeding scale11 that defines bleed grades (0, none; 1, mild; or 2, marked) by objective criteria of 9, based on events that occurred since the last study visit; or (3) rescue treatment administered because of severe thrombocytopenia, bleeding, or a planned invasive procedure	Median 1 year (IQR, 0-3.5, with 28 new diagnosed pts)
(9) (NCT00344149)	RCT,14 centres in Norway, Tunisia, and France	RTX vs. PLC	375 mg/m^2	55 vs. 54	78W	Rate of treatment failure within 78 weeks—a composite of splenectomy or meeting criteria for splenectomy after week 12 if splenectomy was not done	Median (IQR): 37 (8-288) vs 50 (14-211) W RTX vs PLC (with 30 new diagnosed pts)

b) For all trials (included and excluded trials from the NMA), please provide a detailed table reporting all (unadjusted and adjusted for discontinuation, where applicable) data for all outcomes at different time points (follow-up of assessment) and for different dose regimens used in the trials.

The requested information is provided in the excel file below. **Please note this information is considered AIC**

Sent as separate attachment.

c) Please provide adequate justification for the exclusion of trials from the NMA.

Consistent with the eligibility criteria for NMA, described in Section B.2.9.2.2 Criteria for inclusion in NMA of the core submission, 7 RCTs were excluded from the NMA:

- **5 RCTs** comparing ELT vs. PLC
- **2 RCTs** comparing ROM vs. PLC

Brief characteristics and reasons for exclusion are provided below.

5 RCTs comparing ELT vs. PLC were excluded from the NMA:

- **Tomiyama 2012** was a multicentre, double-blind trial conducted on 28 Japanese patients allocated to ELT and PLC in 2:1 ratio for 6 weeks. The treatment assignment was unblinded at week 7 and all patients who completed the double-blind phase were enrolled in the open-label phase, in which patients either continued to receive eltrombopag (eltrombopag arm) for an additional 19 weeks or switched to eltrombopag (placebo arm) with initial dose of 12.5 mg and continued to receive eltrombopag once daily for a total of 26 weeks. Therefore, this study was excluded from the analysis due to:
    - Inadequate population: Japanese patients only
    - Inadequate dose regimen: initial dose of ELT of 12.5mg per day instead if 50mg per day
    - Inadequate duration of treatment: parallel phase lasted 6 weeks, then patients from the PLC group started receiving ELT
- **Yang 2012** was a multicentre, double-blind trial conducted on 155 Chinese patients allocated to ELT and PLC in 2:1 ratio for 8 weeks (stage 1) followed by additional 24 weeks of open-label study (stage 2), during which all patients received ELT. The initial dose of ELT was 25 mg and could be adjusted to max 75 mg based on platelet response. Therefore, this study was excluded from the analysis due to:
    - Inadequate population: Chinese patients only

    - Inadequate dose regimen: Initial dose of ELT of 25 mg per day instead of 50 mg per day
    - Inadequate duration of treatment: Parallel phase lasted 8 weeks, then patients from the PLC group started receiving ELT
- **Huang 2018** was a randomised, single-centre, 6 weeks, placebo-controlled trial. A total of 18 patients were assigned to receive placebo. The initial dose of ELT was 25 mg and could be adjusted to max 75 mg based on platelet response. Therefore, this study was excluded from the analysis due to:
    - Inadequate population: Chinese patients only
    - Inadequate dose regimen: Initial dose of ELT of 25 mg per day instead of 50 mg per day
    - Inadequate duration of treatment: Comparison based on 6 weeks
- **Bussel 2017** was a randomised, multicentre, double-blind, placebo-controlled dose-ranging study. A total number of 118 patients were randomised in 1:1:1:1 ratio to ELT initiated at 30, 50, 70 mg daily or PLC for up to 6 weeks. The primary outcome was assessed at 43rd day of the study. Therefore, this study was excluded from the analysis due to:
    - Inadequate dose regimen: Refers to arms with the initial ELT dose of 25 mg and 70 mg per day
    - Inadequate duration of treatment: Comparison based on 6 weeks only
- **Bussel 2017** was a randomised, multicentre, double-blind study, placebo-controlled study. A total number of 114 patients were randomised in 2:1 ratio to ELT initiated at 50 mg daily or PLC for up to 6 weeks. The primary outcome was assessed at 43rd day of the study. Therefore, this study was excluded from the analysis due to:
    - Inadequate duration of treatment: Comparison based on 6 weeks.

2 RCTs comparing ROM vs. PLC were excluded from the NMA:

- **Kuter 2010** was a randomised, multicentre, open-label, in which 234 patients without splenectomy were randomised in 2:1 ratio to ROM initiated at 3 µg daily or the medical standard of care. The initial dose of ROM could be adjusted to max 10 µg based on platelet response. The total duration of the study was 52 weeks. Therefore, this study was excluded from the analysis due to:
    - Inadequate dose regimen: Initial dose of ROM of 3 µg daily instead of 1 µg daily per day

- **Shirasugi 2011** was a randomised, double-blind study, placebo-controlled study. A total number of 34 Japanese patients were randomised in 2:1 ratio to ROM initiated at 3 µg daily or PLC for 12 weeks. Therefore, this study was excluded from the analysis due to:
    - Inadequate population: Japanese patients only
    - Inadequate dose regimen: ROM of 3 µg daily instead of 1 µg daily per day
    - Inadequate duration of treatment: Comparison based on 12 weeks

Full text PDFs of these publications will be provided.

A16. Priority. Please conduct separate NMAs for all outcomes and report the corresponding results of both fixed and random effects models for the following:

a) Inclusion of the two excluded studies of avatrombopag: Study CL003 (20mg and placebo arms) and Study 305 (which was excluded from efficacy outcomes);

b) Inclusion of the seven excluded trials that did not meet the NMA's inclusion criteria (Tomiyama 2012, Yang 2017, Huang 2018, Bussel 2007, Bussel 2009, Kuter 2010, and Shirasugi 2011). [Note Kuter 2010 should be included with standard of care as a separate intervention in the NMA.]

c) Inclusion of the rituximab trials;

d) Inclusion of all ten excluded trials (i.e., Study CL003, Study 305, the seven excluded trials that did not meet the NMA's inclusion criteria, and rituximab trials).

e) For trials with outcomes reported at different time points (follow-up of assessment) and different dose regimens used in the trials, results of separate NMA should be reported or meta-regression used to report results by time point or dose regimen.

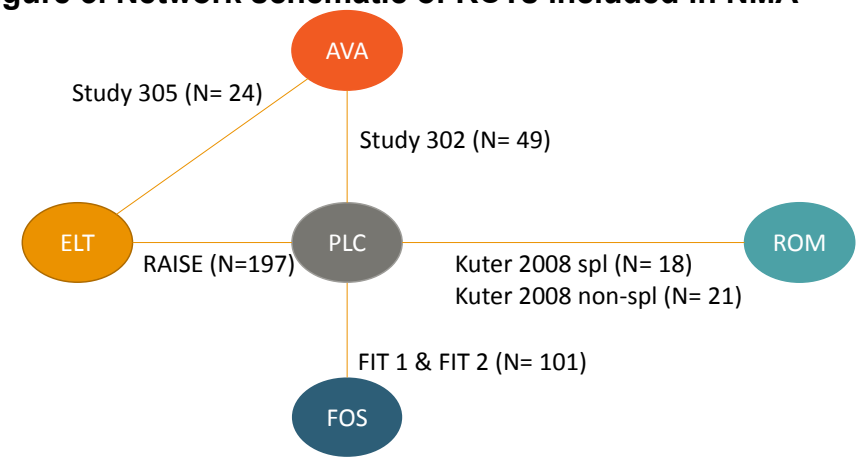
Following discussion with the ERG/NICE, we are unable to provide the requested analyses within the requested timeframe. Instead, it was agreed that we would provide further information and references for all studies that were identified from the SLR but were excluded from the NMA.

A17. The company submission states that fostamatinib was included in the NMAs *"because it broadens the NMA network, which may enhance robustness"*. Please justify the inclusion of the fostamatinib studies in the NMAs, explain how they enhance robustness, and discuss the implications of including these studies on each of the outcomes.

Two RCTs assessing FOS versus PLC were included in the analysis (FIT 1 & FIT 2). The characteristics of these RCTs was presented in Section B.2.9.3 Studies included in the NMA. As presented in the network below (Figure 3), FOS did not form a closed loop within the network of evidence, therefore the inclusion of FIT 1 and FIT 2 trials did not impact the estimates for relative safety and efficacy between other regimens in the network.

However, since FIT 1 & FIT 2 trials assessed the same pairwise comparison, the inclusion of these studies could improve the estimation of the between-trial heterogeneity for random-effects models.

Figure 3. Network schematic of RCTs included in NMA



A18. Priority. Table 22 discusses the impact of premature discontinuation on study outcomes.

a) Please comment on the extent of imbalanced discontinuation in all studies included in the NMAs.

There was a noticeable between-trial heterogeneity in the proportion of patients prematurely discontinuing their allocated treatment in all studies (Figure 4). In the pivotal Study 302 trial, 94% of patients discontinued prematurely from the PLC arm, predominantly due to inadequate therapeutic effect, while 31% of patients dropped out from the avatrombopag arm at the same time due to adverse events (9%) and inadequate therapeutic effect (22%). This discrepancy between proportions of patients discontinuing due to insufficient efficacy from avatrombopag and placebo groups clearly suggest higher efficacy of avatrombopag over placebo. However, at the same time, the higher rate of early drop-outs in placebo groups reduced the total

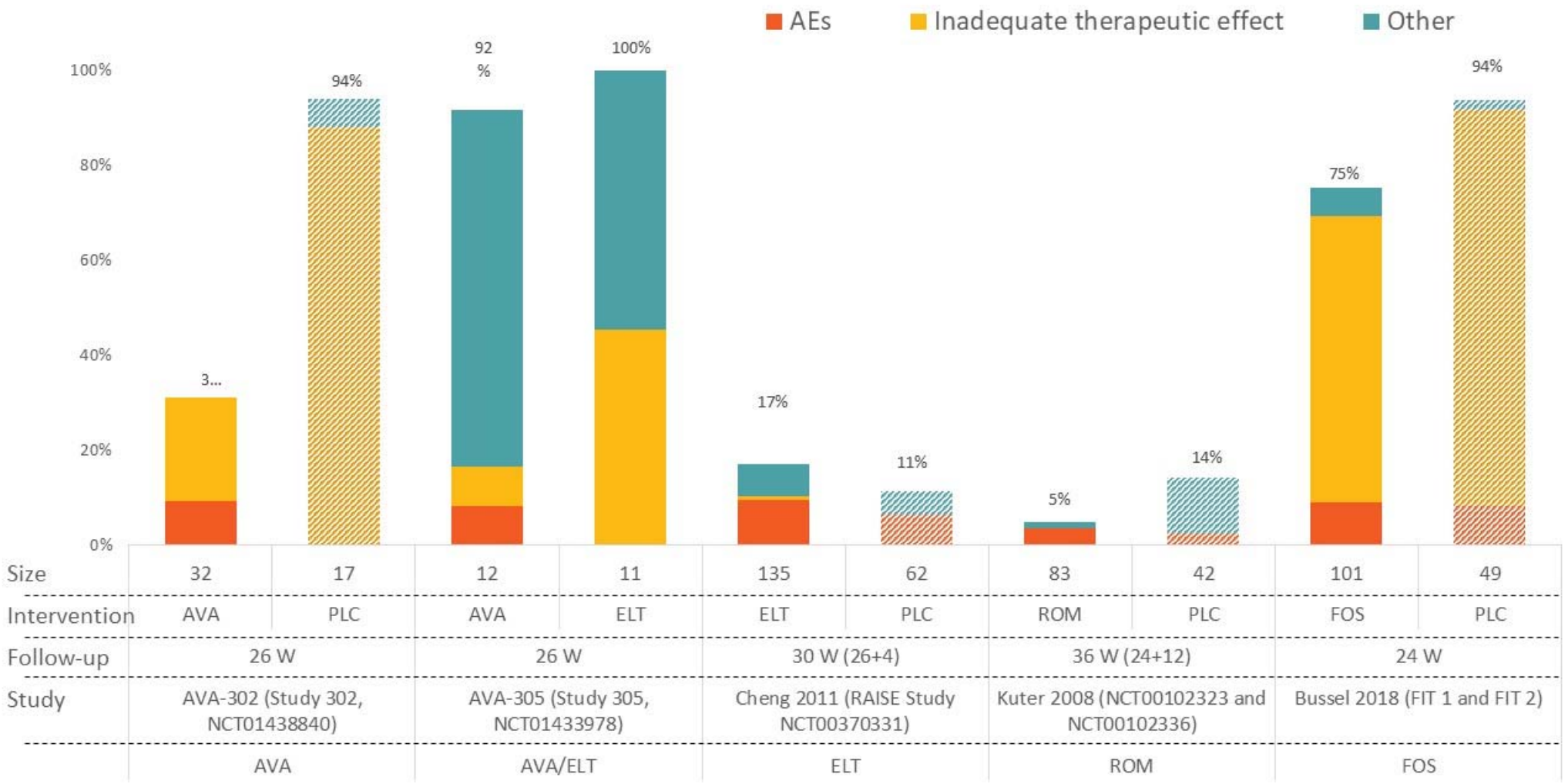
exposure time in this group and lead to severe underestimation of the proportion of patients with events in the placebo group. This is because events such as rescue medication or bleeding events were not counted after treatment discontinuation. According to the protocol patients could be discontinued from Study 302 if the investigator considered platelet counts to be dangerously low after 7 days of treatment at the maximum dose, if patients required rescue therapy more than 3 times, or if they required continuous rescue therapy for more than 3 weeks. Extensive discontinuation was also observed in both FIT 1&2 trials, in which 94% and 75% of patients prematurely discontinued from the placebo and fostamatinib groups, respectively. The main reason for discontinuation from active and placebo arms was lack of response at 12 weeks (60% and 84%, respectively), (with response defined as a platelet count ≥50 000/μL) within the first 12 weeks without rescue medication in the preceding 4 weeks. (Figure 4).

On the contrary, much lower rates of premature discontinuation was observed in studies comparing eltrombopag (RAISE) and romiplostim (Kuter 2008) versus PLC. Overall, 11% and 14% of patients discontinued from the placebo groups of the RAISE and both studies reported by Kuter 2008, respectively. In contrary to Study 302 and FIT 1&2 trials the main reasons for exclusion from studies assessing eltrombopag and romiplostim were from “other” category, none efficacy-related (Figure 4).

Noticeably lower discontinuation rates observed in studies assessing eltrombopag or romiplostim (RAISE, Kuter 2008) could be likely explained by the fact that these agents were the first thrombopoietin receptor agonists (TPO-RA) tested in this indication. At the time when these trials were conducted, there was no effective treatment alternative, therefore the placebo arms of RAISE and Kuter 2008 trials were representative of best available comparators at that time. Based on the findings from these trials, in 2008 eltrombopag and romiplostim received market authorisation for the treatment of patients with chronic ITP.

Study 302 and FIT trials were initiated in 2011 and 2014, respectively (10) . Therefore, the assessment of avatrombopag and fostamatinib were being carried out in the presence of approved alternative ITP therapies. Due to this reason non-responders from both Study 302 and FIT trials could not be maintained in the experimental studies, in particular in placebo groups, due to ethical considerations. These different circumstances in which the trials were being conducted explains the higher proportion of patients discontinuing from Study 302, Study 305 and FIT 1&2 compared with RAISE and Kuter 2008.

Figure 4. Baseline characteristic of included RTCs – proportion of patients who discontinued study



b) Please clarify whether the adjustment for premature discontinuation was applied only to Study 302, or applied to other studies included in the NMAs. If applied to other studies, please provide details of the studies and reasons for adjustment. Please clarify which NMAs were affected by the adjustment.

Premature, imbalanced discontinuation significantly affected the total exposure time in the included studies and therefore could interact with the results for relative efficacy and safety. For example, the mean reported duration of exposure with Study 302 trial was approximately 2.6-fold longer than that in PLC group (22.78 weeks versus 8.93 weeks in the avatrombopag and placebo groups, respectively). This large disproportion in the effective treatment duration very likely influenced the results by decreasing the chance of events to occur in the PLC group. It is therefore highly likely that placebo groups in Study 302 and FIT 1&2 trials were favoured, since considerable drop-out reduced the exposure time and therefore the probability of events such as need for rescue treatment, bleeding events or adverse events to occur. Thus, observed percentages of patients with such outcomes may underestimate the true risk of events in the PLC groups.

Due to this reason, we adopted a method that allowed adjustment for early and imbalanced discontinuation, which was in principle based on the comparison of event rates rather than comparison of crude proportions. For consistency, this approach was applied in all studies included in the NMA, regardless of the extent of imbalance discontinuation.

As already described in the Section *B.2.9.3.3 Adjustment for premature discontinuation,* not all outcomes are equally affected by the early and imbalanced discontinuation. Therefore, the adjustment was applied for highly impacted outcomes (as already presented in Table 22 of the core submission), namely:

- Need for rescue treatment
- Bleeding events
- Safety outcomes

Therefore, 'durable platelet response' and 'reduction in the use of concomitant ITP medications' were assessed using traditional principles based on comparison of proportions of responders.

c) **Please provide details about the adjustment applied. In particular, please provide a step-by-step description of the calculations applied in the adjustment to Study 302 (or any other study) and discuss the implications of the adjustment on study outcomes.**

The method for the estimation of event rates was briefly presented in Section B.2.9.3.3 Adjustment for premature discontinuation. This consisted of the following steps:

1. **Estimation of the mean treatment exposure** accounting for early discontinuation. The time on treatment in all arms of the respective studies was estimated assuming an exponential survival curve for time to discontinuation:

$$\boldsymbol{c(t) = e^{-\lambda t}}$$

Where,

$\boldsymbol{c(t)}$ – proportion of patients, who remained on treatment

$\boldsymbol{\lambda}$ - rate of discontinuation

$\boldsymbol{t}$ – time

The mean exposure was estimated by calculating the surface below the survival curve for time to discontinuation:

$$\text{mean exposure time} = \int_0^{observation\ time} c(t)dt = -\frac{1}{\lambda}\left(e^{\left(\frac{observation\ time}{\lambda}\right)} - 1\right)$$

Mean exposure times were reported for each arms of Study 302 and Study 305 trials. The reported values were highly consistent with estimated ones. We therefore used reported data for the adjusted analysis.

2. **Estimation of incidence rate**

   Event rates were estimated as ratio of the number of patients with event and

the mean exposure time. This method requires the assumption that each patient could experience only one event.

Below please find an excel file providing step-by-step description of all calculations conducted for the adjusted analyses. **Please note this information contains AIC**

Sent as separate attachment.

d) For NMAs that included studies with an adjustment, please provide unadjusted data before the adjustment was made (i.e., data with follow-up of around 8-9 weeks) for all studies (included and excluded, as listed above). Please provide the corresponding NMA results using the unadjusted data.

Any bleeding

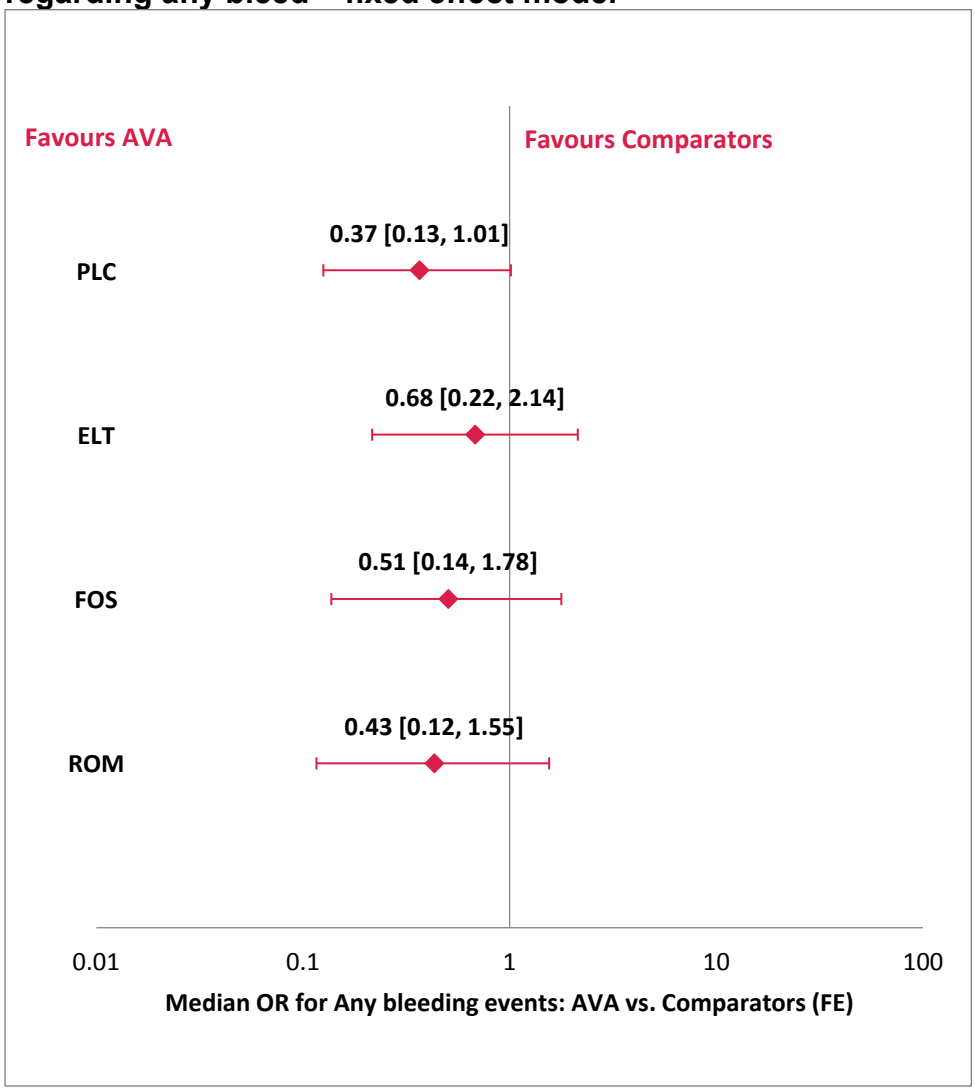
Table 23. Summary of the data for the NMA for the proportion of patients with any bleed

Characteristic		Value
Number of studies		6
Number of treatment regimens		5
Number of patients		545
DIC	Fixed-effects model	**61.02**
	Random-effects model	59.77
$\bar{D}_{res}$	Fixed-effects model	51.95
	Random-effects model	49.76

Table 24. Input data for the NMA of proportion of patients with any bleed

Study	Treatment	Event rate n/N (%)
Study 302	AVA	14/32 (43.8%)
	PLC	9/17 (52.9%)
Study 305	AVA	6/13 (46.2%)
	ELT	9/11 (81.8%)
RAISE	ELT	106/135 (78.5%)
	PLC	56/62 (90.3%)
Kuter 2008 (spl&non-spl)	ROM	48/84 (57%)
	PLC	25/41 (61%)
FIT 1 & FIT 2	FOS	28/101 (27.7%)
	PLC	17/49 (34.7%)

Figure 5. Forest plot for odds ratio for comparison AVA vs comparators regarding any bleed – fixed effect model



Median OR for proportion of patients with any bleed: AVA vs. comparators (FE)

Table 25. Odds ratios and rankings for proportion of patients with any bleed – fixed effect model

	OR for all comparisons (FE model)					Probability of being best	SUCRA	Probability AVA better than comparator
	vs. PLC	vs. AVA	vs. ELT	vs. FOS	vs. ROM			
PLC	PLC	2.73 [0.99, 7.98]	1.85 [0.85, 4.31]	1.38 [0.66, 2.89]	1.18 [0.55, 2.57]	0%	15%	97%
AVA	0.37 [0.13, 1.01]	AVA	0.68 [0.22, 2.14]	0.51 [0.14, 1.78]	0.43 [0.12, 1.55]	67%	87%	-
ELT	0.54 [0.23, 1.17]	1.47 [0.47, 4.62]	ELT	0.74 [0.24, 2.18]	0.63 [0.20, 1.91]	20%	67%	75%
FOS	0.72 [0.35, 1.52]	1.98 [0.56, 7.29]	1.35 [0.46, 4.11]	FOS	0.86 [0.30, 2.50]	8%	46%	85%

ROM	0.85 [0.39, 1.82]	2.31 [0.64, 8.62]	1.58 [0.52, 4.90]	1.17 [0.40, 3.38]	ROM	5%	34%	90%

SUCRA - surface under the cumulative ranking curve; Significant results were reported in bold

Table 26. Odds ratios and rankings for proportion of patients with any bleed – random effect model

	OR for all comparisons (RE model)					Probability of being best	SUCRA	Probability AVA better than comparator
	vs. PLC	vs. AVA	vs. ELT	vs. FOS	vs. ROM			
PLC	PLC	2.96 [0.31, 31.08]	1.47 [0.14, 12.08]	1.38 [0.10, 18.88]	1.18 [0.08, 16.50]	2%	32%	86%
AVA	0.34 [0.03, 3.21]	AVA	0.49 [0.04, 4.57]	0.47 [0.01, 14.64]	0.40 [0.01, 12.48]	50%	77%	-
ELT	0.68 [0.08, 7.38]	2.02 [0.22, 27.16]	ELT	0.93 [0.03, 33.20]	0.79 [0.03, 29.45]	13%	50%	76%
FOS	0.72 [0.05, 9.88]	2.15 [0.07, 73.60]	1.08 [0.03, 30.13]	FOS	0.86 [0.02, 34.57]	19%	49%	71%
ROM	0.85 [0.06, 12.14]	2.50 [0.08, 90.95]	1.26 [0.03, 35.32]	1.17 [0.03, 49.58]	ROM	16%	43%	75%

SUCRA - surface under the cumulative ranking curve; Significant results were reported in bold

Bleeding events WHO grade 2-4

Table 27. Summary of the data for the NMA for the proportion of patients with WHO grade 2-4 bleed

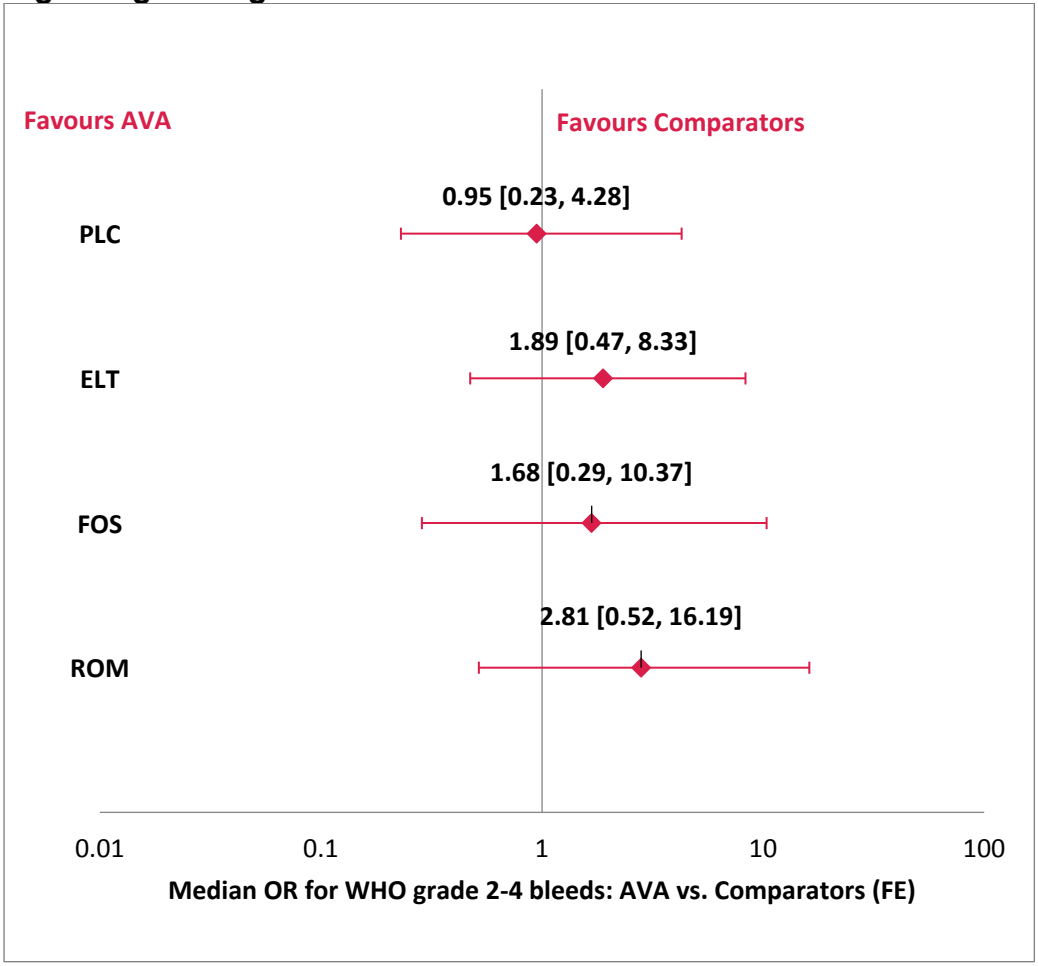
Characteristic		Value
Number of studies		6
Number of treatment regimens		5
Number of patients		545
DIC	Fixed-effects model	**64.89**
	Random-effects model	64.84
$\bar{D}_{res}$	Fixed-effects model	54.84
	Random-effects model	53.63

Table 28. Input data for the NMA of proportion of patients with WHO grade 2-4 bleed

Study	Treatment	Event rate n/N (%)
Study 302	AVA	3/32 (9.4%)
	PLC	0/17 (0.0%)
Study 305	AVA	4/13 (30.8%)
	ELT	4/11 (36.4%)
RAISE	ELT	44/135 (32.6%)
	PLC	32/62 (51.6%)
Kuter 2008 spl	ROM	9/42 (21.4%)
	PLC	8/21 (38.1%)
Kuter 2008 non-spl	ROM	4/42 (9.5%)
	PLC	6/20 (30.0%)

FIT 1 & FIT 2	FOS	10/101 (9.9%)
	PLC	8/49 (16.3%)

Figure 6. Forest plot for odds ratio for comparison AVA vs comparators regarding WHO grade 2-4 bleeds – fixed effect model



Median OR for proportion of patients with any bleed: AVA vs. comparators (FE)

Table 29. Odds ratios and rankings for proportion of patients with WHO grade 2-4 bleed – fixed effect model

	OR for all comparisons (FE model)					Probability of being best	SUCRA	Probability AVA better than comparator
	vs. PLC	vs. AVA	vs. ELT	vs. FOS	vs. ROM			
PLC	PLC	1.06 [0.23, 4.36]	1.99 [1.09, 3.65]	1.77 [0.62, 4.89]	2.95 [1.20, 7.40]	0%	16%	53%
AVA	0.95 [0.23, 4.28]	AVA	1.89 [0.47, 8.33]	1.68 [0.29, 10.37]	2.81 [0.52, 16.19]	7%	28%	-
ELT	0.50 [0.27, 0.92]	0.53 [0.12, 2.12]	ELT	0.89 [0.27, 2.88]	1.48 [0.50, 4.43]	15%	66%	19%

FOS	0.56 [0.20, 1.61]	0.60 [0.10, 3.50]	1.13 [0.35, 3.77]	FOS	1.67 [0.43, 6.63]	17%	56%	28%
ROM	0.34 [0.14, 0.83]	0.36 [0.06, 1.93]	0.68 [0.23, 2.00]	0.60 [0.15, 2.33]	ROM	61%	85%	12%

Table 30. Odds ratios and rankings for proportion of patients with WHO grade 2-4 bleed – random effect model

	OR for all comparisons (RE model)					Probability of being best	SUCRA	Probability AVA better than comparator
	vs. PLC	vs. AVA	vs. ELT	vs. FOS	vs. ROM			
PLC	PLC	0.76 [0.04, 6.59]	1.53 [0.13, 8.75]	1.76 [0.15, 20.50]	2.97 [0.49, 19.14]	1%	32%	60%
AVA	1.32 [0.15, 25.87]	AVA	1.94 [0.20, 22.25]	2.28 [0.10, 122.50]	3.96 [0.25, 138.90]	6%	27%	-
ELT	0.65 [0.11, 7.76]	0.52 [0.04, 5.00]	ELT	1.16 [0.06, 42.46]	1.99 [0.18, 45.60]	14%	53%	74%
FOS	0.57 [0.05, 6.82]	0.44 [0.01, 10.42]	0.86 [0.02, 15.57]	FOS	1.68 [0.08, 37.56]	26%	58%	72%
ROM	0.34 [0.05, 2.04]	0.25 [0.01, 3.97]	0.50 [0.02, 5.65]	0.59 [0.03, 12.50]	ROM	53%	80%	85%

Rescue treatment

Table 31. Summary of the data for the NMA for the proportion of patients with any bleed

Characteristic		Value
Number of studies		6
Number of treatment regimens		5
Number of patients		521
DIC	Fixed-effects model	**58.22**
	Random-effects model	58.77
$\bar{D}_{res}$	Fixed-effects model	49.15
	Random-effects model	49.08

Table 32. Input data for the NMA of proportion of patients with a need for rescue treatment

Study	Treatment	Event rate n/N (%)
Study 302	AVA	7/32 (21.9%)
	PLC	2/17 (11.8%)
RAISE	ELT	24/135 (17.8%)
	PLC	25/62 (40.3%)

Kuter 2008 spl	ROM	11/42 (26.2%)
	PLC	12/21 (57.1%)
Kuter 2008 non-spl	ROM	7/41 (17.1%)
	PLC	13/21 (61.9%)
FIT 1 & FIT 2	FOS	27/101 (26.7%)
	PLC	22/49 (44.9%)

Figure 7. Forest plot for odds ratio for comparison AVA vs comparators regarding the need for rescue treatment – fixed effect model

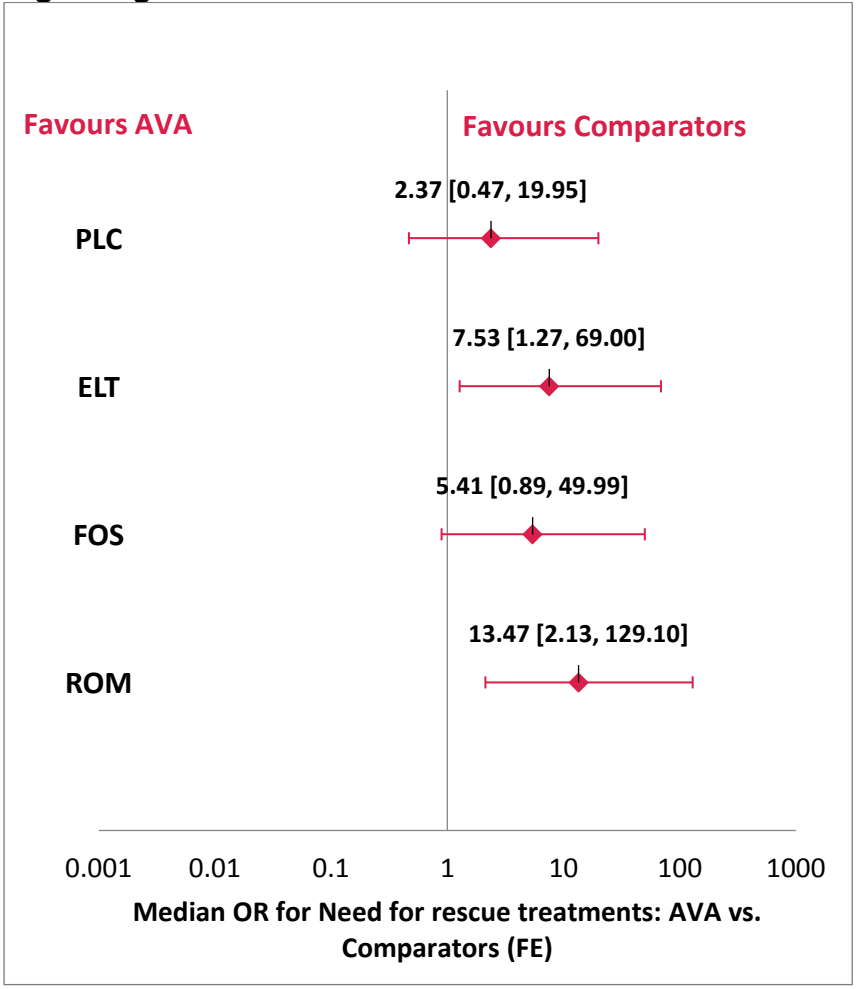


Table 33. Odds ratios and rankings for proportion of patients with need for rescue treatment – fixed effect model

OR for all comparisons (FE model)						Probability of being best	SUCRA	Probability AVA better than comparator
	vs. PLC	vs. AVA	vs. ELT	vs. FOS	vs. ROM			
PLC	PLC	0.42 [0.05, 2.15]	3.15 [1.59, 6.22]	2.25 [1.09, 4.66]	5.57 [2.48, 13.01]	0%	21%	16%
AVA	2.37 [0.47, 19.95]	AVA	7.53 [1.27, 69.00]	5.41 [0.89, 49.99]	13.47 [2.13, 129.10]	0%	5%	-

ELT	0.32 [0.16, 0.63]	0.13 [0.01, 0.79]	ELT	0.72 [0.26, 1.93]	1.78 [0.61, 5.24]	13%	72%	1%
FOS	0.44 [0.21, 0.92]	0.18 [0.02, 1.12]	1.40 [0.52, 3.79]	FOS	2.49 [0.83, 7.47]	3%	56%	3%
ROM	0.18 [0.08, 0.40]	0.07 [0.01, 0.47]	0.56 [0.19, 1.63]	0.40 [0.13, 1.20]	ROM	83%	95%	0%

SUCRA - surface under the cumulative ranking curve

Table 34. Odds ratios and rankings for proportion of patients with need for rescue treatment – random effect model

OR for all comparisons (RE model)						**Probability of being best**	**SUCRA**	**Probability AVA better than comparator**
	vs. PLC	vs. AVA	vs. ELT	vs. FOS	vs. ROM			
PLC	PLC	0.43 [0.03, 6.01]	3.12 [0.32, 29.30]	2.23 [0.23, 21.51]	5.64 [1.02, 31.22]	0%	27%	24%
AVA	2.31 [0.17, 39.85]	AVA	7.28 [0.22, 259.30]	5.22 [0.16, 184.70]	13.25 [0.57, 362.30]	2%	13%	-
ELT	0.32 [0.03, 3.12]	0.14 [0.00, 4.56]	ELT	0.71 [0.03, 17.93]	1.82 [0.11, 31.69]	23%	68%	10%
FOS	0.45 [0.05, 4.40]	0.19 [0.01, 6.27]	1.40 [0.06, 33.31]	FOS	2.54 [0.15, 43.57]	13%	56%	14%
ROM	0.18 [0.03, 0.98]	0.08 [0.00, 1.77]	0.55 [0.03, 9.20]	0.39 [0.02, 6.86]	ROM	62%	86%	5%

SUCRA - surface under the cumulative ranking curve

Unadjusted data analyses for rescue treatments yield unfavourable results for avatrombopag. This result is most likely biased by the premature drop-out of 94% patients from the placebo group, mostly due to insufficient efficacy. This phenomenon lead to severe underestimation of the proportion of patients with events in the placebo group, since those who dropped-out early could not receive rescue medication within Study 302. As a consequence, the estimate for the relative efficacy was biased towards superiority of placebo. Indeed, there was no statistically significant difference in the use of rescue therapies between the avatrombopag-treated patients (21.9%) and placebo-treated (11.8%) patients (P = 0.4668 using Fisher's exact test). There was a 2.6 fold shorter period of exposure to avatrombopag in placebo-treated individuals due to a high rate of early discontinuations due to lack of treatment event, suggesting that lower use of rescue therapy in the placebo treatment group is artefactual. All other endpoints including bleeding events, concomitant medication and rescue therapy usage were secondary or exploratory outcomes. The adjusted analysis

submitted in the core submission document attempts to account for this uncertainty. As noted in the core submission, the NMA results should therefore be interpreted with caution and pragmatism, which is consistent with our conclusion that avatrombopag is at least similar to other TPO-RAs across a range of endpoints, with some numerical trends in favour of avatrombopag.

Section B: Clarification on cost-effectiveness data

Population

B1. The cost-effectiveness model is based on the patient baseline characteristics of Study 302, which did not include any UK patients. Please justify the selection of this trial to inform the baseline patient characteristics in the model over the wider set of clinical trials used in the NMA. Please discuss the comparability of patient characteristics in Study 302, the wider set of comparator clinical trials, including Study 305, with that of the UK patient population (as defined by the NICE scope).

The baseline characteristics included in the model were demographics (age and gender), patient weight and splenectomy status. Study 302 was selected as it is the most robust study in the avatrombopag clinical development programme and most closely aligned to the UK patient population in these key areas. Although Study 305 has an active comparator arm (i.e. eltrombopag), it is limited by small patient numbers and low duration of patient exposure arising from early study termination.

The most robust real-world data source on UK ITP patients is the Adult ITP Registry. A 2018 congress abstract/poster from the European Haematology Association annual meeting provides data from this registry on patient characteristics and management approaches for ITP (11). In terms of demographics, the mean age at diagnosis was 50 years and 57% of patients were female. In Study 302, the mean age at baseline was 44.6 years and 63.3% of patients were female. Although some minor discrepancies are observed, the Study 302 demographics included in the model are broadly comparable to UK practice and any differences are likely to have only a negligible impact on the model results. The proportion of patients who were splenectomised in Study 302 (32.7%) is greater than that observed in UK practice (9.83%). However, this is unlikely to bias the model results in favour of avatrombopag.

Rather, it is likely to understate the efficacy of avatrombopag as it includes a greater proportion of patients who have a more severe form of ITP and increasingly refractory to treatment.

In terms of patient weight, there is limited existing UK real-world data for the ITP population. However, a cross study comparison of trials included in the NMA suggests that the patient weight in Study 302 is similar to those observed in other studies (Table 20; p.50 of the main evidence submission). The median patient weights at baseline for available studies were 83kg (Study 302), 79kg (Study 305), 77kg (NCT00102323; romiplostim) and 78kg (NCT00102336, romiplostim).

Treatment response assessment time point

B2. Priority. Please justify the appropriateness of waiting a full 24 weeks to assess non-response to TPO-RAs in the model. Please comment on whether patients would remain on TPO-RA treatment for up to 24 weeks in UK clinical practice if no response is observed. Please discuss this in the context of the summary of product characteristics for treatment with romiplostim which advocates discontinuation after only four weeks of high-dose therapy.

The model assumption that patients initiating TPO-RA treatment remain on therapy for a period of 24 weeks to determine response/non-response has sought to take into account the following factors: use of TPO-RAs in clinical practice, inclusion of best available data on comparative effectiveness between the TPO-RAs and previously published approaches to economic modelling in ITP (12, 13).

In clinical practice, patients initiate treatment with a TPO-RA at the recommended starting dose (as per product SmPCs). If no response is observed within 2 weeks of starting treatment, dose titration will occur. For both avatrombopag and romiplostim, multiple dose titrations are permitted up to the maximum doses of 40mg daily and 10mcg/kg weekly, respectively. With eltrombopag, a dose titration from 50mg daily to 75mg daily is permitted. Once reaching the maximum dose, patients can remain on therapy for a further 4 weeks to establish response. As a result, response to treatment with a TPO-RA is usually observed within a window of around 8-12 weeks dependent on which product is used. However, this window does not consider circumstances where patients are also receiving concomitant ITP medication (such as those specified

in the model), which may lead to further dose adjustments in order to achieve a stable platelet response

Although response to treatment in clinical practice is usually determined in a shorter time window than 24 weeks, there is limited available data to model this across the TPO-RA treatments. As per section B.2.9 of the main evidence submission, the only platelet count metric which can be estimated through a network meta-analysis is durable platelet response, defined as a platelet count ≥ $50x10^9$/L in at least 6 weekly platelet counts in the final 8 weeks of a 24/26 week study. In order to include platelet response in the model, the key measure used in clinical practice estimate treatment effect, we have taken a pragmatic approach and assumed a longer timeframe to assess response to TPO-RA treatment.

The approach taken in this submission is supported by previous economic evaluations in ITP, most notably the manufacturer submission in the NICE eltrombopag appraisal (TA293) and the (13) study, which permit a longer time to response than what is commonly observed in clinical practice.

B3. Please justify the appropriateness of waiting 8 weeks to assess non-response to rituximab in the model. Please comment on whether patients would remain on rituximab treatment for up to 8 weeks in UK clinical practice if no response is observed.

As an off-label treatment, there is no formally defined dosing regimen for rituximab in adult patients with ITP. However, based on ASH guidelines and a 2019 international consensus report on the management of ITP, treatment with rituximab is most commonly administered on a weekly basis for 4 weeks with a determination of response being made 4 weeks after the final rituximab infusion (i.e., week 8) (14-16)

Sobi has also validated this assumption with clinical experts from across the UK who were able to confirm that response/non-response to rituximab would usually be established 8 weeks after starting treatment.

Comparators

B4. Priority. Please explain why rituximab is not considered a relevant comparator in the model, in light of the treatment pathway and variable use of

rituximab in UK clinical practice. Please explain how the response rates used in the model for rituximab were derived.

An earlier NICE appraisal for romiplostim positioned rituximab prior to the TPO-RA in the sequence of ITP therapies, consistent with the model presented for avatrombopag. In the romiplostim appraisal, clinical specialists considered that the positioning of the TPO-RA in clinical practice would be for patients who are refractory or poorly tolerate rituximab (NICE TA 221).

International clinical experts in the management of ITP no longer consider that rituximab is a relevant comparator to TPO-RAs including avatrombopag in the ITP treatment paradigm (discussions with two UK-based ITP experts, October 2021). There is a comparative paucity of evidence favouring use of rituximab in ITP management as compared to the TPO-RAs including avatrombopag, all of which carry a UK license for use in ITP in contrast to rituximab.

In the context of the COVID-19 pandemic, national guidance was issued favouring the use of other agents instead of rituximab for management of ITP patients where possible, given the potential for “severe infectious events” and an impaired immune response to COVID-19 vaccination with rituximab (Pavord *et al.* 2020 *Br J Haem* **189**:1038-1043). Indeed, evidence elsewhere suggests that rituximab-treated patients show impaired seroconversion rates following COVID-19 vaccination as compared to controls (Mrak *et al.* 2021 *Annals of the Rheumatic Diseases* **80**, 1345-1350; Cattaneo *et al.* 2021 *Blood Cancer Journal* **11**:151).

In a recently published prospective real-world study of 318 UK ITP patients managed during the COVID-19 pandemic, 4 patients (1.3% of the total population) received a rituximab-based ITP treatment regimen in contrast to 56 patients (17.6% of the total population) who received an TPO-RA-containing regimen, further underlying an ongoing shift away from the usage of rituximab in UK clinical practice (Pavord *et al.* 2021 *Br J Haem* - online ahead of press).

Current guidelines for ITP following diagnosis recommend initial treatment of either corticosteroid and/or immunoglobulin therapy. Owing to the risk of adverse events and reduced long-term efficacy, corticosteroid therapy is transient, and most patients

progress to receive subsequent lines of therapy (Neunert, Terrell et al. 2019, Provan, Arnold et al. 2019).

While TPO-RAs, rituximab and splenectomy are all treatment options in the refractory setting, the TPO-RAs are considered the well-established standard of care. For rituximab, its use is highly varied across treatment centres and lines of therapy. Therefore, it does not represent established clinical practice for the population under consideration in this appraisal. It would be inappropriate to include rituximab given there are TPO-RA alternatives available. Furthermore, based on clinical opinion sought by Sobi, avatrombopag will only be considered for use in the population who currently receive a TPO-RA, if approved by NICE (i.e. only eltrombopag or romiplostim will be displaced).

Finally, the response rates for rituximab were derived from STA for Romiplostim for the treatment of chronic immune or idiopathic thrombocytopenic purpura (12).

Treatment sequences

B5. Priority. Table 38 provides the proportion of active therapies used for subsequent lines of treatment in the cost-effectiveness model.

a) **Please justify the modelled proportion of active therapies at second and third line, in light of the treatment pathway and full range of treatment options in UK clinical practice, and on the average duration of treatment with TPO-RAs over the lifetime of the patient. Please identify any relevant empirical evidence.**

In the refractory setting, a range of different treatment options are considered if a patient is non-responsive to a TPO-RA treatment. This includes, switching to an alternative TPO-RA, immunosuppressive therapy (e.g. rituximab, mycophenolate), splenectomy or a range of other agents such as vinca alkaloids (i.e. vincristine and vinblastine). To reflect this heterogeneity, the model base case assumes a mixed treatment strategy rather than a fixed treatment sequence following discontinuation of TPO-RA treatment. The modelled active therapies in second and third line were based on data from independent market research commissioned by Sobi which sought to explore the treatment paradigm in ITP, including use of current therapies, drivers of

decision making and switching behaviour among physicians across the UK and Europe (18). In the UK subset, data on active therapy post TPO-RA was obtained through a series of 1-2-1 interviews (n=5) and an online survey (n=20) with consultant haematologists.

b) **Please justify why a mixed treatment strategy is considered for second and third line rather than a single alternative TPO-RA treatment strategy (or other alternative single treatments such as rituximab). Please justify this in light of the fact that the treatment response rate for subsequent lines of therapy (using a mixed treatment strategy) may be higher than the treatment response rate on first line active therapy. For example, the response rate used in the base case analysis for first line eltromobopag is 27%, while the response rates used in the same analysis for second and third line therapies are 40.3% and 36.0%, respectively. Please consider providing additional scenario analyses that consider a reduction in treatment effect in second and third lines of therapy relative to the first line of therapy.**

As discussed in our response to B5a), there are many different options of treatment available for refractory ITP patients if they are non-responsive to TPO-RA therapy. The mixed treatment strategy has sought to reflect different treatment utilization rates across each line of therapy in the model (dependent on which initial TPO-RA was selected). The estimated proportions of patients receiving various treatments at each subsequent line were obtained from market research which was conducted to inform understanding and provide data on the current treatment of ITP across Europe and the UK. This included a survey as well as structured interviews with 113 physicians across the EU, and included 20 physicians from the UK.

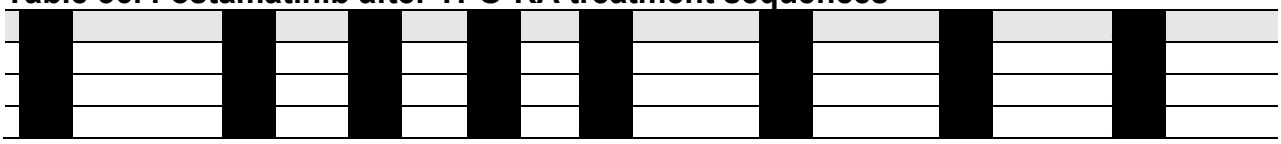
The model has the flexibility to override the mixed treatment assumption and apply a fixed treatment sequence. Although no fixed treatment sequences are presented in our evidence submission, their inclusion is unlikely to impact the base case conclusions. For example, if a sequence of ROM-RTX-'Watch and rescue' (or ELT-RTX-'Watch and rescue') is applied (as suggested in the question), the model still yields results which are consistent with the base case (i.e. avatrombopag dominant vs eltrombopag and romiplostim).

Table 35. Romiplostim-rituximab-watch and wait treatment sequence model results

Abbreviations: AVA, avatrombopag; ELT, eltrombopag; ROM, romiplostim; ICER, incremental cost-effectiveness ratio; QALYs, quality adjusted life years; LY, life years

Likewise, reduction in treatment effect in second and third lines of therapy relative to the first line of therapy does not impact the base case conclusions. For example, assuming the use of fostamatinib after discontinuation of TPO-RAs followed by 'Watch and rescue', avatrombopag is still dominant treatment vs eltrombopag and romiplostim.

Table 36. Fostamatinib after TPO-RA treatment sequences



c) Note that the submission suggests that the proportion of active therapies used at second and third line is dependent on the comparator (eltromobopag or romiplostim). However, the cost-effectiveness results presented are based on a model that only uses the proportion of second and third line therapies ascribed to eltromobopag as a comparator (columns 3 and 5 of Table 38), which excludes patients on avatrombopag or romiplostim from receiving eltromobopag as a subsequent line of therapy. Please comment on the reasons for excluding eltromobopag as a subsequent line of therapy. If this is an error in the presentation of cost-effectiveness results, please provide revised cost-effectiveness results that reflect the proportion of second and third line therapies specific to each comparator.

There appears to be a small error in the base results for avatrombopag vs romiplostim. The defined treatment sequence for romiplostim was incorrectly based on the treatment sequence if patients had initiated treatment with eltrombopag. Updated results with corrected assumptions are presented in the tables below.

Table 37. Model base case results

Technologies	Total costs (£)	Total QALYs	Total LY	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental LY
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 38. Cost per QALY breakdown

Costs (£)	AVA	ROM
Treatment costs	[redacted]	[redacted]
Active treatment	[redacted]	[redacted]
Treatment I	[redacted]	[redacted]
Treatment II	[redacted]	[redacted]
Treatment III	[redacted]	[redacted]
Treatment IV	[redacted]	[redacted]
Rescue therapy	[redacted]	[redacted]
Concomitant ITP medications	[redacted]	[redacted]
Treatment administration costs	[redacted]	[redacted]
Active treatment	[redacted]	[redacted]
Treatment I	[redacted]	[redacted]
Treatment II	[redacted]	[redacted]
Treatment III	[redacted]	[redacted]
Treatment IV	[redacted]	[redacted]
Rescue therapy	[redacted]	[redacted]
Concomitant ITP medications	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]
Treatment I	[redacted]	[redacted]
Treatment II	[redacted]	[redacted]
Treatment III	[redacted]	[redacted]
Treatment IV	[redacted]	[redacted]
Bleeding costs	[redacted]	[redacted]
Minor bleeds	[redacted]	[redacted]
Outpatient bleeds	[redacted]	[redacted]

Inpatient bleeds		[redacted]			[redacted]	
Intracranial haemorrhage		[redacted]			[redacted]	
Gastrointestinal		[redacted]			[redacted]	
Other bleed		[redacted]			[redacted]	
Total costs		[redacted]			[redacted]	
Number of life years		[redacted]			[redacted]	
Health state utility		[redacted]			[redacted]	
Disutility due to AEs - active treatment		[redacted]			[redacted]	
Disutility to AE – rescue therapy		[redacted]			[redacted]	
Total QALYs		[redacted]			[redacted]	

d) **Please justify why a shorter treatment duration of 8 weeks is used to assess time to response for second and third line therapy, while a longer treatment duration of 24 weeks is used for first line therapy.**

Time to response in the model is only dependent on the type of treatment and not by the line of therapy. For example, a shorter time to response is observed for RTX, which can be observed soon after the final infusion is administered (see section B3). Time to response applied in the model has been sourced from the best available data from a small evidence base. That being said, the values applied are unlikely to be a significant driver of costs and QALYs in the model (as exemplified by the DSA (All parameters varied +/- 1 cycle) which shows similarity to the base case where the cost effectiveness of avatrombopag vs. eltrombopag and romiplostim remained consistent with the base case (i.e., dominant).

e) **The response rates for non-TPO-RA treatments in subsequent lines of therapy have been adopted from the romiplostim NICE appraisal. Please comment on the source of the data/evidence used to inform the response rates for non-TPO-RA treatments from the romiplostim NICE appraisal and the relevance of the data to current UK clinical practice.**

As ITP is an orphan indication, there is limited available evidence to populate the model in the number of key areas. Romiplostim appraisal was the most reliable source of response rates for these drugs that was identified during the model development. Although the romiplostim appraisal was conducted 2010/2011, the sourced data from non-TPO-RA treatments response rates are unlikely to have changed since that time and is thus still likely to be accurate. However, as shown in the sensitivity analyses, these response rates are unlikely to have a material impact on the model results.

Treatment discontinuation

B6. Priority. Table 51 provides information on the time on treatment and discontinuation rates per cycle.

a) **Please clarify whether a systematic literature review was undertaken to identify treatment specific discontinuation rates and long-term treatment effectiveness. If not, please comment on why a literature review was not undertaken.**

Although both clinical and HRU (healthcare resource utilization) SLRs were performed for this submission, neither specifically explored treatment discontinuation rates or long-term effectiveness. As a result, they yielded no results to include in the model. Instead, the model parameters reflecting treatment discontinuation and long-term effectiveness were established based on targeted desk research. Given the paucity of data in this area, we are uncertain as to the extent to which an SLR would provide more relevant data than that obtained from the targeted literature review.

Applied estimates regarding discontinuation rates and long-term treatment effectiveness, unlikely to be a significant driver of costs and QALYs in the model (as exemplified by the DSA which shows similarity to the base case in these areas).

b) Please comment on the appropriateness of the assumption that the discontinuation rates (long-term treatment effectiveness) between the TPO-RAs is expected to be the same. Please justify the choice of treatment response duration of 109 cycles and discontinuation rate of 0.9% per cycle for the TPO-RAs. Please comment on this choice in light of the fact that some patients will remain on treatment over a lifetime (time horizon of 56 years in the model).

There is insufficient data to suggest any differences in long-term response/discontinuation between the respective TPO-RAs. Therefore, we have taken a conservative approach and assumed a similar discontinuation rate for avatrombopag, eltrombopag and romiplostim.

That being said, we believe that avatrombopag has important product features which are available to patients and will help maintain adherence, and thus improve LT response. However, given the limited data, these have not been reflected in the model.

Indeed, assumed discontinuation rate allows some patients to be on treatment over a lifetime, but it is very low proportion of patients i.e. 0.001%. Moreover, like many other assumptions in the model, treatment discontinuation is not a significant driver of model results. If increased rates of treatment discontinuation are assumed, avatrombopag remains cost-effective vs eltrombopag and romiplostim.

Rescue therapy

B7. Priority. Table 47 provides information on the proportion of patients using rescue therapy by platelet count and Table 48 provides the response rates for rescue treatment.

a) **Please comment on the source of data/evidence used to inform the proportion of patients using rescue therapy from the eltromobopag NICE appraisal and the relevance of the data to current UK clinical practice. Please comment on how and why the number of patients using rescue therapy from this source differs from Study 302. Please comment on the appropriateness of using Study 302 to inform the proportions of rescue therapy use attributed to bleeding and non-bleeding events.**

Study 302 was not powered to address use of rescue therapy. As a result, the inclusion of rescue therapy data in the model would be based on a very small sample size, n=9/49 (and thus subject to uncertainty).

Given the limited available data, we have instead used rates from the ELT submission, which were accepted by NICE in their decision making for that appraisal. Moreover, NICE concluded that using higher rates of rescue medication was more appropriate.

Additionally, we have provided scenario analyses in our submission using Study 302 data and the results from these analyses remain consistent with the base case.

b) **Please comment on the appropriateness of using the response rates for rescue therapy based on the source of data/evidence from the eltromobopag NICE appraisal and avatrombopag chronic liver disease indication.**

Given limited available data, we believe that the eltrombopag appraisal is an acceptable data source for response rates on rescue therapy. These rates have been previously accepted by NICE.

For platelet transfusions, we have sourced the response rate from the PBO arm of the ADAPT trial which assesses patient platelet count when an urgent platelet

transfusion is required. We believe that the response rate obtained from this study is broadly reflective of response to platelet transfusion when utilised in the ITP population.

Bleeding events

B8. Priority. Table 42 provides information on the proportion of patients experiencing bleeding events per cycle, by bleeding type and response status.

a) Please comment on

- **the source of data/evidence used to inform the proportion of patients experiencing bleeding events from the eltromobopag NICE appraisal and the relevance of the data to current UK clinical practice.**
- **Please comment on how and why the number of patients experiencing bleeding events from this source differs from Study 302.**
- **In particular, please comment on the reasons for a low incidence of serious bleeding events in Study 302.**

The primary data source in the eltrombopag NICE appraisal for patients experiencing bleeding events was the RAISE study (Cheng *et al.* 2010 *Lancet* **377**(9763)), which included chronic ITP patients of a comparable severity of disease to Study 302. Of the 115 study sites participating in the RAISE study, 10 were located in the UK, allowing for a reflection of local clinical practice in the wider study population. Furthermore, approaches to identification and grading of bleeding events in the RAISE study – using the WHO bleeding scale – are consistent with contemporary UK clinical practice. In more recently published real-world observations from 118 ITP patients (86 patients [72.8%] had chronic disease) in the UK treated with another TPO-RA, 29% of patients experienced at least one bleeding event during the 6-month observational period (Doobaree *et al.* 2019 *Eur J Haematol* **102**:416-423). This is similar to and modestly higher than the incidence of on-treatment bleeding events reported in the placebo (31%) and eltrombopag (19%) randomised subjects of the RAISE study respectively (Cheng *et al.* 2010 *Lancet* **377**(9763)). Most recently, the frequency and nature of

bleeding events in the RAISE study has been validated by UK clinical experts as being broadly reflective of contemporary UK clinical practice.

The low incidence of serious bleeding events in Study 302 is related to a small sample size and relatively short follow up of this study. Study 302 was not designed or powered to address reductions in bleeding events with avatrombopag. In Study 302:

- eleven patients experienced a bleeding Grade 1,
- only 2 patients experienced a bleeding Grade 2,
- one patient experienced a bleeding Grade 3.

Therefore, based on these data, estimation of bleeding events per response was possible only for WHO bleeding Grade 1. In the absence of data from Study 302, we believe the bleeding event data from the ELT submission is a suitable proxy given it was accepted in the context of prior NICE appraisal for ITP.

b) Please comment on the source of data/evidence used in the eltromobopag and romiplostim NICE appraisals to inform the increase in the probability of patients experiencing an inpatient bleed (doubled) when patients enter final line no treatment. Please comment on the appropriateness and relevance of this data to current UK clinical practice.

When patients enter the final line of therapy in the model, they are assumed to be refractory to all treatments and move onto a 'watch and rescue' treatment plan. Given these patients are likely to have severe and uncontrolled disease, we believe it is credible to assume that they are at a substantially increased risk of serious bleeding events. Therefore, in line with eltrombopag and romiplostim NICE submissions in the base case a double rate of inpatient bleeds for these patients was assumed. Also, in the referred NICE submissions the increase of probability of patients experiencing an inpatient bleed was also based on an assumption only. The model includes the functionality to remove the assumption of increased inpatient bleeding risk in the final line of therapy. When this assumption is removed, avatrombopag remains dominant vs both eltrombopag and romiplostim.

c) Please justify the modelled assumption that risk of bleeding is only dependent on a platelet count threshold of 50x10^9/L.

The platelet count threshold of $50x10^9$/L is the standard measure of treatment effect defined in ITP clinical studies and prescribing recommendations for TPO-RAs (18-23). Although the data shows the impact of ITP is greatest when platelet counts $<30x10^9$/L, a risk of bleeding is still observed when platelet counts are between $30\text{-}50x10^9$/L (25). In the refractory ITP setting, platelet counts of $50\text{-}70x10^9$/L are recommended to prevent clinically significant bleeding (25).

Furthermore, as all of the studies for avatrombopag and comparators identified in the NMA defined platelet response as $50x10^9$/L, the only way to capture estimates of comparative effectiveness is to define the responder health state at the $50x10^9$/L threshold. This approach is also consistent with previous economic evaluations that have been conducted in ITP, including both the romiplostim and eltrombopag NICE appraisals which define response to treatment at the higher platelet count threshold of $50x10^9$/L (TA221 & TA293).

Concomitant ITP medication usage

B9. Please comment on the appropriateness of using Study 302 to inform concomitant ITP medication usage for all TPO-RAs. Please comment on the relevance of this data to current UK clinical practice. Please compare concomitant medication usage in Study 302 with usage in the pivotal trials for eltromobopag and romiplostim.

As summarised in Table 39, the proportion of patients receiving concomitant ITP medications at baseline in Study 302 was 46.9% and 41.2% respectively for avatrombopag and placebo-randomised subjects. This is broadly comparable to that of the pivotal study for eltrombopag, where 46.6% and 50.0% of eltrombopag and placebo-randomised subjects respectively received concomitant ITP medications at baseline (Cheng *et al.* 2011 *Lancet* **377**:393-402). By contrast, there were reduced proportions of patients in both arms of the romiplostim pivotal trial who received concomitant ITP medications than subjects in the pivotal trials for the other TPO-RAs (27.7% and 38.1% respectively for romiplostim and placebo-randomised subjects) (Kuter *et al.* 2008 *Lancet* **371**:395-403).

The considerable use of concomitant ITP medications alongside TPO-RAs observed in these pivotal studies is reflective of real-world clinical practice in the UK and overseas (Thachil *et al.* (2016) *Br J Haem* 180: 591-594; Lofkhandwala *et al.* (2017)

JCO **35**(15) suppl.) and is a recognised strategy to enhance platelet response, particularly in multi-refractory patients with a high risk of bleeding (Mahevas *et al.* (2016) *Blood* **128**(12):1626-1630). Contemporary treatment guidelines adopted in UK clinical practise often advocate for the use of concurrent ITP medications (Provan *et al.* (2019) *Blood Adv.* **3**(22):3780-3817; Neunert *et al.* (2019) **3**(23):3829-3866).

The pivotal study for avatrombopag in ITP – Study 302 – showed that 5/15 (33.3%) of patients in the avatrombopag treatment group were able to reduce their use of concomitant ITP medications, as compared with 0/7 placebo-treated patients (33.3% vs. 0%, respectively; 95% CI, 9.48, 57.19). These RCT data appear to be recapitulated in early real-world use in patients being switched to avatrombopag from another TPO-RA; of 19 patients in one real-world study requiring concomitant corticosteroids while on treatment with another TPO-RA, 12 (63.2%) were able to discontinue steroids, 6 (31.5%) reduced their steroid dose, and none increased steroid dose following a switch to avatrombopag (Al-Samkari H *et al.* (2021) *EHA Annual Congress*, Poster EP1144).

Table 39. Usage of concomitant ITP therapies in TPO-RA pivotal licensing studies for ITP

TPO-RA (Pivotal Phase 3 Study)	Proportion of patients in pivotal study receiving concomitant ITP medications at baseline	
	Study drug arm, %	Placebo arm, %
Avatrombopag (Study 302)	46.9	41.2
Eltrombopag1 (RAISE)	46.6	50.0
Romiplostim2 (NCT00102323/NCT00102336)	27.7	38.1

1: Cheng et al. (2011) Lancet 377:395-402
2: Kuter et al. (2008) Lancet 371:395-403

It should be noted that concomitant ITP medications have negligible impact on the model results. The cost of concomitant ITP treatments constitutes only around 1% of total costs estimated by the model, whereas the incremental costs between arms is much higher. Hence, any differentiation of concomitant ITP medications between considered TPO-RAs will not impact the assessment of cost-effectiveness of avatrombopag.

Treatment doses and administration costs

B10. Priority. Table 37 provides the base case doses of TPO-RAs used in the model.

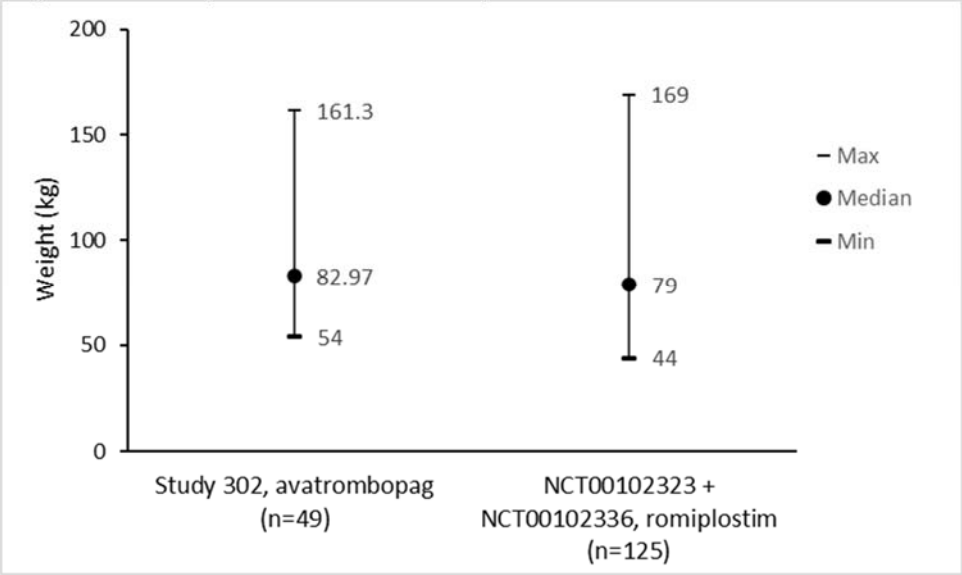
a) **Please justify the use of starting doses based on the respective product SmPCs for avatrombopag and eltromobopag, but use of a median dose for romiplostim from its long-term pivotal trial.**

A recently published survey of UK haematology consultants by the UK ITP forum provides insights on the real-world use of TPO-RAs (26). A key finding from the study was that patients treated with eltrombopag would initiate treatment on the SmPC recommended starting dose of 50mg once daily. We have therefore assumed both oral TPO-RAs (eltrombopag and avatrombopag) would be used at the SmPC starting dose. For romiplostim, the majority of respondents in the clinician survey reported that they would use a starting dose of 3mcg/kg, which was higher than the SmPC dose of 1mcg/kg, in order to achieve a more rapid platelet response (26) . Initiating romiplostim at a higher dose than that specified in the SmPC has been confirmed by Sobi through various expert engagements that have been made in the development of this evidence submission.

b) **Please comment on how the weight distribution of patients in the romiplostim pivotal trials differ from the distribution of patients in Study 302.**

The patient weight distributions from Study 302 and the pivotal romiplostim studies (NCT00102323 + NCT00102336; pooled analysis) are presented in Figure 8 below (10) (20). Minimal between study differences in patient weight are observed based on the median and minimum/maximum values.

Figure 8. Weight distribution of patients across ITP studies



c) Please provide details on the vial wastage assumptions used for the modelled dosing of romiplostim. Please clarify how the drug acquisition costs are calculated for romiplostim, and list any underlying assumptions.

The vial wastage with romiplostim was included in the model base case in a standard manner consistent with routine clinical practice.

The model assumes patients with romiplostim receive a weekly dose of 4mcg/kg with a weight of 82.97kg. This provides a weekly dose of 331.88mcg. Our model assumes patients will require 3 vials (125mcg per vial) per week with all outstanding dose (i.e., 375mcg subtract 331.88mcg = 43.12mcg) will be classed as wastage (i.e., non-transferrable).

We believe this is a credible assumption given small patient numbers across individual centres and a high rate of self-administration, both scenarios preventing the possibility of widespread vial sharing.

In addition to this, vial sharing or re-using vials is not advised since romiplostim is a sterile but unpreserved medicinal product and is intended for single use only (23). Romiplostim should therefore be reconstituted in accordance with good aseptic practice. Any compromise to this would risk microbiological contamination.

d) Please justify the maintenance doses for avatrombopag, eltromobopag and romiplostim used throughout the modelled time horizon, which is assumed to be equivalent to the starting dose for these therapies.

The model assumes patients remain on their starting dose throughout the course of their TPO-RA because these doses were close to the median doses observed in the relevant trials. In addition, DSA analyses showed that varying dosing assumptions still yielded results consistent with the base-case, i.e. that avatrombopag is cost-effective versus other TPO-RAs.

For the oral TPO-RAs, avatrombopag and eltrombopag, the SmPC starting doses have been applied, 20mg and 50mg once daily, respectively. Throughout Study 302, the median daily dose was 22.34mg (10). In the long-term extension study of eltrombopag (RAISE), the median daily dose was 51.5mg (28). For romiplostim, the median dose observed throughout the pivotal studies (NCT00102323 + NCT00102336) was between 3-4 mcg/kg (20).

e) Please justify the assumptions regarding the administration costs of treatments. Please support these assumptions with empirical evidence

Across the respective TPO-RA treatments, only romiplostim has administration costs which are considered to be relevant for the economic analysis (i.e. administration of drug ay community clinic or at home by specialist nurse). To our knowledge, there is limited data available which reports on rates of patient self-administration with romiplostim. Therefore, the model uses data available from the pivotal romiplostim studies (published via a congress abstract). That being said, administration costs only represent a small proportion of total costs in the romiplostim arm of the model and if removed completely, would have limited impact on the overall cost-effectiveness results. In the base case analysis, the total administration costs in the romiplostim arm which also administration costs for subsequent lines of therapy, were approximately 3.7% of total costs (£27,691/£740,332 - see table 69 of the main evidence submission).

Health-related quality of life

B11. Priority. Table 57 provides TOBIT model parameters for health-related quality of life based on Study 302.

a) **Please provide the EQ-5D summary data from Study 302. Please provide this data by treatment arm, numbers of patients, standard deviation or standard error, by assessment time point, baseline score, change from baseline, and, if available, stratified by responder status. Note that the company submission refers to Table 14.2.5.2 of the Study 302 CSR but the CSR was not included with the submission.**

Please be advised the EQ-5D data is contained within the provided CSR with this response at table 14.2.5.2. For convenience please also finds the tables embedded below. **Please be advised these tables are AIC**

Sent as separate attachment.

b) **Please comment on the appropriateness of using the EQ-5D data from Study 302 to inform utility values in the model. Please comment on whether alternative EQ-5D utility values are available from the eltromobopag and romiplostim NICE appraisals and/or respective pivotal clinical trials. If so, please provide a comparison of the utility values.**

The values from the eltrombopag NICE submission are available and are presented below together in Table 40 with the values sourced from Study 302.Values from both sources differ, however, each source confirms impact of platelet count and presence of bleeds on health state utilities. The use of Study 302 allowed consideration of minor bleeds regarding their impact on utilities.

Table 40. Model inputs

State/Source	Eltrombopag NICE submission		Avatrombopag CEM (Study 302)	
	< 50 x 10^9/L	≥ 50 x 10^9/L	< 50 x 10^9/L	≥ 50 x 10^9/L
No bleed	0.841	0.863	0.760	0.801
Minor bleed	N/A	N/A	0.715	0.756
Outpatient bleed	0.732	0.734	0.584	0.625
Inpatient bleed				
Intracranial hemorrhage	0.038	0.038	0.038	0.038
Gastrointestinal bleed	0.45	0.45	0.45	0.45
Other bleed requiring inpatient	0.45	0.45	0.45	0.45

We believe that using EQ-5D data from Study 302 to inform utility values in the model is appropriate and consistent with the general modelling approach, according to which Study 302 was the main source of all data in the model, if only specific information was available. If utilities from the eltrombopag submission were used, the conclusion of cost-effectiveness assessment would remain the same, I.e. avatrombopag would still be dominant treatment over both comparators.

c) Please provide full details of the methods used in the TOBIT model to derive the parameters in Table 57, including numbers of patients informing the estimates, time periods, and the extent of missing data (including any data manipulation required such as details of any imputation methods used to handle missing data).

A total of 100 patients were screened, and 49 subjects were randomized: 32 to avatrombopag and 17 to placebo and included in the FAS (Full Analysis Set) and the Safety Analysis Set. The Tobit model has been used to model utilities adjusted on response, bleeds, splenectomy at baseline and adverse events. A Mixed Model for Repeated Measures (MMRM) approach was used to handle any missing data. The repeated data used in this model included1544 observations; of which only 189 observations are complete (there were1355 observations with missing data on utility values). The numbers of complete observations available at each visit are presented in Table 41 below.

Table 41. Observations at each visit

Visit	Frequency	Percent	Cumulative Frequency	Cumulative Percent
Baseline	48	25.4	48	25.4
Visit 10 (Week 10)	3	1.59	51	27
Visit 11 (Week 12)	29	15.3	80	42.3
Visit 13 (Week 16)	3	1.59	83	43.9
Visit 14 (Week 18)	2	1.06	85	45
Visit 17 (Week 21)	1	0.53	86	45.5
Visit 18 (Week 22)	2	1.06	88	46.6
Visit 21 (Week 25)	1	0.53	89	47.1
Visit 22 (Week 26)	22	11.6	111	58.7
Visit 5 (Week 2)	1	0.53	112	59.3
Visit 7 (Week 4)	4	2.12	116	61.4
Visit 8 (Week 6)	7	3.7	123	65.1
Visit 9 (Week 8)	3	1.59	126	66.7
Visit E1 (Day 1)	39	20.6	165	87.3
Visit E13 (Week 24)	23	12.2	188	99.5
Visit E15 (Week 32)	1	0.53	189	100

d) Please comment on the appropriateness, and relevance to UK clinical practice, of the source of data/evidence used to inform the utility values for serious bleeding events from the eltromobopag NICE appraisal.

As explained in our response to question B8a), for serious inpatient bleedings, there was only 1 >grade 3 AE event reported throughout the Study 302. Therefore, it was not possible to obtain reliable utility values for serious bleeding events from this study. In the absence of data from Study 302, we believe the utility values from the eltrombopag submission are suitable given they were accepted in the context of a prior NICE appraisal for ITP (TA293).

e) Please provide details of the data sources and assumptions used to derive utility decrements for the following events in the model:

– adverse events included in the model;
– from initial and subsequent lines of treatment.

As explained in the dossier, AEs were grouped into serious AEs and other AEs in the model. AEs were associated with a standard disutility value, lasting for 1 model cycle (4 weeks). For both serious and other AEs, a standard disutility value of 0.1 was applied for all TPO-RA therapies, as in the romiplostim NICE appraisal. Other (non-serious) AEs for non-TPO-RA treatments (which are only considered when patients move onto later lines of therapy) were also associated with a disutility value of 0.1, whereas serious AE for non-TPO-RA therapies were associated with a value of 0.4 as in the romiplostim NICE appraisal. Rescue therapy was associated with a disutility of 0.1 for both other and serious AEs, irrespective of treatment agent used. Utility decrements applied in the model were related to AEs while on a given treatment not the treatment itself. The risk of AEs as well as utility decrements were the same for a given treatment used as an initial and subsequent line of therapy. We believe that considering limited available data the approach undertaken in terms of utility decrements in the model is appropriate, especially it was previously accepted by NICE. Moreover, as shown in DSA, base case model conclusions are consistent while changing assumptions regarding utility decrements due to AEs.

f) Please comment on whether the utility values in the model have been adjusted by age over time.

Utility values in the model were estimated based on Study 302 i.e., are representative for ITP patients of assumed average 44.6 years of age. No further age adjustment was applied in the model over time mostly due to lack of data for such age adjustment specific to ITP population and independent on the presence of bleeds and platelet count. Nonetheless, any age adjustment would have been applied to both modelled arms impacting slightly the absolute difference in QALYs between avatrombopag and comparators. Age adjustment of utility values would not change the direction of estimated differences i.e., placebo would sustain its dominance over eltrombopag and romiplostim.

Cost-effectiveness results

B12. Priority. Please provide additional cost-effectiveness results where the response rates are informed by the alternative NMAs requested in section A, namely (corresponding to request A19):

a) **Inclusion of the two excluded studies of avatrombopag;**

b) **Inclusion of the seven excluded trials that did not meet the NMA's inclusion criteria;**

c) **Inclusion of the rituximab trials;**

d) **Inclusion of all ten excluded trials (i.e., Study CL003, Study 305, the seven excluded trials that did not meet the NMA's inclusion criteria, and rituximab trials);**

e) **Outcomes at different time points (follow-up of assessment) and different dose regimens**

Additionally, provide additional cost-effectiveness results for a sensitivity analysis where the response rates from the NMAs are informed by the random effects model.

Please include in your submission updated versions of the model with the functionality to vary the source of treatment effectiveness evidence.

As per A16, we are unable to provide the additional NMA analyses within the timeframe requested. Therefore, additional cost-effectiveness results using the alternative NMA results are also unavailable

Model functionality

B13. The executable model only permits the presentation of cost-effectiveness results for a pairwise comparison of the intervention and a single comparator. Although the results of deterministic analysis can be generated from the pairwise comparison to permit a comparison of the intervention with multiple alternative comparators, it is not possible to provide results of a probabilistic analysis with multiple alternative comparators evaluated simultaneously (only in a pairwise fashion as presented in Tables 70 and 71 of the company submission). Please provide a more flexible executable model with functionality that permits a simultaneous comparison of cost-effectiveness results for multiple alternative comparators and enables a full incremental analysis with the PSA outputs.

Following discussion with the ERG/NICE, we are unable to provide an updated version of the model within the requested timeframe.

Probabilistic sensitivity analysis

B14. The probabilistic sensitivity analysis assumes a common standard error/standard deviation of 20% of the deterministic mean value for many of the model parameters (utility values, event probabilities with the exception of response time, concomitant medications and administration costs), while variation in time to response is limited to +/- 1 week, and eltrombopag dosage to +/- 10%. Please justify the variation used for each of the model parameters and please report the variability observed in the actual data corresponding to the source used.

Base case values of many model parameters were based on limited sources or assumptions. Hence, assumptions were needed for a standard error/standard deviation tested in the probabilistic sensitivity analysis. We believe that in such situation testing 20% variation of base case parameters in the PSA gives reliable reflection of uncertainty of model inputs. Moreover, as shown in the DSA the cost effectiveness of avatrombopag vs. eltrombopag and romiplostim remained consistent

with the base case (i.e., dominant) irrespective to change of inputs. Therefore, testing thinner/wider confidence intervals in PSA would likely not change its conclusion. Variation in time to response was limited to +/- 1 cycle (not week) in order to obtain a confidence interval determined by integer number of cycles. Variation in ELT dosage was limited to +/- 10%, taking into account the variation of romiplostim dosing that occurred in its clinical study, which was lower than 10%. Assuming 10% variation of eltrombopag dosage instead of 20% is a conservative approach as it reduces uncertainty related to eltrombopag.

Section C: Textual clarification and additional points

Searches

C1. There appear to be mistakes in the line combinations of 2 search strategies in Appendix D:

- in Table 2 at line 74
- in Table 7 at line #16

Please check and correct.

The research question in Table 7 at line #16 was wrongly copy to the word document however, the number of returned hits is correct.

In Table 2 at line 74 research questions included combination of keywords for observational studies (or/53-73) as well as duplicated fragment of research questions for RCTs (exclusion of case report, case study, letter, historical article and abstract report). This mistake has no impact on the final results and there is no risk of missing any relevant study.

C2. The search strategies for MEDLINE and Embase (Tables 1, 2, 6, 9, 11, 14 in Appendix D) are limited by study design (RCTs and observational studies). Please clarify if validated study design search filters were used and if yes please give the source or reference where possible.

The search strategies were limited by study design with use of filters which were developed based on recommendations of Cochrane Collaboration, CRD's guidance

for systematic reviews and examples of filter used by HTA agency (e.g. CADTH). The filters had previously been used in many systematic reviews.

Sources:

- https://work.cochrane.org/rct-filters-different-databases
- https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home/search-filters-by-design
- https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters#syst

C3. Please clarify if validated search filters were used in the search strategies shown in the following tables**:**

- Appendix G: Tables 35, 36, 37 and 38
- Appendix H: Tables 40, 41
- Appendix I: Tables 45 and 46
- If yes, please give the source or reference for the filter where possible.

The search strategies were limited by study design with use of filters which were developed based on recommendations of Cochrane Collaboration, CRD's guidance for systematic reviews and examples of filter used by HTA agency (e.g. CADTH). The filters had previously been used in many systematic reviews.

Sources:

- https://work.cochrane.org/rct-filters-different-databases
- https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home/search-filters-by-design
- https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters#syst

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24. EMA. Avatrombopag SmPC [Available from: https://www.ema.europa.eu/en/documents/product-information/doptelet-epar-product-information_en.pdf.
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NICE National Institute for Health and Care Excellence

Patient organisation submission

Avatrombopag in combination for treating chronic immune thrombocytopenia [ID3838]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	The ITP Support Association
3. Job title or position	Chief Executive
4a. Brief description of the organisation (including who funds it). How many members does it have?	The organisation is a registered charity with approximately 1,000 members, who are sufferers of ITP, or their careers. which shall be the relief of sickness of persons with Immune Thrombocytopenia and in particular to promote, improve, develop and maintain the general welfare of ITP Patients and the families of children with ITP including the provision of: Patient and family support Internet and telephone contact network with other patients and families Information pamphlets and newsletters Guidelines for schools Guidelines for dentists of patients Advice for patients and families on referrals to specialists National conventions for patients and families The collation of information for and consultation with medical and ancillary professions in order to advance the knowledge and treatment of ITP. Funding comes from a variety of sources but mainly from charitable events that patients and their carers undertake, donations and from unrestricted grants from pharmaceutical companies. The organisation is not dependent on funding from any one company.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator	The charity received support for Phase 2 of its ITP Patient Toolkit Project - Paediatric Toolkit - £5,000

products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The organisation carried out a bi-annual written survey of patient and carers opinions on treatment options and their attitudes to the current treatments available. The survey has been supported by a number of on-line meetings with members, (previously face to face before lockdown), to discuss aspects of treatment and in particular the risks and benefits of the options in the current treatment pathway. We also hold an annual patient convention at which patients are encouraged to ask questions about treatment options and their views on treatment pathways.These are often highlighted in our quarterly newsletter, The Platelet.
Living with the condition	
6. What is it like to live with the condition? What do carers	The condition is characterised by a reduction in platelets which may lead to spontaneous or excessive bleeding, the latter being out of line for the type of 'insult'. Approximately 40% of patients do not require

experience when caring for someone with the condition?	treatment at presentation but the platelet levels are labile and may fluctuate in response to state of health, infection, vaccinations or more commonly unexpectedly and without obvious cause. Patients (and carers) are aware that when the platelet count falls below a level of 20-30x10^9/l that is when they are particularly at risk from bleeding. This causes significant worry, and in many quite marked anxiety, and is especially prominent in those with refractory or relapsed disease who are in the persistent or chronic categories of disease. In addition to the bleeding risk patients with low platelet counts often have fatigue, that is marked in up to a third and present in another third which affects their quality of life. Many also have side-effects from the treatments used of which infection is a major risk. Although mortality is low in ITP in those who have failed splenectomy and are immune suppressed half of the deaths are related to infection, which is also responsible for significant morbidity. There is a real desire to look for treatments that minimise toxicity and can be personalised for the individual patient.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Patients and carers generally accept what treatments are available, as they appreciate that the need for treatment to prevent bleeding may outweigh the side-effects of the treatment. However, there is a general consensus that treatment to increase the platelet count to a safe level should be with minimal toxicity and should optimise health-related quality of life. In those who have failed first-line treatment with steroids +/- iv immunoglobulin historically splenectomy has been a standard second-line treatment in ITP. But due, in considerable part, to patient resistance the rate of splenectomy has dropped significantly in the UK (and now also in Europe and the USA) with an increased reliance on medical therapies. Patients have become much more critical of the various medical options and their potential side-effects and whether these can easily be alleviated, or avoided.
8. Is there an unmet need for patients with this condition?	Yes, in adults in particular ITP is a chronic or persistent disease that may be life-long. As the disease has a fluctuating course treatment may need to be continued indefinitely, or at best the patient may require recurrent courses of treatment. Cure is rare and many patients will have periodic relapses. The thrombopoietin-receptor agonists (TPO-RAs) are generally being accepted as the second-line treatment of choice in the patient who has relapsed first-line treatment, if they are eligible for them.

	However, although they have a high response rate many patients are not suitable. The average patient with ITP is male and over 60 and many will have co-morbidities, or risk factors that increase their thrombotic risk, and in these a decision has to made in conjunction with the patient as to whether TPO-RAs are appropriate. Real-World data on treatment has also shown that up to 40% of patients will stop taking TPO-RAs for a variety of reasons. Standard immune suppression has more general side-effects that are well recognised and the infections risks of rituximab are increasingly recognised, particularly when used recurrently. We are aware that Avatrombopag does not appear to disturb liver function, unlike the alternative oral TPO RA (eltrombopag), which does this in approximately 6% of patients. The TPO RA treatments are of particular importance to patients since the onset of the COVID 19 pandemic, because alternatives in the form of immunosuppression (e.g. rituximab, steroids) represent a risk factor for poor outcome following COVID 19 infection in what has already been shown to be a typically older population. Since COVID vaccine itself is known to result in a fall in platelets for some ITP patients, this is an additional stress that we would prefer to avoid. We are also aware that this treatment can be effective for patients who have previously received other TPO RA treatments but still require treatment Al-Samkari H et al B J Haem 2022 PMID 35179784. The reduction in splenectomy rate has been mentioned previously and this has been recognised in the two recent updated guidelines where it is recommended that it is not considered until at least 12 months, and then if only after radio-labelled predictive tests, if these are available. • An International Consensus Guideline (Provan D et al Blood Advances 2019 PMID: 31770441) • American Society of Hematology Guidelines (Neunert C et al Blood Advances 2019 PMID 31794604)

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	One of the main advantages of taking avatrombopag is that it is an oral medication and can be taken without food restrictions, when compared with other treatments. Our recent survey on patients' attitudes to treatment (TRAPeze study) highlighted their preference for oral treatment but there was a significant dislike of the food restrictions, which they find quite irksome Up to two thirds of patients suffer from fatigue which is severe in up to half of these. Many feel this is a result of a low platelet count and can often pin-point relapses by their change in energy levels. The thrombopoietin receptor agonists increase the platelet count in a significant proportion of patients and may be associated in some with improvement if their fatigue and general quality of life. This has been shown in specific health related QoL studies, although some still find fatigue is a side-effect of their treatment. Avatrombopag is generally well tolerated, and we would expect it to show the same impact as the two currently available agents (Romiplostim and Eltrombopag). In addition, as has been said about other medicines, this provides the health care professional with another item in their tool box of treatments if another TPO-RA does not work or the patient has suffered from side effects from the use of other treatments.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Avatrombopag, although it is generally well tolerated, like many medicines in this class can leave patients with some side effects: Very common (may affect more than 1 in 10) Feeling tired Headache Common (may affect up to 1 in 10)

	back pain, muscle pain, joint pain, pain in arms or legs discomfort or pain of bones, muscles, ligaments, tendons, and nerves.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	With ITP no one patient is the same, what treatment works for one patient may not work for another, as with all treatments this must be taken into account when making an assessment.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**None known**

Other issues	
13. Are there any other issues that you would like the committee to consider?	The treatment is for adults and is an outpatient based oral treatment. It should be prescribed in a secondary care setting by a haematologist. As an oral treatment it has no resource implications over and above the other oral medications and has fewer demands on patient and clinical time than alternate options of IV immunoglobulin, rituximab and romiplostim. There are no dietary restrictions as seen with eltrombopag.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- The TPO RA class of drugs are important for ITP patients because they offer a good response rate, and importantly, do not suppress the immune system.
- Avatrombopag is an important treatment advance because it is given by a preferred treatment route (oral), without the dietary restrictions of the alternative oral medication, and provides a non-immunosuppressive option, with a good response rate, for those patients who do not tolerate or respond to the alternative TPO RA drugs.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Avatrombopag in combination for treating chronic immune thrombocytopenia [ID3838]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	UK ITP Forum

3. Job title or position	Chair
4. Are you (please tick all that apply):	x☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The UK ITP forum is a national working group of health care professionals with a special interest in the care of patients with immune thrombocytopenia (ITP) (http://ukitpforum.org/index.php/en/) The objectives and aims of the forum are: • To improve care and outcomes for patients with immune thrombocytopenia (ITP) in the UK • To provide a forum for the interaction of UK healthcare professionals with an interest in ITP • To develop a network of specialist centres able to provide high quality care and tertiary review • To advance the education of health care professionals and the general public in all aspects of the disease. • To promote best practice and raise awareness of developments in translational research • To encourage collaborative research and trial recruitment into ITP studies Membership of the UK Forum is free and includes haematologists, paediatric haematologists, specialist and interested nurses, and a patient representative. As a voluntary organisation, the forum has no funds. It has received practical support from the British Society of Haematology which has provided teleconference facilities and rooms for meetings. The costs of the forum website have been met by the ITP Support Association (https://www.itpsupport.org.uk/index.php/en/).

4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	No.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve	We would agree with the recommendations for treatment in the recently published international consensus document (Provan et al 2019 PMID 31770441): 1. Treatment goals should be individualized to the patient and the phase of the disease. 2. Treatment should prevent severe bleeding episodes.

mobility, to cure the condition, or prevent progression or disability.)	3. Treatment should maintain a target platelet level >20-30 x 10^9/L at least for symptomatic patients (because risk for major bleeding increases below this level). 4. Treatment should be with minimal toxicity. 5. Treatment should optimize health-related quality of life (HRQoL). We also recognise that higher platelet counts are sometimes required. For example to cover periods of increased bleeding risk such as surgery or delivery.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	In 2009, an international working group published a consensus document for the standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura (PMID: 19005182). This group defined a response as: • A platelet count of ≥ 30 x 10^9/L and at least 2-fold increase the baseline count and absence of bleeding. Platelet counts should be confirmed on at least 2 separate occasions (at least 7 days apart when used to define response) • Also supplemental outcomes (whenever possible) o Bleeding symptoms measured by a validated scale (requires additional studies) o Health-related quality of life assessment measured by a validated instrument (requires additional studies) Clinicians also recognise that some patients with severe thrombocytopenia and haemorrhagic symptoms can achieve clinical benefit from treatment that increases the platelet count and/or reduces bleeding, even if not achieving the response criteria listed above. For example, increasing a platelet count from 5-10, to 20-30 can translate to reduced bleeding symptoms and improved quality of life. Since titration of avatrombopag during the phase III study was with a platelet target range of 50 - 150 x 10^9/L, and the primary end point required a platelet count ≥50 x 10^9/L, it is likely that a clinically meaningful response will be achieved in more patients than is suggested by the primary end point.
8. In your view, is there an	Yes. ITP is often a chronic condition for adults with the majority of patients relapsing after first line steroids.

unmet need for patients and healthcare professionals in this condition?	There are a number of second line medical therapies including two NICE approved thrombopoietin receptor agonists (TPO RA) eltrombopag and romiplostim (NICE technology appraisals TA293 & TA221) but not all patients respond to, or tolerate currently available treatments.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Adult patients with ITP requiring initial treatment will usually receive corticosteroids and/or intravenous immunoglobulins. Patients subsequently requiring treatment will typically receive a TPO-RA. Alternative treatment options include rituximab, mycophenolate or azathioprine. Due to different efficacy and side effect profiles, the choice of medical therapy is individualised. Evidence from the adult UK ITP registry showed that the use of surgical splenectomy to treat ITP is in decline (EHA 2019 PF691 Splenectomy in immune thrombocytopenia: do changing treatment patterns for ITP affect outcomes? Data from the UK ITP Registry). There are currently no UK specific guidelines. The British Society of Haematology previously signposted clinicians to the first international consensus guideline (2010 PMID: 19846889) and practice in the UK has been broadly in line with that. The international consensus guideline was updated in 2019 (PMID: 31770441). ITP is a rare condition with relatively little high grade evidence. The guideline is therefore permissive for the selection of second and third line therapies and clinicians will typically make individualised decisions about these treatments in partnership with their patients. Impact of the COVID-19 pandemic: In response to the global COVID-19 pandemic, the WHO recommended the avoidance of immunosuppression to treat other conditions where there are alternatives. UK guidance was subsequently issued which recommended that TPO-RA were considered as up-front treatment in order to avoid immunosuppression (PMID: 32374026). This practice was subsequently endorsed by NHS England https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2021/02/C1066-interim-clinical-commissioning-policy-tpo-ra-for-itp-rps-v1.1.pdf. Subsequent studies confirmed that patients receiving

	immunosuppression such as steroid, rituximab and mycophenolate e.g. PMID 33268442, 32471903 are at greater risk of severe COVID-19 infection.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	There are three recently published guidelines for the treatment of this condition. 1) An international consensus guideline (Provan D et al Blood Advances 2019 PMID: 31770441) 2) American Society of Hematology guidelines (Neunert C et al Blood Advances 2019 PMID 31794604) 3) UK guidelines for the management if ITP in adults during the COVID-19 pandemic (Pavord et al BJH 2020 PMID: 32374026) The international consensus lists Avatrombopag as a medical therapy with robust evidence for treatment of ITP requiring treatment subsequent to first line therapy (Figure 1 & Table 5)
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Discussed above
• What impact would the technology have on the current pathway of care?	SPC licence “Doptelet is indicated for the treatment of primary chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).” Avatrombopag is a TPO RA and is likely to be used at a similar position in the treatment pathway to other TPO RA.
10. Will the technology be used (or is it already used) in the same way as current care	Yes

in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	The health care resource use would be similar to the alternative oral TPO RA eltrombopag, but could be less than the once weekly subcutaneous injection romiplostim which requires delivery on a haematology day unit for some patients, who are unable to make up and deliver treatment themselves.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Avatrombopag would be prescribed within secondary care by the treating haematologist.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, patients who are intolerant or who fail to respond to one TPO RA have a reasonable chance of responding to an alternative TPO RA (studies suggest that up to 46-80% can successfully switch PMID: 31073079). Patients who respond to TPO RA thereby avoid the risks and side effects associated with immunosuppressive therapies including the risk of more severe COVID-19 infection.
• Do you expect the technology to increase length of life more than	Mortality attributed to ITP or its treatments is caused by fatal bleeding events or infection associated with immunosuppressive agents. Since avatrombopag does not suppress the immune system, responding patients are at reduced risk of fatal events. Fatal events are rare and it is unlikely that a study will ever be sufficiently powered to detect a difference in survival between treatment and placebo or standard of care

current care?	arms. ITP is thought to have a heterogeneous pathogenesis, not all patients respond to current SOC and as an additional effective medical therapy, avatrombopag has the potential to save lives.
• Do you expect the technology to increase health-related quality of life more than current care?	We are not aware of HRQoL data published for avatrombopag. Evidence from other TPO RA treatments would suggest that HRQoL improves in patients who respond to treatment (Kuter PMID 22460421).
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional	The two main advantages of avatrombopag over the alternative oral TPO RA eltrombopag is 1) The lack of liver upset as a side effect reported in patients receiving avatrombopag 2) The fact that there are no dietary restrictions with avatrombopag. This may improve compliance with medication and provide a better patient experience/HRQoL

clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The goals of treatment are outlined in question 6 and the indication for starting treatment would be the same for avatrombopag as any other patient with ITP requiring treatment. Patients would typically have a platelet count <30 x 10^9/l and be symptomatic of their condition but an individual assessment would be needed to balance the burdens and benefits of treatment. Avatrombopag is a maintenance treatment and likely to be continued in the long term for responding patients who tolerate therapy. However an accepted treatment approach for ITP patients is titrating to the minimum effective dose after a period of stability. Hence treatment is likely to be tapered and potentially stopped in patients achieving and maintaining a good response.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year	ITP has been shown to reduce HRQoL. Validated HRQoL scales specific for ITP have been developed capture the adverse impact of ITP on HRQoL (Trotter & Hill PMID: 30568522). QALY assessment using EQ-5D may lack sensitivity for ITP specific impact on HRQoL.

(QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Efficacy and tolerance appear similar to other TPO RAs, but there are additional benefits outlined in question 13. The relatively quick onset of action (65% had responded by day 8 in the main phase III study) compared with other TPO RA may enable clinicians to avoid steroid rescue for some patients.
• Is the technology a 'step-change' in the management of the condition?	No, this is a drug within the class of existing TPO RA. However not all patients respond to existing TPO RA and the class of drug is particularly valuable for patients because they do not suppress the immune system.
• Does the use of the technology address any particular unmet need of the patient population?	Greater patient convenience over a subcutaneous injection and no dietary restrictions.
17. How do any side effects or adverse effects of the technology affect the management of the condition	In the core study, non-bleeding adverse events occurring in at least 10% of subjects in avatrombopag-treated versus placebo-treated patients included headache (37.5% vs. 11.8%), upper respiratory tract infection (18.8% vs. 5.9%), arthralgia (12.5% vs. 0%), and fatigue (12.5% vs. 5.9%). In the core and extension study together, 4/47 patients developed a thromboembolic event. 50% of patients who were on

and the patient's quality of life?	steroids at baseline, were able to wean or stop steroids. The symptoms of upper respiratory tract infection and headache are in keeping with known side effects of this class of treatment. The risk of thromboembolism is thought to be increased in patients with ITP. Whether that risk increases further with TPO RA treatments is debated, but is a possibility. Despite their potential side effects, the HRQoL is often improved in responding patients to this class of drug (TPO RA) The published data on tolerance for avatrombopag does not appear greatly different from other treatments in this class. Advantages are convenience (oral, no dietary restriction) and potential to reduce steroid burden.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, the requirements for an ITP diagnosis were appropriate, as was a platelet count <30 at time of entry. Target platelet count of 50-150 is a dosing regimen consistent with other TPO RA treatments.
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Platelet count response is the standard efficacy assessment used in ITP studies/trials. This acts as a surrogate for the prevention of severe and or fatal bleeding complications (Hill 2017 PMID 28480957) since these are rare events in actively managed patients. We would also consider HRQoL to be a further

	consideration.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Longer term safety and efficacy was addressed in the open-label extension study.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	None known.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	None known
20. Are you aware of any new evidence for the comparator treatment(s) in relevant guidance?	The control arm was placebo.
21. How do data on real-world experience compare with the	We are not aware of published real world data in ITP.

trial data?	Real world data was consistent with clinical trials for avatrombopag when used for its other licence indication (chronic liver disease): https://dmr.amegroups.com/article/view/7256/html Additionally, an oral presentation at the ASH conference 2020 reported a head to head study (study 305) comparing avatrombopag with eltrombopag, that was discontinued early due to recruitment challenges. In this study 12 patients with avatrombopag were compared to 11 patients receiving eltrombopag. Achieving a platelet count ≥ 50 on Day 8 was noted in 45.5% avatrombopag and 36.4% eltrombopag. Although numbers were insufficient for definitive conclusions, platelet count response to avatrombopag may be quicker. https://www.sciencedirect.com/science/article/abs/pii/S000649711871834X
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	n/a

Key messages
23. In up to 5 bullet points, please summarise the key messages of your submission. • Avatrombopag is the third licenced thrombopoietin receptor agonist (TPO RA), but is a welcome addition to current treatments since not all patients respond to the current standard of care. • The TPO RA class of agents are particularly important during the COVID-19 pandemic as they do not suppress the immune system and are currently the only class of drug licenced in ITP (other than fostamatinib, which is currently unavailable NICE TA 10387) with robust evidence of efficacy. • Unlike eltrombopag, avatrombopag does not cause liver derangement and is more convenient for patients as there are no dietary restrictions • Some patients who are intolerant or unresponsive to one TPO RA can successfully switch and tolerate or respond to an alternative TPO RA.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient expert statement

3838 - Avatrombopag in combination for treating chronic immune thrombocytopenia

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

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Information on completing this expert statement

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition?

	☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	The ITP Support Association
4. Did your nominating organisation submit a submission?	☒ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	I have lived with chronic ITP since 1992 and experienced the range of treatments, approaches to the condition, the advances in science in understanding the condition and developing new drugs and the changes in perception of what it is like to live with chronic ITP. It is a frightening condition to live with and I suffer from impaired QOL, chronic fatigue and have experienced the following side effects from Steroids, immunosuppressants, IVig, TPo's: severe and prolonged gut problems, blood clots in my brain, constant severe shoulder and neck pain, headaches, insomnia, high levels of anxiety, hair loss, impaired haemoglobin levels.

	I have many visits to hospital and have had many “rescue” trips, x rays, MRI scans, CT scans and ultrasounds over the years. Steroids particularly resulted in my having 22 infections within one 18-month period. Any kind of infection or even food poisoning can drop the platelet count dramatically and very quickly and additional blood counts and hospital visits then occur. Family and friends struggle to understand both the anxiety and fatigue surrounding living with this condition and how distressing the bruising and spontaneous bleeding can be, including difficulty stopping bleeding from what would be very innocuous cuts for a person with a normal platelet count. There is also the issue of potential internal haemorrhaging should I fall or have an accident. I always carry tranexamic acid tablets with me, in the events of spontaneous bleeding (mucal mainly) and going to the dentist, even for a regular hygiene appointment is problematical and extremely stressful. I quite frequently wake up to find I have had a bleed in the night and blood on my pillows and bedding. It is difficult to travel or plan a trip around injecting and not practicable to try and carry drugs which need to be kept at a specific cold temperature. Equally drugs that have dietary restrictions and timings around eating which make family life eating and socialising difficult for all involved. Living with ITP impacts social confidence, abilities to work, physical hobbies that are at risk of accidents and above all else it is a random condition that reacts differently in individuals across the board - one size does not fit all in terms of medication. Some people bleed at platelet counts of 30 and under and some like me bleed at counts over 50. I have had cuts that have taken 3 days to stop bleeding even when my platelet count was 114 and I was taking tranexamic acid.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Repercussions, especially long term, of immune suppression drugs are concerning, bone health, adrenal damage, depression and even more anxiety and loss of confidence because of the weight gains and moon face effects, isolate patients even more from society and result in more medication for depression, stomach problems and so on. Ivig is a temporary fix in most cases and not practicable long term as requires day care in hospital. TPO's Eltrombopag - higher incidence of blood clots, dietary restrictions, personally I experienced hair loss, brain clots, depletion of iron (not unusual) and caused problems with eating times and any kind of social life at home or outside the home. I experienced horrendous head pain and thought I was going to die on several occasions, this has affected my mental health to this day. It also severely impacted my haemoglobin count and I had to take very high doses of iron which affects the gut. A head scan identified blood clots in my brain because of this drug. Romiplostim - anxiety around long term self-injection, adds to bruising incidents around injection, little training on doing this, difficult for a lot of people to diligently inject correct doses. Sustainably wise - a lot of packaging to be disposed of, lots of wastage - syringes, wipes, glass containers - for anyone on high doses. Difficult to store in refrigerator at home in the quantities that are needed. I personally dispose of annually conservatively 96 unused syringes,288 unused sterile wipes,192 glass vials,96 boxes and plastic packaging, plus 48 used syringes, 48 unused needles! Whilst, without doubt it is good that the technology development has currently provided these drugs to ITP patients, oral tablets with minimal side effects and so few restrictions would have a massively positive impact for patients going forward.
10. Is there an unmet need for patients with this condition?	Yes, as above, this new drug would have such a positive impact for patients physically and mentally and improve quality of life without a doubt.

Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	It is oral, no restrictions around diet, research shows a more durable response, lesser disadvantages, improves QOL and mental health. ELTROMBOPAG is difficult for patients because fundamentally too much calcium can negate the efficacy of the drug. So, the drug needs to be taken ideally 4 hours after eating - I was always advised to take last thing at night, so a good 3-4 hours after last meal. So, one has to be careful to avoid too much of the following foods - dairy products (yoghurt, cheese, milk, orange juice, cereal and bread (last three are invariably fortified with calcium content, also leafy green vegetables (spinach and collards). All of this makes life very difficult at home, with family or partner and restricts a normal social life - be it at home or outside the home environment AVATROMBOPAG does not have any food or time restrictions. ROMIPLOSTIM: This must be done by injection, this is stressful, anxiety provoking and there is the worry of not administering the correct dosage for old and young alike. For those with ITP it also translates into more bruising at injection sites - this can affect mental health. There are significant problems around storage, the boxes are large and must be refrigerated and kept at a cool temperature. This also makes planning short breaks or holidays difficult and air travel limiting. As stated earlier there are also significant disposal issues that cost the NHS money. Both the TPOs above have their place in ITP treatment, however, Avatrombopag would make significant improvements, the studies of this drug confirm more robust and durable responses in patients, particularly for those patients who do not display high platelet responses or for whom the other 2 TPOs do not actually work. There are far less and distressing side effects documented and research says that the rescue incidents are also reduced in patients receiving Avatrombopag.

	By example the ISTH (International Society on Thrombosis and Haemostasis) Congress Abstracts of 2021 shows statistics of ITP response evaluation of Avatrombopag being extremely enhanced by patients switching to this drug from Eltrombopag and Romiplostim. The reasons for switching to Avatrombopag were convenience, ineffectiveness of the other two TPOs and adverse events (This was a report on a Multi Centre Study of US ITP Referral Centres). I believe that having this drug available, should it be deemed as suitable for some individual chronic ITP patients, should their consultants feel the drug is appropriate to them, would make a significant difference to their general wellbeing, it should be noted that there is very little counselling or mental health support available across the UK for patients who at the end of the day have to live with a very unpleasant condition for whom there is no end in sight. To eliminate food and eating time restrictions, injections and their storage and reduce rescue episodes and other drugs that they may need to take to alleviate side effects, can only be a positive move in the progress of ITP treatment and approach and benefit the economic impact on the NHS.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	The documented disadvantages of Avatrombopag are only comparable with the LESSER disadvantages of the other 2 TPOs currently available. So to be able to access this drug would be a major step forward in treatment options for patients and clinicians alike.
Patient population	
13. Are there any groups of patients who might benefit more or less from the	Patients young and old who lack the diligence and confidence to inject safely and competently, those who cannot cope with the dietary restrictions and timings of the medications, those at most risk of thrombosis because of other underlying conditions, those who must travel for work or who have young families and find the other drugs restrictions and applications untenable - lack of storage space, family eating, sleep times can be affected because tablets must be taken a minimum of 4 hours after food at night.

technology than others? If so, please describe them and explain why.	Also, those for whom the TPOs to date have undoubtedly made a difference, but arguably a better response might be achieved for them if the issues surrounding the drugs used to date are not around as in avatrombopag.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	Both the current TPOs do in many cases necessitate the use of other drugs - pain relief, stomach relief, anti-depressants, beta blockers and in the case of Romiplostim significant disposal costs of packaging and glass vials, syringes, antiseptic wipes and present storage issues and travel issues. Avatrombopag would be a breath of fresh air for many patients, would add to the arsenal of available drugs to help keep ITP patients stable (and sane!), it also, I believe, is an economically more viable drug. As a patient I would also like the following to be considered: Because of the random behaviour of the condition and the medication impact on individual patients I would ask that if this drug is passed for use in the UK, there are no accessibility restrictions around relativity to platelet count when clinicians can prescribe.

	The 30-count benchmark is in a potentially critical situation, but equally some of us bleed at a count over 50. Clinicians need the freedom to make prescribing decisions on an individual patient basis to translate into lesser rescue visits and costs across the NHS.

Topic-specific questions

Key messages

16. In up to 5 bullet points, please summarise the key messages of your statement:

- This TPO is another move in the right direction of non-immunosuppressant drugs, especially given there are new global infections such as Covid affecting people, and these are more impactful on people with chronic immune conditions.
- This is an oral drug with no restrictions surrounding food or eating times, which will enhance the QOL for patients.
- There are no storage implications and there are no packaging, wastage, or clinical disposal costs.
- Given the reduction in side effects and the good response rate documented, as opposed to the current 2 TPOs, this would translate in a reduction in rescue visits, plus reduce number of other drugs needed to be prescribed to alleviate the side effects of current treatments and therefore impact the NHS savings overall.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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Evidence Review Group's Report

Avatrombopag in combination for treating chronic immune thrombocytopenia

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None

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Rider on responsibility for report

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Contributions of authors

Edward Cox performed the economic analyses and wrote Sections 4, 5 and 6 of the report.

Mark Corbett performed the clinical effectiveness review and wrote Sections 3.1-3.3 of the report.

Pedro Saramago Goncalves performed the ERG network meta-analyses and wrote section 3.5 of the report.

Hollie Melton performed the clinical effectiveness review and wrote Sections 2 and 3.2.2.5 of the report.

Melissa Harden performed database searches and provided information and library support.

Simon Walker provided expert advice on the economic analyses.

Sofia Dias performed the network meta-analysis review and wrote section 3.4 of the report.

Claire Rothery performed the critical review of the economic analyses, contributed to the writing of Sections 4, 5 and 6 of the report, led the overall economic analyses and takes joint responsibility for the report as a whole.

Alison Eastwood contributed to the writing of Sections 2 and 3 of the report, led the overall clinical effectiveness review and takes joint responsibility for the report as a whole.

Note on the text

All commercial-in-confidence (CIC) data have been [redacted], all academic-in-confidence (AIC) data are [redacted], all depersonalised data (DPD) are [redacted].

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List of abbreviations

AE	Adverse event
ASH	American Society of Haematology guidelines
AVA	Avatrombopag
BCSH	British Committee for Standards in Haematology
BNF	British National Formulary
CHE	Centre for Health Economics
CHMP	Committee for Medicinal Products Human Use
CrI	Credible interval
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
ELT	Eltrombopag
EQ-5D	EuroQol - 5 Dimension
EMA	European Medicines Agency
EPAR	European public assessment report
ERG	Evidence review group
HR	Hazard ratio
HRG	Healthcare resource group
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ICH	Intracranial haemorrhage
IRR	Incidence rate ratio
ITP	Immune thrombocytopenia
IV	Intravenous
IVIg	Intravenous immunoglobulin
N/A	Not Applicable
NR	Not Reported
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
PAS	Patient access scheme
PLA	Placebo
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSSRU	Personal social services research unit
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
ROM	Romiplostim
RR	Relative risk
SAE	Serious adverse event
SLR	Systematic literature review
SmPC	Summary of product characteristics
TEAE	Treatment-emergent adverse event
TPO-RA	Thrombopoietin receptor agonist
TTO	Time trade-off
UK	United Kingdom
WHO	World Health Organisation

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 Overview of the ERG's key issues

Table 1: Overview of the ERG's key issues

ID	Summary of issue	Report sections
1.	The treatment pathway and positioning of avatrombopag relative to rituximab is unclear.	Sections 2.3 and 4.2.4.2
2.	The limited evidence-base for avatrombopag due to recruitment and attrition issues	Section 3.2
3.	Exclusion of some TPO-RA trials from the NMAs in the company's submission	Section 3.3.1
4.	The company estimates of comparative effectiveness between TPO-RAs for the outcome of durable platelet response	Sections 3.4 and 3.5
5.	The modelled time to treatment response. In clinical practice TPO-RA treatment duration is likely below 24-weeks for patients not responding to treatment.	Section 4.2.2.2
6.	The composition of subsequent treatments in the model only allows pairwise comparisons of treatment strategies.	Section 4.2.4.2
7.	The company's mixed treatment sequencing approach cannot determine the optimum position for avatrombopag among TPO-RAs.	Section 4.2.4.2
8.	Source to inform dosages for non-TPO-RAs is outdated.	Section 4.2.9.2
9.	Different definitions of response for TPO-RAs and non-TPO-RAs	Section 4.2.6.3
10.	The long-term treatment duration of TPO-RAs	Section 4.2.6.5
11.	Proportion of patients receiving rescue therapy	Section 4.2.6.9
12.	The longer-term mortality risks associated with ITP	Section 4.2.7.2
13.	Health-related quality of life utility values used in the model	Section 4.2.8.2
14.	Overestimation of administration costs for romiplostim	Section 4.2.9.2
15.	Overestimation of treatment acquisition costs for romiplostim	Section 4.2.9.2
16.	Approach to costing bleeding and recue therapy events in the model	Section 4.2.9.2

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are (i) removing TPO-RAs from subsequent lines of therapy to provide a fully incremental comparison of treatment sequences each with a common set of subsequent therapies; (ii) drug dosing schedules matching the latest guidance; (iii) estimates of comparative effectiveness from the ERG frequentist fixed-effect ITC; (iv) utility values adjusted by age; (v) romiplostim administration costs based on one initial clinic visit followed by 12.5% of patients administering at a haematological outpatient visit; (vi) romiplostim drug acquisition costs aligned with median doses from the pivotal romiplostim trial in the first 24-weeks of active treatment; (vii) rescue therapy rates and costs configured to Study 302 + Extension and bleeding event costs aligned to NHS reference costs.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing the proportion of patients who achieve a durable platelet response ($\geq 50 \times 10^9$/L), as response is associated with better health-related quality of life, lower risk of bleeds and rescue therapy and greater life expectancy.

Overall, the technology is modelled to affect costs by:

- Increasing the proportion of patients who achieve a durable platelet response ($\geq 50 \times 10^9$/L), as response is associated with lower risk of bleeds and a reduced dependency for rescue therapies and concomitant medications.
- Reduced administration costs compared with romiplostim.

The modelling assumptions that have the greatest effect on the ICER are:

- Durable platelet response rates
- Long-term TPO-RA treatment duration
- Rates and costs of bleed and rescue therapy events

1.3 The decision problem: summary of the ERG's key issues

Issue 1 Positioning of rituximab in the treatment pathway

Report section	2.3
Description of issue and why the ERG has identified it as important	The treatment pathway and positioning of avatrombopag relative to non-TPO-RAs such as rituximab is unclear. The ERG has identified this as a potential issue as it is uncertain whether rituximab should be considered a relevant comparator.
What alternative approach has the ERG suggested?	The ERG notes that in TA293 (eltrombopag), if rituximab was considered an appropriate treatment option, patients were assumed to have already received it, i.e., rituximab was assumed to come before eltrombopag or romiplostim. In TA221 (romiplostim), rituximab was positioned after romiplostim, but clinical specialists at the committee meeting for appraisal TA221 suggested that romiplostim would be used in clinical practice (at that time) in people whose condition is refractory to rituximab, or who are intolerant of rituximab. In the most recent NICE Technology Appraisal of fostamatinib for treating refractory chronic immune thrombocytopenia (ID1087), the treatment pathway for chronic ITP positioned TPO-RAs before rituximab, splenectomy, azathioprine, mycophenolate, cyclosporine, dapsone and danazol. The ERG clinical advisor reported that there is variation in the use of rituximab in UK clinical practice, and the variation in use has changed further in the last few years in the context of the COVID-19 pandemic, where TPO-RAs are now more likely to be given before rituximab. The ERG considers the company's position that eltrombopag and romiplostim are the most relevant comparators to be reasonable, but recognises that there is uncertainty about the positioning of rituximab in the treatment pathway.
What is the expected effect on the cost-effectiveness estimates?	Not applicable.
What additional evidence or analyses might help to resolve this key issue?	Not applicable.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

Issue 2 Limited evidence-base for avatrombopag due to recruitment and attrition issues

Report section	3.2
Description of issue and why the ERG has identified it as important	Both of the two main avatrombopag trials had methodological limitations. Study 302 was small (n=49) and had an important imbalance in missing outcome data due to lack of efficacy in the placebo group (only one placebo patient completed the trial). Study 305 of avatrombopag vs eltrombopag was terminated early due to significant enrolment challenges [redacted]. The study aimed to recruit [redacted] patients but only [redacted] were randomised when the trial was terminated.
What alternative approach has the ERG suggested?	No alternative data exist.
What is the expected effect on the cost-effectiveness estimates?	The limited evidence adds uncertainty to the cost-effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	Another trial comparing avatrombopag with eltrombopag would help to resolve uncertainty about comparative effectiveness. Invasive endoscopies would not be needed, though the feasibility of recruiting enough patients is still uncertain.

Issue 3 Exclusion of some TPO-RA trials from the NMAs in the company's submission

Report section	3.3.1
Description of issue and why the ERG has identified it as important	The company excluded seven TPO-RA comparator trials from their NMAs, despite these trials being included in their systematic review. The exclusions were based on judgements on one or more of the following issues: treatment durations, initial TPO-RA doses, and population ethnicity.
What alternative approach has the ERG suggested?	The ERG and their clinical adviser reviewed these decisions and disagreed with the company's reasons for excluding these trials.
What is the expected effect on the cost-effectiveness estimates?	The expected effect on cost-effectiveness is uncertain because the only outcome included in the company's model that is dependent on treatment is durable platelet count.
What additional evidence or analyses might help to resolve this key issue?	Conduct NMAs with these trials included. Although the short duration of follow up of most of these trials means they do not have data for the key outcome in the model, durable response. The excluded trials could contribute data to the more clinically-important bleeding event outcomes.

Issue 4 Comparative effectiveness estimates from the NMA for durable platelet response

Report section	3.4 and 3.5

Description of issue and why the ERG has identified it as important	The ERG has major concerns about the company's NMA for the primary efficacy outcome of durable platelet response used in the cost-effectiveness analysis: • The NMA results for avatrombopag vs. placebo (common comparator) lack face validity with respect to the trial results from Study 302 (i.e., odds ratio reported from NMA for avatrombopag vs. placebo is 102.80 [95% CrI: 3.87 - 2,796,449] compared to the study-specific odds ratio of 18.72 [95% CI: 1.02 - 340]); • The appropriateness of the continuity corrections used in the NMA to correct for the presence of zero events in study arms of the trials (Study 302 for avatrombopag and Kuter 2008 SPL for romiplostim); • Response outcomes for the pivotal study of eltrombopag (RAISE) were estimated for the observed population, whereas for all other studies included in the NMA the ITT population was used; • The appropriateness of the inclusion of fostamatinib trials in the NMA; • Heterogeneity in placebo response rates across the trials included in the NMA.
What alternative approach has the ERG suggested?	The ERG has undertaken additional analyses to correct the issues identified in the company's NMA for the outcome of durable platelet response. These estimates suggest that romiplostim is expected to be the most effective treatment (odds ratio of 29.61 [95% CI: 5.42 - 161.58] for romiplostim vs. placebo), followed by avatrombopag (odds ratio of 18.72 [95% CI: 1.03 - 340.54] for avatrombopag vs. placebo), and then eltrombopag (odds ratio of 10.60 [95% CI: 3.64 – 30.87] for eltrombopag vs. placebo).
What is the expected effect on the cost-effectiveness estimates?	The ERG alternative estimates for the response rates of avatrombopag, eltrombopag, and romiplostim have a major impact on the cost-effectiveness results: ERG Scenario 5 demonstrates that the company's base case incremental QALYs and cost saving decreases from [redacted] to [redacted] and [redacted] to [redacted] for the comparison of avatrombopag vs. eltrombopag, and decreases from 0.378 to [redacted] and [redacted] to [redacted] for the comparison of avatrombopag vs. romiplostim, respectively. The scenario ICER is [redacted] /QALY for romiplostim compared to avatrombopag. Eltrombopag remains dominated when compared to avatrombopag.
What additional evidence or analyses might help to resolve this key issue?	The ERG considers that the issues related to the company's NMA are resolved in the ERG's base-case. However, additional evidence on the comparative effectiveness between avatrombopag, eltrombopag, and romiplostim for the outcome of durable platelet response is required.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

Issue 5 Modelled time to treatment response

Report section	4.2.2.2
Description of issue and why the ERG has identified it as important	The company's model assumes that patients wait a full 24 weeks to assess non-response to TPO-RA treatment (avatrombopag, eltrombopag and romiplostim). The product SmPCs for the TPO-RAs all stipulate stopping treatment if response is not achieved within a short time window after establishment of maximum dose. The ERG considers non-response to treatment with a TPO-RA to be observed within clinical practice within a time-frame of around 8 weeks rather than 24 weeks as used in the company's model. Furthermore, the ERG considers there to be little evidence of a specific time-to-response effect in Study 302 to suggest that TPO-RAs warrant a longer 24-week timeframe to assess response to treatment.
What alternative approach has the ERG suggested?	Extending treatment for non-responders by a further 16 weeks (from 8 to 24 weeks) will increase costs but it does not appear to meaningfully increase response to treatment; however, the latter cannot be assessed using the durable platelet response definition as used in the model as this refers to at least 6 weekly platelet counts $\geq 50\times10^9$/L in the final 8 weeks of a 24-26-week study. The modelled timeframe for treatment response is further complicated by the fact that patients in Study 302 were also receiving concomitant ITP medication, which may lead to further dose adjustments in order to achieve a stable platelet response. The ERG undertook an exploratory analysis to assess the impact on costs of treatment at first line for a response assessment time point of 8 weeks.
What is the expected effect on the cost-effectiveness estimates?	The difference in avatrombopag acquisition costs for an 8-week vs. 24 week stopping rule is [redacted]. ERG Scenario 1 demonstrates that the company's corrected base case incremental cost saving increases from [redacted] to [redacted] for the comparison of avatrombopag vs. eltrombopag, and decreases from [redacted] to [redacted] for the comparison of avatrombopag vs. romiplostim, respectively. Avatrombopag was the dominant strategy compared to eltrombopag and romiplostim (most effective with the lowest cost).
What additional evidence or analyses might help to resolve this key issue?	Alternative response criterion and assessment time points for response to treatment are required.

Abbreviations: TPO-RA, thrombopoietin receptor agonist.

Issue 6 Cost-effectiveness modelling only permits pairwise comparisons

Report section	4.2.4.2
Description of issue and why the ERG has identified it as important	The approach used by the company to model subsequent treatments after discontinuation of first-line treatment (avatrombopag, eltrombopag or romiplostim) restricts the cost-effectiveness analysis to a comparison of only two mutually exclusive treatment strategies simultaneously, i.e., results are

	presented for avatrombopag vs. eltrombopag and avatrombopag vs. romiplostim separately. This occurs because the proportion of active therapies modelled at subsequent lines (mixed treatment strategy) is dependent on the comparator technology (eltrombopag or romiplostim).
What alternative approach has the ERG suggested?	To establish the most cost-effective treatment sequence from a series of possible strategies, it is necessary to undertake a fully incremental analysis comparing all the sequences simultaneously. This is a core principle of cost-effectiveness analysis that involves assessing the incremental cost of generating additional health effects when moving from one strategy to a more effective one, and assessing this against the NICE cost-effectiveness threshold as the measure of opportunity cost. The ERG suggests removing TPO-RAs from the mixed treatment strategy at subsequent lines to enable a fully incremental comparison of avatrombopag, eltrombopag and romiplostim.
What is the expected effect on the cost-effectiveness estimates?	Removing TPO-RAs from the mixed treatment strategy at subsequent lines has limited effect on the cost-effectiveness estimates; however, it permits a fully incremental comparison of avatrombopag, eltrombopag and romiplostim.
What additional evidence or analyses might help to resolve this key issue?	Not applicable as the ERG has provided a revised version of the model with functionality that permits a simultaneous comparison of cost-effectiveness results for multiple alternative treatment strategies and enables a fully incremental analysis.

Abbreviations: TPO-RA, thrombopoietin receptor agonist.

Issue 7 Modelled treatment sequences

Report section	4.2.4.2
Description of issue and why the ERG has identified it as important	The company has not used the modelled treatment sequences to determine the most efficient use and positioning of avatrombopag among the TPO-RAs.
What alternative approach has the ERG suggested?	If treatment sequencing is considered a valid approach then the company should consider the use of avatrombopag at alternative points within a treatment sequence. For example, assuming that the TPO-RAs may be used in any order and avatrombopag may be positioned before or after an alternative TPO-RA, then there is a minimum of six relevant treatment sequences for avatrombopag. If non-TPO-RAs were also to be considered in the sequence, then the decision problem gets exponentially large. Importantly, a more formal evaluation of the positioning of avatrombopag among the TPO-RAs would allow the optimum position for avatrombopag to be determined.
What is the expected effect on the cost-effectiveness estimates?	The most cost-effective treatment sequence will depend on the response rates of the alternative TPO-RAs and the time spent between treatments as non-responders, as well as the treatment costs where it might be anticipated that it is more cost-effective to start treatment with cheaper therapies before progressing to more expensive options. An exploratory analysis by the ERG on the positioning of avatrombopag among TPO-RAs demonstrated limited impact on cost-effectiveness conclusions but this was

	based on the company's modelled assumptions where treatment discontinuation rates for the TPO-RAs were assumed to be identical.
What additional evidence or analyses might help to resolve this key issue?	Additional evidence on the comparative effectiveness between avatrombopag, eltrombopag, and romiplostim and the duration of each treatment (long-term discontinuation rates) is required to assess the most efficient use and positioning of avatrombopag among the TPO-RAs.

Abbreviations: TPO-RA, thrombopoietin receptor agonist.

Issue 8 Drug dosages for non-TPO-RAs

Report section	4.2.9.2
Description of issue and why the ERG has identified it as important	The dosages for non-TPO-RAs used in the cost-effectiveness analysis were based on those from TA293 (eltrombopag) and sourced from Provan et al (2010) [1]. The ERG notes that the guidelines reported in Provan et al (2010) have been superseded with updated guidance published in Provan et al (2019) [2].
What alternative approach has the ERG suggested?	The ERG believes that the updated guidance provides a more relevant source to inform dosages for the non-TPO-RAs.
What is the expected effect on the cost-effectiveness estimates?	The revised dosages for non-TPO-RAs have a very minor impact on the cost-effectiveness results: ERG Scenario 4 demonstrates that the company's corrected base case incremental cost savings marginally increase from [redacted] to [redacted] for the comparison of avatrombopag vs. eltrombopag, and increase from [redacted] to [redacted] for the comparison of avatrombopag vs. romiplostim, respectively. Avatrombopag was the dominant strategy compared to eltrombopag and romiplostim (most effective with the lowest cost).
What additional evidence or analyses might help to resolve this key issue?	The ERG considers that this issue is resolved in the ERG's base-case assumptions.

Abbreviations: TPO-RA, thrombopoietin receptor agonist.

Issue 9 Modelled treatment response rates for TPO-RAs and non-TPO-RAs

Report section	4.2.6.3
Description of issue and why the ERG has identified it as important	Treatment response estimates for first and subsequent lines of therapy used in the model are based on different definitions of response for TPO-RAs and non-TPO-RAs. At first-line for TPO-RAs, the definition of response is durable platelet count, while for subsequent lines of therapy, not involving a TPO-RA, the definition of response is unclear. The ERG notes that the response rates used in subsequent lines of treatment for non-TPO-RAs are very high relative to the response rates used in the model for TPO-RAs. This suggests that the definition of treatment response for non-TPO-RAs is most likely reflecting a treatment response (platelet count $\geq 50\times10^9$/L) at a single point in time rather than a sustained response over a fixed time period. Consequently, the treatment response estimates used in the model for subsequent lines of therapy are based on a mixed treatment response definition

	because subsequent lines of therapy include a mix of both TPO-RAs and non-TPO-RAs.
What alternative approach has the ERG suggested?	The assumption that 'response' and 'durable platelet count' are interchangeable is unlikely to hold, i.e., those experiencing a platelet response of $\geq 50 \times 10^9$/L at least once are unlikely to be considered as achieving the same response as those who maintain a durable or sustained response over a period of at least 6 weekly platelet counts. The ERG believes that either the same definition of treatment response should be used across all treatments or a fixed treatment strategy (not mixed by different proportions of TPO-RAs and non-TPO-RAs) should be used in subsequent treatment lines.
What is the expected effect on the cost-effectiveness estimates?	The impact on cost-effectiveness of the assumption that 'response' and 'durable platelet count' are the same is difficult to assess because the company has used a mixed treatment strategy (involving both TPO-RAs and non-TPO-RAs) in subsequent treatment lines.
What additional evidence or analyses might help to resolve this key issue?	Further clarity on the definition of treatment response and corresponding estimates for non-TPO-RAs. The company submission only refers to response rates for non-TPO-RAs as those adopted from TA221 (romiplostim). Recent and up-to-date estimates of treatment response rates and time to response for non-TPO-RAs is required.

Abbreviations: TPO-RA, thrombopoietin receptor agonist.

Issue 10 Long-term treatment duration

Report section	4.2.6.5
Description of issue and why the ERG has identified it as important	The longer-term durability of treatment response on TPO-RA treatment (avatrombopag, eltrombopag or romiplostim) was assumed to be an average of 109 model cycles (436 weeks or 8.4 years) over a patients' lifetime, which equates to a constant discontinuation rate of 0.9% per 4-week model cycle. This estimate was based on the lowest of the mean times on treatment of 109 cycles for eltrombopag and 393 cycles for romiplostim reported in Lee et al [3]. The difference in mean time on treatment for eltrombopag and romiplostim suggests that there could be a notable difference in long-term discontinuation rates between the TPO-RAs.
What alternative approach has the ERG suggested?	Even if the treatment duration is assumed to be identical between the TPO-RAs, the actual mean estimate used in the model (e.g., 109 cycles vs. 393 cycles) will have an impact on the cost-effectiveness of avatrombopag relative to eltrombopag and romiplostim. This is because the higher the response rate between the alternative TPO-RAs, the longer (greater mean time on treatment) or shorter (lower mean time on treatment) this response is maintained over time, which impacts the time to the 'no treatment no response' health state that incurs an elevated risk of bleeding (and associated high costs of hospitalisation and mortality) and need for rescue therapy. The ERG undertook an exploratory analysis to assess the impact of a longer treatment duration of 393 cycles applicable to all TPO-RAs (ERG Scenario 6a) and another scenario considering

	393 cycles for romiplostim only (109 for eltrombopag and eltrombopag) (ERG Scenario 6b).
What is the expected effect on the cost-effectiveness estimates?	Lower discontinuation rates for a more effective treatment will only result in improved cost-effectiveness when the movement to the 'no treatment no response' health state occurs late enough in time so that the elevated risk of severe bleeding events and need for rescue therapy are significantly discounted, and the next subsequent line of therapy is less cost-effective than the TPO-RA. The ERG exploratory analysis had a notable impact on the cost-effectiveness results: ERG Scenario 6a (treatment duration of 393 cycles for all TPO-RAs) demonstrates that the company's corrected base case incremental QALYs and cost savings increase from [redacted] to [redacted] and [redacted] to [redacted] for the comparison of avatrombopag vs. eltrombopag, and increases from [redacted] to [redacted] and [redacted] to [redacted] for the comparison of avatrombopag vs. romiplostim, respectively. Avatrombopag was the dominant strategy compared to eltrombopag and romiplostim (most effective with the lowest cost). ERG Scenario 6b (treatment duration of 393 cycles for romiplostim and 109 for avatrombopag and eltrombopag) demonstrates that the company's base case incremental QALYs decrease from [redacted] to [redacted] and incremental costs increase from [redacted] to [redacted] for the comparison of avatrombopag vs. romiplostim. The scenario ICER is [redacted]/QALY for romiplostim compared to avatrombopag. Estimates for the comparison of avatrombopag vs. eltrombopag were comparable to company base case results.
What additional evidence or analyses might help to resolve this key issue?	Evidence on the long-term treatment duration for initial responders to TPO-RAs is required.

Abbreviations: TPO-RA, thrombopoietin receptor agonist.

Issue 11 Rates of rescue therapy

Section 4.2.6.9	4.2.6.9
Description of issue and why the ERG has identified it as important	The ERG has two main concerns with the rates of rescue therapy used in the model: (1) The rates of rescue therapy for responders and non-responders are uncertain. The rates used in the company's model of 3% and 22% per model cycle for responders and non-responders, respectively, are reported to be based on TA293 (eltrombopag); however, the ERG is unable to validate the rates reported as the source used in TA293 is unclear. (2) The company stratified rescue therapy into two attributable causes: bleeding and non-bleeding events. Rates for each of the attributable cause are informed by nine patients from Study 302, therefore highly uncertain.
What alternative approach has the ERG suggested?	The ERG is unable to validate the rates reported by the company as the source is unclear.

What is the expected effect on the cost-effectiveness estimates?	This is explored in ERG Scenario 11.
What additional evidence or analyses might help to resolve this key issue?	Evidence on the rates of rescue therapy.

Abbreviations:-TPO-RA, thrombopoietin receptor agonist.

~~Issue 12:~~ Mortality risks associated with ITP

Report section	4.2.7.2
Description of issue and why the ERG has identified it as important	The company only consider fatal bleeds for disease-related mortality. The ERG considers there to be significant uncertainty surrounding the longer-term survival of ITP patients. This could be important as health gains from improvements in longer-term survival may be overestimated.
What alternative approach has the ERG suggested?	The ERG considered the impact of applying the following hazard ratios to the company's base case age- and sex-adjusted UK general population mortality rate: ERG Scenario 7a: Enger et al's (2010) – 4.2 ERG Scenario 7b: Frederisken et al (2014) – 1.5 ERG Scenario 7c: Schoonen et al (2009) – 1.6 ERG Scenario 7d: Schoonen et al (2009) – 1.408 (when adjusting for bleed- and infection-related mortality)
What is the expected effect on the cost-effectiveness estimates?	The ERG exploratory analysis had a minor impact on the cost-effectiveness results: ERG Scenario 7a (that applying the highest hazard ratio) demonstrates that the company's corrected base case incremental QALYs decrease from [redacted] to [redacted] and [redacted] to [redacted] for the comparison of avatrombopag vs. eltrombopag, and decreases from [redacted] to [redacted] and [redacted] to [redacted] for the comparison of avatrombopag vs. romiplostim, respectively. Avatrombopag was the dominant strategy compared to eltrombopag and romiplostim (most effective with the lowest cost). Scenarios 7b-7d provided results between Scenario 7a and company base case results.
What additional evidence or analyses might help to resolve this key issue?	Bleed and non-bleed related long-term mortality risks for patients with chronic ITP.

Abbreviations: TPO-RA, thrombopoietin receptor agonist.

Issue 13 Health-related quality of life utility values

Report section	4.2.8.2
Description of issue and why the ERG has identified it as important	The company did not adjust the utility values by age over time in the model. The general population sex- and age-adjusted utilities used to calculate health-state utility values apply to 45–54 year-olds. When utility values are considered over the 56-year lifetime horizon, the utility values assigned to ITP patients can eventually exceed the general population utility estimates.

What alternative approach has the ERG suggested?	In ERG Scenario 8, the ERG adjusted the utility values by age over time.
What is the expected effect on the cost-effectiveness estimates?	The age-adjusted utility values have a very minor impact on the cost-effectiveness results: ERG Scenario 8 demonstrates that the company's corrected base case incremental QALYs decrease from [redacted] to [redacted] for the comparison of avatrombopag vs. eltrombopag, and decrease from [redacted] to [redacted] for the comparison of avatrombopag vs. romiplostim, respectively. Avatrombopag was the dominant strategy compared to eltrombopag and romiplostim (most effective with the lowest cost).
What additional evidence or analyses might help to resolve this key issue?	The ERG considers that this issue is resolved in the ERG's base-case assumptions.

Abbreviations: TPO-RA, thrombopoietin receptor agonist.

Issue 14 Administration costs for romiplostim

Report section	4.2.9.2
Description of issue and why the ERG has identified it as important	The ERG has three main concerns with the company assumed administration costs for romiplostim: (i) costing the first four romiplostim administrations within a clinic setting (as supposed to only the first dose as stated in the CS) (ii) the 27.7% long-term proportion of patients administering romiplostim within a clinic setting which may not be representative of current clinic practice the costs associated with administering romiplostim in a clinic setting are potentially overestimated
What alternative approach has the ERG suggested?	To resolve these concerns, the ERG has conducted the following additional analyses: ERG Scenario 9a: All patients are assumed to receive their first dose at clinic visit with 27.7% assumed at clinic thereafter (as opposed to the first four doses received in cycle 1) ERG Scenario 9b: 12.5% of romiplostim administrations are conducted in clinic after the 1st cycle (as opposed to 27.7%) ERG Scenario 9c: Romiplostim clinic administrations costed as clinical haematology outpatient visits (£165.57) (as opposed to £241.06) (1) ERG Scenario 9d: All three scenarios combined.
What is the expected effect on the cost-effectiveness estimates?	The alternative approaches have a minor impact on the cost-effectiveness results: ERG Scenario 9d demonstrates that the company's corrected base case incremental cost savings decrease from [redacted] to [redacted] for the comparison of avatrombopag vs. romiplostim, respectively. ERG Scenario 9 did not impact the comparison between avatrombopag or eltrombopag. Avatrombopag was the dominant strategy compared to eltrombopag and romiplostim (most effective with the lowest cost).

What additional evidence or analyses might help to resolve this key issue?	The ERG considers that these issues are resolved in the ERG's base-case assumptions.

Issue 15 Romiplostim treatment acquisition costs

Report section	4.2.9.2
Description of issue and why the ERG has identified it as important	The company's romiplostim acquisition costs do not take account of the weight distribution of the study population or the up-titration of dosing.
What alternative approach has the ERG suggested?	To resolve these concerns, the ERG has conducted the following additional analyses: ERG Scenario 10a: applies median doses from the pivotal romiplostim trial (non-splenectomised: 0.002mg/kg; splenectomised: 0.003mg/kg) to model romiplostim doses in the first 24-weeks of active treatment. ERG Scenario 10b: applies romiplostim doses from TA293 (eltrombopag) calculated from the distribution of patient weights from RAISE and average romiplostim usage for patients in the first 24 weeks of treatment from the pivotal romiplostim trial, averaged over the 4 week cycle length
What is the expected effect on the cost-effectiveness estimates?	The alternative approaches have a significant impact on the cost-effectiveness results: ERG Scenario 10a demonstrates that the company's corrected base case incremental cost savings decrease from [redacted] to [redacted] for the comparison of avatrombopag vs. romiplostim, respectively. ERG Scenario 10b demonstrates that the company's corrected base case incremental cost savings decrease from [redacted] to [redacted] for the comparison of avatrombopag vs. romiplostim, respectively. ERG Scenario 10a and 10b did not impact the comparison between avatrombopag or eltrombopag. Avatrombopag was the dominant strategy compared to eltrombopag and romiplostim (most effective with the lowest cost).
What additional evidence or analyses might help to resolve this key issue?	The ERG considers that these issues are resolved in the ERG's base-case assumptions.

Issue 16 Costs and configuration of bleeds and rescue therapy events used in the model

Report section	4.2.9.2
Description of issue and why the ERG has identified it as important	The ERG has three main concerns with the rates of rescue therapy used in the model: (i) The rates of rescue therapy for responders and non-responders is uncertain while company acquired rescue therapy rates could not be verified from their source by the ERG [TA293].

	(ii) Bleed-related rescue therapy event probabilities and associated costs are assumed to be nested within those for bleeding events. The ERG believes this new approach complicates the interpretation of bleed and rescue costs, represents a significant departure from the approach used in previous appraisals [TA293 and TA221] and is unwarranted. (iii) the bleed costs applied in the model are derived from a company commissioned paradigm review with markedly higher costs compared to NHS reference costs and those applied in previous appraisals.
What alternative approach has the ERG suggested?	To resolve these concerns, the ERG has conducted a scenario analysis (ERG Scenario 11) using the following model inputs: 1. Company non-bleed related rescue therapy event costs applied to bleed-related and non-bleed related rescue therapy events to aid consistency and interpretability. 2. Bleed-related rescue therapy events costed independently using NHS reference costs (i.e. not containing bleed-related rescue therapies). 3. Applies rescue therapy rates observed in Study 302 + extension.
What is the expected effect on the cost-effectiveness estimates?	This alternative approach has a significant impact on costs and cost-effectiveness. ERG Scenario 11 demonstrates that the company's corrected base case cost savings from [redacted] to [redacted] for the comparison of avatrombopag vs. eltrombopag, and [redacted] to [redacted] for the comparison of avatrombopag vs. romiplostim, respectively. QALY differences were marginal. The ICER in this scenario was [redacted]/QALY for avatrombopag versus eltrombopag. Avatrombopag was the dominant strategy compared to romiplostim.
What additional evidence or analyses might help to resolve this key issue?	The ERG considers that issues (ii) and (iii) are resolved in the ERG's base-case assumptions. For issue (i) see issue 7.

1.6 Other key issues: summary of the ERG's view

None

1.7 Summary of ERG's preferred assumptions and resulting ICER

Table 2 summarises the ERG's preferred assumptions and resulting ICER. For further details of the exploratory and sensitivity analyses conducted by the ERG, please see Section 6.

Table 2: Summary of ERG's preferred assumptions and resulting ICER

Scenario	**Incremental cost**	**Incremental QALYs**	**ICER (change from company base case)**
Company base case			
avatrombopag vs. eltrombopag	[redacted]	[redacted]	[redacted]
avatrombopag vs. romiplostim	[redacted]	[redacted]	[redacted]
ERG Scenario 2: a fully incremental comparison of treatment strategies with subsequent therapies aligned across comparators			
Avatrombopag	-	-	-
Eltrombopag	[redacted]	[redacted]	[redacted]
Romiplostim	[redacted]	[redacted]	[redacted]
ERG Scenario 4: updated guidance to inform dosages for non-TPO-RAs in the model			
Eltrombopag (vs. avatrombopag)	[redacted]	[redacted]	[redacted]
Romiplostim (vs. avatrombopag)	[redacted]	[redacted]	[redacted]
ERG Scenario 5: applying ERG estimates of comparative effectiveness for durable platelet response			
Eltrombopag (vs. avatrombopag)	[redacted]	[redacted]	[redacted]
Romiplostim (vs. avatrombopag)	[redacted]	[redacted]	[redacted]
ERG Scenario 8: applying age-adjusted utilities			
Eltrombopag (vs. avatrombopag)	[redacted]	[redacted]	[redacted]
Romiplostim (vs. avatrombopag)	[redacted]	[redacted]	[redacted]
ERG Scenario 9d: Administration costs for romiplostim based on one initial clinic visit and alternative rates and costs for administrations			
Romiplostim (vs. avatrombopag)	[redacted]	[redacted]	[redacted]
ERG Scenario 10a: Romiplostim dosing in the first 24-weeks from medium dosages in pivotal trial			
Eltrombopag (vs. avatrombopag)	[redacted]	[redacted]	[redacted]
Romiplostim (vs. avatrombopag)	[redacted]	[redacted]	[redacted]
ERG Scenario 11			
Eltrombopag (vs. avatrombopag)	[redacted]	[redacted]	[redacted]
Romiplostim (vs. avatrombopag)	[redacted]	[redacted]	[redacted]
ERG base-case **ERG Scenarios 2+4+5+8+9d+10a+11**			
Avatrombopag			
Eltrombopag	[redacted]	[redacted]	[redacted]
Romiplostim	[redacted]	[redacted]	[redacted]

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

In this report the ERG has reviewed the clinical and cost-effectiveness evidence submitted by Sobi AB in support of avatrombopag (Doptelet) for adults with chronic immune thrombocytopenia (ITP) that is refractory to other treatments.

ITP is defined by the company as:

> a rare autoimmune disorder characterised by the destruction and impaired production of platelets, and defined by an abnormal platelet count of $<100\times10^9$/L (normal adult platelet count range is $150–450\times10^9$/L). […] ITP develops into a chronic disorder in 80% of adult patients. […] the platelet response threshold of 50×10^9/L is an accepted measure for treatment response in both ITP clinical studies and clinical practice. While data indicate that the impact of ITP is greatest when platelet counts are $<30\times10^9$/L, a risk of bleeding is still observed when platelet counts are between $30–50\times10^9$/L *(CS, p11)*

The ERG considers the company's description of the health condition is broadly appropriate and relevant to the decision problem. The ERG's clinical advisor indicated that in practice patients are treated on a case-by-case basis, wherein the platelet count in isolation would not dictate treatment, unless posing a severe threat.

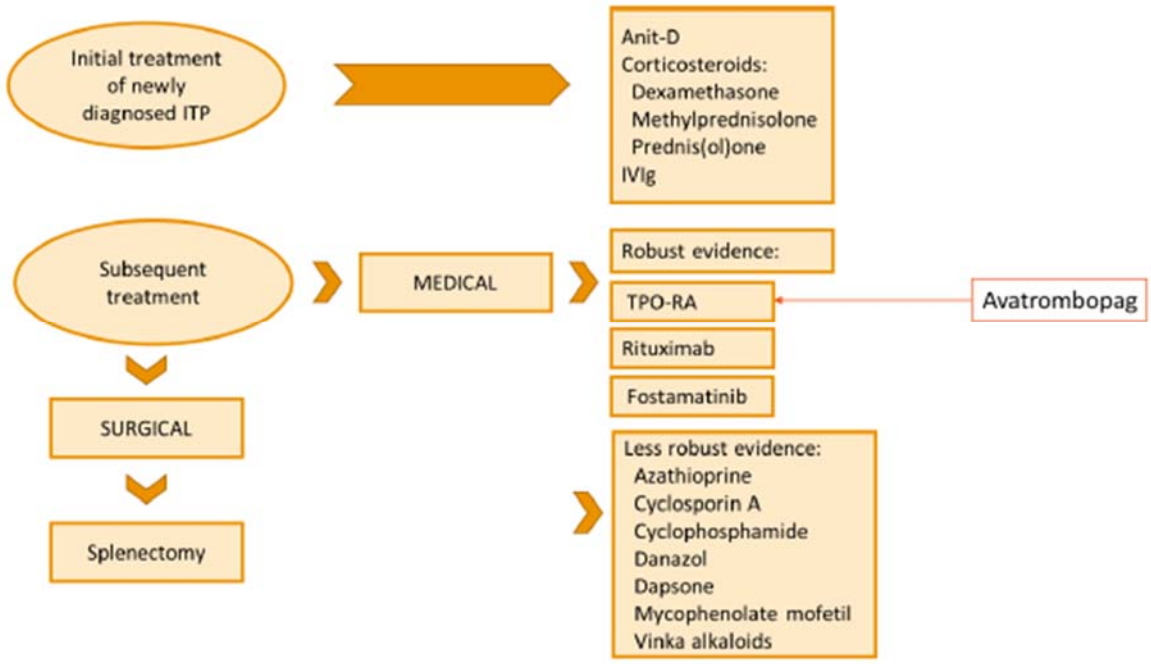
In this section the ERG critiques the company's proposed positioning of avatrombopag in the treatment pathway and its definition of the decision problem when compared to the NICE scope.

2.2 Background

The proposed position of avatrombopag in the treatment pathway is presented in Figure 1 of the CS, and reproduced below for reference. The ERG's clinical advisor broadly agreed with the presented treatment pathway. Corticosteroids are used as first-line treatment; the clinical advisor noted though that anti-D is no longer manufactured. Patients used to then proceed to rituximab but can move quickly through the pathway, and treatment selection is based on patient characteristics and consultation. Due to the pandemic, the clinical advisor commented that patients are now proceeding straight to TPO-RAs. This part of the pathway may vary across the NHS, and across recent timelines. The clinical advisor also added that splenectomy is no longer carried out in the UK, and may be more prevalent in other countries.

The ERG and their clinical advisor agree with the suggested position of avatrombopag as an additional TPO-RA option, for patients who have failed initial treatment for ITP. The ERG acknowledges that avatrombopag offers a new option for treatment.

Figure 1 Clinical care pathway of ITP and avatrombopag positioning



Abbreviations: IVIg, intravenous immunoglobulin g; TPO-RA, thrombopoietin receptor agonist
Source: CS, Figure 1

The company stated that an additional option to existing TPO-RAs (eltrombopag and romiplostim) is important because a loss of response or adverse events lead to treatment discontinuation. Avatrombopag is administered as a once-daily oral dose, taken with food. Existing TPO-RAs require fasting and dietary restriction (eltrombopag) or administration via injection (romiplostim). In the CS the company report improved adherence in comparison to approved TPO-RAs, though there was no direct evidence reported to support this claim. Table 23 in the CS reported completion rates across included trials, in which avatrombopag had the lowest completion rate. Table 51 in the CS reported the assumed discontinuation per cycle within the economic model and all TPO-RAs were assumed equal. ASH guidelines reflect on this with reference to eltrombopag and its dietary requirements being a challenge to adherence; the ERG's clinical adviser agreed this is a consideration when selecting suitable treatment. There are no dietary restrictions for romiplostim, and issues of adherence are not reported in guidelines known to the ERG. The CS refers to a 2016 publication regarding adherence to injectable medication for type 2 diabetes to infer possible challenges faced with romiplostim. The ERG is unaware of any similar research within the target population.

The duration of avatrombopag treatment presented was 24 weeks, which the ERG's adviser said was appropriate for evaluating durable platelet response. However, in clinical practice, the clinical advisor reported that patients would be assessed for response at 8-12 weeks. If patients were not responding by that time, they would not continue treatment to the full 24 weeks, which differs from assumptions made in the CS.

The ERG notes the uncertainty and variation in current clinical practice, as highlighted by the clinical advisor. Prior to the COVID-19 pandemic, rituximab was increasingly being used before TPO-RAs. The pandemic changed treatment preferences due to the immune suppression rituximab can cause and TPO-RAs are now being used prior to rituximab. It is unclear whether this will change again.

2.3 Critique of company's definition of decision problem

The CS is generally reflective of the NICE decision problem, although the ERG has some concerns about the exclusion of rituximab as a comparator given the current uncertainty regarding its use.

A summary and critique of the company's definition of the decision problem is presented in Table 1.

Table 3 Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	Adults with chronic immune thrombocytopenia that is refractory to other treatments.	Adults with chronic immune thrombocytopenia that is refractory to other treatments.		Applicability of the included trials to the NHS setting is broadly adequate. See section 3.
Intervention	Avatrombopag	Avatrombopag in addition to current clinical management		The intervention in the CS matches that of the final scope. Avatrombopag is a TPO-RA that mimics the biological effect of endogenous thrombopoietin to stimulate platelet production. CHMP approved, and EMA approved in the given population.
Comparator(s)	Established clinical management without avatrombopag, which may include: • Thrombopoietin receptor agonists (romiplostim and eltrombopag) • Immunosuppressive agents (rituximab, mycophenolate mofetil, azathioprine, dapsone, danazol and cyclosporin A [currently none have a marketing authorisation in the UK for this indication]) • watch and rescue • splenectomy	Eltrombopag and romiplostim	TPO-RAs are considered the well-established standard of care for ITP. It would be inappropriate to include either splenectomy or rituximab given there are multiple TPO-RA alternatives available. In the former case, clinical opinion now positions splenectomy as a later-line treatment procedure once all medical treatment options have been exhausted owing to risk of relapse and mortality. For	The company chose to omit comparator treatments excepting other approved TPO-RAs; eltrombopag and romiplostim. The company has not reported consultation with clinical opinion as a basis for the exclusion of rituximab, instead referring to variable use. Clinical advisor to the ERG noted that rituximab is still a considered intervention, particularly as it offers a curative outcome for

			rituximab, its use is highly varied across treatment centres and lines of therapy. Therefore, it does not represent established clinical practice for the population under consideration in this appraisal. It is anticipated that the population eligible for avatrombopag will be exactly the same as those who currently receive a TPO-RA.	some patients. However, the COVID-19 pandemic changed treatment preferences due to the immune suppression rituximab can cause and TPO-RAs are now being used prior to rituximab. The clinical advisor agreed splenectomy is no longer used, or as a very last resort in the UK. There is a minority of patients who have had a prior splenectomy when this was more common practice.
Outcomes	The outcome measures to be considered include: • platelet count • response rate and duration • use of concurrent treatments and rescue treatments • reduction in symptoms • mortality • adverse effects of treatment HRQoL	The outcome measures to be considered include: • platelet count • response rate and duration • use of concurrent treatments and rescue treatments • reduction in symptoms • mortality • adverse effects of treatment HRQoL		The outcomes matched the final scope issued by NICE. The CS only reports durable response for platelet response, and did not report any shorter term response outcomes before 24 weeks. Per advice from the clinical advisor, patients would be assessed at 8-12 weeks and discontinue treatment if not responsive.
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. If the technology is likely to provide	Sobi believes that avatrombopag is suitable for a fast-track appraisal because it is anticipated to be a highly cost-effective use of NHS		The economic analysis is in line with the NICE Reference case and the approach used to assess cost-effectiveness is broadly appropriate. However, the ERG notes that

	similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account	resources, with an ICER <£10,000.		the company have only presented cost-effectiveness results for a pairwise comparison of avatrombopag vs. eltrombopag and a separate pairwise comparison for avatrombopag vs. romiplostim.
Subgroups	If the evidence allows the following subgroups will be considered: • Prior rituximab	N/A	Subgroup analyses of patients with prior rituximab treatment were not appropriate for this appraisal owing to limited clinical data.	Prior ritxuimab may be relevant as a subgroup comparison as there are eligible patients who are rituximab exposed, as reported by the clinical advisor to the ERG.
Special considerations including issues related to equity or equality		It is not anticipated that this appraisal will exclude from consideration any people protected by the equality legislation, lead to a		

		recommendation that has a different impact on people protected by equality legislation than on the wider population, or lead to recommendations that have any adverse impact on people with a particular disability or disabilities.		

Abbreviations: ITP, immune thrombocytopenia; ICER, incremental cost-effectiveness ratio; HRQoL, health-related quality of life; TPO-RA, thrombopoietin receptor agonist

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review

The company conducted a systematic literature review to identify all relevant evidence regarding the clinical efficacy and safety of licensed pharmacological treatments for ITP. Details of the SLR are reported in Appendix D of the CS. In the absence of sufficient direct evidence comparing avatrombopag with all relevant comparators, a network meta-analysis (NMA) was conducted (CS Section B2.9).

3.1.1 Searches

The search strategies to identify studies of avatrombopag and comparators for the treatment of chronic immune thrombocytopenia were included in Appendix D of the CS. The ERG appraisal of the literature searching can be found in Table 4 below.

Table 4 ERG appraisal of evidence identification

Topic	ERG response	Notes
Is the report of the search clear and comprehensive?	YES	
Were appropriate sources searched?	PARTLY	- Limited searching for previous non-Cochrane systematic reviews. As the searches of MEDLINE and Embase were restricted to RCTs and observational studies, they may have missed relevant systematic reviews. Epistimonikos, a source of systematic reviews, was not searched. - Conference abstracts were identified via Embase, however no further sources of conference abstracts were searched. - Sources of ongoing or completed Health Technology Assessments were not searched eg: International HTA (INAHTA) database, HTA Database, websites of HTA agencies. - Checking of reference lists for further relevant studies was not reported.
Was the timespan of the searches appropriate?	YES	Databases were searched from inception to July 2021.
Were appropriate parts of the PICOS included in the search strategies?	PARTLY	- ITP (**P**opulation) AND (avatrombopag (**I**ntervention) OR relevant comparators (**C**omparators)) AND (RCTs OR observational studies (**S**tudy design)) - Two extra comparators were included in the search strategy – fostamatinib and lustutrombopag. It is unclear why they were included in the search strategies. - The reliability of the search could have been improved by removing the limit to RCTs and observational studies to allow retrieval of all study designs. Inappropriate study designs could then have been identified and removed at the screening stage.

Were appropriate search terms used?	YES	
Were any search restrictions applied appropriate?	NOT APPLICABLE	
Were any search filters used validated and referenced?	UNCLEAR	It appears that study design search filters were used to limit to RCTs and observational studies in MEDLINE and Embase. However, references to particular study design search filters were not reported in the submission or in the response to the points for clarification. Although the company clarified that their search filters were developed following recommendations from the Cochrane Collaboration, CRD, ISSG search filter resource and CADTH, they did not clarify which recommendations or which particular filters were used to develop them from. Therefore, it is unclear if the search filters used were validated. In addition, previous research has shown that current search filters to limit to non-randomised/observational studies are not sensitive enough for use in systematic reviews.[4]

ERG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

3.1.2 Inclusion criteria

The eligibility criteria used to select studies for inclusion in the systematic review of treatment effectiveness were presented in Table 17 of the CS. The ERG considers these criteria to be broadly appropriate, with the exception of including studies of lusutrombopag and fostamatinib; neither were part of the NICE scope and lusutrombopag is not licensed for treating patients with chronic immune thrombocytopenia. However, the ERG do not consider this to be an important issue, given that no trials of lusutrombopag were included in the network meta-analyses and it is unlikely that the inclusion of fostamatinib studies in the NMAs would have affected the effect estimates for the TPO-RAs, given the absence of closed network loops including fostamatinib (discussed in Section 3.4).

3.1.3 Critique of data extraction

No data extraction methods were reported in the submission for the clinical effectiveness systematic review. It is therefore unclear whether or not the processes used may have been affected by errors or bias.

3.1.4 Quality assessment

Studies included in the systematic review were quality assessed using the 2011 version of the Cochrane risk of bias tool (a more recent version was published in 2019, but was not used). The results were reported in Section D.1.1.6 of the CS Appendix D. Studies included in the NMA were reported to have been assessed differently from those included in the systematic review, using criteria based on CRD guidance (stated in Section B.2.9.3.2) but the assessment results (p51 of the CS) suggest that the Cochrane risk of bias tool was used. A commentary on the results of the quality

assessments is given in Section 3.3. No assessment was made of trial external validity or applicability to the NHS setting.

3.1.5 Evidence synthesis

The evidence synthesis presented in the CS was a network meta-analysis (NMA). Details and further commentary on this analysis and the results are given in Section 3.4.

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

The company's submission documented three RCTs of avatrombopag: one phase two trial (Study CL-003 (NCT00441090)) and two phase III trials (Study 302[5] and Study 305 (NCT01433978)). Studies CL-003 and 302 had placebo comparators (study CL-003 compared four doses of avatrombopag with placebo) and study 305 compared avatrombopag with eltrombopag. Each study also had a single-arm extension phase.

3.2.1 Design and methods of the avatrombopag trials

Study 302

Study 302 was a phase III, multicentre, randomised, parallel group trial, which compared avatrombopag 20mg with dose titration up to 40mg or down to 5mg (n=32) with placebo (n=17) using a 2:1 allocation ratio. Design details and eligibility criteria were reported in Table 4 and section B.2.3.1.1 of the CS. The key population eligibility criteria appeared largely appropriate and relevant although it was possible for patients to be excluded because they had not responded (platelet count $>50\times10^9$/L) to a previous ITP therapy the company clarified that no such exclusions had occurred. No evaluation of external validity was presented; there were no UK trial sites. The ERG's clinical adviser was not aware of any patient characteristics or factors which were considered as likely predictors of treatment response to TPO-RAs, with the exception of previous response to steroids, which may possibly predict a TPO-RA response. With this in mind it appears likely that the results of study 302 will be applicable and relevant to an NHS population.

Study 302 appears to have a low risk of bias for most domains of the submission's quality assessment (see p47 of the CS Appendix file). However, the exception is the domain for evaluating bias arising from missing outcome data. There was an important imbalance in discontinuation rates between the treatment groups, with a higher discontinuation rate seen in the placebo group, due to lack of efficacy. This resulted in the mean treatment durations being 22.8 and 8.9 weeks in the avatrombopag and placebo groups, respectively. Only one placebo patient completed the trial. Although this information

was reported in the submission, the risk of bias judgement for missing outcome data was judged to be 'unclear', based on there being "no information" to form a risk of bias judgement. The submission did though describe more generally the possible risks of bias due to early discontinuation for five outcomes in Table 22 of the CS. For the outcomes, durable response and reduction in the use of concomitant ITP medication the risk was judged to be low. The ERG agrees with this, providing 'no response' imputation is assumed for participants with missing data for these outcomes i.e. absence of durable response and no reduction in the use of concomitant ITP medication.

For safety outcomes, the need for rescue treatment, and bleeding events the risk was judged to be high so the analysis was based on estimated incidence using incidence rate ratios.

Study 305

Study 305 was a phase III, multicentre, randomised, parallel group trial, which compared avatrombopag 20mg with dose titration up to 40mg or down to 5mg (n=12) with eltrombopag (n=11) with dose titration up to 75mg or down to 25mg, using a 1:1 ratio. The eligibility criteria were similar to those used in study 302. The CS stated that study 305 was terminated early due to "significant enrolment challenges", though few details were provided on the reasons, and no results were presented in the CS. The ERG sought clarification on the reasons for the termination of the trial. The company stated that study 305 was initiated at a time when eltrombopag was approved and became commercially available so patients were less likely to enrol since they could be randomised to a non-approved drug (avatrombopag). Also, protocol amendments included criteria mandating that subjects undergo [redacted]. The study aimed to recruit [redacted] patients but only [redacted] had been randomised when the trial was terminated (one patient was randomised in error and did not receive any study treatment.

Study CL-003

Study CL-003 was a phase II trial evaluating different doses of avatrombopag. Patients were assigned to avatrombopag at 2.5 mg, 5 mg, 10 mg or 20 mg, or placebo in a 3:3:3:3:1 ratio, respectively. The treatment arms relevant to this appraisal are 20mg (the licensed dose) and placebo. However, only 15 patients received avatrombopag 20mg and only 5 patients received placebo. Moreover, the follow up duration was only 28 days and platelet response was the only scope-relevant efficacy outcome reported.

3.2.2 Results of the avatrombopag trials

3.2.2.1 Baseline characteristics

The baseline characteristics of participants recruited to the three avatrombopag trials were reported in Tables 8-10 of the CS. The ERG's clinical adviser considered these characteristics to be quite well aligned with those of patients expected to be treated with TPO-RAs in UK clinical practice. The main

difference noted was that in the UK there would be fewer patients with prior splenectomy; in Study 302 this figure was 33% whereas the ERG's clinical adviser estimated that in NHS practice the proportion of patients eligible for avatrombopag who had prior splenectomy would be around 10-15%. Study 302 also had an imbalance in sex across treatment groups with 72% being female in the avatrombopag group and 47% being female in the placebo group. However, the ERG's adviser did not think this would have a meaningful impact on the trial results.

The ERG asked the company to state which specific concomitant ITP medications were being used at baseline. A table was provided in response to clarification question A2 which showed that by far the most frequently taken concomitant medication was prednisone (a corticosteroid), taken by around 35% of participants. The ERG also requested a table comparing the baseline characteristics of splenectomised participants with those of non-splenectomised participants (provided in response to question A3 and presented in Table 5 below, in modified form). This showed that splenectomised participants were generally older, had lower baseline platelet counts, were more likely to have previously used rituximab and were more likely to be using concomitant ITP medications.

Table 5 Baseline characteristics of splenectomised versus non-splenectomised patients in Study 302 of avatrombopag versus placebo

Characteristic	Non-splenectomised n=33 (%)	Splenectomised n=16 (%)
Age (years), mean (SD)	43.2 (15)	47.6 (12)
<65 years, n (%)	29 (88)	16 (100)
Female, n (%)	18 (55)	12 (75)
Ethnicity, n (%)		
Caucasian	30 (91)	6 (38)
Black or African American	0	1 (6)
Asian	2 (6)	0
Weight (kg), mean (SD)	81.1 (20)	86.8 (25)
Height (cm), mean (SD)	169.1 (8)	168.1 (8)
BMI (kg/m^2), mean (SD)	28.4 (7)	30.5 (7)
Baseline platelet count, n (%)		
≤15x10^9/L	15 (45)	13 (81)
15-30x10^9/L	18 (55)	2 (13)
≥30x10^9/L	0	1 (6)
Prior TPO-RA, n (%)	9 (27)	9 (56)
Prior rituximab, n (%)	2 (6)	7 (44)
Use of concomitant ITP medication at baseline, n (%)	12 (36)	10 (63)

3.2.2.2 Main efficacy results

Clinical efficacy results data for the avatrombopag trials were presented in Section B.2.6 of the CS. This reported results for Study 302 and brief results for study CL-003 but no results were presented for Study 305 (which was terminated early).

Study 302

The results for Study 302 showed that treatment with avatrombopag resulted in statistically significant improvements, when compared with placebo, for the following outcomes: durable platelet response (defined as having a platelet response for ≥6 of the last 8 weeks of treatment); cumulative number of weeks with platelet response of $\geq 50 \times 10^9$/L; and platelet response at day 8. Incidence of bleeding events and use of concomitant ITP medications were reduced in patients receiving avatrombopag compared with placebo, but both these results were not statistically significant. Rescue therapy was required by 22% of avatrombopag-treated patients and 12% of those who received placebo. Interpretation of some of these results is difficult due to the impact of the imbalance in missing data which resulted in a mean treatment duration of only 8.9 weeks in the placebo group (see Section 3.2.1 for more details). For the network meta-analyses, the company sought to address this issue by using incidence rate ratios (instead of odds ratios, see Appendix D of the CS) for some outcomes (see Section 3.4.1).

The CS did not present platelet response data across different follow-up time points. The ERG extracted data from the CSR for study 302 which are presented in Figure 2. These data suggest that [redacted].

Figure 2 Variation in platelet response rate over time in the 32 patients receiving avatrombopag in study 302

[redacted]

Study 305

Results for study 305 were available only in the CSR.

[redacted]

[redacted]

Study CL-003

Results from Study CL-003 were limited by the very small placebo group (n=5) and the short (28-day) follow up duration.

[redacted]

3.2.2.3 Subgroup analyses

On page 7 of the submission the company stated that "*Subgroup analyses of patients with prior rituximab and splenectomy treatment were not appropriate for this appraisal owing to highly varied use of rituximab by treatment centre and clinical opinion increasingly positioning splenectomy as a later-line treatment once medical interventions are exhausted, respectively*". However, this reasoning does not take account of there being current NHS patients who have already had splenectomies and have already taken rituximab.

Despite this statement some subgroup results were reported in Section B.2.7 of the CS and also in Appendix E. These results were also reported in the CSR for Study 302 and in the EMA's CHMP report. There were no results based on prior rituximab status. The reported subgroup results showed that cumulative platelet response was notably lower in splenectomised subjects compared to non-splenectomised subjects (4.9 weeks versus 15.9 weeks) and in subjects with baseline platelet counts of ≤15 x10^9/L compared to subjects with baseline counts of >15 to <30 x10^9/L (5.3 versus 19.2 weeks).[6] Considering that data in Table 5 (above) suggested that baseline platelet counts of ≤15 x10^9/L are more frequently seen in splenectomised participants than in non-splenectomised participants, it seems possible that any subgroup effect may be driven by baseline platelet count, which itself may be related to splenectomy status. However, the ERG's clinical adviser thought that although his experience was that splenectomised patients appear to be more resistant to achieving responses with eltrombopag and romiplostim (than non-splenectomised patients), almost all splenectomised patients would have failed all other treatments and he did not think that baseline platelet count predicts resistance to achieving treatment responses.

In the romiplostim trials no splenectomy was significantly associated (p=0·0306) with increased rates of durable response.[7] For eltrombopag there was no evidence of a splenectomy subgroup effect with the ERG report stating that "*among non-splenectomised participants, 57% (20/35) of participants in the eltrombopag group had a platelet response ≥50x10^9/L at the end of the intervention compared*

with 17% (4/24) in the placebo group. The results for splenectomised participants were similar (62% [19/31] vs. 15% [2/14]).”[8]

Post-hoc subgroup results (CS, p42) found no differences in efficacy for subgroups based on prior TPO-RA use nor on the number of lines of prior ITP treatments (<3 vs >3).

3.2.2.4 Longer-term clinical efficacy

Efficacy results relating to longer-term follow up data on avatrombopag were reported on p41 of the CS. This section noted only that, in Study 302, platelet counts above 50×10^9/L were maintained up to week 38 (9 months) but that after that timepoint platelet response was lower and more variable, with the small number of patients (n<15) at these time points limiting further interpretation.

3.2.2.5 Adverse events

Adverse events were presented for study 302 in Table 30, study 305 in Table 31 and study CL-003/004 in Table 32, of the CS. Treatment emergent adverse events (TEAEs) were reported for all studies, and serious adverse events were reported for study 302 within Table 30. The company provided further data on severe grade 3-4 TEAEs, and deaths for all 3 studies in their response to the points for clarification.

The definition of TEAE used differed across studies presented in the CS which did not allow for easy comparison between trials (exposure adjusted in study 302 in Table 30, occurring in at least 20% in study 305, not adjusted for duration of exposure in Table 31, and occurring in at least 5% of patients in CL-003/004 not adjusted for duration of exposure in Table 32). In the response to points for clarification, the company also provided unadjusted incidence rates for TEAEs in study 302, reported below in Table 6.

The company reported adjusted TEAEs by exposure for the core study 302, due to excessive attrition in the placebo group. The company report low incident rates of TEAEs in the avatrombopag and placebo arms (placebo 6.6% vs avatrombopag 4.3%). The incident rates of any TEAE are notably smaller than those reported in study 305 or CL-003/004 which the company clarified is due to exposure adjustment for study 302 (TEAEs occurring in at least 20% of patients in study 305, for any TEAE [redacted] TEAEs occurring in at least 5% of patients in study CL-003/004, for any TEAE[redacted]). Relative to comparator arms within the trials, avatrombopag patients experienced a comparable amount of TEAEs. Considering the unadjusted incidence rate of TEAEs in core study 302 (presented in Table 6), they remain similar to comparators.

The rate of serious grade 3-4 adverse events is also similar across avatrombopag and comparators (unadjusted incidence of serious TEAEs in study 302 =28.1%, unadjusted incidence of severe TEAEs

grade 3-4 in study 302 =18.8%, severe TEAEs grade 3-4 in study 305 = [redacted] severe TEAEs grade 3-4 in study CL-003/004 = [redacted]). [redacted]

Table 6. TEAEs in Study 302 Core and Extension Phase, Safety Analysis Set, presented in response to the points for clarification

	Core study incidence of TEAEs		Core study + extension phase incidence of TEAEs
	PLC (N=17) n (%)	AVA (N=32) n (%)	AVA (N=47) n (%)
TEAEs	10 (58.8)	31 (96.9)	45 (95.7)
TEAEs with CTCAE grade 3 or 4	0	6 (18.8)	14 (29.8)
Serious TEAEs	1 (5.9)	9 (28.1)	15 (31.9)
Deaths (CTCAE grade 5)	0	0	0

*Rate is calculated as 100 x (the number of subjects with events/total exposure in subject-weeks) within each category. Abbreviations: AVA, avatrombopag; CTCAE, common terminology criteria for adverse events; TEAE, treatment-emergent adverse event; PLC, placebo

Data source: Table 17 and 18, Study 302 CSR

Replicated from Table 11, Company response to points for clarification

3.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

The methods used in the company's systematic review (reported in Appendix D of the CS) were largely appropriate and have been discussed in Section 3.1. A PRISMA flow diagram was presented in Appendix D of the CS, along with a table of the included studies and a list of excluded studies. Fourteen RCTs were initially identified in the systematic review for inclusion in the NMA (Table 18 of the CS). As mentioned in section 3.1.2, the ERG disagrees with the company's decision to include two trials of fostamatinib, which was not listed as a comparator in NICE's scope (see Section 3.4.)

Risk of bias judgement details (see Appendix D.1.1.6 of the CS) were reported for 13 of the 14 randomised trials included in the systematic review. The assessment results were limited as they did not provide judgements on overall risk of bias and did not indicate which judgements might vary by trial outcome.

As described in section 3.2.1, the ERG considers the pivotal avatrombopag trial - trial 302 - to be at high risk of bias due to an important imbalance in missing outcome data, although this risk may be reduced by the use of non-responder imputation or incidence rate ratios (depending on the outcome of interest). For study 305 the allocation concealment judgement was given in the CS as

[redacted].

3.3.1 Studies excluded from the NMA

The company then applied further exclusion criteria for the 14 identified trials when identifying studies for inclusion in the NMA. Consequently, seven of the 14 trials were excluded based on one or more of the following criteria:

- Studies conducted exclusively on Asian patients were excluded to minimise the potential bias caused by ethnic differences. This was based on the differences in recommended posology of eltrombopag between patients with Asian and non-Asian ethnicity.
- Studies assessing dose regimens approved by the EMA only were included. Studies or study arms assessing treatment schemes exclusively used in other ethnicities were excluded.
- Studies in which patients received the investigated treatment for a period shorter than 9 weeks (corresponding to the mean duration of treatment in the placebo group in Study 302), were excluded "*to minimise the bias associated with a wide range of treatment durations*".

The ERG considered the specific reasons for the company's decision to exclude each trial and also asked their clinical adviser for his opinion on the appropriateness of these exclusions. The ERG and their adviser were of the opinion that all seven trials should be deemed eligible for inclusion in the NMAs. The reasons for exclusion given by the company, together with the ERG's rationale for including the seven studies are presented in Table 7. The fairly short follow-up durations of most of these trials precludes them from contributing to the durable platelet response NMA. The ERG examined the excluded trials for data which might be used in other NMA efficacy outcomes. Table 8 shows that nearly all trials had data on bleeding events and three trials had data on the use of rescue treatment. None of the trials had data on reductions in concomitant ITP medication. Five trials reported platelet response data at week 6. The ERG therefore considers that for several outcomes the CS NMA did not make full use of all the available evidence when comparing treatments. Incidence rate ratios could have been calculated in studies where sufficient data were available. In a clarification question the ERG requested further NMA analyses, asking the company to include relevant data from the 7 excluded trials, rituximab trials and all the avatrombopag trials but the company said they could not produce the requested analyses within the specified timeframe.

3.3.1.1 Platelet response data

There may be differences in comparative efficacy between durable platelet response (defined as having a platelet response for ≥6 of the last 8 weeks of treatment) and fixed time point platelet responses. This may be important to know, since in clinical practice avatrombopag (and the other

TPO-RAs) should be discontinued after 4 weeks of no response with maximal dose, but in the avatrombopag (and other TPO-RA) trials non-responders did not have to discontinue trial treatments. It is therefore possible that in the trials short-term non-responders could go on to become durable responders for that particular TPO-RA, although the ERG's clinical adviser thought it was unlikely that a patient would respond to a TPO-RA later if they were unresponsive initially.

In light of this uncertainty the ERG requested the company to perform NMAs based on platelet response rates at different time points, and including the trials excluded from the company's NMAs which the ERG considered relevant. This was in order to obtain a more complete picture of the platelet response data and make better use of the available evidence. These analyses would also provide comparative efficacy estimates of platelet response nearer the timepoints where decisions are made on discontinuation due to lack of efficacy. The company stated that they did not have time to perform these analyses. The ERG notes that although 4- and 6-week platelet response data are available for avatrombopag (via the CSR for study 302) and eltrombopag (several trials), no such data at any specific time points are available for any of the romiplostim trials. Therefore, an NMA comparing all three TPO-RAs for platelet response at four or six weeks is not possible. However, the EMA CHMP report on avatrombopag reported results for NMAs comparing avatrombopag with eltrombopag[6] (see Section 3.6).

Table 7 ERG and clinical adviser opinion on trials excluded from the NMA by the company

Excluded trial	Treatments	Company's reasons for excluding trial from NMA	ERG and clinical adviser comments
Tomiyama 2012[9]	ELT vs PLA N=28	**1. Population**: Japanese patients only **2. Dose regimen**: Initial dose of eltrombopag of 12.5 mg/day instead of 50 mg/day **3. Duration of treatment**: Parallel phase lasted 6 weeks	**Disagree with exclusion** **1.** Disagree. The ERG's clinical adviser thought that trial data from Asian cohorts should be utilised. **2.** Disagree. Although the SmPC states that for patients of East-/Southeast-Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily the ERG's clinical adviser did not think that the difference between starting doses of 12.5mg and 25mg was likely to be important in terms of efficacy outcomes. **3.** Disagree. Results from timepoints earlier than 9 weeks have clinical value and avoid the need for adjustment to avoid bias associated with imbalanced premature discontinuation.
Yang 2017[10]	ELT vs PLA N=155	**1. Population**: Chinese patients only **2. Dose regimen**: Initial dose of eltrombopag of 25mg mg/day instead of 50 mg/day **3. Duration of treatment**: Parallel phase lasted 8 weeks	**Disagree with exclusion** **1.** Disagree. The ERG's clinical adviser thought that trial data from Asian cohorts should be utilised. **2.** Disagree. The dose for Asian patients is in line with the SmPC. **3.** Disagree. Results from timepoints earlier than 9 weeks have clinical value and avoid the need for adjustment to avoid bias associated with imbalanced premature discontinuation.
Huang 2018[11]	ELT vs PLA N=35	**1. Population**: Chinese patients only **2. Dose regimen**: Initial dose of eltrombopag of 25mg mg/day instead of 50 mg/day **3. Duration of treatment**: Comparison based on 6 weeks	**Disagree with exclusion** **1.** Disagree. The ERG's clinical adviser thought that trial data from Asian cohorts should be utilised. **2.** Disagree. The dose for Asian patients is in line with the SmPC. **3.** Disagree. Results from timepoints earlier than 9 weeks have clinical value and avoid the need for adjustment to avoid bias associated with imbalanced premature discontinuation.
Bussel 2007[12]	ELT 30mg vs ELT 50mg vs ELT 70mg vs PLA	**1. Dose regimen**: Inadequate dose for 25mg and 75mg arms **2. Duration of treatment**: Comparison based on 6 weeks	**Disagree with exclusion** **1.** Agree though 50mg dose still eligible. 50mg vs placebo comparison should be included in NMA. The company appears to agree with this.

	N=118		**2.** Disagree. Results from timepoints earlier than 9 weeks have clinical value and avoid the need for adjustment to avoid bias associated with imbalanced premature discontinuation.
Bussel 2009[13]	ELT vs PLA N=114	**1. Duration of treatment**: Comparison based on 6 weeks	**Disagree with exclusion** 1. Disagree. Results from timepoints earlier than 9 weeks have clinical value and avoid the need for adjustment to avoid bias associated with imbalanced premature discontinuation.
Kuter 2010[14]	ROM vs Standard of care N=234	**1. Dose regimen**: Initial dose of romiplostim 3µg/kg instead of 1 µg/kg	**Disagree with exclusion** 1. Disagree. The ERG's adviser stated that although the initiating dose of romiplostim is 1 µg/kg in reality it is hardly ever started at this dose and it is mostly either started at 2µg/kg or 3µg/kg.
Shirasugi 2011[15]	ROM vs PLA N=34	**1. Population**: Japanese patients only **2. Dose regimen**: Initial dose of romiplostim 3 µg/kg instead of 1 µg/kg **3. Duration of treatment**: Comparison based on 12 weeks	**Disagree with exclusion** 1. Disagree. The ERG's clinical adviser thought that trial data from Asian cohorts should be utilised. There is no restriction in the SmPC for Asian ethnicity. 2. Disagree. The ERG's adviser stated that although the initiating dose of romiplostim is 1 µg/kg in reality it is hardly ever started at this dose and it is mostly either started at 2µg/kg or 3µg/kg. 3. Disagree. 12 weeks duration is within the company's own criteria for NMA inclusion.

Table 8 Availability of efficacy outcome data for studies excluded from some, or all, of the company's NMAs

Excluded trial	Treatments studied and sample size	Outcome reported?			
		Platelet count at 4 or 6 weeks	Use of rescue treatment	Bleeding events	Reduction in concomitant ITP medication
Study 305[16]	AVA vs ELT, N=24	No	No	Yes, used in company NMA	No
Tomiyama 2012[9]	ELT vs PLA, N=23	Weeks 4 & 6	No	Only for ELT	Not by treatment group
Yang 2017[10]	ELT vs PLA, N=155	Week 6	Yes	Yes*	No
Huang 2018[11]	ELT vs PLA, N=35	Week 6	Yes	Yes	Unclear (published in Chinese)
Bussel 2007[12]	ELT 50mg vs PLA, N=59	Week 6	No	Yes**	No
Bussel 2009[13]	ELT vs PLA, N=114	Week 6	No	Yes	No
Kuter 2010[14]	ROM vs Standard of care N=234	No	No	Yes	No
Shirasugi 2011[15]	ROM vs PLA N=34	No	Yes	Yes	No

* In supplementary file **Only in graph form

3.3.2 ERG's assessment of heterogeneity across trials

Baseline characteristics of the seven trials included in the company's NMA were reported in Table 20 (p50) of the CS. Details of the key eligibility criteria and baseline characteristics across the 12 trials considered eligible for NMA by the ERG are presented in Table 9 and Table 10. Although ethnicities varied across trials the ERG's clinical adviser did not expect this to have a meaningful impact on efficacy outcomes. The only trial which differed notably from other trials was the romiplostim study reported by Kuter et al 2010.[14] This trial had much higher baseline platelet counts and excluded patients with prior splenectomy. The platelet count difference is likely a consequence of its eligibility criteria which also differed from other trials in terms of pre-treatment platelet count ($< 50\times10^9$/l). It is also the only trial to use standard of care as a comparator, so would have had to have formed its own node in a network.

Table 9 Comparison of key eligibility criteria across trials considered eligible for NMA by the ERG

Trial	Eligibility criteria	
	Response to a previous ITP therapy	Definition of chronic ITP

Study 302[5] (AVA)	Must have had either initially responded to a previous ITP therapy or have had a bone marrow examination consistent with ITP within 3 years	More than 12 months' duration (ASH/ BCSH)
Study 305[16] (AVA, ELT)	Must have had either initially responded to a previous ITP therapy or have had a bone marrow examination consistent with ITP within 3 years	More than 12 months' duration (ASH/ BCSH)
CL003[17] (AVA)	Relapsed or refractory patients eligible	More than 6 months' duration (ASH)
RAISE[18] (ELT)	Must have responded to one or more previous ITP treatments	More than 6 months' duration (ASH)
Kuter 2008[7] (ROM)	No restrictions reported	More than 6 months' duration (ASH)
Tomiyama 2012[9] (ELT)	Refractory to one or more previous ITP therapies	More than 6 months' duration
Yang 2017[10] (ELT)	Insufficient response or relapse after prior ITP treatment	More than 12 months' duration
Huang 2018[11] (ELT)	Data unavailable	Data unavailable
Bussel 2007[12] (ELT)	Patients had to have failed at least one treatment	More than 6 months' duration
Bussel 2009[13] (ELT)	Patients had to have failed at least one treatment	More than 6 months' duration
Kuter 2010[14] (ROM)	No restrictions reported	Not reported
Shirasugi 2011[15] (ROM)	No restrictions reported	More than 6 months' duration

ASH American Society of Haematology guidelines, BCSH British Committee for Standards in Haematology guidelines

Table 10 Key baseline characteristics of trials considered eligible for NMA by the ERG

Trial	Age (yrs)	Weight (Kg)	Main ethnicities	Platelet count (10^9/l)	% with prior splenectomy	% taking concomitant ITP treatment	No. of previous ITP therapies
Study 302[5] (AVA)	45	83	94% White	14	33	45	[redacted]
Study 305[16] (AVA, ELT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CL003[17] (AVA)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RAISE[18] (ELT)	Median ~ 50	74	74% White 17% Asian	Median 16	36	48	54% ≥3 therapies
Kuter 2008[7] (ROM)	Median 52	79	82% White 7% Black	16	50	31	63% ≥3 therapies
Tomiyama 2012[9] (ELT)	Median 60	60	100% Japanese	17	70	83	100% ≥1 therapy

Yang 2017[10] (ELT)	44	63	100% Chinese	Median 14	16	52	19% ≥1 therapy
Huang 2018[11] (ELT)	Median 42	Unavailable	100% Chinese	14	Unavailable	Unavailable	Unavailable
Bussel 2007[12] (ELT)	Median 50	NR	79% White 18% Asian	48% <15	47	32	51% ≥3 therapies
Bussel 2009[13] (ELT)	Median 48	NR	74% White 25% Other	48% <15	39	43	51% ≥3 therapies
Kuter 2010[14] (ROM)	Median 57	Median 77	88% White	Median 29	0	11	73% ≥2 therapies
Shirasugi 2011[15] (ROM)	55	58	100% Japanese	18	44	68	Median 4

Age, weight and platelet counts are reported as means unless stated. AVA=avatrombopag, ELT=Eltrombopag, ROM=Romiplostim, NR=Not reported, Splen=splenectomised, non-splen=non- splenectomised, yrs years

3.3.3 ERG check of data extracted for the NMA

The ERG checked the NMA input data reported in Appendix D of the CS and in the Excel file provided by the company in response to clarification question A18. In the Kuter 2008 trial(s) of Romiplostim,[7] for the outcome *proportion of patients with any bleed* the ERG considers the figures for the romiplostim group to be 45/84 (as reported in the romiplostim ERG's report, Table 4, p47)[19] instead of the 48/84 reported in the CS. Additionally, the denominator varied by outcome because "*One non-splenectomised patient randomly assigned to placebo received three doses of romiplostim in error and was included in the safety analysis as a patient given romiplostim and in the efficacy analysis as a patient given placebo*",[7] resulting in denominators for safety outcomes (bleeding being classed as a safety outcome) of 84 for romiplostim and 41 for placebo and denominators for efficacy outcomes of 83 romiplostim and 42 for placebo.

In the eltrombopag RAISE trial the denominators were based on the observed population (patients who completed the study), whereas for all other studies ITT population denominators were used. The ITT numbers in RAISE were n=62 and n=135 for the placebo and eltrombopag arms, respectively.

The ERG disagreed with some of the follow-up time periods reported in Table 19 of the CS, which were used in the incidence rate ratio NMAs. Specifically, the ERG considers that 24 weeks' duration of follow up is correct for the Kuter romiplostim trials,[7] rather than the (24+12=)36 weeks used in the CS NMAs. In these trials there were 24 weeks of trial treatment (romiplostim versus placebo), then a pause in trial treatment of up to 12 weeks, then an open-label phase of romiplostim treatment:

"*After 24 weeks, study treatment was discontinued and platelet counts monitored every week. Patients completed the study at week 36 or once platelet counts were less than* 50×10^9*/L. All patients who completed the study were eligible to be screened for participation in an open-label extension study of romiplostim*."[7]

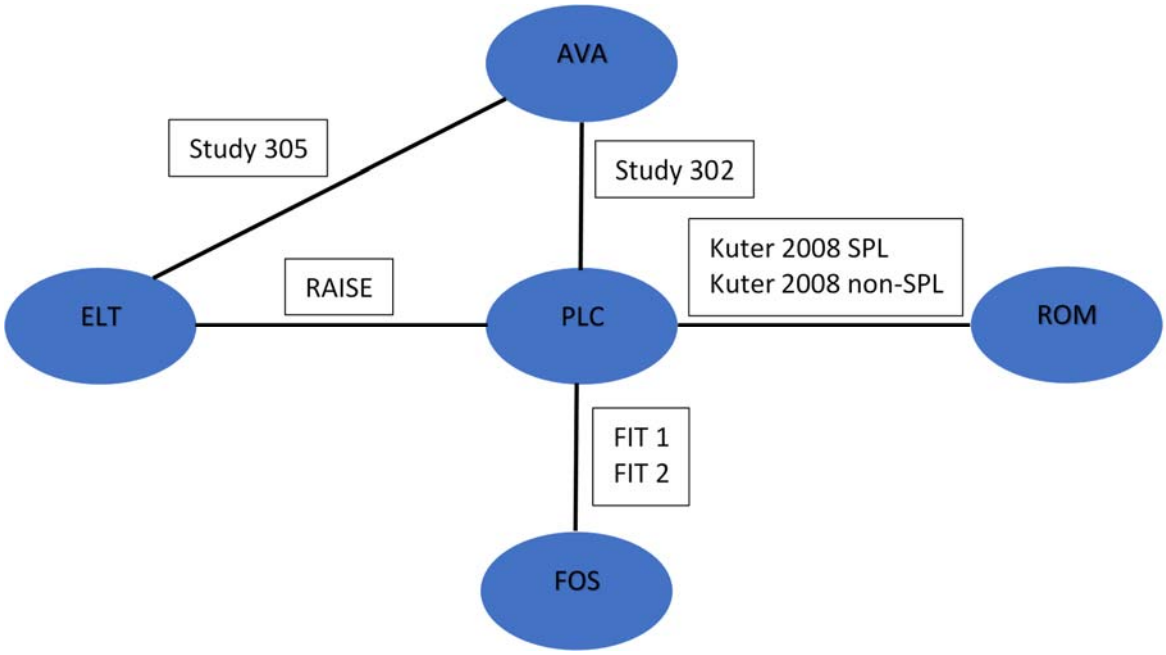
3.4 Critique of the indirect comparisons and/or multiple treatment comparisons

Due to the absence of head-to-head comparisons between avatrombopag and most alternative TPO-RAs, the company conducted an indirect treatment comparison (ITC) to compare the efficacy and safety of avatrombopag with the following TPO-RAs: eltrombopag, romiplostim and fostamatinib. Only Study 305 compared avatrombopag directly with eltrombopag, for the remaining 6 studies placebo was used to connect avatrombopag to comparator TPO-RAs.

ITCs or network meta-analyses (NMAs, where evidence comparing avatrombopag directly with eltrombopag is also included) were conducted for six outcomes: durable platelet response and reduction in the use of concomitant ITP medication, treated as binary; and need for rescue therapy, any bleeding events, bleeding events WHO grade 2-4 and any adverse events, treated as count/rate data due to differential drop-out and different study follow-up times. These outcomes were selected because they were commonly reported across comparator trials and were deemed by the company to be the most clinically meaningful and relevant for market access purposes. Except for the outcomes relating to bleeding events and any adverse events, where evidence from Study 305 was utilised, the remaining network structures were star-shaped.

The overall network for all outcomes is presented in Figure 3 which is replicated from Figure 9 in the CS, and the studies included for each outcome assessed are presented in Table 11.

Figure 3 Network of included studies and interventions



Abbreviations: AVA, avatrombopag; ELT, eltrombopag; FOS, fostamatinib; NMA, network meta-analysis; PLC, placebo; ROM, romiplostim.
Replicated from Figure 9 in the CS.

Table 11 Studies informing the NMAs for each outcome

Comparator	Studies per outcome					
	Binary		Rate data			
	Durable response	Reduction in the use of concomitant ITP medication	Need for rescue therapy	Any bleeding events	Bleeding events WHO grade 2-4	Any adverse events
vs Placebo						
Avatrombopag	Study 302	Study 302	Study 302	Study 302	Study 302	Study 302
Eltrombopag	RAISE	RAISE	RAISE	RAISE	RAISE	RAISE
Romiplostim	Kuter SPL Kuter non-SPL	Kuter SPL Kuter non-SPL	Kuter SPL Kuter non-SPL	Kuter SPL & Kuter non-SPL*	Kuter SPL Kuter non-SPL	Kuter SPL & Kuter non-SPL*
Fostamatinib	FIT 1 FIT 2	----------	FIT 1 & FIT 2*	FIT 1 & FIT 2*	FIT 1 & FIT 2*	FIT 1 & FIT 2*
vs Eltrombopag						
Avatrombopag	----------	----------	----------	Study 305	Study 305	Study 305

*Included as a single study

Abbreviations: SPL= splenectomised; non-SPL: Non-splenectomised

Network plots for each outcome are given in Appendix D, Section 1.1.5 of the CS. Note however that the network presented for the outcome 'Any bleeding events' (Figure 5, CS Appendix D page 44) is

incorrect and the correct network is the same as for the outcome 'Any adverse events' (Figure 7, CS Appendix D page 46).

3.4.1 Data and methods

One NMA analysis per outcome was conducted, each within a Bayesian framework using Markov Chain Monte Carlo (MCMC) sampling and the software WinBUGS.[20] No detail was provided in the original CS with respect to the synthesis models or data used in each implemented NMA. After points for clarification the company provided WinBUGS codes, data lists and sets of initial values' lists for each NMA to allow the analyses to be reproduced. All WinBUGS codes followed recommendations in the NICE DSU Technical Support Document 2.[21] For the two binary outcomes the analyses assumed that data followed a binomial likelihood and outcomes were represented as odds ratios (the logit link was used). For the four rate outcomes, data were first transformed to log incidence rate ratios (IRR) with a standard error, and the analyses assumed that the IRRs followed a normal likelihood (the identity link was used).

The company argued that premature, imbalanced discontinuation between active and placebo groups in some included studies significantly affected the total exposure time and could interact with the results for relative efficacy and safety by decreasing the chance of events to occur in the placebo group. In particular Study 302 and FIT 1 & 2 had considerable drop-out which reduced the exposure time and therefore the probability of events such as need for rescue treatment, bleeding or adverse events to occur. Thus, observed percentages of patients with such outcomes may underestimate the true risk of events in the placebo groups and an analysis on the odds ratio scale could be biased. The company therefore analysed these outcomes using a method that takes the differential exposure times into account, comparing event rates rather than proportions. This approach was applied to all studies included in the NMA, regardless of the extent of imbalance of discontinuation, for the outcomes need for rescue treatment, bleeding and adverse events. The company used the incidence rate ratio (IRR) which is the ratio of two incidence rates (the incidence rate in arm 2 of a study, divided by the incidence rate in arm 1 of that study). The incidence rate is the number of events divided by the person-time at risk (in weeks or years) in that study arm. The IRR gives a relative measure of the effect of a given treatment compared to another and approximates the relative risk or the odds ratio only if the occurrences are rare.

To calculate the incidence rates in each arm of each study, the mean treatment exposure time for each study arm needs to be available. This is then multiplied by the total number of patients in that study arm to give the estimated total person-time at risk for that study arm (E_k , for study arm k). The incidence rate is then calculated by dividing the number of patients with the event in a study arm (r_k for study arm k) by total person-time at risk, E_k , which is then used to calculate the IRR. However,

the company only had access to the mean treatment exposure and total person-time at risk for Study 302 and Study 305. For the other studies included in the NMAs the mean treatment exposure time in each arm of each study was estimated by assuming an exponential survival curve for time to discontinuation as described in Section B.2.9.3.3, page 52 of the CS. Note that the equation for the calculation of the mean treatment exposure time is

$$\text{mean exposure time} = -\frac{1}{\lambda}\left(e^{(\lambda F)} - 1\right)$$

where F is the study follow-up time and λ is the rate of discontinuation. (Note that there is an error in the equation presented in page 53 of the CS, but details of all calculations provided at the clarification stage use the correct formula).

Data extracted from the relevant studies and data used as input for the ITCs with binary data are presented in Table 12. Study specific odds ratios and 95% CI are also shown, these were estimated by using the standard continuity correction approach i.e. adding the constant 0.5 to all study cells in order to obtain non-infinite estimates of treatment effects and non-infinite variance.[21]

In the company's ITC for durable platelet response, the response outcome for the eltrombopag RAISE study was estimated for the observed population, whereas all other studies used the ITT population. The ITT population for the RAISE study considered n=62 and n=135 for the placebo and eltrombopag arms, respectively.

The durable platelet response data showed the presence of zero events (cells) for Study 302, Kuter 2008 SPL and FIT 1 studies. To address the zero cells issue the company added a value to the number of durable response events. Different adjustment values were used across treatment arms within a study but also across studies (Table 12). The company performed adjustments to durable platelet response events (numerator), but did not perform any adjustment to the total participants' number (denominator). It is common practice to adjust both numerator and denominator when performing zero cells corrections. These continuity adjustments were done externally to the evidence synthesis and, despite the ERG request, at points for clarification, for further details on all adjustments performed to the data used in the ITCs, no explanation was provided to clarify how or why these adjustment values were obtained. The ERG was unable to verify the source, calculus and appropriateness of the continuity adjustments calculated and used by the company. **Table 12 Extracted study data and input data informing the ITCs by binary outcome.**

Study	Binary outcomes						
	Treatment	Durable response			Reduction in the use of concomitant ITP medication		
		Event rate (extracted) n / N (%)	Event rate (used in ITC) n / N (%)	OR* (95% CI)	Event rate (extracted) n / N (%)	Event rate (used in ITC) n / N (%)	OR* (95% CrI)
Study 302	Avatrombopag	**11 / 32 (34.38)**	**11.604 / 32 (36.26)**	18.72	**5 / 15 (33.33)**	**5.577 / 15 (37.18)**	7.86

	Placebo	**0 / 17 (0.00)**	**0.321 / 17 (0.02)**	(1.02, 340.20)	**0 / 7 (0.00)**	**0.269 / 7 (0.04)**	(0.38, 163.88)
RAISE**	Eltrombopag	Observed: 57 / 95 (60.00) ITT: 57 / 135 (42.22)	Observed: 57 / 95 (60.00) ITT: 57 / 135 (42.22)	Observed: 13.13 (4.34, 39.74) ITT: 10.60 (3.65, 30.81)	37 / 63 (58.73)	37 / 63 (58.7)	2.99 (1.25, 7.15)
	Placebo	Observed: 4 / 39 (10.26) ITT: 4 / 62 (6.45)	Observed: 4 / 39 (10.26) ITT: 4 / 62 (6.45)		10 / 31 (32.25)	10 / 31 (32.3)	
Kuter 2008 SPL	Romiplostim	**16 / 42 (38.10)**	**16.627 / 42 (39.59)**	26.77 (1.52, 472.10)	12 / 12 (100.00)	12 / 12 (100.00)	91.67 (3.28, 2,565.44)
	Placebo	**0 / 21 (0.00)**	**0.313 / 21 (0.01)**		1 / 6 (16.67)	1 / 6 (16.67)	
Kuter 2008 non-SPL	Romiplostim	25 / 41 (60.98)	25 / 41 (60.98)	31.25 (3.82, 255.70)	8 / 11 (72.72)	8 / 11 (72.72)	2.67 (0.48, 14.70)
	Placebo	1 / 21 (4.76)	1 / 21 (4.76)		5 / 10 (50.00)	5 / 10 (50.00)	
FIT 1	Fostamatinib	**9 / 51 (17.65)**	**9.638 / 51 (18.90)**	11.40 (0.64, 204.19)	----------	----------	----------
	Placebo	**0 / 25 (0.00)**	**0.313 / 25 (0.01)**		----------	----------	----------
FIT 2	Fostamatinib	9 / 50 (18.00)	9 / 50 (18.00)	5.05 (0.60, 42.34)	----------	----------	----------
	Placebo	1 / 24 (4.17)	1 / 24 (4.17)		----------	----------	----------

Studies with zero event cells in **bold**;
*Study specific odds ratio and 95% confidence interval, estimated using standard continuity correction of 0.5;
** For the RAISE study the observed data was extracted and used by the company, while the ITT data was extracted and used in remaining studies.

Data extracted from the relevant studies and data used as input for the NMAs with rate data are presented in Table 13 to Table 16 for outcomes 'need for rescue therapy', 'any bleeding events', 'bleeding events WHO grade 2-4' and 'any adverse events', respectively. The input data to the NMAs were the log-IRRs and their standard errors obtained from the study specific event rates, and exposure and incidence rate estimates for each arm, which are also shown.

Table 13 Input data for the NMA of the estimated incidence of the need for rescue therapy.

Study	Treatment	Event rate n/N (%)	Mean exposure (years)	Total pt years (E)	Incidence rate (/pts-yrs)	IRR [95%CI]	lnIRR (SE)**
Study 302	AVA	7/32 (21.9)	0.44	14.02	0.4993	0.73	-0.3150
	PLC	2/17 (11.8)	0.17	2.92	0.6842	[0.15, 3.51]	(0.8018)
RAISE	ELT	24/135 (17.8)	0.46	61.57	0.3898	0.46	-0.7863
	PLC	25/62 (40.3)	0.47	29.22	0.8557	[0.26, 0.80]	(0.2858)
Kuter 2008	ROM	11/42 (26.2)	0.68	28.38	0.3876	0.45	-0.8055
(Splenectomised)	PLC	12/21 (57.1)	0.66	13.83	0.8674	[0.20, 1.01]	(0.4174)
Kuter 2008	ROM	7/41 (17.1)	0.68	27.69	0.2528	0.25	-1.3670
(Non-splenectomised)	PLC	13/21 (61.9)	0.62	13.11	0.9920	[0.10, 0.64]	(0.4688)
FIT 1 & FIT 2*	FOS	27/101 (26.7)	0.25	25.12	1.0747	0.37	-0.9907

	PLC	22/49 (44.9)	0.16	7.60	2.8944	[0.21, 0.65]	(0.2872)

Abbreviations: AVA, avatrombopag; ELT, eltrombopag; FOS, fostamatinib; PLC, placebo; ROM, romiplostim; RR, relative risk; IRR, incidence rate ratio; SE, standard error.
*Included as a single study; **calculated by the ERG based on calculations presented in response to clarification question A18.
Adapted from Table 23, CS Appendix D page 33

Table 14 Input data for the NMA of proportion of patients with any bleed

Study	Treatment	Event rate n/N (%)	Mean exposure (years)	Total pt years (E)	Incidence rate (/pts-yrs.)	IRR [95%CI]	lnIRR (SE)**
Study 302	AVA	14/32 (43.8)	0.44	14.02	0.9986	0.32	-1.1260
	PLC	9/17 (52.9)	0.17	2.92	3.0789	[0.14, 0.75]	(0.4272)
Study 305	AVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ELT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RAISE	ELT	106/135 (78.5)	0.43	58.62	1.8084	0.90	-0.1059
	PLC	56/62 (90.3)	0.45	27.86	2.0103	[0.65, 1.24]	(0.1652)
Kuter 2008*	ROM	48/84 (57.1)	0.68	56.74***	0.8459***	0.89***	-0.6965
(SPL and non-SPL)	PLC	25/41 (61.0)	0.64	26.31***	0.9504***	[0.55, 1.44]***	(0.3075)
FIT 1 & FIT 2*	FOS	28/101 (27.7)	0.25	25.12	1.1145	0.50	-0.6965
	PLC	17/49 (34.7)	0.16	7.60	2.2366	[0.27, 0.91]	(0.3075)

Abbreviations: AVA, avatrombopag; ELT, eltrombopag; FOS, fostamatinib; PLC, placebo; RR, relative risk; IRR, incidence rate rate; SPL, splenectomised; SE, standard error.
*Included as a single study; **calculated by the ERG based on calculations presented in response to clarification question A18; ***Not presented by the company - values based on calculations presented in response to clarification question A18 and data presented in Table 27, Appendix D
Adapted from Table 27, CS Appendix D page 44

Table 15 Input data for the NMA of proportion of patients with bleed WHO grade 2–4

Study	Treatment	Event rate n/N (%)	Mean exposure (years)	Total pt years (E)	Incidence rate (/pts-yrs)	IRR [95%CI]	lnIRR (SE)**
Study 302	AVA	3/32 (9.4)	0.44	14.02	0.2140	4.63	1.5316
	PLC	0/17 (0.0)	0.17	2.92	0.0000	[0.04, 575.58]	(2.4612)
Study 305	AVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ELT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RAISE	ELT	44/135 (32.6)	0.43	58.62	0.7506	0.65	-0.4255
	PLC	32/62 (51.6)	0.45	27.86	1.1488	[0.41, 1.03]	(0.2323)
Kuter 2008	ROM	9/42 (21.4)	0.68	28.38	0.3171	0.55	-0.6007
(Splenectomised)	PLC	8/21 (38.1)	0.66	13.83	0.5783	[0.21, 1.42]	(0.4859)
Kuter 2008	ROM	4/42 (9.5)	0.68	28.36	0.1410	0.29	-1.2263
(Non-splenectomised)	PLC	6/20 (30.0)	0.62	12.48	0.4807	[0.08, 1.04]	(0.6455)
FIT 1 & FIT 2*	FOS	10/101 (9.9)	0.25	25.12	0.3981	0.38	-0.9724
	PLC	8/49 (16.3)	0.16	7.60	1.0525	[0.15, 0.96]	(0.4743)

Abbreviations: AVA, avatrombopag; ELT, eltrombopag; FOS, fostamatinib; PLC, placebo; RR, relative risk; IRR, incidence rate rate; SE, standard error.

*Included as a single study; **calculated by the ERG based on calculations presented in response to clarification question A18.
Adapted from Table 29, CS Appendix D page 45.

Table 16 Input data for the NMA of the estimated incidence of any AE.

Study	Treatment	Event rate n/N (%)	Mean exposure (years)	Total pts years (E)	Incidence rate (/pts-yrs.)	IRR [95%CI]	lnIRR (SE)**
Study 302	AVA	31/32 (96.9)	0.44	14.02	2.2112	0.65	-0.4364
	PLC	10/17 (58.8)	0.17	2.92	3.4211	[0.32, 1.32]	(0.3637)
Study 305	AVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ELT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RAISE	ELT	118/135 (87.4)	0.46	61.57	1.9165	0.98	-0.0164
	PLC	56/61 (91.8)	0.47	28.74	1.9482	[0.72, 1.35]	(0.1623)
Kuter 2008*	ROM	83/83 (100.0)	0.68	56.07	1.4804	1.00	-0.0015
(SPL and non-SPL)	PLC	39/41 (95.1)	0.64	26.31	1.4826	[0.68, 1.46]	(0.1941)
FIT 1 & FIT 2*	FOS	85/102 (83.3)	0.25	25.37	3.3503	0.69	-0.3668
	PLC	36/48 (75.0)	0.16	7.45	4.8350	[0.47, 1.02]	(0.1989)

Abbreviations: AVA, avatrombopag; ELT, eltrombopag; FOS, fostamatinib; PLC, placebo; RR, relative risk; IRR, incidence rate rate; SPL, splenectomised; SE, standard error.
*Included as a single study; **calculated by the ERG based on calculations presented in response to clarification question A18.
Adapted from Table 31, CS Appendix D page 46

3.4.2 Results

Fixed-effect and random-effects NMA models were fitted to all outcomes. The fixed-effect models were chosen based on comparing the deviance information criteria (DIC) across models for each outcome. Further details on the methods and results of the NMAs are presented in CS Document B Section 2.9 and Appendix D Section 1.1.5. The ERG appreciates and agrees with the range of limitations associated with the NMAs and highlighted by the company in CS Document B Section 2.9.6. A summary of the key results for each of the outcomes is presented below in Table 17, which also includes evidence provided by the company at points for clarification.

Table 17 Summary of the company's main results for each outcome using a FE model.

Comparator	Efficacy Outcome					
	Binary		Rate data			
	Durable response	Reduction in the use of concomitant ITP medication	Need for rescue therapy	Any bleeding events	Bleeding events WHO grade 2-4	Any adverse events
vs Placebo	Odds Ratio (95% CrI)		IRR (95% CrI)			

Avatrombopag	102.80 (3.87, 2,796,448.5)	48.75 (1.34, 1,769,074.94)	0.73 [0.15, 3.52]	0.34 [0.18, 0.66]	0.50 [0.12, 2.02]	0.63 [0.36, 1.10]
Eltrombopag	14.27 (5.14, 53.73)	3.08 (1.25, 7.98)	0.46 [0.26, 0.79]	0.89 [0.65, 1.22]	0.67 [0.42, 1.05]	0.99 [0.73, 1.34]
Romiplostim	46.49 (9.12, 670.61)	13.72 (2.84, 88.83)	0.35 [0.19, 0.64]	0.90 [0.55, 1.46]	0.44 [0.20, 0.93]	1.00 [0.68, 1.46]
Fostamatinib	10.94 (2.13, 181.70)	----------	0.37 [0.21, 0.65]	0.50 [0.27, 0.91]	0.38 [0.15, 0.96]	0.69 [0.47, 1.02]
Synthesis model outputs*						
Total residual deviance (mean)	11.14	14.40	4.81	4.04	5.51	4.02
Number of data points **	12	8	5	5	6	5

*Obtained by the ERG based on the company's models and data; ** Number of data points to which the Total residual deviance should be compared to.
Odds ratios and IRR presented are posterior medians.

The company's base case NMA analysis for durable platelet response, reduction in the use of concomitant ITP medication and for the safety outcomes of 'any bleeding' and 'any AE' showed trends favouring avatrombopag compared to other TPO-RAs, with avatrombopag having the largest point estimate for durable platelet response compared to placebo and the lowest for the safety outcomes, although credible intervals were extremely wide for durable platelet response.

For durable platelet response a sizable variation placebo effect was observed in all studies included in the ITC, and this varied substantially between trials. The response observed in the placebo arm in all the trials ranged from 0% (in Study 302 and Kuter 2008 SPL, to 10.3% (in the RAISE study, when observed data is used).

3.4.3 Points for Critique

The ERG identified a number of important limitations in the ITCs presented by the company. The focus of the ERG's critique is on the limitations of the ITC presented for the binary outcome durable platelet response as this is the only outcome, from all efficacy outcomes evaluated by the company, that directly informs the economic model, with its results being identified as key drivers of the cost-effectiveness of avatrombopag compared to alternative treatments. Nonetheless, many of the following limitations are common to the other efficacy outcomes.

The company included two studies on fostamatinib in this ITC, stating that fostamatinib was included "because it broadens the NMA network, which may enhance robustness". Further clarifications were sought by the ERG on the inclusion of fostamatinib trials, to which the company indicated that these studies could improve the estimation of the between-trial heterogeneity for random-effects models.

The ERG considers that, given the star-shaped characteristics of the network, the inclusion of these two fostamatinib trials have no impact on the fixed-effect model results, and will not be considering them from now onwards. Furthermore, the ERG considers that a random-effects model using weakly informative prior distributions for the between-study heterogeneity would not be appropriate given the characteristics of the network and small number of trials informing each contrast of interest. Empirically-based or other informative prior distributions for the heterogeneity parameter could have been considered in order to better fit the random-effects models.[22-24] However, the fixed-effect models showed a very good fit to the data for all outcomes (assessed by comparing the total mean residual deviance to the number of data points) indicating that the additional complexity of random-effects models is unlikely to be necessary.

The company did not present details of the number of iterations used for burn-in or to obtain the posterior summaries presented for the rate data outcomes. However, the ERG was able to verify the results obtained for these outcomes using a burn-in of 10,000 iterations and 20,000 posterior samples from 3 independent chains. A more specific critique of the convergence issues observed for the binary data is given below.

Durable platelet response

For durable platelet response the network of comparator therapies consisted of only placebo-controlled trials. As there were no head-to-head comparisons, consistency could not be checked which is an essential assumption of any network meta-analysis. Only one study of avatrombopag was included in this ITC, Study 302. The company excluded Study 305 from this ITC due to data not being available for the outcome of interest, durable platelet response.

No adjustments were made in the ITC, despite a number of potential differences in patient characteristics between the trials included, as discussed in Section 3.3, and heterogeneity in placebo responses. Though the ERG appreciates that in sparse networks such as these, limited adjustments can be achieved. The placebo effect and differences in placebo responses identified may have contributed to high between-study heterogeneity, which can be a source of bias when comparing treatment effects. However, due to the sparse nature of the network, this between-study heterogeneity cannot be estimated. Some differences in the definition of durable platelet response, in the evaluation timepoints and population definitions between studies may have also introduced bias favouring avatrombopag. The ERG notes that data from the observed population of the RAISE trial was included in the analysis, where for other included studies the ITT population was considered. The ERG considers that the ITT population should be used across trials included in the ITC for durable platelet response.

As highlighted above, for durable platelet response several studies had a zero cell in their placebo arms. Typically, this is not an issue in a Bayesian MCMC approach as a binomial likelihood would be

able to deal with the case of the occasional study with a zero-cell count. However, in this ITC for durable platelet response we have an extreme scenario where several trials have zero cells, many trials are small, most contrasts of interest are only informed by one trial, and the network is star-shaped, meaning there is no additional indirect evidence to strengthen the relative effect estimates where a zero-cell is present. Under these circumstances it is inevitable that the model will be numerically unstable and either fails to converge and no treatment effects are estimated, or converges to posterior distributions with very high standard deviations for some of the relative treatment effects of interest.[21] The ERG ran the ITC model for durable platelet response with the observed zero counts in the placebo arms of Study 302 and Kuter 2008 SPL, including and excluding the fostamatinib trials. The ERG verified that the fixed-effect model presented several convergence issues, particularly for the estimation of the treatment effect for avatrombopag where chain convergence was not achieved and an extremely wide and skewed posterior distribution was obtained.

As described above by the ERG, the company corrected the placebo zero cells and corresponding active treatment events externally to the synthesis model. The ERG was not provided with any explanation on how these adjustment values were obtained and why these were applied just to the numerators. The ERG acknowledges that any zero-cell adjustments will inherently introduce bias to the ITC pooled results. Without any information on how the correction values were obtained, the ERG considers the company adjustment values as valid and as arbitrary as the usual continuity correction of 0.5 typically used. The ERG considers that both the company adjustment approach and the standard approach of adding 0.5 will provide more favourable ORs to avatrombopag and romiplostim, for study 302 and Kuter 2008 SPL, respectively. The ERG acknowledges that both approaches introduce bias, nevertheless the company's chosen continuity correction adjustment values provide more favourable ORs to avatrombopag and romiplostim than the standard continuity correction approach of adding 0.5 to numerators and 1 to denominators.

The ITC results (with continuity corrected data) presented by the company for durable platelet response, still showed convergence problems, though not to the extent of the ITC without any zero-cells correction. As evidenced by the company’s results, the treatment effects for avatrombopag relative to comparators, and particularly relative to placebo, has a large point estimate and very wide 95% credible interval, indicating that convergence issues still prevail. Table 18 below shows the fixed-effect results for durable platelet response, zero-cell adjusted with the unexplained company values, reported by the company, and the study-specific results using the standard 0.5 continuity correction. If ITC chain convergence were to be obtained, and due to the star-shape characteristics of the network, the ERG would have expected the results of the ITC for avatrombopag and eltrombopag (treatments informed by only one study) to be similar to the results directly obtained from the corresponding individual trials. While for eltrombopag that similarity is verified, staggering

differences are observed for the avatrombopag comparison, indicating that numeric instability and lack of convergence endured. For the reasons listed above, the ERG considers the company's ITC results for durable platelet response to be neither satisfactory nor reliable, in particular for avatrombopag.

Table 18 Summary of the company's main ITC fixed-effect results and study-specific results

Comparator *vs* placebo	Outcome: Durable platelet response		
	Company ITC results, zero-cell adjusted*		Study-specific results**
	Odds Ratio, median (95% CrI)	Prob best (%)	Odds Ratio (95% CI)
Avatrombopag	102.80 (3.87, 2,796,448.5)	69%	Study 302: 18.72 (1.02, 340.20)
Eltrombopag***	14.27 (5.14, 53.73)	1%	RAISE: 13.13 (4.34, 39.74)
Romiplostim	46.49 (9.12, 670.61)	30%	Kuter 2008 SPL: 26.77 (1.52, 472.10)
			Kuter 2008 non-SPL: 31.25 (3.82, 255.70)

* Zero-cell adjustment performed by the company; ** Study specific odds ratio and 95% confidence interval, estimated using standard continuity correction of 0.5; *** Using the observed data from the RAISE study; Prob best (%) is the probability of the treatment being the best.

Reduction in the use of concomitant therapies

The outcome on the reduction in the use of concomitant treatments shared many of the issues listed above for durable platelet response, the key aspects being: having a study with a zero cell in the placebo arm, adjusted by the company without any explanation being provided to the ERG, and the ITC model convergence issues. This is mainly driven by the shared evidence base between the two outcomes (that is, both outcomes are informed by the same studies) which is again translated in a star-shaped network informed by placebo-controlled studies only, with small trials informing each contrast and with only one trial informing most comparisons. Inevitably, under these circumstances, the ITC model for reduction in the use of concomitant treatments presented convergence issues, particularly for the estimation of the treatment effect for avatrombopag where chain convergence was difficult to achieve and an extremely wide and skewed posterior distribution was obtained.

Rate data outcomes

The company analysed outcomes relating to the need for rescue treatment, bleeding and adverse events on the log-IRR scale, to take into account the differential times of exposure to treatment across arms within a study and between studies. The company's models converge quickly and results were verified by ERG.

The ERG agrees with the company's approach in principle, although it requires some assumptions to be made. Due to the lack of available data on mean exposure time for studies other than Study 302 and 305, an assumption of an exponential discontinuation rate had to be made in order to estimate the mean exposure time. This seems a reasonable assumption, in the absence of any evidence to the contrary, and the company's calculations have been verified by the ERG. Having calculated the total exposure time in each treatment arm of each study, the company then transformed these into log-IRR with standard errors, to include as data in a relative effect meta-analysis model.[21] Although this is also an acceptable approach, it does make the additional assumption that the log-IRRs follow a normal distribution which may not hold when exposure times are low and events are rare. This may particularly affect the outcome 'bleeding events WHO grade 2-4' which is relatively uncommon in the included studies and was zero for the placebo arm of Study 302 – possibly due to the low exposure time. An alternative model using arm-level data could be used, which assumes the events in each arm k of each study follow a Poisson distribution with mean $\lambda_k E_k$ where the synthesis model is placed on the rate λ_k (see example 2 in the Appendix of Dias et al [21]). This would avoid the approximate normality assumption and the need to add a correction to the zero-cells, but may be less stable to fit due to network sparseness. Overall the company's modelling of the rate outcomes is appropriate.

Three of the networks using IRR had one loop of evidence due to the inclusion of Study 305, that is there was direct and indirect evidence informing the comparisons of avatrombopag, eltrombopag and placebo. However, the company did not perform inconsistency checks to assess whether there is conflict between the different sources of evidence (direct vs indirect).[25] Methods and results of the ERG's inconsistency checks are presented in Section 3.5

The ERG noticed some discrepancies in the number of participants and in the number of events occurring in the romiplostim arm of Kuter 2008 for the outcomes 'any bleed' and 'any AE' (see Section 3.3.3). These were corrected by the ERG and revised results are presented in Section 3.5. Discrepancies in the assumed study duration for the Kuter 2008 study by the company and the ERG (Section 3.3.3) do not affect the IRR since the overall study duration is the same in both arms of each study and therefore cancels out when calculating the ratio of the incidence rates. However, if the alternative arm-level data (Poisson likelihood) approach was taken, data would differ depending on the assumed study duration, which may affect the overall uncertainty in the estimates, particularly in sparse networks.

3.5 Additional work on clinical effectiveness undertaken by the ERG

3.5.1 Durable platelet response

As mentioned in 3.4.1, the company added a continuity correction to the ITC for durable platelet response which may be incorrect and for which no detail was provided. The ERG repeated the

analysis with the standard continuity correction of 0.5 affecting both numerators and denominators (Section 3.5.1). The ERG considered also the ITT data for all trials, instead of the observed data for RAISE and ITT population data for the remaining studies (section 3.5.2). Finally, the ERG explored performing the ITC for durable platelet response in a frequentist approach, instead of a Bayesian one, so that the potential noise brought by flat prior information is discarded and only trial data are considered (3.5.3).

3.5.1.1 Continuity correction

The ERG repeated the ITC for durable platelet response (excluding fostamatinib trials) without the continuity-correction and with the standard continuity correct of 0.5, presenting the results compared to those estimated by the company using the unexplained adjustments. Results are presented in Table 19. The point estimates for the model with 0.5 continuity correction are lower (i.e. less favourable to avatrombopag) than those observed when using the zero-cells corrections done by the company, i.e. with unexplained values and applied just to numerators.

Table 19 Results for ITC for durable platelet response with (company's and 0.5 adjustments) and without continuity correction for zero counts

Comparator *vs* placebo	Outcome: Durable platelet response						
	No CC	CC by the company		CC of 0.5 (ERG analysis)		Studies with CC	Total Studies
		Odds Ratio, median (95% CrI)	Prob best (%)	Odds Ratio, median (95% CrI)	Prob best (%)		
Avatrombopag	Not converged	96.96 (3.89, 5,960,000.00)	60%	37.82 (2.93, 13,340.00)	50%	1	1
Eltrombopag	Not converged	14.30 (5.06, 52.90)	4%	14.31 (5.03, 52.34)	7%	0	1
Romiplostim	Not converged	45.71 (9.21, 653.50)	36%	38.21 (8.46, 432.70)	48%	1	2
Model outputs							
DIC	----------	38.51		39.16			
Total residual deviance (mean)	----------	6.85		6.73			
Number of data points	8						

Abbreviations: CC= continuity correction, CrI= credible interval, Prob best (%)= probability of the treatment being the best.

3.5.1.2 ITT population

The ERG considered the ITC for durable platelet response with a continuity correction of 0.5 and the ITT data for the RAISE study and compared its results with the same continuity adjustments but with the observed data for RAISE. Table 20 shows the results for both scenarios. As expected, using the ITT data for RAISE had minimum impact on the estimated treatment effects for avatrombopag and romiplostim. Results of the ITT data were less favourable to eltrombopag on the point estimate, with wide credible intervals and of similar range.

Table 20 Results for ITC for durable platelet response with CC of 0.5 for zero counts and ITT data for the RAISE study

Comparator *vs* placebo	Outcome: Durable platelet response			
	CC of 0.5 and observed RAISE data		CC of 0.5 and ITT RAISE data	
	Odds Ratio, median (95% CrI)	Prob best (%)	Odds Ratio, median (95% CrI)	Prob best (%)
Avatrombopag	37.82 (2.93, 13,340.00)	50%	39.78 (2.89, 18,150.00)	50%
Eltrombopag	14.31 (5.03, 52.34)	7%	11.43 (4.33, 41.37)	4%
Romiplostim	38.21 (8.46, 432.70)	48%	38.45 (8.41, 452.60)	46%
Model outputs				
DIC	39.16		39.67	
Total residual deviance (mean)	6.73		6.77	
Number of data points	8			

Abbreviations: CC= continuity correction, CrI= credible interval, Prob best (%)= probability of the treatment being the best.

3.5.1.3 Frequentist approach

The ERG considered that the Bayesian inference using MCMC methods was not the ideal approach to derive a treatment effect for avatrombopag and its comparators in this network. The ERG implemented the ITC in a frequentist approach using the STATA[26] package *mvmeta* and the *network* suite[27] supported on multivariate meta-analysis and meta-regression methods. The key assumption of this analysis method is that it relies on a normal approximation to the distribution of the estimated study-specific treatment effects. Also, this frequentist analysis does not demand the specification of a prior distribution for the parameters of interest (informative or non-informative), depending solely on the probabilities of observed and unobserved event data. Results of the frequentist ITC analysis of this data showed a substantial reduction of the effect of avatrombopag compared to placebo on the point estimate and an ample reduction on the confidence intervals range. As expected, the frequentist ITC analysis results were aligned and consistent with the study-specific results.

Table 21 Results for ITC for durable platelet response with CC of 0.5 for zero counts and ITT data for the RAISE study using a Bayesian and a Frequentist approach

Comparator *vs* placebo	Outcome: Durable platelet response				
	Bayesian MCMC model CC of 0.5 and ITT RAISE data		Frequentist model CC of 0.5 and ITT RAISE data		Study-specific results, CC of 0.5 and ITT RAISE data
	Odds Ratio, median (95% CrI)	Prob best (%)	Odds Ratio, median (95% CrI)	Prob best (%)	Odds Ratio (95% CI)
Avatrombopag	39.78 (2.89, 18,150.00)	50%	18.72 (1.03, 340.54)	38%	Study 302: 18.72 (1.02, 340.20)
Eltrombopag	11.43 (4.33, 41.37)	4%	10.60 (3.64, 30.87)	8%	RAISE: 10.60 (3.65, 30.81)
Romiplostim	38.45 (8.41, 452.60)	46%	29.61 (5.42, 161.58)	55%	Kuter 2008 SPL: 26.77 (1.52, 472.10)
					Kuter 2008 non-SPL: 31.25 (3.82, 255.70)

Abbreviations: CC= continuity correction, CrI= credible interval, Prob best (%)= probability of the treatment being the best.

3.5.2 Reduction in use of concomitant ITP medications

The ERG repeated the analysis described above for the reduction in the use of concomitant ITP therapies outcome. Table 22 shows the results of the ITC on the reduction in the use of concomitant therapies with CC of 0.5 for zero counts using the Bayesian and frequentist approaches. The point estimates compared to placebo from the frequentist model are lower (i.e. less favourable to avatrombopag) than those from the Bayesian model and there was an ample reduction in the confidence intervals range. As expected, the frequentist ITC analysis results were aligned and consistent with the study-specific results.

Table 22 Results for ITC for reduction in the use of concomitant therapies with CC of 0.5 for zero counts using a Bayesian and a Frequentist approach

Comparator *vs* placebo	Outcome: Reduction in the use of concomitant therapies				
	Bayesian MCMC model, CC of 0.5		Frequentist model, CC of 0.5		Study-specific results, CC of 0.5
	Odds Ratio, median (95% CrI)	Prob best (%)	Odds Ratio, median (95% CrI)	Prob best (%)	Odds Ratio (95% CI)
Avatrombopag	15.55 (0.93, 5,085.00)	53%	7.86 (0.37, 164.74)	54%	Study 302: 7.86 (0.38, 163.88)
Eltrombopag	3.07 (1.25, 7.89)	1%	2.99 (1.21, 7.39)	8%	RAISE: 2.99 (1.25, 7.15)
Romiplostim	13.63 (2.83, 88.18)	46%	5.95 (1.20, 29.35)	38%	Kuter 2008 SPL: 91.67 (3.28, 2,565.44)
					Kuter 2008 non-SPL: 2.67 (0.48, 14.70)

Abbreviations: CC= continuity correction, CrI= credible interval, Prob best (%)= probability of the treatment being the best.

3.5.3 Rate data outcomes

The ERG conducted inconsistency checks on three NMAs conducted by the company which had an evidence loop, and re-ran the company's NMA models for two outcomes where data from Kuter 2008 were corrected by the ERG. Inconsistency checks were also performed for these new analyses.

3.5.3.1 Inconsistency checks

Three of the networks using IRR have one loop of evidence due to the inclusion of Study 305. These are the network for outcomes 'any bleeding events', 'bleeding events WHO grade 2-4' and 'any adverse events'. The ERG checked whether there was evidence of disagreement between direct and indirect evidence in the loop formed by Placebo—Avatrombopag—Eltrombopag in these three networks.[25] As these are all networks with a single three-treatment loop and only include 2-arm studies, the approach suggested in Section 7.4 of Dias et al 2018[28] was adopted. Briefly, a fixed effect unrelated mean effects (UME) model was used to estimate relative treatment effects based only on direct evidence[25] and code was added to the model to calculate an indirect estimate for each relative effect in that loop using the Bucher approach. The probability, *prob*, that the direct estimate is

greater/lower than the indirect estimate was calculated using the MCMC simulations and a Bayesian p-value was calculated as 2×*prob* when *prob* < 0.5 or 2×(1-*prob*) when *prob* > 0.5.[28] BUGS code used by the ERG is given in Box 1 in the Appendix. Although the code calculates multiple probabilities, these will all give the same p-value as there is a single loop.[28]

Convergence occurred by 10,000 iterations after which posterior samples were obtained from 20,000 iterations on 3 independent chains.

For each network, inconsistency was assessed by comparing the fit of the UME to the NMA model using the mean residual deviances and by assessing the Bayesian p-value. Results are presented in Table 23. The inconsistency model does not show improved model fit compared to the NMA model (similar total residual deviances) and all p-values are large, indicating that there is no evidence of inconsistency in these networks.

Table 23 Model fit and Bayesian p-value for inconsistency assessment of the company's NMAs.

	Any bleeding events	Bleeding events WHO grade 2-4	Any adverse events
Total residual deviance (mean)	5.01	5.61	5.01
Number of data points *	5	6	5
p-value for inconsistency	0.86	0.34	0.91

***** Number of data points to which the Total residual deviance should be compared to.

3.5.3.2 NMAs with corrected data

The ERG re-ran the company's NMA for the outcomes 'any bleed' and 'any AE', correcting the number of participants and number of events occurring in the romiplostim arm of Kuter 2008. Corrected data used in the analyses are given in Table 24 for 'any bleed' and Table 25 for 'any AE'. Only data related to the Kuter 2008 study are changed from Section 3.4. The company's NMA code and initial values for IRR data were used; convergence occurred by 10,000 iterations after which posterior samples were obtained from 20,000 iterations on 3 independent chains.

Table 24 Input data for the NMA of proportion of patients with any bleed – corrected by the ERG.

Study	Treatment	Event rate n/N (%)	Mean exposure (years)	Total pt years (E)	Incidence rate (/pts-yrs.)	IRR [95%CI]	lnIRR (SE)
Study 302	AVA	14/32 (43.8)	0.44	14.02	0.9986	0.32	-1.1260
	PLC	9/17 (52.9)	0.17	2.92	3.0789	[0.14, 0.75]	(0.4272)
Study 305	AVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ELT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RAISE	ELT	106/135 (78.5)	0.43	58.62	1.8084	0.90	-0.1059

	PLC	56/62 (90.3)	0.45	27.86	2.0103	[0.65, 1.24]	(0.1652)
Kuter 2008*	ROM	45**/84 (53.6)	0.67	56.41	0.80	0.85	-0.1633
(SPL and non-SPL)	PLC	25/41 (61.0)	0.65	26.62	0.94	[0.52, 1.38]	(0.2494)
FIT 1 & FIT 2*	FOS	28/101 (27.7)	0.25	25.12	1.1145	0.50	-0.6965
	PLC	17/49 (34.7)	0.16	7.60	2.2366	[0.27, 0.91]	(0.3075)

Abbreviations: AVA, avatrombopag; ELT, eltrombopag; FOS, fostamatinib; PLC, placebo; RR, relative risk; IRR, incidence rate rate; SPL, splenectomised; SE, standard error.
*Included as a single study; **corrected by the ERG based on values extracted from the Romiplostim ERG report[19] and Kuter 2008[7]
Adapted from Table 27, CS Appendix D page 44

Table 25 Input data for the NMA of the estimated incidence of any AE – corrected by the ERG.

Study	Treatment	Event rate n/N (%)	Mean exposure (years)	Total pts years (E)	Incidence rate (/pts-yrs.)	IRR [95%CI]	lnIRR (SE)
Study 302	AVA	31/32 (96.9)	0.44	14.02	2.2112	0.65	-0.4364
	PLC	10/17 (58.8)	0.17	2.92	3.4211	[0.32, 1.32]	(0.3637)
Study 305	AVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ELT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RAISE	ELT	118/135 (87.4)	0.46	61.57	1.9165	0.98	-0.0164
	PLC	56/61 (91.8)	0.47	28.74	1.9482	[0.72, 1.35]	(0.1623)
Kuter 2008*	ROM	84/84** (100.0)	0.67	56.41	1.4892	1.02	0.0162
(SPL and non-SPL)	PLC	39/41 (95.1)	0.65	26.62	1.4653	[0.70, 1.49]	(0.1938)
FIT 1 & FIT 2*	FOS	85/102 (83.3)	0.25	25.37	3.3503	0.69	-0.3668
	PLC	36/48 (75.0)	0.16	7.45	4.8350	[0.47, 1.02]	(0.1989)

Abbreviations: AVA, avatrombopag; ELT, eltrombopag; FOS, fostamatinib; PLC, placebo; RR, relative risk; IRR, incidence rate rate; SPL, splenectomised; SE, standard error.
*Included as a single study; **corrected by the ERG based on values extracted from the Romiplostim ERG report[19]
Adapted from Table 31, CS Appendix D page 46

Results obtained from the NMAs with revised data are compared to the company's original results in Table 26. The fixed-effect models fitted equally well to the corrected and original data and estimates of the IRR were similar, although there were slight changes to the IRR of romiplostim compared to placebo for both outcomes. Inconsistency checks were performed following the methods described in Section 3.5.3.1 with results identical to those presented in Table 23, i.e. there was no evidence of inconsistency in these networks.

Table 26 Comparison of the company's main analysis results to the ERG's results using corrected data for Kuter 2008 (FE model).

	Any bleeding events: IRR [95%CrI]		Any adverse events: IRR [95%CrI]	
Comparator vs Placebo	Company's original analysis	ERG corrected data	Company's original analysis	ERG corrected data
Avatrombopag	0.34 [0.18, 0.66]	0.34 [0.18, 0.67]	0.63 [0.36, 1.10]	0.63 [0.36, 1.11]

Eltrombopag	0.89 [0.65, 1.22]	0.89 [0.65, 1.22]	0.99 [0.73, 1.34]	0.99 [0.73, 1.34]
Romiplostim	0.90 [0.55, 1.46]	0.85 [0.52, 1.38]	1.00 [0.68, 1.46]	1.02 [0.69, 1.48]
Fostamatinib	0.50 [0.27, 0.91]	0.50 [0.27, 0.91]	0.69 [0.47, 1.02]	0.69 [0.47, 1.02]
Model fit statistics				
Total residual deviance (mean)	4.04	4.04	4.02	4.02
Number of data points *	5	5	5	5

* Number of data points to which the Total residual deviance should be compared to.
IRR presented are posterior medians.

3.6 Conclusions of the clinical effectiveness section

Avatrombopag trial evidence

The trial evidence on the efficacy and safety of avatrombopag is based on the results of three RCTs, with most of the evidence being derived from one placebo-controlled RCT, Study 302. This study reported statistically significant and clinically important benefits of avatrombopag when compared to placebo across platelet response outcomes. Avatrombopag can therefore be assumed to be an effective treatment for improving symptoms of ITP. However, there were no statistically significant differences in incidence of bleeding events, use of concomitant ITP medications and use of rescue therapy. This may be a consequence both of small numbers of events, and the bias arising from missing outcome data in Study 302; there was an important imbalance in discontinuation rates between the treatment groups, with a higher discontinuation rate (due to lack of efficacy) seen in the placebo group. This made interpretation of the results difficult because the company did not adjust for different discontinuation rates when presenting their pivotal trial results (although they did adjust the results in later sections of the CS, when comparing trials in the NMA).

Although the avatrombopag trials were conducted in populations which were broadly applicable to NHS patients, all the trials had small sample sizes with the one trial which used an active comparator (eltrombopag, in Study 305) being terminated early due to recruitment issues. Avatrombopag appears to have an acceptable safety profile. Subgroup analyses of Study 302 suggested that efficacy might be lower in splenectomised patients and in patients with baseline platelet counts $\leq 15 \times 10^9$/L.

Network Meta-analyses

The company excluded seven TPO-RA comparator trials from their NMAs, despite these trials being included in their systematic review. The exclusions were based on judgements on one or more of the following issues: treatment durations, initial TPO-RA doses, and population ethnicity. The ERG and

their clinical adviser disagreed with the company's reasons for excluding the trials. Their inclusion would have broadened the available evidence for some outcomes, particularly the clinically-important bleeding outcomes, although none could contribute data to the outcome used in the economic modelling: durable platelet response. The company also excluded trials of rituximab, based on its uncertain position in the treatment pathway, but there appears to be no clear consensus of clinical opinion on the positioning of rituximab.

Estimates obtained from the NMAs were uncertain, having wide credible intervals for all outcomes. Results were particularly uncertain for durable platelet response, the key outcome used in the economic modelling. This was partly due to the evidence sparseness, both in terms of the network structure and the fact that there were several study arms with no observed events, meaning that the company's Bayesian NMA provided numerically unstable results. These results were revised by the ERG for inclusion in the economic model although data limitations still mean that uncertainty in the relative efficacy of avatrombopag versus its comparators remains.

The company's NMA suggested that avatrombopag was better than eltrombopag for durable platelet response, a result driven by the uncertainty in results and convergence issues in the company's Bayesian NMA. The EMA assessment report[6] has some limited results of an alternative NMA which suggest that avatrombopag and eltrombopag have similar durable platelet response. The ERG believes there is considerable uncertainty in how these interventions compare.

The company's approach to deal with the effect that premature, imbalanced discontinuation between active and placebo groups may have in terms of biasing results for the outcomes relating to the need for rescue treatment, bleeding and adverse events to occur was broadly appropriate. However, interpretation of results from these analyses is still limited by the short exposure time and low number of events and the company's approach cannot totally remove the potential bias from not having actually observed some patients over an appropriate follow-up time.

4 COST EFFECTIVENESS

4.1 ERG comment on company's review of cost-effectiveness evidence

4.1.1 Summary of company's submission

The company conducted systematic literature reviews to identify published evidence on the cost-effectiveness of avatrombopag for the treatment of chronic ITP. The company's literature review did not identify any relevant economic evaluations for avatrombopag but did identify twenty economic evaluations in other treatments for ITP. A detailed description of the search criteria and findings can be found in Appendix G of the CS.

4.1.2 Points for critique

The ERG considers that the searches undertaken by the company were not as thorough as would be expected for a systematic literature review. In particular, the search filter used to limit the searches to economic evaluations was quite restrictive. The search filter was not referenced; therefore, it was unclear if the filter had been designed and tested for use in highly sensitive search strategies of the type needed for systematic reviews. In addition, the sources searched for unpublished studies were fairly limited, which may have resulted in missed studies. The ERG appraisal of the searches can be found in Table 27 below. In the absence of any relevant economic evaluations for avatrombopag, the ERG considers the de-novo cost-effectiveness analysis reported in the CS to be the most relevant source of evidence to inform the decision problem.

Table 27: ERG appraisal for the identification of economic evaluation evidence in CS

Topic	ERG response	Note
Is the report of the search clear and comprehensive?	YES	The original and update search strategies and were both included in Appendix G. A reference for the study design search filter was missing.
Were appropriate sources searched?	PARTLY	- Conference abstracts were identified via Embase, however no further sources of conference abstracts were searched. - Limited searching for previous Health Technology Assessments - the International HTA (INAHTA) database or websites of HTA agencies were not searched. - Checking of reference lists for further relevant studies was not reported.

Was the timespan of the searches appropriate?	YES	The searches covered the period from database inception to March 2021.
Were appropriate parts of the PICOS included in the search strategies?	PARTLY	- ITP (**P**opulation) AND economic evaluations (**S**tudy design). - It was inappropriate to limit the searches of NHS EED, DARE and the HTA database by study design. Population terms only should have been used to search these three databases.
Were appropriate search terms used?	YES	
Were any search restrictions applied appropriate?	NOT APPLICABLE	
Were any search filters used validated and referenced?	UNCLEAR	Searches were limited to economic evaluations in MEDLINE and Embase. The search filter used was not referenced in the submission or in the points for clarification and was not recognised by the ERG. Therefore it was unclear if the filter used was validated.

4.2 Summary and critique of the company's submitted economic evaluation

The company submitted a de-novo Markov economic model to assess the cost-effectiveness of avatrombopag, within its licensed indication for chronic ITP, relative to the comparators of eltrombopag and romiplostim. In the model, patients initiate active treatment, with concomitant ITP medication such as corticosteroids, and remain in an uncontrolled non-responder disease state until treatment response is assessed. Response was defined as a platelet count of $\geq 50x10^9$/L. Following a response, patients can either remain on treatment or relapse into a 'no response' health-state ($<50x10^9$/L) and discontinue treatment. Patients failing to achieve a response at 24-weeks transition into the no response health-state where active treatment is discontinued and a "watch and wait" strategy is adopted. Patients within the no response health-state may transition to a new active subsequent treatment when a bleeding event or need for rescue therapy occurs. All patients in the model are at risk of death.

Avatrombopag is modelled to reduce NHS costs and improve the expected quality-adjusted life-years of patients with chronic ITP by increasing treatment response ($\geq 50x10^9$/L) rates, which are associated with lower risks of bleeding events, reduced dependency for rescue therapies and concomitant medications, greater life expectancy (by avoiding severe life-threatening bleeds) and improved health-

related quality of life. A broader overview of the company's economic evaluation is presented in Appendix Box 1.

4.2.1 NICE reference case checklist

Table 28: NICE reference case checklist

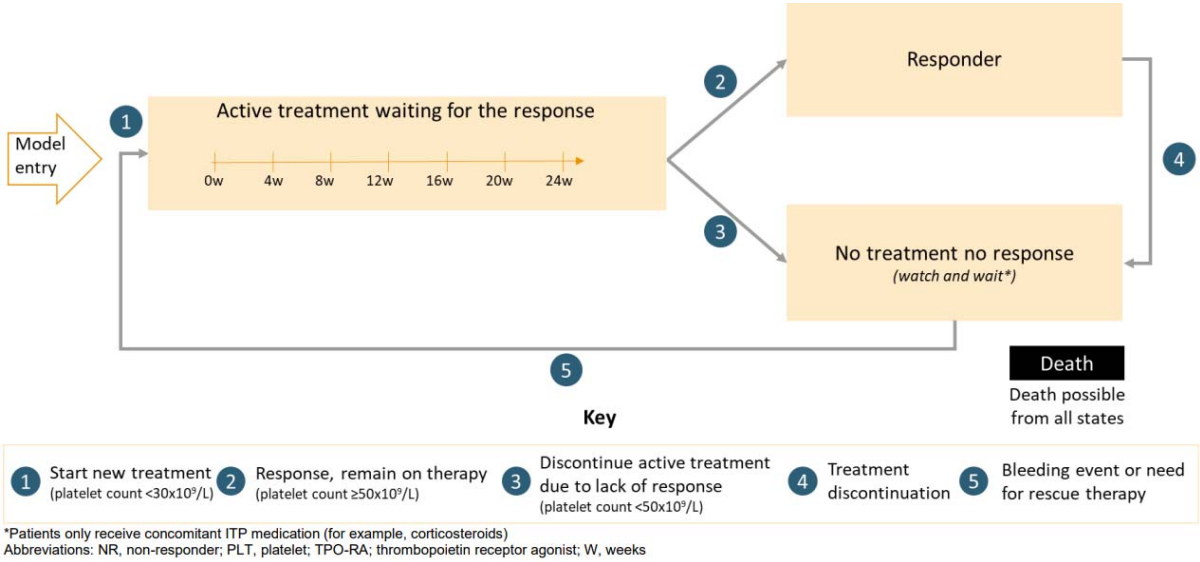
Element of health technology assessment	Reference case [29]	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The CS is appropriate.
Perspective on costs	NHS and PSS	The CS is appropriate.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The CS is appropriate.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The CS is appropriate, the time horizon is 56 years, by when more than 99.6% of the cohort have died.
Synthesis of evidence on health effects	Based on company NMA	The approach used by the company is appropriate but the methods used in the NMA are unclear.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	The CS is appropriate. Health-state utility values are modelled from EQ-5D-3L data.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	The CS is appropriate.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The CS is appropriate.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	The CS is appropriate.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	The CS is appropriate. Resources obtained from previous appraisals, survey findings, guidelines, and pivotal trial data. Unit costs from national representative sources [30, 31].
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	The CS is appropriate.
CS: company submission; NMA: Network meta analysis; EQ-5D: standardised instrument for use as a measure of health outcome; HRQoL: health-related quality of life; PSS: personal social services; QALYs: quality-adjusted life years; RCT: randomised controlled trial.		

4.2.2 Model structure

4.2.2.1 Summary of company submission

The company's economic model is a Markov cohort model which consists of four mutually exclusive health states: (i) Active treatment (up to 24 weeks waiting for response), (ii) Responder, (iii) No treatment no response (watch and wait), and (iv) Death (see Figure 4). Patients with a platelet count $<30x10^9$/L enter the model in Cycle 0, which represents the point at which treatment with avatrombopag or one of the comparator TPO-RAs (eltrombopag or romiplostim) starts. These treatments are given in addition to current clinical management. Patients remain in state (i) Active treatment until their response status is determined. Response is defined as achieving a platelet count of $\geq 50\times10^9$/L. For first-line active treatment, this is determined at 24 weeks (for subsequent lines of treatment this is determined at 8 weeks). Following 24-weeks of active treatment, patients transition into either the (ii) Responder ($\geq 50x10^9$/L), or the (iii) No treatment no response ($<50x10^9$/L) health-state, in accordance with their response status. Patients who are classified as responders remain in the (ii) Responder health-state receiving active treatment until relapse and treatment discontinuation occurs. At this point, these patients transition into the (iii) No treatment no response health-state. Patients who are classified as non-responders following active treatment move to the (iii) No treatment no response health-state, where a 'watch and wait' strategy is adopted and patients only receive ITP medication such as corticosteroids. Patients in the no treatment no response health state are at an increased risk of a bleeding event or need for rescue therapy (and reduced health-related quality of life). Once rescue therapy is required to re-establish a safe platelet count, or a bleeding event occurs, these patients may return to the (i) Active treatment health-state, where they receive an alternative active treatment from their first-line treatment option. The model allows up to two lines of subsequent active treatment and a third line defined as being a watch and wait strategy (i.e. no active treatment, only ITP medication such as corticosteroids). All patients in the model are at risk of death due to all-cause mortality and ITP-related mortality, where ITP-related mortality is a function of ITP-related hospitalisations for severe bleeds. The model cycle length is 4-weeks long, and a half-cycle correction is implemented. The company justified a 4-week cycle length on the basis that the timing is consistent with the frequency of haematologist consultations in early management and the schedule adopted for longer-term blood testing.

Figure 4: Company model structure (reproduced from CS Figure 12, page 81)



*Patients only receive concomitant ITP medication (for example, corticosteroids)
Abbreviations: NR, non-responder; PLT, platelet; TPO-RA; thrombopoietin receptor agonist; W, weeks

4.2.2.2 Points for critique

The ERG considers the model structure to be broadly representative of the natural course of ITP and appropriate for characterising the mechanism of effect for TPO-RAs. In the model, treatment effect and related impact on patient outcomes is determined solely by response to active treatment, where response is defined as a platelet count of ≥50x10^9/L. The company justified the ≥50×10^9/L response threshold on the basis that it is regularly used to define treatment response in clinical studies and that it has been used in previous economic models and NICE appraisals for ITP [32, 33]. The ERG clinical advisor indicated that although active treatment is typically given to patients with a low platelet count, treatment would not normally be determined solely on the basis of platelet count. Other factors such as the symptoms of the patient and likelihood of a bleeding event are important considerations. However, the platelet response threshold of ≥50×10^9/L is an accepted measure for treatment response. Therefore, the ERG considers the use of a response threshold of ≥50×10^9/L by the company to be broadly acceptable.

It is important to note that a response threshold of ≥50×10^9/L means that the difference in response rates between the active treatments, in terms of platelet count, is a critical parameter for determining the cost-effectiveness of avatrombopag relative to its comparators. This is because the risk of bleeding and need for rescue therapy is modelled independent of treatment and only according to platelet count, with patients with a platelet count ≥50×10^9/L having a lower probability of experiencing bleeding events and need for rescue therapy compared to those with a platelet count <50×10^9/L. Also, a higher platelet count is associated with greater health-related quality of life. This means that time in the responder health-state accrues benefits via lower bleeding event risks (and associated mortality), reduced dependency for rescue therapies and concomitant medications, greater life expectancy and improved health-related quality of life.

The ERG has concerns about the inconsistency in definition of response to active treatment that is used at first and subsequent lines of treatment in the model. At first-line active treatment with avatrombopag, eltrombopag or romiplostim, durable platelet response is the platelet response measure used to model response, which is defined as a platelet count $\geq 50\times10^9$/L in at least 6 weekly platelet counts in the final 8 weeks of a 24-26-week study. This was used on the basis that it was the only platelet response measure which yielded comparative effectiveness data between avatrombopag and the other TPO-RAs (eltrombopag and romiplostim). However, in subsequent lines of treatment, when patients switch to an alternative second- or third-line active treatment, the definition of response appears to be a mixed definition of either platelet count $\geq 50\times10^9$/L (not based on durable or sustained response, although the definition used is unclear) or durable platelet response. The CS does not discuss the definition of response used in subsequent lines of therapy and only refers to response rates for non-TPO-RA treatments in subsequent lines as those adopted from TA221 for romiplostim NICE appraisal (Appendix Table 58). However, the ERG notes that the response rates in subsequent lines of treatment for the non-TPO-RAs are all higher than the response rate for first-line treatment with eltrombopag in the company's base-case analysis, while response rates for some non-TPO-RAs are higher or similar (e.g. rituximab, splenectomy, azathioprine, mycophenolate mofetil, cyclosporine) compared to the response rate for first-line romiplostim. This suggests that the company is using a different definition of treatment response at first-line compared to subsequent lines of therapy. Furthermore, the company has modelled second- and third-line treatment as a mixed treatment strategy (percentage of patients receiving different active treatments at second- and third-line) rather than a single alternative treatment option. As part of this mixed treatment strategy, patients who become non-responders to a TPO-RA at first-line may receive an alternative TPO-RA at second- or third-line. The response rates for the TPO-RAs are always durable platelet response in all lines of therapy, while it appears to be an alternative metric of platelet count $\geq 50\times10^9$/L (not based on durable or sustained response) for non-TPO-RAs. This means that the mixed treatment strategy for subsequent lines of therapy is based on a mixed treatment response definition of durable platelet response for TPO-RAs and platelet count $\geq 50\times10^9$/L for non-TPO-RAs.

The ERG is raising the point about definition of response because the model structure assumes that patients wait a full 24 weeks to assess non-response to TPO-RAs after initiating first-line active treatment, while they wait 8 weeks to assess non-response in subsequent lines of therapy. Following ERG points for clarification, the company justified this approach on the basis that durable platelet response is the only metric which could be estimated through a network meta-analysis to compare response rates for avatrombopag, eltrombopag and romiplostim. Therefore, they adopted a pragmatic approach and assumed a 24-week timeframe to assess response to TPO-RA treatment. The company supported this further by indicating that durable platelet count is the key measure used in clinical practice to estimate treatment effect.

The ERG clinical advisor supported the view that durable platelet count is the best metric of treatment response. However, he indicated that it is very unlikely that patients would remain on treatment up to 24 weeks to determine response to treatment. In clinical practice, patients would initiate treatment with a TPO-RA at the recommended starting dose, as per the product SmPC. If no response is observed within a short timeframe of monitoring (1-2 weeks), dose titration will occur up to the maximum dose permitted in the product SmPCs (a maximum dose of 40 mg once daily for avatrombopag, 75 mg once daily for eltrombopag (50 mg for East Asian heritage), and 10 micrograms/kg once weekly for romiplostim). The product SmPCs for the TPO-RAs all stipulate stopping treatment if response is not achieved within a short time window after establishment of maximum dose:

> Avatrombopag SmPC: *"Discontinue avatrombopag if the platelet count does not increase to ≥ 50 x 109/L after 4 weeks of dosing at the maximum dose of 40 mg once daily. Discontinue Doptelet if the platelet count is greater than 250 x 109/L after 2 weeks of dosing at 20 mg once weekly."*;
>
> Eltrombopag SmPC: *"Treatment should be stopped if the platelet count does not increase sufficiently to avoid clinically significant bleeding after 4 weeks of therapy at a dosage of 75 mg once daily."*;
>
> Romiplostim SmPC: *"Treatment with romiplostim should be stopped if the platelet count does not increase sufficiently to avoid clinically significant bleeding after 4 weeks of romiplostim therapy at the highest weekly dose of 10 micrograms/kg"*.

On this basis, the ERG considers non-response to treatment with a TPO-RA to be observed within clinical practice within a time-frame of around 8 weeks rather than 24 weeks as used in the company's model. A timeframe of 8 weeks to assess non-response to TPO-RAs in first-line treatment would be consistent with the modelled timeframe of 8 weeks used to assess non-response in subsequent lines of therapy.

The ERG considers there to be little evidence of a specific time-to-response effect to suggest that TPO-RAs warrant a longer 24-week timeframe to assess response to treatment. The evidence for platelet count from weeks 8 to 24 of Study 302 (Figure 6, page 39 of CS) suggest a fairly stable maintenance of response over this period. Therefore, extending treatment for non-responders by a further 16 weeks will increase costs but it does not appear to meaningfully increase response to treatment (although the latter cannot be assessed using the durable platelet response definition as this refers to at least 6 weekly platelet counts $\geq 50 \times 10^9$/L in the final 8 weeks of a 24-26-week study). The modelled timeframe for treatment response is further complicated by the fact that patients in Study

302 were also receiving concomitant ITP medication, which may lead to further dose adjustments in order to achieve a stable platelet response. The extent to which concomitant ITP medication would be used in clinical practice to achieve the desired level of response is unclear.

Item 1. It is unlikely that patients would remain on active first-line TPO-RA treatment for a duration of 24 weeks before non-response to treatment is assessed in clinical practice.

4.2.3 Population

4.2.3.1 Summary of company submission

The patient population considered in the company's economic model are adults with primary chronic ITP who are refractory to other treatments (e.g. corticosteroids or immunoglobulins), in line with the Study 302 population. The baseline characteristics of the modelled population are: 44.6 years of age, 36.7% male, 82.97 kg, 1.94 m^2 body surface area, and 32.7% of patients are post-splenectomy.

The company did not consider any separate subgroup populations in the economic model, thereby omitting the prior rituximab sub-group specified within the NICE scope or the splenectomy status sub-group considered in previous appraisals [32, 33]. The company justification for the exclusion of subgroup analyses of patients with prior rituximab and splenectomy treatment was that this was "*not appropriate for this appraisal owing to highly varied use of rituximab by treatment centre and clinical opinion increasingly positioning splenectomy as a later-line treatment once medical interventions are exhausted, respectively*" (CS, page 7).

4.2.3.2 Points for critique

The ERG considered how well the patient population of Study 302 aligns with the population seen in UK clinical practice. Study 302 was a small study with no UK patients. However, as discussed in Section 3.3 the baseline patient characteristics for this trial population are not dissimilar to the patient characteristics of the trials included in the NMA of RAISE (eltrombopag) and Kuter et al (2008) (romiplostim), in terms of age, sex, weight and body surface area. In response to ERG points for clarification, the company indicated that the most robust real-world data source on UK ITP patients is the Adult IT Registry, where a 2018 congress abstract from the European Haematology Association (based on clinical data from 2010- Jan 2018) reports a mean age of diagnosis of 50 years and 43% of patients are male. The proportion of patients who were splenectomised in Study 302 (32.7%) is greater than that observed in UK clinical practice (9.83%); however, changing this percentage in the model has minimal impact on the cost-effectiveness results because the model does not consider separate response outcomes for splenectomised and non-splenectomised patients. Therefore, the ERG is satisfied that the choice of Study 302 to inform the baseline patient characteristics in the model is reasonable.

The company justification for excluding subgroup populations by splenectomised status and prior use of rituximab is discussed in the next Section 4.2.4 under interventions and comparators.

4.2.4 Intervention and comparators

4.2.4.1 Summary of company submission

The intervention considered is avatrombopag in addition to standard of care (which includes concomitant ITP medication and rescue therapy as defined in Study 302). The company considered eltrombopag and romiplostim as the relevant comparators because these are the two existing TPO-RA treatments approved by NICE in 2013 and 2011, respectively [32, 33]. The company justified the choice of comparators on the basis that the population eligible for avatrombopag will be identical to those who currently receive a TPO-RA, with eltrombopag and romiplostim the only TPO-RA treatments representing established clinical management.

Rituximab is listed as a potential comparator in the NICE scope but the company justified its exclusion due to the high variability in its use across treatment centres and lines of therapy. Splenectomy was also listed as a potential comparator in the NICE scope but the company justified its exclusion on the grounds that clinical opinion now positions splenectomy as a later treatment procedure once all medical treatment options have been exhausted due to a risk of relapse and procedure-related mortality. Other potential comparators listed in the NICE scope include immunosuppressive agents of azathioprine, mycophenolate mofetil, dapsone, danazol, and cyclophosporin A, and watch and rescue.

For patients who require subsequent therapy after discontinuation of their TPO-RA (i.e., when a bleed has occurred or patients require rescue therapy), the cost-effectiveness of the TPO-RAs is assessed by allowing patients to receive two subsequent lines of active treatment (i.e. second- and third-line treatment). In the fourth line of therapy, patients are assumed to be in a 'watch and wait' state, where patients only receive ITP medication such as corticosteroids. For the subsequent lines of active treatment, the company adopts a mixed treatment strategy, where the strategy consists of a percentage of patients each receiving different active treatments (see Table 38, page 85 of CS). For example, when eltrombopag is the first-line comparator treatment, the second-line treatment is a mixed treatment strategy consisting of 12.5% romiplostim, 20.5% rituximab, 10.2% splenectomy, 2.8% for each of the immunosuppressive and chemotherapy agents (azathioprine, mycophenolate mofetil, cyclosporine, danazol, dapsone, cyclophosphamide, vincristine, and vinblastine) and 34.1% on watch and rescue, while the third-line treatment is also a mixed treatment strategy (19.5% romiplostim, 12.6% rituximab, 10.3% splenectomy, 2% for each of the immunosuppressive and chemotherapy agents and 41.4% on watch and rescue). When romiplostim is the first-line comparator treatment, the company adopts a different mixed treatment strategy for second- and third-lines. For example, the

second-line treatment strategy consists of 13.5% eltrombopag, 20.2% rituximab, 10.1% splenectomy, 2.8% for each of the immunosuppressive and chemotherapy agents and 33.7% on watch and rescue, while the third-line consists of 17.6% eltrombopag, 12.6% rituximab, 10.3% splenectomy, 2.1% for each of the immunosuppressive and chemotherapy agents and 42.4% on watch and rescue. The company indicated that the percentages for the mixed treatment strategies were based on a survey and structured interviews with 113 physicians across the EU, including 20 physicians from the UK.

The included doses for the intervention and comparators was based on the starting dosages specified in the product SmPC for avatrombopag (20mg once daily) and eltrombopag (50mg once daily), while the dosage for romiplostim was taken from a pivotal long-term study of romiplostim (0.004 mg/kg once weekly) [34]. The company assumes avatrombopag and its comparators will be administered over a 24-week schedule. The dosage for non-TPO-RAs used in subsequent lines of therapy was based on those used in TA293 for eltrombopag and sourced from Provan et al (2010) [1].

4.2.4.2 Points for critique

In line with the marketing authorisation for avatrombopag, the company assumed that all patients entering the model have ITP that is refractory to first-line treatment with corticosteroids or immunoglobulins. The ERG considers this appropriate and in line with the positioning of the comparator TPO-RAs, as previously assessed in TA293 for eltrombopag and TA221 for romiplostim. In TA293, when guidance was first developed for eltrombopag it had a marketing authorisation for the treatment of chronic ITP in patients who have had a splenectomy (and whose condition is refractory to other treatments) or as a second-line treatment in patients who have not had a splenectomy because surgery is contraindicated. However, the guidance in TA293 and in TA221 (romiplostim) was reviewed in 2018 and an amended change was made with respect to prior splenectomy, which now permits patients with or without prior splenectomy to receive eltrombopag and romiplostim [35]. The ERG clinical advisor indicated that splenectomy is rarely used in UK practice and would not be considered as a comparative treatment option to TPO-RAs and would only be used in those resistant to other treatments. Therefore, the ERG supports the company's view that splenectomy is not a relevant comparator to avatrombopag.

With respect to rituximab, in TA293 (eltrombopag), if rituximab was considered an appropriate treatment option, patients were assumed to have already received it, i.e., rituximab was assumed to come before eltrombopag or romiplostim. This was not the case in TA221 (romiplostim) where rituximab was positioned after romiplostim, but clinical specialists at the committee meeting for appraisal TA221 suggested that romiplostim would be used in clinical practice (at that time) in people whose condition is refractory to rituximab, or who are intolerant of rituximab. The ERG clinical advisor reported that there is variation in the use of rituximab in UK clinical practice, and the variation in use has changed further in the last few years in the context of the COVID-19 pandemic,

where TPO-RAs are now more likely to be given before rituximab. In response to ERG points for clarification, the company also indicated that national guidance during the pandemic was issued favouring the use of other agents instead of rituximab given the potential for severe infectious events and an impaired immune response to COVID-19 vaccination with rituximab. In the most recent NICE Technology Appraisal of fostamatinib for treating refractory chronic immune thrombocytopenia (ID1087), August 2021, the treatment pathway for chronic ITP positioned TPO-RAs before rituximab, splenectomy, azathioprine, mycophenolate, cyclosporine, dapsone and danazol [36]. Given this uncertainty, the ERG considers the company's position that eltrombopag and romiplostim are the most relevant comparators to be reasonable, while the company's positioning of rituximab, splenectomy and immunosuppressive agents after TPO-RAs is also reasonable.

Item 2. The treatment pathway and positioning of avatrombopag relative to non-TPO-RAs such as rituximab and splenectomy is unclear.

The ERG has concerns about the approach used by the company to model subsequent lines of therapy after discontinuation of TPO-RAs. The company used a mixed treatment strategy rather than a single alternative treatment option. This deviates from the approach used in the previous appraisals of TA293 and TA221 for eltrombopag and romiplostim, respectively, where each of the subsequent non-TPO-RAs were modelled as separate lines of subsequent treatment. In response to ERG points for clarification, the company justified their approach on the grounds that there is a wide range of agents in use across the UK. To reflect this heterogeneity in use and switching behaviour among physicians the market research commissioned by the company, that involved structured interviews and an online survey by consultant haematologists, provided the best source of data to inform a mixed treatment approach (note that the ERG cannot comment on the survey itself as no information was provided in the company submission). The use of a mixed treatment strategy means that the response rate, time to response, and duration of treatment (discontinuation rate) for the subsequent lines of therapy is comprised of a percentage of the response rates, time to responses, and treatment durations for each of the individual therapies that follow first-line TPO-RA. This makes interpretation of outcomes at second- and third-line more challenging. For example, the response rate used in the company's base case analysis for first-line treatment with eltrombopag is 27%, while the response rates used in the same analysis for second- and third-line therapies are higher at 40.3% and 36.0%, respectively. The reason for the higher response rates in subsequent lines of therapy are partly driven by the different definitions of treatment response that appear to be used for TPO-RAs (durable platelet count over a 24-week study) compared to non-TPO-RAs (an alternative platelet count measure), but also by the fact that in subsequent lines of therapy for first-line eltrombopag, a percentage of patients are assumed to receive romiplostim (12.5%) and rituximab (20.5%) that have higher response rates than eltrombopag (durable platelet response rate of 55.21% for romiplostim and 58% response rate for

rituximab). The time to response for second- and third-line treatment is also modelled to be shorter (8 weeks) compared to first-line treatment (24 weeks). Another concern with the interpretation of the mixed treatment approach relates to the presence of splenectomy in the sequence. Approximately 10% of patients are assumed to receive splenectomy at second- and third-line for any comparator, but clearly patients could only receive a splenectomy once in their lifetime; thereby making the interpretation of second- and third-line treatments in the modelled sequences more difficult.

A key concern for the ERG in the modelling of subsequent treatments is the fact that the proportion of active therapies used at second- and third-line in the mixed treatment strategy is dependent on the comparator technology (eltrombopag or romiplostim) because patients who fail to respond (or discontinue treatment after initial response) to one TPO-RA are permitted to switch to an alternative TPO-RA. This means that in the company's model the mixed treatment strategy at second- and third-line is different across the three interventions (avatrombopag, eltrombopag and romiplostim). As a result, the company has developed a model that only permits two treatment sequences to be compared, i.e., one that compares avatrombopag to eltrombopag, and one that compares avatrombopag to romiplostim. However, to establish the most cost-effective treatment sequence from a series of possible strategies, it is necessary to undertake a fully incremental analysis comparing all the sequences simultaneously. This is a core principle of cost-effectiveness analysis that involves assessing the incremental cost of generating additional health effects when moving from one strategy to a more effective one, and assessing this against the NICE cost-effectiveness threshold as the measure of opportunity cost. The approach used by the company means that it is not possible to conduct a probabilistic fully incremental analysis, which is the reason why the probabilistic results for the company's base-case analysis are presented in the submission as pair-wise comparisons. At ERG points for clarification, the ERG requested a revised version of the model with functionality that permits a simultaneous comparison of cost-effectiveness results for multiple alternative treatment strategies and enables a fully incremental analysis; however, the company responded that they were unable to provide an updated version of the model within the requested timeframe.

> ***Item 3. The approach used by the company to model subsequent treatments after discontinuation of a first-line TPO-RA restricts the cost-effectiveness analysis to a comparison of only two mutually exclusive treatment strategies simultaneously.***

The mixed treatment approach used by the company is very pragmatic and an oversimplification of modelling treatment sequences. A more appropriate approach would involve a comprehensive assessment of fixed treatment sequences, which are then weighted by the percentage of patients in UK clinical practice that are likely to follow each treatment pathway, in order to reflect the variability in treatment options in practice. The company model has flexibility to override the mixed treatment strategy used in subsequent lines with a fixed treatment sequence; however, the model only permits

up to two subsequent lines of active therapy before a fourth line of watch and wait. The impact of a fixed treatment sequence is explored by the ERG in Section 6. More importantly, the company has not used the treatment sequencing to determine the optimum position for avatrombopag among the TPO-RAs. The approach used by the company is not a sufficient basis to inform the most efficient use and positioning of avatrombopag among TPO-RAs (and non-TPO-RAs). It is unclear to the ERG whether a cost-effectiveness analysis comparing treatment sequences is an appropriate approach to the decision problem because it is not directly defined in the final NICE scope; however, if treatment sequencing is considered a valid approach then the company should consider the use of avatrombopag at alternative points within a treatment sequence. For example, assuming that the three TPO-RAs could be used in any order and avatrombopag could be positioned before or after an alternative TPO-RA, then there is a minimum of six relevant treatment sequences for avatrombopag which should be compared:

- Avatrombopag → eltrombopag → romiplostim → non-TPO-RAs
- Avatrombopag → romiplostim → eltrombopag → non-TPO-RAs
- Eltrombopag → avatrombopag → romiplostim → non-TPO-RAs
- Eltrombopag → romiplostim → avatrombopag → non-TPO-RAs
- Romiplostim → avatrombopag → eltrombopag → non-TPO-RAs
- Romiplostim → eltrombopag → avatrombopag → non-TPO-RAs

Clearly if non-TPO-RAs were also to be considered in the sequence, then the decision problem gets exponentially large. Importantly, a more formal evaluation of the positioning of avatrombopag among the TPO-RAs would allow the optimum position for avatrombopag to be determined. The most cost-effective treatment sequence will depend on the response rates of the alternative TPO-RAs and the time spent between treatments as non-responders, as well as the treatment costs where it might be anticipated that it is more cost-effective to start treatment with cheaper therapies before progressing to more expensive options. An exploratory analysis on the positioning of avatrombopag among TPO-RAs is presented in Section 6.

Item 4. The company has not used the modelled treatment sequencing to determine the optimum position for avatrombopag among the TPO-RAs.

The base-case doses of TPO-RAs used in the model appear to be appropriate and in line with the product SmPCs for avatrombopag and eltrombopag. However, the dosage used for avatrombopag and eltrombopag do not directly align with the respective clinical trials for these treatments; in Study 302, dose adjustment based on platelet count took place during the core and extension phases of the trial, while over the 6-month study period of the RAISE trial for eltrombopag, the mean daily dose was 54.7 mg per person (the SmPC starting dose of 50mg once daily was used in the model). For

romiplostim, the mean dose from the pivotal long-term trial of Kuter et al (2008) was used (0.004 mg/kg).

The dosages for non-TPO-RAs were based on those used in TA293 for eltrombopag and sourced from Provan et al (2010) [1]. The ERG notes that the guidelines reported in Provan et al (2010) have been superseded with updated guidance published in Provan et al (2019) [2]. The ERG believes that the updated guidance provides a more relevant source to inform dosages of non-TPO-RAs. This is discussed in detail in Section 4.2.9.2 and explored in Section 6.

Item 5. The company has not used updated guidance to inform dosages for non-TPO-RAs in the model.

4.2.5 Perspective, time horizon and discounting

4.2.5.1 Summary of company's submission

The perspective of the company's economic analysis is NHS and Personal Social Services (PSS). The time horizon used in the model is 56 years, which is assumed to represent a lifetime horizon. The model predicts approximately 99.6% of the patient cohort have died at this point (100 years-old). A discount rate of 3.5% per annum was applied to model long-term costs and QALYs.

4.2.5.2 Points for critique

The company's submission adheres to the NICE Methods Guide [29] and the ERG considers the approach used by the company to be appropriate.

4.2.6 Treatment effectiveness and extrapolation

4.2.6.1 Summary of company's submission

The primary mechanism for treatment effectiveness and its long-term extrapolation in the model is through treatment-related platelet response rates. All other outcomes in the model are assumed to be independent of treatment but a platelet count of $\geq 50 \times 10^9$/L (responder) drives three surrogate elements of treatment-effectiveness: (i) the probability of bleeding (where rates of severe bleeds determine hospitalisation type and mortality); (ii) the probability of requiring rescue therapy; and (iii) the probability of requiring concomitant ITP medication.

4.2.6.2 Treatment-related platelet response rates

As noted in Section 3.3 durable platelet response was the only platelet response measure which yielded comparative effectiveness data between avatrombopag, eltrombopag, and romiplostim, and represented the primary efficacy outcome from Study 302. The company's base case analysis applies treatment response rates and time to response for avatrombopag and comparator TPO-RAs based on the company's NMA estimates for durable platelet count over a follow-up period of 24-26 weeks,

which corresponds to response rates of 73%, 27% and 55% for avatrombopag, eltrombopag and romiplostim, respectively. In the model, all patients receive treatment for a full 24 weeks, at the end of which patients whose condition does not respond stop treatment. The company also conducted a scenario analysis which considered the impact of equalising the efficacy of avatrombopag and its comparators.

Treatment effectiveness estimates for non-TPO-RAs were sourced from TA293 for eltrombopag, which itself sourced estimates from a systematic literature review conducted by Amgen for TA221 for romiplostim (Appendix Table 58) [32, 33]. Time to response for non-TPO-RAs was also sourced from TA221, which was based on a systematic literature review conducted in 2008. The response rates ranged from 49% (dapsone) to 85% (splenectomy), while the time to response ranged from 4 weeks to 16 weeks for the non-TPO-RAs. The response rates for rescue therapies were based on TA293 (eltrombopag) and for platelet transfusion from TA626 for avatrombopag in chronic liver disease, which sourced response rates from two pivotal trials (ADAPT I and II) [37 38].

4.2.6.3 Points for critique

As discussed in Section 3.4, the ERG has major concerns about the company's NMA for the primary effectiveness outcome of durable platelet response. The key concerns are:

- The NMA results for avatrombopag vs. placebo (common comparator) lack face validity with respect to the trial results from Study 302 (i.e., odds ratio reported from NMA for avatrombopag vs. placebo is 102.80 [95% CrI: 3.87 - 2,796,449] compared to the study-specific odds ratio of 18.72 [95% CI: 1.02 - 340]);
- The appropriateness of the continuity corrections used in the NMA to correct for the presence of zero events in study arms of the trials (Study 302 for avatrombopag and Kuter 2008 SPL for romiplostim);
- Response outcomes for the pivotal study of eltrombopag (RAISE) were estimated for the observed population, whereas for all other studies included in the NMA the ITT population was used;
- The appropriateness of the inclusion of fostamatinib trials in the NMA;
- Heterogeneity in placebo response rates across the trials included in the NMA.

In Section 3.5, the ERG has undertaken additional analyses to produce comparative effectiveness estimates between avatrombopag, eltrombopag and romiplostim for the outcome of durable platelet response. These estimates suggest that romiplostim is expected to be the most effective treatment (odds ratio of 29.61 [95% CI: 5.42 - 161.58] for romiplostim vs. placebo), followed by avatrombopag (odds ratio of 18.72 [95% CI: 1.03 - 340.54] for avatrombopag vs. placebo), and then eltrombopag

(odds ratio of 10.60 [95% CI: 3.64 – 30.87] for eltrombopag vs. placebo). These estimates form the ERG's preferred base-case assumptions for treatment-related platelet response rates in Section 6.

Item 6. The company's NMA providing comparative effectiveness between avatrombopag, eltrombopag and romiplostim for the outcome of durable platelet response used in the model is subject to considerable uncertainty.

The ERG also has a concern about the definition of treatment response used in the model between first and subsequent lines of therapy. At first-line for TPO-RAs, the definition of response is durable platelet count (defined as a platelet count $\geq 50\times10^9$/L in at least 6 weekly platelet counts in the final 8 weeks of a 24-26-week study), while for subsequent lines of therapy, not involving a TPO-RA, the definition of treatment response is unclear. The maximum time to response in the model for non-TPO-RAs is 16 weeks suggesting that the durable platelet count metric, as defined for TPO-RAs, is not used for non-TPO-RAs. The ERG also notes that the response rates used in subsequent lines of treatment for non-TPO-RAs are very high relative to the response rates used in the model for TPO-RAs. This suggests that the company is using a different definition of treatment response for TPO-RAs and non-TPO-RAs, with the latter most likely reflecting a treatment response (platelet count $\geq 50\times10^9$/L) at one point in time rather than a sustained response over a fixed time period. This means that the treatment response estimates for subsequent lines of therapy in the model are based on a mixed treatment response definition because subsequent lines of therapy include both TPO-RAs and non-TPO-RAs. The assumption that 'response' and 'durable platelet count' are interchangeable is unlikely to hold, i.e., those experiencing a platelet response of $\geq 50\times10^9$/L at least once are unlikely to be considered as achieving the same response as those who maintain a durable or sustained response over a period of at least 6 weekly platelet counts. The impact of this assumption on the cost-effectiveness results is difficult to assess because of the mixed treatment strategy (involving both TPO-RAs and non-TPO-RAs) used in subsequent treatment lines.

The CS does not discuss the definition of response used in subsequent lines of therapy and only refers to response rates for non-TPO-RAs as those adopted from TA221 for romiplostim. The ERG has concerns that the company made no attempt to provide more recent and up-to-date estimates of treatment response rates and time to response for non-TPO-RAs. At ERG points for clarification, the ERG requested the company to comment on the source of the data and evidence used to inform the response rates for non-TPO-RAs and the relevance of the data to current UK clinical practice. The response from the company provided no additional clarification over and above that already presented in the CS, which only referred to TA221. However, the company did indicate that the response rates for non-TPO-RAs are unlikely to have changed since the appraisal for romiplostim.

Item 7. Treatment response estimates for first and subsequent lines of therapy used in the model are based on different definitions of response for TPO-RAs and non-TPO-RAs.

4.2.6.4 Duration of treatment

The longer-term durability of treatment response on TPO-RA treatment (avatrombopag, eltrombopag or romiplostim) was assumed to be an average of 109 model cycles (436 weeks or 8.4 years) over a patients' lifetime, which equates to a constant discontinuation rate of 0.9% per model cycle from the 'responder' health state to the 'no treatment no response' health state. This estimate was based on the lowest of the mean times on treatment of 109 cycles for eltrombopag and 393 cycles for romiplostim reported in Lee et al [3], which was based on fitting log-normal curves to Kaplan-Meier data for the eltrombopag and romiplostim arms of the respective long-term, open label, extension studies (EXTEND for eltrombopag and Kuter et al, 2008 for romiplostim, respectively).

The treatment duration for non-TPO-RAs were sourced from TA221 for the romiplostim appraisal and ranged between 1 (vina alkaloids) and 364 (splenectomy) model cycles. Although not mentioned in the company submission, splenectomy response duration was sourced from Cuker (2018) [39].

4.2.6.5 Points for critique

The company assumed an identical length of treatment duration (discontinuation rate per model cycle) for each of the TPO-RAs, which the company states is a conservative assumption. The ERG notes that the assumption of identical treatment duration is only conservative for avatrombopag when it is estimated to have a higher response rate relative to eltrombopag and romiplostim and when the same set (and proportions) of subsequent treatments (with an expected lower duration of response over time) are used in further lines of therapy.

At ERG points for clarification, the ERG requested further details on (i) why a systematic literature review had not been undertaken to identify treatment-specific discontinuation rates; (ii) the appropriateness of the assumption that discontinuation rates between the TPO-RAs are expected to be the same; and (iii) justification for the choice of treatment response duration of 109 cycles in light of the fact that this estimate implies that some patients will remain on treatment over their entire lifetime (time horizon of 56 years in the model). The response to these clarification questions provided very limited further information over and above that already presented in the CS. The company used "targeted desk research" to establish the treatment duration estimates for the model, whilst indicating that there is insufficient data to suggest any differences in long-term discontinuation between the respective TPO-RAs and adding that avatrombopag has important product features that will help maintain adherence that have not been reflected in the model (the company does not clarify what product features they are referring to, but the ERG believes that these are likely related to less dietary restrictions associated with avatrombopag which may increase longer term adherence).

The difference in mean time on treatment of 109 cycles for eltrombopag and 393 cycles for romiplostim reported in Lee et al suggests that there could be a notable difference in long-term discontinuation rates between the TPO-RAs [3]. Furthermore, even if the treatment duration is assumed to be identical between the TPO-RAs, the actual mean estimate used in the model (e.g., 109 cycles vs. 393 cycles) will have an impact on the cost-effectiveness of avatrombopag relative to eltrombopag and romiplostim because the higher the response rate between the alternative TPO-RAs, the longer (greater mean time on treatment) or shorter (lower mean time on treatment) this response is maintained over time, which delays the time to the 'no treatment no response' health state that incurs an elevated risk of bleeding (and associated high costs of hospitalisation and mortality) and need for rescue therapy. Lower discontinuation rates for a more effective treatment will only result in improved cost-effectiveness when the movement to the 'no treatment no response' health state occurs late enough in time so that the elevated risk of severe bleeding events and need for rescue therapy are significantly discounted, and the next subsequent line of therapy is less cost-effective than the TPO-RA. This is explored further by the ERG in Section 6.

Item 8. The longer-term treatment duration for TPO-RAs is uncertain.

4.2.6.6 Bleeding events

The risk of bleeding was modelled according to platelet count, with a platelet count $\geq 50x10^9$/L associated with a lower probability of bleeding events, while a platelet count $<50x10^9$/L was associated with an elevated risk of bleeding. Bleeding events were categorised into minor, outpatient, and inpatient bleeds, with inpatient bleeds further stratified by type (intracranial haemorrhage, gastrointestinal and other serious bleeds). Severity was defined in accordance with the WHO Bleeding Scale Score (WHO grade 1: minor; WHO grade 2 and 3: outpatient; WHO grade 4: inpatient) with risks at each severity level differentiated according to response status. Minor bleed rates were aligned to findings from Study 302: 10% in patients with platelet response $\geq 50x10^9$/L and 17.1% in patients without platelet response ($<50x10^9$/L). Outpatient and inpatient bleed rates and the proportion of inpatient bleeds of each type were sourced from TA293 for eltrombopag NICE appraisal (CS – Table 42), which itself applied the bleed risks and types from TA221 for romiplostim NICE appraisal (that used findings from the romiplostim phase 3 trials – see Appendix Table 58: Company base case model input comparison used in appraisals for avatrombopag, eltrombopag [TA 293] and romiplostim [TA 221]Table 58) [7, 32, 33]. Outpatient and inpatient bleeding events were assumed in all cases to be treated with rescue therapy. Bleed-associated rescue therapy schedules were stratified by bleed severity and defined according to a commissioned epidemiology and treatment paradigm review. This is explained in more detail in Section 4.2.9.2. The company also assumes that once patients enter the final line of watch and wait (i.e., refractory to all prior therapies) 'no treatment no response' health-state the risk of experiencing an inpatient bleed is doubled (8.6%). This assumption, along with the

characterisation and differentiation of bleeding events, was consistent with TA293 (eltrombopag) and TA221 (romiplostim) NICE appraisals [32, 33].

4.2.6.7 Points for critique

The relationship between risk of bleeding and platelet count ($\geq 50x10^9$/L or $<50x10^9$/L) means that the bleeding events in the model are driven by the treatment response rates. The ERG notes that the difference in bleeding costs (associated with outpatient and inpatient bleeds) is a key driver of cost-effectiveness.

The approach used by the company is consistent with the previous NICE Technology Appraisals of TA221 and TA293, and the same estimates from these appraisals are used to inform the risk of outpatient and inpatient bleeding by response status. The company justified the omission of Study 302 data for informing outpatient and inpatient bleed rates by reporting the limited number of serious events recorded in this study (3 >WHO grade 2 bleed events). The ERG considers the approach used by the company to be reasonable.

4.2.6.8 Recue therapy

The probability of patients requiring rescue therapy by platelet response was sourced from TA293 (eltrombopag) [33]. Patients within the responder health-state had rescue therapy rates of 3% per model cycle, while patients in the 'no treatment no-response' health state has an elevated rate of 22% per cycle (CS - Table 47). Rates of rescue therapy based on findings from Study 302 (with and without extension phase data) were explored in the company's scenario analyses.

The company stratified rescue therapy into two attributable causes: bleeding and non-bleeding events. The proportion of rescue therapies attributable to bleeding events was based on Study 302, in which 4/9 rescue therapy events were due to a bleed (44.4%). Bleeds and the advent of rescue therapies not attributable to bleeds informed transition probabilities between the no treatment no response (watch and wait) health-state and subsequent therapy. Rescue therapies attributable to bleeds were assumed to be already accounted for within bleeding events. Assumed rescue therapy schedules were nested within bleeding events with resource and cost implications specific to event type (Section 4.2.9.2).

4.2.6.9 Points for critique

In response to ERG points for clarification, the company indicated that Study 302 was not powered to address use of rescue therapy. As a result, rates of rescue therapy by platelet response were sourced from TA293. The ERG considers the approach used by the company to be reasonable; however, it is very unclear to the ERG where the estimates for the rates of rescue therapy for responders and non-responders of 3% and 22% per model cycle, respectively, are sourced from. At ERG points for clarification, the ERG requested the company to comment on the source of data used to inform the proportion of rescue therapies in TA293 and the relevance of the data to current UK clinical practice.

However, the company did not provide the source of data and only referred to TA293. The ERG is unable to validate the rates reported by the company as the source is unclear. The ERG notes that the values reported in TA293 for rates of rescue therapy are 0% for responders and 33% and 68% for non-responders in non-splenectomised and splenectomised patients, respectively (see Appendix Table 58) [33]. The ERG also notes that the approach to stratify rescue therapy by bleeding and non-bleeding events was not undertaken in TA293 and appears to be used by the company mainly for costing purposes (Section 4.2.9.2).

Item 9. The proportion of patients receiving rescue therapy is uncertain (with and without treatment response)

4.2.6.10 Concomitant medication use

The company estimated rates of concomitant ITP medication usage based on data from Study 302, with adjustment by treatment response. Concomitant ITP medication usage for non-responders was based on baseline use in Study 302 (44.9%), while usage for patients with response to treatment in the model was based on a discontinuation rate of concomitant ITP medication usage of 20% in the core phase of Study 302 to 35.9% for responders (Table 45, page 89 of CS). Concomitant ITP medication dose reductions for patients within the responder health-state were applied in line with those observed in Study 302 (equivalent to 5.8% of patients). The composition of treatments and dosages used in concomitant ITP medication were based on those used in Study 302 and published guidelines for the diagnosis and management of primary ITP [1], respectively (Table 46, page 89 of CS).

4.2.6.11 Points for critique

At ERG points for clarification, the ERG requested the company to comment on the appropriateness of using Study 302 to inform concomitant ITP medication usage for all TPO-RAs, the relevance of this data to current UK clinical practice, and comparison of usage in the pivotal trials for eltrombopag and romiplostim. The company indicated that the baseline usage in Study 302 (46.9% and 41.2% in the avatrombopag and placebo arms, respectively) was broadly comparable to that of the pivotal study for eltrombopag (46.6% and 50% in eltrombopag and placebo arms, respectively), but differed to that of the romiplostim pivotal trial (27.7% and 38.1% in romiplostim and placebo arms, respectively). The company also indicated that the considerable use of concomitant ITP medications alongside TPO-RAs observed in these pivotal studies is reflective of clinical practice in the UK and elsewhere [40] and is a recognised strategy to enhance platelet response.

The ERG notes that concomitant ITP medication usage has minimal impact on the cost-effectiveness results. The baseline usage is assumed to be the same for all TPO-RAs until treatment response is established. At response, concomitant ITP medication usage is reduced but the difference between

non-response and response status is relatively small. The costs of concomitant ITP medication accounts for around 1% of total costs estimated by the model.

4.2.7 Safety

4.2.7.1 Summary of company's submission

Adverse events

The model includes treatment-specific adverse events, categorised as either serious events or other events. It was assumed that all TPO-RAs shared the same risk of serious and other adverse events. Treatment-related serious and other adverse events rates were adopted from TA221 (romiplostim). The company's justification for their approach was that it provides consistency with the eltrombopag and romiplostim appraisals (see Table 58), and that the results from the company NMAs (see Section 3.4) indicated comparable safety profiles for TPO-RAs. In the company model, treatment-specific adverse events have a one-off health-related quality of life decrement and do not affect costs (summarised in Section 4.2.8). The risk of bleed events, rescue therapy and the need for concomitant ITP medications are summarised in Section 4.2.6.

Mortality

The model includes two separate causes of mortality: all-cause and disease-related/ITP mortality. All-cause mortality was informed using ONS life tables for average age and sex characteristics of patients in Study 302. Disease-related mortality was modelled exclusively through severe bleeding events. The mortality risk associated with each inpatient bleed type (see Section 4.2.6.6) was sourced from Danese et al (2009) [41].

4.2.7.2 Points for critique

The ERG is broadly satisfied with the company's approach to adverse events and mortality in the economic model. However, the ERG considers there to be significant uncertainty surrounding the longer-term survival of ITP patients. For example, a Danish population-based cohort study by Frederisken et al (2014) reported adjusted hazard ratios for mortality due to cardiovascular disease, infection, and haematological cancers of 1.5, 2.4 and 5.7 relative to the general population, respectively [42]. Enger et al's (2010) assessment of a US cohort of 3,131 chronic ITP patients found the adjusted incident rate ratios of 1.73 for diabetes, 2.05 for renal failure, 1.70 for any vascular event, 5.91 for lymphoma, 19.83 for leukemia, and 4.21 in all-cause mortality relative to a control sample [43]. Schoonen et al (2009) cohort study of 1145 UK ITP patients registered in the General Practice Research Database estimated an all-cause mortality hazard ratio of 1.6 compared to age- and sex-matched comparisons and reported bleeds and infections responsible for approximately 13% and 19%

of all computerised plausible causes of death [44]. The ERG acknowledges that many of these studies are derived from historic cohorts and hence may over-estimate mortality compared to current practice.

The ERG believes Danese et al (2009) provides a suitable source for bleed-related mortality risk, while expert clinical advice sought by the ERG suggested responding patients are likely to have good outcomes, with infrequent hospital admissions and no excess morbidity. In addition, the relative risks of mortality in the company model predominately fall within or above those values reported in the literature. In the absence of robust evidence for treatment-related AE, the ERG considers the company's application of consequences from TA221 (romiplostim) to be broadly appropriate. The ERG expects the omission of any cost-consequences from treatment-related AEs to have minimal impact on cost-effectiveness results.

Item 10. The longer-term mortality risks associated with ITP are uncertain

4.2.8 Health related quality of life

4.2.8.1 Summary of company's submission

Section B.3.4 of the CS reports the systematic literature review conducted to identify relevant health-related quality of life data, the values used in the model and methods used for their derivation.

The company conducted a systematic literature review to identify studies assessing the health-related quality of life of patients with chronic ITP. Six studies were identified for data-extraction: three cost-effectiveness studies using health-state utility values and three elicitation studies. Two cost-effectiveness studies applied utilities from the identified utility elicitation studies. The company did not use any of the studies identified in the systematic literature review to inform utility values in the model.

The health-related quality of life (HRQoL) utility values used in the company's base-case analysis were derived from Study 302 where possible. HRQoL was dependent on the proportion of patients with prior splenectomy, treatment response status and adverse events. The company derived a baseline utility value based upon EQ-5D values from the UK general population for the average patient characteristics of Study 302 (44.6 years of age and 37% male). Using EQ-5D data from Study 302, a multivariate TOBIT regression model was used to estimate the association between platelet response, bleeding events (minor and outpatient bleeds), splenectomy status and adverse events (serious and not serious AEs) with patient-reported health-related quality of life (Table 57, page 97 of CS). Treatment response was associated with an increase in baseline utility, while disutility values were estimated for minor and outpatient bleeds and serious AEs.

For serious bleeding events (i.e., all inpatient bleeds) the company used utility values sourced from TA293 (eltrombopag) because lack of data from Study 302 precluded the use of the TOBIT model for these estimates (Table 58, page 97 of CS) [33]. Utility decrements for treatment-related AEs were assumed to last for 1 model cycle (4 weeks). In the model, all treatment-related AEs incur a disutility value of 0.1, with the exception of serious AEs from non-TPO-RA therapies which incur a 0.4 utility decrement.

4.2.8.2 Points for critique

Appendix H of the CS included the searches to identify studies of quality of life or utility values in patients with ITP. The ERG considers the searches to be generally appropriate. However, further studies may have been identified by searching some additional sources of HRQoL studies, through reference checking or searching further sources of conference abstracts. The search filter used to limit the searches to HRQoL studies or utilities was not referenced, therefore it was unclear if the filter had been previously validated. The ERG appraisal of the searches is presented in Table 29 below.

Table 29: ERG appraisal of company's identification of health-related quality of life evidence

Topic	ERG response	Note
Is the report of the search clear and comprehensive?	YES	The original and update search strategies and were both included in Appendix G. A reference for the study design search filter was missing.
Were appropriate sources searched?	PARTLY	- Conference abstracts were identified via Embase, however no further sources of conference abstracts were searched. - Further sources of HRQoL studies were not searched: - ScHARRHUD (https://www.scharrhud.org/) - CEA Registry (https://cevr.tuftsmedicalcenter.org/databases/cea-registry) - Checking of reference lists for further relevant studies was not reported.
Was the timespan of the searches appropriate?	YES	The searches covered the period from database inception to March 2021.
Were appropriate parts of the PICOS included in the search strategies?	YES	- ITP (**P**opulation) AND HRQoL/utilities (**O**utcomes).
Were appropriate search terms used?	YES	

Were any search restrictions applied appropriate?	NOT APPLICABLE	
Were any search filters used validated and referenced?	UNCLEAR	Searches were limited to studies reporting HRQoL or utilities in MEDLINE and Embase. The search filter used was not referenced in the submission or in the points for clarification, therefore it is unclear if the filter used was validated.

ERG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

The ERG considers the approach used by the company to estimate health-related quality of life to be broadly appropriate and in line with the NICE Reference case. However, the ERG notes that the company did not adjust the utility values by age over time in the model. The general population sex- and age-adjusted utilities used to calculate health-state utility values apply to 45–54 year-olds. When utility values are considered over the 56-year lifetime horizon it is evident that the utility values assigned to ITP patients can eventually exceed the general population utility estimates, which naturally decline with age (from individuals beyond 54 years of age in the model). In response to ERG points for clarification the company stated that this omission was: "*due to lack of data for such age adjustment specific to ITP population and independent on the presence of bleeds and platelet count.*" and that "ag*e adjustment of utility values would not change the direction of estimated differences i.e., placebo would sustain its dominance over eltrombopag and romiplostim*". The ERG disagrees with the company's assessment made in clarification. A more appropriate approach would reflect the decreasing utility of patients as they age through the model over time. The ERG understands that a paucity in data may prohibit an assessment of the likely dynamics and interactions between age and events associated with an ITP patient's HRQoL, however, the omission of any longer-term age-adjustment to utility values is not warranted over the long-term because it overestimates health gains from improvements in longer-term survival. For these reasons the ERG believes that utilities should be age-adjusted over the model time horizon (i.e., beyond the 45-54 year stratum). This issue has been addressed in the ERG's base-case in Section 6.

Item 11. The company has not age-adjusted HRQoL values over the model time-horizon

The ERG considers the presentation of summary EQ-5D utility data from Study 302, the description of the regression methods used to calculate the utility values, and the justification for using external sources to inform some of the utility values in the model, to be very limited in the CS. In response to ERG points for clarification, the company referred to EQ-5D summary data published in the clinical study report for Study 302, provided a comparison of utility values with those used in TA293 (eltrombopag), and commented on the appropriateness of the source of data/evidence used to inform utility values.

The EQ-5D data made available in the clinical study report includes aggregated responses for each EQ-5D-3L domain and level at baseline and 12-week and 26-week study follow-up for avatrombopag and placebo. The aggregation of data precludes the ERG from assessing average utility values within and between arms, or to assess responses made outside the primary study follow-up periods. EQ-5D responses appeared generally balanced between arms. Note that it was only from results provided in the clinical study report that the ERG could verify the application of EQ-5D-3L data (rather than EQ-5D-5L data) for the utility values used in the CS.

The estimation of the relationship between response status, minor bleeds, and outpatient bleeds on health-related quality of life was informed from subjects included in the Full Analysis Set and the Safety Analysis Set (32 randomised to avatrombopag and 17 to placebo). To handle missing data the company applied a Mixed Model for Repeated Measures (MMRM) approach (1355 missing from 1544 observations). In broad terms, the ERG considers the modelling approach to be appropriate, in terms of included EQ-5D data, regression model selection (TOBIT) and imputation methods employed; however, the information presented is limited. The exploration of interaction effects between the bleed and response status in the regression framework would have been desirable.

The company's assessment of utility values between those used in the model and TA293 (eltrombopag) is limited to stating that "*values from both sources differ, however, each source confirms impact of platelet count and presence of bleeds on health state utilities*". The company further clarified that the paucity of inpatient bleedings observed in Study 302 (1 >grade 3 AE event) necessitates the need for the company to apply values from the eltrombopag submission (which itself uses values from Szende (2010)[45]). The ERG compared the utility values with those reported in TA221 (romplostim) on account that these were absent from both the CS and response to clarification. The utility values in the response- and event-related health states from TA221 (derived from a Time Trade-Off utility study commissioned by Amgen) were higher than those reported in the CS [32]. The ERG considers the omission of utility values from TA221 to be appropriate. A comparison of utility values with those reported in TA293 and TA221 is presented in Appendix Table 58.

Expert clinical advice received by the ERG indicated that patients responding to treatment could expect to achieve a health-related quality of life comparable to the general population. As a result, the ERG believes that the utility values used by the company appear reasonable with face validity. The company concluded in clarification that: "*We believe that considering limited available data the approach undertaken in terms of utility decrements in the model is appropriate, especially it was previously accepted by NICE*". The ERG believes that the company's estimated health-state utility values in conjunction with utilities from Szende (2010) for inpatient bleeds provide the best available evidence on the health-related quality of life for ITP patients in the model.

4.2.9 Resource use and costs

4.2.9.1 Summary of company's submission

The company conducted a systematic literature review to identify relevant resource use and cost data for patients with chronic ITP. Three studies were identified (Table 59, page 98 of CS), two cost-effectiveness analyses of eltrombopag (Allen et al (2016) and Lee et al (2013) [3, 46]), and a summary article of the evidence review groups' (ERG) report of the eltrombopag technology appraisal (Boyers et al (2010) [47]). No studies identified in the systematic literature search were used to inform resource use and costs in the model.

The resource utilisation and costs included in the CS relate to: (i) treatment acquisition; (ii) treatment administration; (iii) monitoring; and (iv) bleeding and rescue therapy events.

Treatment acquisition

Treatment acquisition costs were calculated according to modelled treatment and maintenance schedules, drug dosages, and associated unit costs.

TPO-RA treatment schedules were 24-weeks in length, with avatrombopag and eltrombopag administered daily, and romiplostim weekly (see Section 4.2.4.1). Non-TPO-RA active treatments, rescue therapies and concomitant ITP medication schedules were adopted according to the time to response assumptions used in TA221 (romiplostim) and those reported in Proven et al (2010) management guidelines (for rituximab and splenectomy) [1], and varied from 1 day (e.g. dapsone in rescue therapy) to 16 weeks (e.g. Azathioprine active treatment).

Maintenance therapy following a response was assumed to persist for an exponential length of time, where each treatment had an associated exponential rate of discontinuation scaled in proportion to the treatment's expected time in response. All TPO-RA treatments were discontinued at a constant rate of 0.9% per model cycle (averaging 109 cycles - see Section 4.2.4.1). The discontinuation rate for non-TPO-RA therapies ranged between 0.3%-51% (vinca alkaloids). Although not reported in the CS, the company clarified that romiplostim was assumed to have vial wastage. The model rounded up romiplostim dosages to the nearest vial (3 vials). This equated to approximately a third of a vial being wasted per week for the base case patient characteristics (43.12mcg from a 125 mcg vial).

The dosages were sourced from summary of product characteristics (avatrombopag, eltrombopag), trial data (romiplostim) and ITP management guidelines [1, 7] (Section 4.2.4.1).

Unit costs were obtained from national sources [30]. For avatrombopag, the company applied the list price acquisition cost with a [redacted] PAS discount. The company applied BNF list prices for eltrombopag and romiplostim given that the PAS is confidential for both treatments.

Treatment administration

Avatrombopag and eltrombopag were assumed to incur no administration costs as both are oral treatments which patients may administer independently at home. Romiplostim administration was assumed to incur administration costs in the first model cycle (equivalent to four weekly clinic attendances), and in 27.7% of cases thereafter. The proportion of romiplostim patients having treatment administered in clinic was informed via data reported at the American Society of Haemotology annual meeting (ASH) in 2010 (consistent with eltrombopag appraisal – see Appendix Table 58). The cost per clinic visit was set to £241.06, which equates to NHS reference costs for the delivery of parenteral chemotherapy at first attendance [31]. The company justified the approach on the grounds that it is consistent with that adopted in TA293 (eltrombopag) [33]. Intravenous treatments and rescue therapies, Anti-D injections and platelet transplants also incurred administration costs based on NHS reference costs [31] (see Appendix Table 58).

Monitoring costs

Disease monitoring costs were calculated based on a routine follow-up schedule from TA293 (eltrombopag), with relevant unit costs sourced from the NHS schedule of reference costs [31]. Specifically, the model assumes that all patients receive 1 haematologist consultation, 2 laboratory tests, 1 full blood count and 1 biochemistry assessment each month during treatment. Monitoring costs were assumed independent of treatment.

Bleed and recue therapy costs

The resource use and cost implications associated with each non-minor bleeding event (see Section 4.2.6.1) have been informed by qualitative research commissioned by the company and unit costs from UK sources (Table 63, page 101 of CS). Resource use associated with outpatient and inpatient bleeds included hospitals stays, diagnostic imaging and blood test and therapeutic interventions. Unit costs for each resource were taken from UK sources, and averaged in cases where multiple unit costs were found for the same resource (Table 64, page 101 of CS). The analysis assumes minor bleeds are self-treated and have no associated costs. To avoid double counting for bleed-related rescue therapy, bleed-related costs were assumed to be inclusive of the proportion of recue therapies attributable to bleeding events (55.6%), while rescue therapies attributable to factors other than bleeds (44.4%) were costed separately.

4.2.9.2 Points for critique

The CS included the searches for cost and healthcare resource use studies in ITP. A detailed description of the searches and all search strategies were included in Appendix I. The searches presented in the submission were generally appropriate, however, the sources searched for published

and unpublished studies were fairly limited. The ERG appraisal of the searches can be found in Table 30 below.

Table 30: ERG appraisal of resource use and cost evidence identification

Topic	ERG response	Note
Is the report of the search clear and comprehensive?	YES	The original and update search strategies and were both included in Appendix I.
Were appropriate sources searched?	Partly	Limited range of databases searched - MEDLINE and Embase only.
Was the timespan of the searches appropriate?	YES	The searches covered the period from database inception to March 2021.
Were appropriate parts of the PICOS included in the search strategies?	YES	- ITP (**P**opulation) AND costs/resource use (**O**utcomes).
Were appropriate search terms used?	YES	
Were any search restrictions applied appropriate?	YES	Retrieval limited to studies from the UK.
Were any search filters used validated and referenced?	NOT APPLICABLE	

The ERG considers the majority of the resource use and cost estimates informing the model to be broadly appropriate but have noted some limitations and concerns. Key issues relate to the romiplostim administration and acquisition costs applied in the economic model, assumed drug dosing schedules, the resource use and cost implications for bleeds and rescue therapies, and other methodological issues relating to unit costs, treatment acquisition costs and AE costs.

Administration cost of romiplostim

The ERG has the following concerns regarding the administration costs for romiplostim in the economic model: (i) the company's application of administration costs within the first model cycle; (ii) the assumed proportion of patients administering romiplostim within a clinic setting; and (iii) the resource use associated with an administration of romiplostim in a clinic setting.

First, the company states in submission that the economic model assumes that the first dose of romiplostim, and 27.7% of subsequent doses, are administered in a clinic setting and costed

accordingly. However, the ERG has found that the company has applied clinic administration costs for all scheduled doses within the first model cycle. This means that three subsequent romiplostim administrations are costed as if administered within a clinic setting. Second, the proportion of patients assumed to receive romiplostim in a clinic setting was informed by data (ASH annual meeting 2010) collected prior to romiplostim's approval in UK practice (April 2011). The ERG sought expert clinical feedback on this matter and was informed that "*almost all patients self-administer at home*". This conclusion aligns with more recent research which indicates self-administration is effective, well tolerated and achieves high levels of adherence in eligible patients with ITP [48] [49]. Third, the ERG received expert clinical opinion that NHS patients will be brought to the day ward for administration, and as such costs associated with a regular clinical haematology outpatient visit (£167) may be more applicable in this context than those used by the company (£241 - first attendance of parenteral chemotherapy).

The ERG favours romiplostim administration costs that are correctly aligned with the company's version of initial administration, and for subsequent administrations to be mostly from home, with exceptional clinic visits costed according to regular haematological outpatient visits. This is explored further by the ERG in Section 6.

Item 12. The company's assumed administration schedule for romiplostim overestimates both the proportion of patients receiving doses within a clinic setting and its associated cost

Romiplostim acquisition cost

The model calculates romiplostim costs according to the median dose reported in the extension study of the romiplostim clinical trial (4 mcg/kg) [34] and the average model cohort weight (82.97kg). The company have assumed romiplostim costs are incurred for whole vials, meaning that the corresponding modelled 0.33188mg dose per administration requires three 0.125mg vials, leaving approximately a third of a vial to be wasted (0.04312mg).

The ERG has two concerns regarding the company's approach. First, romiplostim dosing is dependent on efficacy with upward titrations initiated if response is not achieved. The SmPC states that "*the initial dose is 1 mcg/kg*" and that "*the once weekly dose of romiplostim should be increased by increments of 1 mcg/kg until the patient achieves a platelet count ≥ 50 x 10^9/L*" [50]. The company's approach assumes patients initiate treatment at 4 mcg/kg, which means that patients expend three vials immediately from treatment initiation. The ERG believes that, at least in the shorter term, this overestimates treatment acquisition costs for romiplostim. This is exemplified by the median dose administered in the pivotal romiplostim phase 3 trials (non-splenectomised: 0.002mg/kg; splenectomised: 0.003mg/kg) being below the trials' extension-phase median dose (0.004mg/kg) [7, 32,

[34]. Second, romiplostim costs were based on the weight of the average patient in Study 302, which means that the model dosing does not take into account the distribution of weights seen in the patient population. A more accurate approach would have been to fit a parametric distribution to the cumulative density of patient weight with corresponding dosing estimates calculated using a method of moments technique. Assuming complete wastage of romiplostim appears reasonable given that the majority of vials are prescribed for home administration and thrown away, although this does represent the maximum wastage. Given these uncertainties, the ERG sought to explore the impacts of alternative romiplostim dosing on cost-effectiveness results in Section 6.

The ERG considers the romiplostim acquisition costs used in the model to be the upper estimate of the likely costs incurred by the NHS.

A significant concern raised in TA221 (romiplostim) was that some patients received a dose above the recommended maximum weekly limit (10 micrograms/kg) in the romiplostim trials. Since acquisition costs for romiplostim are based on median study doses from TA221, rather than mean values, dosages in the model are not dependent on dosing values from the trial that may not reflect clinical practice (i.e. those greater than 10 micrograms/kg).

Item 13. The company's romiplostim acquisition costs do not take account of the weight distribution of the study population or the up-titration of dosing.

Drug dosing schedules

The dosing schedules used for costing active treatments, concomitant ITP medication and rescue therapies were derived from a variety of sources, including SmPCs, previous appraisals, label information and trial findings (see Appendix Table 58). The majority of dosing schedules however, were defined according to an international consensus report on the investigation and management of primary immune thrombocytopenia published by Provan et al (2010) [1]. The ERG notes that in 2019 a revised international consensus report was published, and with it updated dosing schedules [2]. Table 31 reports differences between active treatment drug dosing schedules the ERG identified from Provan (2019) and those from Provan et al (2010) used by the company. The ERG believes the medical therapies reported in Provan et al (2019) provide more contemporary estimates of treatment scheduling. Within the time constraints of this report, the ERG only updated treatment schedules for active treatment. The impact of the updated dosing schedule on cost-effectiveness results is minimal.

Table 31: Differences between drug dosing schedules used in the CS based on Provan (2010) and those reported in Provan (2019)

Treatment dosages	Assumed from Provan et al (2010)		Provan et al (2019)	
Active treatment	Dose	Duration (pre response)	Dose	Duration (pre response)
Mycophenolate mofetil	1000mg/kg	x2 daily: 3.5 weeks	1.5-2g	For at least 12 weeks
Cyclosporine	5mg/kg	Daily: 4 weeks	2.5-3mg/kg	Daily: 4 weeks
Dapsone	87.5mg	Daily: 4 weeks	50 mg/day for 1 week, then 100 mg/day for 2 months; or 100mg/day	
Cyclophosphamide	1.5mg/kg	Daily: 4 weeks	1-2 mg/kg	Daily: 16 weeks

Bleeds and rescue therapy costs

The ERG has concerns regarding the application of rescue therapy costs in the model and considers the company's bleed event costs to be extremely high relative to national sources and those reported in TA293 (eltrombopag) and TA221 (romiplostim) appraisals.

In the company's base case analysis, the need for rescue therapy and bleeds form two key model events, each incurring significant costs and determine the transitions between 'watch and wait' and subsequent treatment. Patients experience both events at rates sourced from TA293 (eltrombopag), with bleed-related rescue therapies assumed to be captured within bleeding events. The company does not provide a rationale for the departure from the costing approach used in TA293 and TA221, in which independent rates of bleeds and rescue therapies are maintained, with rescue therapy costs aligned to trial rescue treatment rates/schedules and bleed costs from national sources. The company's approach substitutes rescue therapies performed within trial and bleed costs reported in national sources with those calculated from a paradigm review commissioned by the company (Tables 63-65, pages 101-103 of CS). Table 32 displays a comparison of bleed and rescue event costs used in the company analysis, in TA293 (eltrombopag), TA221 (romiplostim), the most recent NICE Technology Appraisal of fostamatinib for treating refractory chronic immune thrombocytopenia (ID1087), and those reported in the latest NHS reference costs (2019/20) [31]. Bleed costs derived from the company's commissioned analysis are markedly higher than NHS reference costs, with modelled bleed events (that encompass 55.6% of rescue therapies) costing up to eight times that defined in national sources. The ERG considers the company's new approach unwarranted (although notes that the CS provides no details on the justification for the approach taken) and confuses the interpretation of bleed and rescue costs. In addition, the company failed to provide any details regarding the methodology used to arrive at the assumed resource utilisation from bleeding events. The ERG is not aware of how the different healthcare services utilised for each respective bleeding event was compiled nor who was asked, when it was compiled, and for what context the findings are applicable to. Alternative bleed-related unit costs and rates of rescue therapy are explored in Section 6.

Table 32: Company, NHS and previous appraisal bleed and rescue therapy event costs

Event costs		Bleed				Rescue therapy	
		Minor bleed	Outpatient	Gastrointestinal or other bleeds	Intracranial haemorrhage	Bleed-related (55.6%)	Other than bleed (44.4%)
Company analysis		Rescue: £0	Rescue: £1538	Rescue: £9,702	Rescue: £12,128	Assumed to fall within bleeding events cost and probabilities	Rescue: £6,500
		Bleed: £0	Bleed: £1597	Bleed: £4,623	Bleed: £13,571		Bleed: £0
		Total: £0	Total: £3134	Total: £14,325	Total: £25,699		Total: £6,500
NHS reference cost 19/20 (see Section 6.1.1.11)		-	£460	£3,092/£2,891 Other/gastrointestinal	£4,691		
TA 293 (eltrombopag) > NHS reference cost 11/12		-	£303	£1,553	£3,451	Company base case values taken from TAA 221 (below)	
TA 221 (romiplostim) >NHS reference costs		-	£220	£1,718/£1,395 Other/gastrointestinal	£3,680	£4,772 splenectomised; £5,195 non-splenectomised	
Fostamatinib for treating thrombocytopenic purpura [ID1087]	Company	-	£450	£3,534	£5,293	Rescue costs per event not reported	
	ERG	-	£362	£2,993	£4,099		

Item 14. The company costs for bleeding events are not adequately detailed or justified and exceed those reported in national sources and previous appraisals.

Other methodological issues

The ERG has identified three further methodological matters related to modelled costs. First, the unit costs sourced by the company have not been inflated to a common year, with older unit cost sources (e.g. bleed-related costs) not aligning with contemporary unit costings. Second, costs relevant to ITP-specific adverse events (e.g. fatigue, menorrhagia, bruising) are not considered in the model, thereby potentially omitting additional cost-savings associated with achieving a response. Third, treatment acquisition costs are costed according to the average schedules of the treatment mix, instead of taking the average across the acquisition costs for each unique subsequent treatment option. To most accurately model average treatment costs, costs for each subsequent therapy should be considered in turn with individual results weighted according to the modelled treatment mix.

The ERG believes the first two issues are unlikely to significantly impact results as their cost-impacts are likely to be small in magnitude. The consequences of the third issue are unknown and remains an area of uncertainty.

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

5.1.1 Summary of company's submission

All analyses presented in the CS include the confidential PAS discount for avatrombopag. The confidential appendix to this ERG report provides the company's updated base-case results with confidential PAS discounts applied to eltrombopag and romiplostim.

The company's base case cost-effectiveness results are presented in the CS using deterministic analysis (Table 68, page 115 of CS). As noted in Section 4.2.4.2, the company developed a model that only permits two treatment sequences to be compared, i.e., one that compares avatrombopag to eltrombopag, and one that compares avatrombopag to romiplostim. Therefore, the results presented in the CS are pair-wise comparisons of avatrombopag vs. eltrombopag and avatrombopag vs. romiplostim.

The ERG identified an error in the presentation of the company's base-case results. This error was related to the proportion of active therapies used in subsequent lines of therapy after first-line TPO-RA. The CS indicated that the proportion of therapies used at second- and third-line is dependent on the comparator (eltrombopag and romiplostim). However, the ERG noted that the cost-effectiveness results presented in the CS were based on a model that only uses the proportion of second- and third-line therapies ascribed to eltrombopag as a comparator (Table 38, page 85 of CS, columns 3 and 5), which excludes patients on avatrombopag or romiplostim from receiving eltrombopag as a subsequent line of therapy, as intended by the company. Following response to ERG points for clarification, the company presented revised deterministic cost-effectiveness results for the comparison of avatrombopag vs. romiplostim, which corrected the technical error identified by the ERG regarding subsequent therapies; however, the ERG notes that this error was only corrected in the romiplostim arm and not in the avatrombopag arm, which means that the subsequent therapies used in the comparison of avatrombopag vs. romiplostim are different by treatment arm.

Table 33 presents the company's revised base case deterministic cost-effectiveness results for the comparison of avatrombopag vs. eltrombopag, and the corresponding results for the comparison of avatrombopag vs. romiplostim. A breakdown of total costs and QALYs by treatment arm is presented in Table 34.

The pairwise comparison approach used by the company means that it is not possible to conduct a probabilistic fully incremental analysis; therefore, the probabilistic results for the company's base-case analysis are presented in the CS as pair-wise comparisons. The company did not present revised

probabilistic cost-effectiveness results in response to the error noted by the ERG above. The ERG has conducted the probabilistic results for the company's revised base-case, which are presented in Table 35.

Table 33: Company's revised base-case deterministic results

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company revised base-case pair-wise comparison for avatrombopag (AVA) vs. eltrombopag (ELT)					
AVA	[redacted]	[redacted]	-	-	-
ELT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company revised base-case pair-wise comparison for avatrombopag (AVA) vs. romiplostim (ROM)					
AVA	[redacted]	[redacted]	-	-	-
ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 34: Breakdown of the company's revised base case deterministic cost-effectiveness results

	Deterministic results		
Costs (£)	**AVA**	**ELT**	**ROM**
Treatment costs	[redacted]	[redacted]	[redacted]
Active treatment	[redacted]	[redacted]	[redacted]
Treatment I	[redacted]	[redacted]	[redacted]
Treatment II	[redacted]	[redacted]	[redacted]
Treatment III	[redacted]	[redacted]	[redacted]
Treatment IV	[redacted]	[redacted]	[redacted]
Rescue therapy	[redacted]	[redacted]	[redacted]
Concomitant ITP medications	[redacted]	[redacted]	[redacted]
Treatment administration costs	[redacted]	[redacted]	[redacted]
Active treatment	[redacted]	[redacted]	[redacted]
Treatment I	[redacted]	[redacted]	[redacted]
Treatment II	[redacted]	[redacted]	[redacted]
Treatment III	[redacted]	[redacted]	[redacted]
Treatment IV	[redacted]	[redacted]	[redacted]
Rescue therapy	[redacted]	[redacted]	[redacted]
Concomitant ITP medications	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]	[redacted]
Treatment I	[redacted]	[redacted]	[redacted]
Treatment II	[redacted]	[redacted]	[redacted]
Treatment III	[redacted]	[redacted]	[redacted]
Treatment IV	[redacted]	[redacted]	[redacted]
Bleeding costs	[redacted]	[redacted]	[redacted]
Minor bleeds	[redacted]	[redacted]	[redacted]
Outpatient bleeds	[redacted]	[redacted]	[redacted]
Inpatient bleeds	[redacted]	[redacted]	[redacted]
Intracranial haemorrhage	[redacted]	[redacted]	[redacted]

Gastrointestinal	[redacted]	[redacted]	[redacted]
Other bleed	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Number of life years	[redacted]	[redacted]	[redacted]
Health state utility	[redacted]	[redacted]	[redacted]
Disutility due to AEs - active treatment	[redacted]	[redacted]	[redacted]
Disutility to AE – rescue therapy	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]

Table 35: Revised company base case probabilistic cost-effectiveness results by ERG

	Avatrombopag vs Eltrombopag			Avatrombopag vs Romiplostim		
Technologies	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard deviation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Minimum	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q 0.025	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Q 0.975	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Probability being CE						
£30,000/QALY threshold			[redacted]			[redacted]
£20,000/QALY threshold			[redacted]			[redacted]
£10,000/QALY threshold			[redacted]			[redacted]
Probability dominant			[redacted]			[redacted]
Probability dominated			[redacted]			[redacted]

For both the deterministic and probabilistic cost-effectiveness results, avatrombopag was the dominant intervention compared to eltrombopag and romiplostim (i.e. cost saving and more effective). The cost-effectiveness plane scatterplot and cost-effectiveness acceptability curve from the probabilistic cost-effectiveness results for the original analysis (before ERG points for clarification) are presented in Figures 13-17 (p118 and p120) of CS, respectively.

5.1.2 Points for critique

A key concern for the ERG is the presentation of cost-effectiveness results as pair-wise comparisons. When there are more than two alternative treatment options, a fully incremental analysis comparing all the sequences simultaneously should be undertaken. This is not straightforward to implement under the company's base-case assumptions because the company has modelled subsequent treatments as a mixed treatment strategy that is dependent on the comparator technology (eltrombopag or romiplostim). The approach used by the company also means that it is not possible to conduct a probabilistic fully incremental analysis. At ERG points for clarification, the ERG requested a revised version of the model with functionality that permits a simultaneous comparison of cost-effectiveness results for multiple alternative treatment strategies and enables a fully incremental analysis; however,

the company responded that they were unable to provide an updated version of the model within the requested timeframe.

The ERG also noted an inconsistency in the company's revised cost-effectiveness results for the comparison of avatrombopag vs. romiplostim. In the company's revised results, patients on first-line avatrombopag are excluded from receiving eltrombopag as a subsequent line of therapy, while patients on first-line romiplostim are permitted to receive eltrombopag as a subsequent line of therapy. This creates an inconsistency in the subsequent treatment lines for the comparison of avatrombopag vs. romiplostim. The ERG has updated the company's revised base-case results for this comparison such that the subsequent treatment lines for avatrombopag are the same as those for romiplostim. Table 36 presents the ERG's revised version of the company's deterministic updated cost-effectiveness results.

Table 36: ERG revised company base-case deterministic results for the comparison of avatrombopag with romiplostim

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG revised company base-case pair-wise comparison for avatrombopag vs. romiplostim					
AVA	[redacted]	[redacted]	-	-	-
ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The ERG identified two issues with the probabilistic sensitivity analysis conducted by the company: (i) cohort characteristics (age, percentage of males, body weight, and body surface) were included as a source of parameter uncertainty, despite differences being due to patient variability rather than parameter uncertainty; and (ii) parameter uncertainty estimates available for TPO-RA response rates from the NMA were not incorporated into the PSA (instead the company used a +/- 20% range). The ERG notes parameter uncertainty was predominantly characterised as being +/- 20% around parameter mean values, however the company assumed a range of +/- 10% for some treatment dosing while using trial evidence to inform others. For example, variability in the dosing of avatrombopag and romiplostim was sourced from trial data, while for eltrombopag it was assumed to vary by approximately +/-10% of the mean value. The company did not provide justifications for the inconsistent characterisation of parameter uncertainty in the model.

Furthermore, the presentation of PSA results in the model precluded a flexible fully incremental comparison of alternatives by the ERG. Within the time constraints of this report, it was not feasible for the ERG to address these issues in the probabilistic analysis. However, the ERG expects that the impact on the mean cost-effectiveness results is moderate because the mean probabilistic ICER is similar to the deterministic ICER.

5.2 Company's sensitivity analyses

5.2.1 Summary of company's submission

The company conducted univariate deterministic sensitivity analyses across a wide range of model inputs, including discount rates, patient characteristics, response rates, time to response, costs, HRQoL, and bleed and mortality probabilities (CS – Table 72). Model inputs were mostly adjusted to either 20% above, or 20% below, mean values. No results from the company's sensitivity analysis were reported. The company concluded that: "*In all deterministic analyses, the cost effectiveness of avatrombopag vs. eltrombopag and romiplostim remained consistent with the base case (i.e. dominant)*" (CS – page 121).

The company also reports six scenario analyses considering alternative rates of response and rescue therapy in the model (summarised in Table 73 of the CS). Aligning response rates across comparators equalised the expected QALYs in each arm, with higher joint response rates associated with larger cost-savings for avatrombopag relative to eltrombopag and romiplostim compared to base case settings. Rescue therapy rates per cycle from Study 302 ($50x10^9$/L = 4.1%; $<50x10^9$/L = 6.1%), Study 302 with extension data ($50x10^9$/L = 3.9%; $<50x10^9$/L = 13.2%), and those if rescue therapies are only used to manage bleeds, reduce the cost savings associated with avatrombopag relative to eltrombopag and romiplostim compared to base case settings ($50x10^9$/L = 3.0%; $<50x10^9$/L = 22.0) with minimal impacts on QALY estimates. The company conclude that heterogeneity in response rates is the most sensitive model input and remains the most significant cause of uncertainty in the model.

5.2.2 Points for critique

The company conducted extensive deterministic sensitivity analyses across a suitable number of model inputs. The results of the scenario analyses reported in the CS are similar to those correcting for technical errors raised in ERG points for clarification. The exploration of structural assumptions was included but limited in scope. The sensitivity analysis surrounding patient characterises should be considered as potential subgroup analyses and were limited (patient sex or prior splenectomy status not considered, only ages of 40.55 and 48.6 years assessed).

The ERG has concerns about the ranges adopted by the company in each of the sensitivity analyses, as these were not justified and appear very narrow. In particular, the ERG believes durable response rates, time to response, and bleed costs all have higher degrees of uncertainty than those explored by the company. For response rates, the assessment of +/- 20% around the mean values falls extremely short of the 95% confidence interval ranges for each TPO-RA reported in the NMA (e.g. avatrombopag vs placebo ranges between 9% and 100%). For bleed costs, inpatient bleeds costed

between 7-10 times more than those reported in TA293 (eltrombopag), which means it's very likely that the uncertainty in this parameter extends well beyond +/- 20% of the mean values. Time and definition of response is a key uncertainty in the evaluation of TPO-RA technologies (Section 4.2.4), where assessing +/- 1 model cycle for time to response is inadequate for assessing the impact response timing has on cost-effectiveness. These uncertainties are explored in greater detail in Section 6.

5.3 Model validation and face validity check

5.3.1 Summary of company submission

The company internally validated the economic model according to a "*quality check*" of model codes, model input sources and intermediary calculations, and model outputs. The company assessed the external validity of the results by comparing findings to those reported in TA293 (eltrombopag) and TA221 (romiplostim) appraisals, and Lee et al and Allen et al for the economic evaluations of eltrombopag versus romiplostim identified in the company's systematic literature review. The company conclude that there are "*no significant differences between those models and the model presented in this submission*". The company did make reference to the fact that QALY estimates in Allen et al were higher on account of the application of higher base case utility values.

5.3.2 Points for critique

The CS reports that the model inputs were verified, checklists were used for technical implementation, stress tests were conducted, and the model was reviewed independently.

Despite validation efforts, the ERG identified errors in the calculation of subsequent therapies for romiplostim and avatrombopag (Section 5.1.2). The company did not submit an updated model with these errors corrected, but instead provided revised results following ERG points for clarification. The ERG was required to implement these corrections into the model in order to validate revised company results and to conduct appropriate exploratory analyses.

The ERG considers the company's choice to reference previous appraisals as the source for model inputs, rather than their ultimate source, hinders model validation. In most cases, the inputs sourced from TA293 (eltrombopag) were themselves sourced from TA221 (romiplostim) but the original source of data used to inform TA221 was not provided in the CS or in response to ERG points for clarification. Consequently, the ERG was required to review model inputs across avatrombopag, eltrombopag and romiplostim in order to appropriately validate the company's approach (Appendix Table 58).

The ERG notes that the company's assessment of external validity does not make reference to the fact that estimated costs for all comparators are considerably higher than any previous cost assessment of a TPO-RA.

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

A summary of the main issues identified and critiqued in Sections 4 and 5 and the additional scenario analyses the ERG uses to address each issue is shown in Table 38. The ERG identified a number of limitations and areas of uncertainty in the company's cost-effectiveness analysis. Where possible, the ERG has explored alternative assumptions and model inputs in a series of scenario analyses on the company's updated base-case analysis (ERG Scenarios 1-11). The ERG's base case consists of the set of assumptions and model inputs that the ERG considers to be most appropriate for assessing the cost-effectiveness of avatrombopag relative to eltrombopag and romiplostim. A thorough description of the ERG scenario analyses are presented in Section 6.1.1, while their impact on the company's cost-effectiveness results are presented in Section 6.2. The effect of making changes simultaneously on elements that are considered to form part of the ERG's preferred base case assumptions is presented in Section 6.3.

Following points for clarification, the ERG corrected technical errors in the company's model for the mixed treatment sequences used at second- and third-line for romiplostim (which was incorrectly aligned to the sequencing used for eltrombopag in the company's original base case results), and for avatrombopag in the comparison with romiplostim (which was incorrectly aligned to the sequencing used for eltrombopag in the company's revised base case results reported in response to ERG points for clarification) (see Section 5.1.2). The proportion of each therapy used in the mixed treatment strategies at second- and third-line in the company's original base case, the company's revised base case following clarification, and the ERG's corrected configuration for the company's base case are presented in Table 37. The ERG scenario analyses in Section 6.2 are based on the ERG's corrected configuration for subsequent lines of therapy.

The ERG notes that eltrombopag and romiplostim are subject to confidential PAS discounts. All analyses provided in this report are those with eltrombopag and romiplostim costed at their respective list prices (i.e. without confidential PAS discounts). Results with confidential PAS discounts applied for eltrombopag and romiplostim are presented in the confidential appendix to this ERG report.

Table 37: Company's original, revised and ERG corrected composition of subsequent therapies

	Company's original mixed treatment strategy								Company's revised mixed treatment strategy								ERG corrected mixed treatment strategy							
	Ava vs ELT		Ava vs ROM		ELT		ROM		Ava vs ELT		Ava vs ROM		ELT		ROM		Ava vs ELT		Ava vs ROM		ELT		ROM	
Line of treatment	II	III	II	III	II	III	II	III	II	III	II	III	II	III	II	III	II	III	II	III	II	III	II	III
Avatrombopag	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	**0.0%**	**0.0%**	0.0%	0.0%	**0.0%**	**0.0%**	0.0%	0.0%	**0.0%**	**0.0%**
Eltrombopag	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	**13.5%**	**17.6%**	0.0%	0.0%	**13.5%**	**17.6%**	0.0%	0.0%	**13.5%**	**17.6%**
Romiplostim	12.5%	19.5%	12.5%	19.5%	12.5%	19.5%	12.5%	19.5%	12.5%	19.5%	12.5%	19.5%	12.5%	19.5%	**0.0%**	**0.0%**	12.5%	19.5%	**0.0%**	**0.0%**	12.5%	19.5%	**0.0%**	**0.0%**
Rituximab	20.5%	12.6%	20.5%	12.6%	20.5%	12.6%	20.5%	12.6%	20.5%	12.6%	20.5%	12.6%	20.5%	12.6%	**20.2%**	**12.9%**	20.5%	12.6%	**20.2%**	**12.9%**	20.5%	12.6%	**20.2%**	**12.9%**
Splenectomy	10.2%	10.3%	10.2%	10.3%	10.2%	10.3%	10.2%	10.3%	10.2%	10.3%	10.2%	10.3%	10.2%	10.3%	**10.1%**	**10.6%**	10.2%	10.3%	**10.1%**	**10.6%**	10.2%	10.3%	**10.1%**	**10.6%**
Watch and wait	34.1%	41.4%	34.1%	41.4%	34.1%	41.4%	34.1%	41.4%	34.1%	41.4%	34.1%	41.4%	34.1%	41.4%	**33.7%**	**42.4%**	34.1%	41.4%	**33.7%**	**42.4%**	34.1%	41.4%	**33.7%**	**42.4%**
Azathioprine	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	**2.8%**	**2.1%**	2.8%	2.0%	**2.8%**	**2.1%**	2.8%	2.0%	**2.8%**	**2.1%**
Mycophenolate mofetil	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	**2.8%**	**2.1%**	2.8%	2.0%	**2.8%**	**2.1%**	2.8%	2.0%	**2.8%**	**2.1%**
Cyclosporine	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	**2.8%**	**2.1%**	2.8%	2.0%	**2.8%**	**2.1%**	2.8%	2.0%	**2.8%**	**2.1%**
Danazol	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	**2.8%**	**2.1%**	2.8%	2.0%	**2.8%**	**2.1%**	2.8%	2.0%	**2.8%**	**2.1%**
Dapsone	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	**2.8%**	**2.1%**	2.8%	2.0%	**2.8%**	**2.1%**	2.8%	2.0%	**2.8%**	**2.1%**
Cyclophosphamide	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	**2.8%**	**2.1%**	2.8%	2.0%	**2.8%**	**2.1%**	2.8%	2.0%	**2.8%**	**2.1%**
Vincristine	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	**2.8%**	**2.1%**	2.8%	2.0%	**2.8%**	**2.1%**	2.8%	2.0%	**2.8%**	**2.1%**
Vinblastine	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	2.8%	2.0%	**2.8%**	**2.1%**	2.8%	2.0%	**2.8%**	**2.1%**	2.8%	2.0%	**2.8%**	**2.1%**

Values changed from company's original mixed treatment strategy are in bold. Note the fourth line of treatment for all strategies is 100% watch and wait.

Table 38: Summary of the main issues identified by the ERG in Section 4 and ERG exploratory analyses

Critique item and description The ERG considers:		Dealt with in the		Area of remaining uncertainty	Significant impact on ICER
		ERG's Scenarios	ERG's Base-case		
1	***It is unlikely that patients would remain on active first-line TPO-RA treatment for a duration of 24 weeks before non-response to treatment is assessed in clinical practice.***	Sc. 1	No	Yes	No
2	***The treatment pathway and positioning of avatrombopag relative to non-TPO-RAs such as rituximab is unclear.***	No	No	Yes	-
3	***The approach used by the company to model subsequent treatments after discontinuation of a first-line TPO-RA restricts the cost-effectiveness analysis to a comparison of only two mutually exclusive treatment strategies simultaneously.***	Sc. 2	Yes	No	No
4	***The company has not used the modelled treatment sequencing to determine the optimum position for avatrombopag among the TPO-RAs.***	Sc. 3	No	Yes	No
5	***The company has not used updated guidance to inform dosages for non-TPO-RAs in the model.***	Sc. 4	Yes	No	No
6	***The company's NMA providing comparative effectiveness between avatrombopag, eltrombopag and romiplostim for the outcome of durable platelet response used in the model lacks face validity and is subject to considerable uncertainty.***	Sc. 5	Yes	Yes	Yes
7	***Treatment response estimates for first and subsequent lines of therapy used in the model are based on different definitions of response for TPO-RAs and non-TPO-RAs.***	No	No	Yes	-
8	***The long-term treatment duration of TPO-RAs is uncertain.***	Sc. 6	No	Yes	Yes
9	***The proportion of patients receiving rescue therapy (with and without treatment response) is uncertain.***	No	No	Yes	-
10	***The longer-term mortality risks associated with ITP are uncertain.***	Sc. 7	No	Yes	No
11	***The company has not age-adjusted HRQoL utility values over the model time-horizon.***	Sc. 8	Yes	No	No
12	***The company's assumed administration schedule for romiplostim overestimates the proportion of patients receiving doses within a clinic setting and its associated costs.***	Sc. 9	Yes	No	No
13	***The company's romiplostim acquisition costs do not take account of the weight distribution of the study population or the up-titration of dosing.***	Sc. 10	Yes	No	No
14	***The company costs for bleeding events are not adequately detailed or justified and exceed those reported in national sources and previous NICE appraisals.***	Sc. 11	Yes	Yes	Yes

6.1.1 Issues explored by the ERG in additional analyses

6.1.1.1 ERG Scenario 1: patients remain on active first-line TPO-RA treatment for a duration of 8 weeks before response to treatment is determined

As discussed in Section 4.2.2.2, the ERG considers there to be little evidence of a specific time-to-response effect to suggest that TPO-RAs warrant a full 24-week timeframe to assess response to treatment. The ERG believes that non-response to active first-line treatment with a TPO-RA is more likely to be assessed within a timeframe of around 8-12 weeks in clinical practice, rather than waiting a full 24 weeks as assumed in the company's base case. An 8-week timeframe would be consistent with the modelled timeframe used to assess non-response in subsequent lines of therapy, and the time at which platelet counts began to stabilise in Study 302.

ERG Scenario 1 is an exploratory analysis that assumes response to first-line TPO-RA treatment is determined at 8-weeks. This scenario removes 16-weeks of treatment costs for patients that are considered as non-responder in the model. The ERG recognises that this scenario does not align the model treatment schedule with the definition of durable platelet response (at least 6 weekly platelet counts ≥50×109/L in the final 8 weeks of a 24-26-week study); however, the ERG also recognises that there are stopping rules in the product SmPCs for when no response is observed in practice and it is unlikely that patients would remain on treatment for a full 24 weeks before response to treatment is assessed.

6.1.1.2 ERG Scenario 2: a fully incremental comparison of treatment strategies, with subsequent therapies aligned across strategies

As discussed in Section 4.2.4.2, the ERG is concerned with the company's approach to modelling subsequent treatments. Because patients who initiate subsequent therapy (i.e., those with no response or discontinue treatment after initial response) are permitted to switch to an alternative TPO-RA in the model, the mixed treatment strategy at second- and third-line is different across the three treatment strategies under consideration (Table 37). As a result, the company's model only permits a pairwise comparison of treatment strategies. To establish the most cost-effective treatment sequence, it is necessary to undertake a fully incremental comparison of all the sequences simultaneously. This is a core principle of cost-effectiveness analysis and is detailed in Section 4.2.4.2. In order to permit a fully incremental comparison, the ERG removed TPO-RAs from the subsequent lines of therapy (i.e. eltrombopag and romiplostim were removed from the proportion of therapies used in the mixed treatment strategy at second- and third-line) so that all treatment sequences had a common set of subsequent non-TPO-RA therapies. This approach was also used in TA293 (eltrombopag) and TA221 (romiplostim), where subsequent lines of therapy only consisted of non-TPO-RAs.

The common set of non-TPO-RA therapies used in subsequent treatment lines is presented in Table 39. ERG Scenario 2 provides a fully incremental comparison of avatrombopag, eltrombopag and romiplostim under this common set of subsequent therapies.

Table 39: The mixed treatment composition for subsequent therapies applied in ERG Scenario 2

	TPO-RA subsequent therapies		
Line of treatment	II	III	IV
Rituximab	23.4%	15.7%	0.0%
Splenectomy	11.7%	12.9%	0.0%
Watch and rescue	39.0%	51.4%	100.0%
Azathioprine	3.2%	2.5%	0.0%
Mycophenolate mofetil	3.2%	2.5%	0.0%
Cyclosporine	3.2%	2.5%	0.0%
Danazol	3.2%	2.5%	0.0%
Dapsone	3.2%	2.5%	0.0%
Cyclophosphamide	3.2%	2.5%	0.0%
Vincristine	3.2%	2.5%	0.0%
Vinblastine	3.2%	2.5%	0.0%

6.1.1.3 ERG Scenario 3: exploratory modelling of treatment sequences to assess the optimum position for avatrombopag among the TPO-RAs

As discussed in Section 4.2.4.2, the company has not considered the optimum position for avatrombopag among the TPO-RAs. The mixed treatment strategy approach by the company for subsequent therapies is an oversimplification of modelling treatment sequences and fails to inform what is the most efficient use and positioning of avatrombopag among TPO-RAs (and non-TPO-RAs). The ERG notes that there is significant uncertainty regarding what the most relevant treatment sequences are for informing the decision problem for avatrombopag as these are not directly defined in the final NICE scope.

ERG Scenario 3 is an exploratory analysis where avatrombopag displaces an alternative TPO-RA in a treatment sequence of TPO-RAs, i.e., a fixed treatment sequence is considered where the use of avatrombopag may be positioned before or after an alternative TPO-RA within the treatment sequence of TPO-RAs. This gives rise to six alternative combinations of avatrombopag, eltrombopag and romiplostim used in sequence (see Section 4.2.4.2). The fourth line of therapy is assumed to be 'watch and wait' as this represents the fourth line of therapy used in the company's model (note that in this sequence of TPO-RAs the more appropriate fourth line treatment would be a non-TPO-RA therapy

such as rituximab, but the company's model was not flexible enough to consider greater than three lines of active therapy). The sequential treatment strategies explored in ERG Scenario 3 are presented in Table 40.

Table 40: Sequential treatment strategies assessed in ERG scenario 3

	Treatment line			
Sequential treatment strategies	I	II	III	IV
AVA → ELT → ROM →WW	Avatrombopag	Eltrombopag	Romiplostim	Watch and wait
AVA → ROM → ELT →WW	Avatrombopag	Romiplostim	Eltrombopag	Watch and wait
ELT → AVA → ROM →WW	Eltrombopag	Avatrombopag	Romiplostim	Watch and wait
ELT → ROM → AVA →WW	Eltrombopag	Romiplostim	Avatrombopag	Watch and wait
ROM → AVA → ELT →WW	Romiplostim	Avatrombopag	Eltrombopag	Watch and wait
ROM → ELT → AVA →WW	Romiplostim	Eltrombopag	Avatrombopag	Watch and wait

6.1.1.4 ERG Scenario 4: using updated guidance to inform dosages for non-TPO-RAs in the model

As discussed in Section 4.2.9.2, the ERG identified that the source used in the company's model for dosing schedules for non-TPO-RA therapies (Provan et al (2010)) was revised in 2019 [1, 2]. Provan et al (2019) reports that there have been numerous developments and changes in treatment practices for the management of patients with immune thrombocytopenia (ITP) since the international consensus report published in 2010 [2]. Table 31 in Section 4.2.9.2 reports these changes identified by the ERG. ERG Scenario 4 applies the active treatment drug dosing schedules from Provan (2019).

6.1.1.5 ERG Scenario 5: applying estimates of comparative effectiveness for durable platelet response between avatrombopag, eltrombopag and romiplostim from the ERGs ITC

As discussed in Section 3.4-3.5, the ERG has major concerns regarding the company's ITC for the primary effectiveness outcome of durable platelet response. Concerns include lack of face validity of the company's estimates when compared to the individual trial results, the appropriateness of the continuity corrections applied for zero events, misalignment of study populations (observed population vs ITT), the inclusion of an uninformative treatment in the network (fostamatinib) and the inclusion of between-trial heterogeneity in placebo response rates.

Table 41 presents the estimates of comparative effectiveness from the ERG's frequentist fixed-effect ITC and the associated probabilities of durable platelet response for avatrombopag, eltrombopag, romiplostim and placebo. ERG Scenario 5 uses these estimates to assess the cost-effectiveness of avatrombopag relative to eltrombopag and romiplostim.

Table 41: ERG estimates of comparative effectiveness for durable platelet response between avatrombopag, eltrombopag and romiplostim relative to placebo

	Comparative effectiveness and probabilities for durable platelet response					
	Mean OR	95% CI		Mean probability	95% CI	
Comparisons		Lower CI	Higher CI		Lower CI	Higher CI
Avatrombopag vs placebo	18.721	1.029	340.539	0.438	0.041	0.934
Eltrombopag vs placebo	10.596	3.637	30.868	0.306	0.132	0.563
Romiplostim vs placebo	29.606	5.425	161.579	0.552	0.184	0.871
Placebo baseline risk	-	-	-	0.040	0.0004	0.6670

6.1.1.6 ERG Scenario 6: assuming alternative and differential longer-term treatment discontinuation rates for TPO-RAs

As discussed in Section 4.2.6.5, the ERG considers there to be significant uncertainty surrounding the length of treatment duration for each of the TPO-RA treatments. The company's assertion that identical treatment discontinuation rates represent a conservative assumption for the cost-effectiveness of avatrombopag are based on the company's ITC estimates for durable platelet response where avatrombopag is more effective than the alternative TPO-RAs. However, the ERG estimates of comparative effectiveness for durable platelet response between avatrombopag, eltrombopag and romiplostim suggests that romiplostim is expected to be the most effective treatment. Furthermore, the company's estimated mean time on treatment of 109 cycles for eltrombopag and 393 cycles for romiplostim from Lee et al suggests that there could be a notable difference in long-term discontinuation rates between the TPO-RAs [3]. ERG Scenario 6 explores the impact of alternative TPO-RA treatment durations on cost-effectiveness results, specifically:

- ERG Scenario 6a: Equal 309 cycle average time on treatment across all treatment strategies (0.2541% discontinuation rate per model cycle)
- ERG Scenario 6b: Differential average time on treatment for romiplostim (309 cycles) and avatrombopag/eltrombopag (109 cycles)

6.1.1.7 ERG Scenario 7: implementing alternative longer-term mortality risk profiles for ITP patients

As discussed in Section 4.2.7.2, the ERG considers there to be significant uncertainty surrounding the longer-term survival of ITP patients. Cohort studies identified by the ERG report significantly higher rates of all-cause and chronic disease-related (e.g. cardiovascular disease, haematological cancer, etc.) mortality in ITP patients compared to that of the general population. Enger et al's (2010) US cohort study estimated an adjusted all-cause mortality hazard ratio of 4.21 for persistent or chronic ITP relative to a control sample [43]. Frederisken et al's (2014) Danish ITP population-based cohort study reported an adjusted all-cause mortality hazard ratio of 1.5 relative to the general population [42]. Schoonen et al's (2009) UK population-based cohort study of 1145 ITP patients estimated an all-

cause mortality hazard ratio of 1.6 compared to age- and sex-matched comparisons [44] and reported that bleeds and infections were responsible for 13% and 19% of all computerised plausible causes of death. ERG Scenario 7 explores the impact of applying the hazard ratios from each of the aforementioned sources to the company's base case age- and sex-adjusted UK general population mortality. Since patient outcomes in the model were already inclusive of bleed-related mortality, a fourth sub-scenario was considered which applied a model background all-cause mortality hazard ratio of 1.408 to UK general population mortality risk. The 1.408 hazard ratio represents Schoonen et al's (2009) estimated hazard ratio down-weighted by the proportion of mortalities that were associated bleed- and infection-related mortalities (32%) (i.e. assuming that of the 60% higher risk of death for ITP patients relative to the general population, only 68% is attributable to non-bleed events).

6.1.1.8 ERG Scenario 8: applying age-adjusted utilities

As discussed in Section 4.2.8.2, the ERG considers that age-adjusted utility values should be incorporated in the model to reflect the decreasing utility of patients as they age through the model over time. This adjustment is incorporated in ERG Scenario 8. The age-adjusted health state utility values applied in the model for this scenario are reported in Table 42.

Table 42: Age-adjusted health-state utility values applied in ERG scenario 8

	<50 x 10^9/L			≥50 x 10^9/L		
	No bleed	Minor bleed	Outpatient bleed	No bleed	Minor bleed	Outpatient bleed
35-44	0.864	0.820	0.689	0.824	0.779	0.648
45-54	0.801	0.756	0.625	0.760	0.715	0.584
55-64	0.753	0.708	0.578	0.713	0.668	0.537
65-74	0.734	0.690	0.559	0.694	0.649	0.518
75+	0.679	0.634	0.503	0.638	0.594	0.463

6.1.1.9 ERG Scenario 9: Administration costs for romiplostim based on one initial clinic visit and alternative rates of haematological outpatient visit administration

As discussed in Section 4.2.9.2, the ERG has concerns relating to: (i) the company's application of romiplostim administration costs within the first model cycle; (ii) the proportion of patients administering romiplostim within a clinic setting; and (iii) the costs associated with administering romiplostim in a clinic setting. First, romiplostim administration is referenced in the company submission as being exclusively in a clinic setting for the first dose. The ERG has identified that in the model the first four doses are costed as being in a clinic setting. Second, literary sources and expert clinical advice sought by the ERG indicate that the vast majority of patients self-administer romiplostim at home. The proportion of clinic administrations used in the model (27.7%) was informed by data presented at the ASH annual meeting in 2010. The ERG questions the

representativeness of these findings to current UK practice. Schipperus et al's (2018) analysis of romiplostim self-administration reported 87.5% of patients correctly administer romiplostim when provided administration training materials [48]. Third, expert opinion received by the ERG suggests that administration usually takes place in the day ward, which means that unit costs aligned to haematology outpatient visits (£165.57) appear more appropriate than those for the delivery of simple parenteral chemotherapy at first attendance (used in the company's base - £241.06).

To correct the economic model for the initial clinic administration setting outlined by the company, and to best align long-term rates and costs of clinic-based romiplostim administration to current NHS practice the ERG considers the following cases in ERG Scenario 9:

- ERG Scenario 9a: All patients are assumed to receive their first dose at clinic visit with 27.7% assumed at clinic thereafter (as opposed to the first four doses received in cycle 1)
- ERG Scenario 9b: 12.5% of romiplostim administrations are conducted in clinic after the 1st cycle (as opposed to 27.7%)
- ERG Scenario 9c: Romiplostim clinic administrations costed as clinical haematology outpatient visits (£165.57) (as opposed to £241.06)
- ERG Scenario 9d: All three scenarios combined.

6.1.1.10 ERG Scenario 10: alternative romiplostim dosages

As discussed in Section 4.2.9.2, the ERG considers that the romiplostim acquisition costs used in the model may overestimate drug costs. The company's application of median doses from the pivotal long-term trial of romiplostim by Kuter et al neglects the lower starting doses administered prior to up-titration. Median doses administered in the pivotal romiplostim trial (non-splenectomised: 0.002mg/kg; splenectomised: 0.003mg) were notably lower than those in the trials' extension-phase (0.004mg/kg) and were selected to inform initial dosing in both the TA292 (eltrombopag) and TA221 (romilpostm) appraisals. The ERG also notes that the company's approach to estimating romiplostim drug costs neglects the distribution of patient weights, which may lead to costing errors. For these reasons, the ERG presents two scenario analyses with alternative romiplostim dosing and associated vial acquisition costs for average Study 302 characteristics (82.97kg; 32.7% post-splenectomy):

- ERG Scenario 10a: applies median doses from the pivotal romiplostim trial (non-splenectomised: 0.002mg/kg; splenectomised: 0.003mg/kg) to model romiplostim doses in the first 24-weeks of active treatment [7].
- ERG Scenario 10b: applies romiplostim doses from TA293 (eltrombopag) calculated from the distribution of patient weights from RAISE and average romiplostim usage for patients in the first 24 weeks of treatment in Kuter 2008, averaged over the 4 week cycle length [7].

The assumed average doses for each scenario are reported in Table 43.

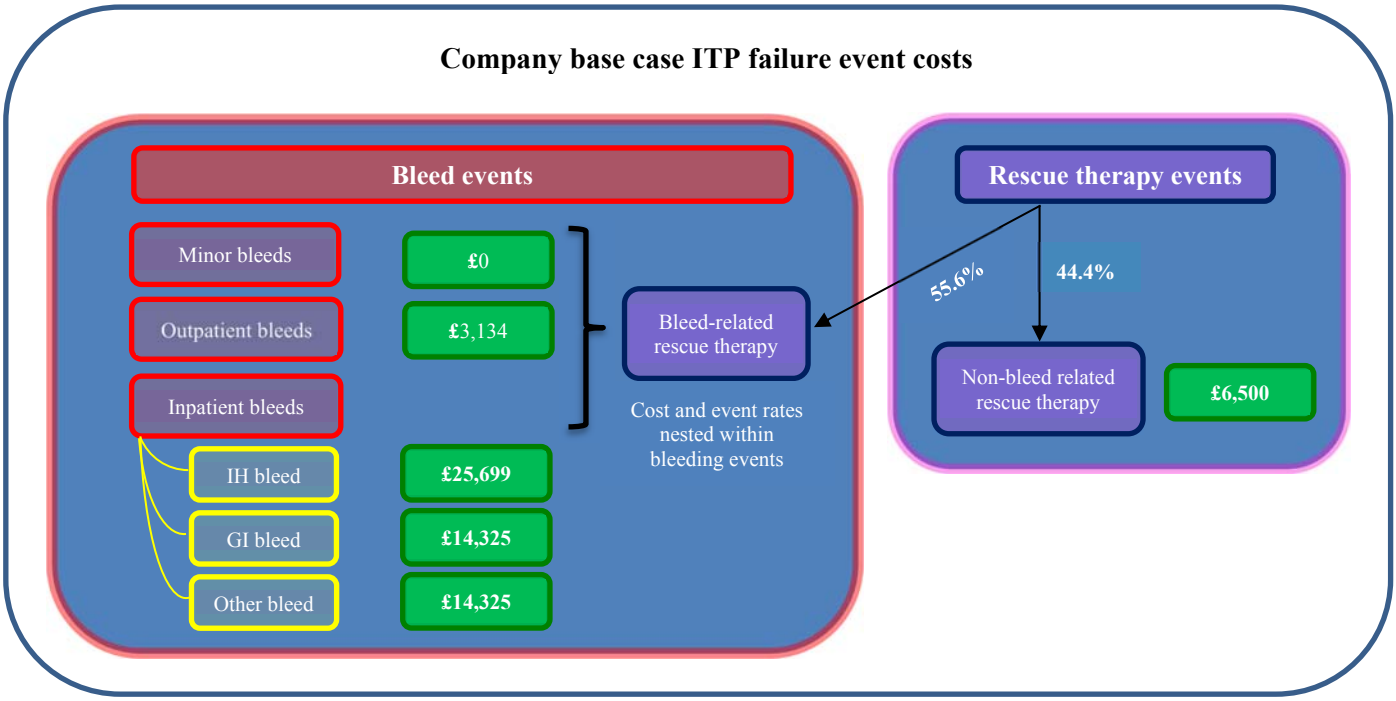
Table 43: Average model romiplostim doses applied in ERG Scenario 10

	Splenectomised		Non-splenectomised		Average	
	10 a) Trial median dose	10 b) TA 293	10 a) Trial median dose	10 b) TA293	10 a) Trial median dose	10 b) TA293
Week 0-3	0.003	0.00206	0.002	0.00149	0.00233	0.00168
Week 4-7	0.003	0.00365	0.002	0.00246	0.00233	0.00285
Week 8-11	0.003	0.00437	0.002	0.00247	0.00233	0.00309
Week 12-15	0.003	0.00489	0.002	0.00272	0.00233	0.00343
Week 16-19	0.003	0.00498	0.002	0.00276	0.00233	0.00348
Week 20-23	0.003	0.00511	0.002	0.00274	0.00233	0.00351
Post-week 28	0.004	0.00511	0.004	0.00274	0.004	0.00351

6.1.1.11 ERG Scenario 11: revising bleed event costs to NHS reference sources and aligning rescue therapy rates and costs to Study 302

As discussed in Section 4.2.9.2, the ERG has concerns regarding the company's configuration of bleed and rescue therapy event risks and associated costs in the model. The company disaggregates rescue therapy according to two attributable causes: bleed-related and non-bleed related. The probability and associated costs of a bleed-related rescue therapy event is assumed to be nested within those for bleeding events. Non-bleed related rescue therapy events are costed separately and directly inform ITP failure events (i.e. those which necessitate a subsequent treatment in the model) (Figure 5). This approach represents a departure from the costing approach used in TA293 and TA221, in which independent bleed and rescue therapy rates and costs were used, with rescue therapy costs aligned to trial rescue treatment rates/schedules and bleed costs from national sources.

Figure 5: Company's modelled approach for bleeds and rescue therapy costs



Specifically, the ERG has the following concerns regarding the company's approach to modelling bleed and rescue therapy events: the bleed costs (which encompass 55.6% of rescue therapies) applied in the model (Table 32) are derived from a company commissioned paradigm review with markedly higher costs compared to NHS reference costs and those applied in previous appraisals; the company's new approach complicates the interpretation of bleed and rescue costs and is unwarranted; rescue therapy rates sourced from TA293 (eltrombopag) could not be verified by the ERG.

ERG Scenario 11 makes the following changes to the company's base case costs:

1. Applies the company's non-bleed related rescue therapy event costs (i.e. that applicable to the Study 302 composition of rescue treatment) to both bleed-related and non-bleed related rescue therapies to aid consistency and interpretability (Table 44).
2. Applies NHS reference costs for bleeding events (Table 44) [31] where bleed-related rescue therapy events are costed independently (see point 1).
3. Applies rescue therapy rates observed in Study 302 + extension (CS – Table 73).

Table 44: NHS reference bleed costs and company rescue therapy costs applied in ERG Scenario 11

	Cost (£)	Source
Outpatient bleed	**£459.65**	NHS reference cost 19/20: assumes average unit cost for a day case bleed procedure (weighted FD03F-FD03H)
Gastrointestinal bleed	**£3,091.79**	NHS reference cost 19/20: assumes average unit cost for non-elective long stay GI admissions with single or multiple intervention (weighted FD03A to FD03E)
Intercranial haemorrhage	**£4,690.02**	NHS reference cost 19/20: assumes average unit cost for non-elective long stay haemorrhagic cerebrovascular disorder admissions, (weighted AA23C to AA23G)
Other inpatient bleed	**£2,890.37**	NHS reference cost 19/20: assumes average unit cost for non-elective short stay GI admissions, (weighted FD03B and FD03E (GI bleed codes with single or multiple intervention, low CC scores only)
Bleed-related rescue therapy*	**£6,499.67**	Company submission: costed according to rescue therapy composition from Study 302, BNF drug costs and international management guidelines on dosing and administration

*Made equivalent to the company's non-bleed related rescue therapy event costs

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

Table 45-Table 55 show the results of each ERG scenario. Scenarios with the largest impact on the ICER are those relating to: (i) comparative effectiveness for durable platelet response between avatrombopag, eltrombopag and romiplostim; (ii) the long-term treatment duration of TPO-RAs; and (iii) rescue and bleeding event costs and probabilities.

6.2.1.1 ERG Scenario 1: patients remain on active first-line TPO-RA treatment for a duration of 8 weeks before response to treatment is determined

Table 45: Cost-effectiveness results for ERG Scenario 1

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG Scenario 1: pair-wise comparison for avatrombopag vs. eltrombopag					
AVA	[redacted]	[redacted]			
ELT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG Scenario 1: pair-wise comparison for avatrombopag vs. romiplostim					
AVA	[redacted]	[redacted]			
ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.2.1.2 ERG Scenario 2: a fully incremental comparison of treatment strategies with subsequent therapies aligned across comparators

Table 46: Cost-effectiveness results for ERG Scenario 2

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG Scenario 2: fully incremental comparison of alternative treatment strategies					
AVA	[redacted]	[redacted]			
ELT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.2.1.3 ERG Scenario 3: alternative modelled treatment sequences to assess the optimum position for avatrombopag among the TPO-RAs

Table 47: Cost-effectiveness results for ERG Scenario 3

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG Scenario 3: Fully incremental comparison of alternative treatment sequences					
AVA → ELT → ROM →WW	[redacted]	[redacted]			
ELT → AVA → ROM →WW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AVA → ROM → ELT →WW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ELT → ROM → AVA →WW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ROM → AVA → ELT →WW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ROM → ELT → AVA →WW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.2.1.4 ERG Scenario 4: using updated guidance to inform dosages for non-TPO-RAs in the model

Table 48: Cost-effectiveness results for ERG Scenario 4

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG Scenario 4: pair-wise comparison for avatrombopag vs. eltrombopag					
AVA	[redacted]	[redacted]			
ELT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG Scenario 4: pair-wise comparison for avatrombopag vs. romiplostim					
AVA	[redacted]	[redacted]			
ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.2.1.5 ERG Scenario 5: applying ERG estimates of comparative effectiveness for durable platelet response between avatrombopag, eltrombopag and romiplostim

Table 49: Cost-effectiveness results for ERG Scenario 5

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG Scenario 5: pair-wise comparison for avatrombopag vs. eltrombopag					
AVA	[redacted]	[redacted]			

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ELT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG Scenario 5: pair-wise comparison for avatrombopag vs. romiplostim					
AVA	[redacted]	[redacted]			
ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.2.1.6 ERG Scenario 6: assuming alternative and differential longer-term treatment discontinuation rates for TPO-RAs

Table 50: Cost-effectiveness results for ERG Scenario 6

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Equal 309 cycle average time on treatment across all treatment strategies (0.2541% discontinuation rate)					
ERG Scenario 6a: pair-wise comparison for avatrombopag vs. eltrombopag					
AVA	[redacted]	[redacted]			
ELT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG Scenario 6a: pair-wise comparison for avatrombopag vs. romiplostim					
AVA	[redacted]	[redacted]			
ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Differential average time on treatment for romiplostim (309 cycles) and avatrombopag/eltrombopag (109 cycles)					
ERG Scenario 6b: pair-wise comparison for avatrombopag vs. eltrombopag					
AVA	[redacted]	[redacted]			
ELT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG Scenario 6b: pair-wise comparison for avatrombopag vs. romiplostim					
AVA	[redacted]	[redacted]			
ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.2.1.7 ERG Scenario 7: implementing alternative longer-term mortality risk profiles for ITP patients

Table 51: Cost-effectiveness results for ERG Scenario 7

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Background non-bleed related hazard ratio x4.2 general population mortality [Enger et al's (2010)]					
ERG Scenario 7a: pair-wise comparison for avatrombopag vs. eltrombopag					
AVA	[redacted]	[redacted]			
ELT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG Scenario 7a: pair-wise comparison for avatrombopag vs. romiplostim					
AVA	[redacted]	[redacted]			
ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Background non-bleed related hazard ratio x1.6 general population mortality [Schoonen et al (2009)]					
ERG Scenario 7b: pair-wise comparison for avatrombopag vs. eltrombopag					
AVA	[redacted]	[redacted]			
ELT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG Scenario 7b: pair-wise comparison for avatrombopag vs. romiplostim					

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
AVA	[redacted]	[redacted]			
ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Background non-bleed related hazard ratio x1.5 general population mortality [Frederisken et al's (2014)]					
ERG Scenario 7a: pair-wise comparison for avatrombopag vs. eltrombopag					
AVA	[redacted]	[redacted]			
ELT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG Scenario 7a: pair-wise comparison for avatrombopag vs. romiplostim					
AVA	[redacted]	[redacted]			
ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Background non-bleed related hazard ratio x1.408 general population mortality [adjusted Schoonen (2009)]					
ERG Scenario 7c: pair-wise comparison for avatrombopag vs. eltrombopag					
AVA	[redacted]	[redacted]			
ELT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG Scenario 7c: pair-wise comparison for avatrombopag vs. romiplostim					
AVA	[redacted]	[redacted]			
ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.2.1.8 ERG Scenario 8: applying age-adjusted utilities

Table 52: Cost-effectiveness results for ERG Scenario 8

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG Scenario 8: pair-wise comparison for avatrombopag vs. eltrombopag					
AVA	[redacted]	[redacted]			
ELT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG Scenario 8: pair-wise comparison for avatrombopag vs. romiplostim					
AVA	[redacted]	[redacted]			
ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.2.1.9 ERG Scenario 9: administration costs for romiplostim based on one initial clinic visit and alternative rates of haematological outpatient visit administration

Table 53: Cost-effectiveness results for ERG Scenario 9

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
All patients are assumed to receive their first dose at clinic visit with 27.7% assumed at clinic thereafter					
ERG Scenario 9a: pair-wise comparison for avatrombopag vs. romiplostim					
AVA	[redacted]	[redacted]			
ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12.5% administrations of romiplostim are assumed at clinic after the 1st cycle					
ERG Scenario 9b: pair-wise comparison for avatrombopag vs. romiplostim					
AVA	[redacted]	[redacted]			
ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Romiplostim clinic administrations costed as clinical haematology outpatient visits (£165.57)					

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG Scenario 9c: pair-wise comparison for avatrombopag vs. romiplostim					
AVA	[redacted]	[redacted]			
ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All three scenarios (Scenarios 10a 10b and 10c) combined					
ERG Scenario 9d: pair-wise comparison for avatrombopag vs. romiplostim					
AVA	[redacted]	[redacted]			
ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.2.1.10 ERG Scenario 10: alternative romiplostim dosages

Table 54: Cost-effectiveness results for ERG Scenario 10

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Kuter (2008) median trial 24-week dosing (splenectomised: 0.003mg/kg; non-splenectomised 0.002 mg/kg) [7]					
ERG Scenario 10a: pair-wise comparison for avatrombopag vs. eltrombopag					
AVA	[redacted]	[redacted]			
ELT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG Scenario 10a: pair-wise comparison for avatrombopag vs. romiplostim					
AVA	[redacted]	[redacted]			
ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Romiplostim doages used in TA293					
ERG Scenario 10b: pair-wise comparison for avatrombopag vs. eltrombopag					
AVA	[redacted]	[redacted]			
ELT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG Scenario 10b: pair-wise comparison for avatrombopag vs. romiplostim					
AVA	[redacted]	[redacted]			
ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.2.1.11 ERG Scenario 11: revising bleed event costs to NHS reference sources and aligning rescue therapy rates and costs to Study 302

Table 55: Cost-effectiveness results for ERG Scenario 11

Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Independent bleed (NHS reference) and rescue therapy (Study 302) costs & Study 302+extension rescue rates					
ERG Scenario 10a: pair-wise comparison for avatrombopag vs. eltrombopag					
ELT	[redacted]	[redacted]			
AVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG Scenario 10a: pair-wise comparison for avatrombopag vs. romiplostim					
AVA	[redacted]	[redacted]			
ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.3 ERG's preferred assumptions

The ERG preferred assumptions are:

- A fully incremental comparison of avatrombopag, eltrombopag and romiplostim, removing TPO-RAs from subsequent lines of therapy so that all treatment sequences have a common set of subsequent non-TPO-RA therapies - ERG scenario 2.
- Active treatment drug dosing schedules aligned to the latest guidance from Provan (2019) [2] – ERG scenario 4
- Estimates of comparative effectiveness for durable platelet response from the ERG's frequentist fixed-effect ITC for avatrombopag, eltrombopag, romiplostim and placebo – ERG scenario 5.
- Age-adjusted utility values reflecting the decreasing utility of patients as they age through the model over time – ERG scenario 8.
- Administration costs for romiplostim based on one initial clinic visit followed by 12.5% of patients administering at a haematological outpatient visit thereafter – ERG scenario 9.
- Median doses from the pivotal romiplostim trial (non-splenectomised: 0.002mg/kg; splenectomised: 0.003mg/kg) used to inform romiplostim drug acquisition costs in the first 24-weeks of active treatment – ERG scenario 10.
- Rescue therapy rates aligned to Study 302 + Extension with rescue therapy and bleed events costed independently from Study 302 rescue treatments and NHS reference costs, respectively – ERG Scenario 11.

Table 56 shows the ERG's preferred assumptions, which form the ERG base-case, and their cumulative impact on the ICER. The ERG base-case ICER is [redacted]/QALY for romiplostim compared to avatrombopag. Eltrombopag is dominated when compared to avatrombopag (i.e., higher costs and lower QALYs). ERG preferred assumptions decrease the incremental costs, and increase the incremental QALYs, associated with eltrombopag and romiplostim relative to avatrombopag. Mean probabilistic results produced by the ERG were comparable to deterministic values, albeit significantly more uncertain when incorporating the response rate parameter uncertainty from the ERG ITC.

6.3.1 ERG base case analysis

Table 56: ERG's preferred model assumptions

ERG Scenario Number	Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
2	**Fully incremental comparison of alternative treatment strategies**					
	AVA	[redacted]	[redacted]			
	ELT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG Scenario Number	Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
	ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2+4	**Using updated guidance to inform dosages for non-TPO-RAs in the model**					
	AVA	[redacted]	[redacted]			
	ELT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2+4+5	**ERG estimates of comparative effectiveness for durable platelet response**					
	AVA	[redacted]	[redacted]			
	ELT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2+4+5+8	**Age-adjusted utility values used in the model**					
	AVA	[redacted]	[redacted]			
	ELT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2+4+5+8+9d	**Administration costs for romiplostim based on one initial clinic visit and alternative rates (12.5%) and costs (£165.57) for administrations**					
	AVA	[redacted]	[redacted]			
	ELT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2+4+5+8+9d+10a	**Romiplostim dosing in the first 24-weeks from medium dosages in pivotal trial (12)**					
	AVA	[redacted]	[redacted]			
	ELT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2+4+5+8+9d+10a+11	**Revising bleed event costs to NHS reference sources and independent rescue therapy costs based to Study 302 rescue therapy definition**					
	AVA	[redacted]	[redacted]			
	ELT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

6.4 Conclusions of the cost effectiveness section

The company submitted a de novo economic model to assess the cost-effectiveness of avatrombopag versus eltrombopag and romiplostim for treating chronic ITP. The ERG considered the model structure broadly appropriate to inform decision-making and notes that the company's approach was

largely based on the assumptions used in previous appraisals (TA 293 (eltrombopag) and TA221 (romiplostim)). The ERG considers the company's model broadly appropriate for reflecting the decision problem defined in the final NICE scope. However, the ERG has identified a number of issues and key uncertainties with the company's cost-effectiveness analysis.

Central issues with the company's approach relate to the estimation of comparative effectiveness for durable platelet response and the bleed and rescue therapy event costs and configuration of the model. The response rates used in the company's model suggests that avatrombopag has the highest response rate out of any of the TPO-RAs under consideration, with response rates 2.6 and 1.3 times higher than eltrombopag and romiplostim, respectively. The evidence supporting these findings is based on the company's ITC which the ERG has major concerns with. Specifically, the ERG takes issue with the company's estimates lacking face validity when compared to the individual trial results, the continuity corrections made for zero events, the inconsistent study population definitions across trials (observed population vs ITT), the inclusion of uninformative treatments into the network (fostamatinib) and the between-trial placebo heterogeneity in response rates. With respect to the costing and configuration of bleed and recue therapy events, the company's disaggregation of rescue therapy events (into bleed and non-bleed related) and the company's paradigm review to inform event costs represents a significant departure from previous appraisals and suggests bleed and rescue therapy event costs are markedly higher than NHS reference costs and those used in previous appraisals. ERG analyses show a significant interaction-effect between response rates and bleed and rescue therapy event costs in the model. This is because the largest cost-saving associated with achieving and maintaining a response is via averting bleed and rescue therapy events. The larger the treatment response rate relative to its comparators, the more influential bleed and rescue therapy costs are for offsetting the long-term treatment costs necessary for maintaining response. Applying the ERG preferred bleed and rescue therapy configuration and costs (ERG Scenario 11) reduced cost savings associated with avatrombopag by approximately [redacted] and [redacted] relative to eltrombopag and romiplostim, respectively. In the ERGs revised base case which includes lower treatment-specific differentials in response rates, bleed and rescue costs had a lesser impact. Other issues identified by the ERG include the pairwise assessment of alternatives (to facilitate common subsequent therapy schedules across alternatives), the likely overestimation of administration costs associated with romiplostim, the failure to account for up titration and patient weight distribution in romiplostim dosing, and omitting longer-term age-adjustments in model utilities.

Key uncertainties and limitations in the evidence base prevent the ERG from making alternative assumptions surrounding: (i) the treatment pathway; (ii) long-term TPO-RA treatment duration; and (iii) non-bleed related mortality for chronic ITP patients. First the ERG note that a fully incremental comparison of defined treatment sequences is required to accurately assess cost-effectiveness and the

optimal positing of avatrombopag among the TPO-RAs. However, the position of rituximab and splenectomy within the treatment pathway remains highly uncertain, making a comparison of sequences relevant to decision making difficult. Second, the long-term treatment duration remains a key area of uncertainty in the model. Considering the absence of compelling evidence to suggest appropriate treatment durations for each TPO-RA comparator, the ERG considers it appropriate to use an equivalent annual treatment discontinuation rate across the comparators, although notes that differential treatment durations are plausible. Third the ERG has identified evidence to suggest ITP patients experience higher mortality risks than the general population. The ERG considers there to be significant uncertainty surrounding the magnitude in chronic (e.g. hematologic cancers) and acute (fatal bleeds) risks associated with chronic ITP. Since the relative risks of mortality in the company model largely fall within or above the range of values reported in the literature, the ERG considers the company's background age- and sex-adjusted general population mortality acceptable.

The ERG's base-case analysis assumes alternative response rates, romiplostim drug acquisition and administration costs, bleed and rescue therapy rates and costs, and corrects for several methodological issues. The assumptions with the largest impact on cost and QALY differentials and cost-effectiveness are the durable platelet response rates, long-term TPO-RA treatment duration, and the rates and costs of bleed and rescue therapy events. The other changes that comprise the ERG base-case have a smaller impact on the cost-effectiveness results. Compared to avatrombopag, the ERG base-case ICER is [redacted]/QALY for romiplostim and eltrombopag is dominated. The ERG base case analysis reduces the incremental costs associated with eltrombopag from [redacted] to [redacted] and increase incremental QALYs from [redacted] to [redacted] relative to avatrombopag. For romiplostim, ERG preferred assumptions decrease incremental costs from [redacted] to [redacted] and increase incremental QALYs from [redacted] to [redacted] (making romiplostim the most effective comparator). The ERG highlights that these results do not include the confidential PAS discount on eltrombopag or romiplostim.

7 END OF LIFE

Due to the nature of the condition and treatment evaluated, the ERG believes that end of life criteria considerations do not apply to this appraisal.

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9 APPENDICES

Box 1 BUGS code for the unrelated mean effects (inconsistency) model code with test for inconsistency in a single loop – adapted from Dias et al 2018[28]

```
model{
for( i in 1 : ns2 ) {
  y[i , 2] ~ dnorm(delta[i , 2], prec[i , 2])
  var[i , 2] <- pow(se[i , 2], 2)
  prec[i , 2] <- 1 / var[i , 2]
  dev[i] <- (y[i , 2] - delta[i , 2]) * (y[i , 2] - delta[i , 2]) * prec[i , 2]
  delta[i , 2] <- d[t[i,1],t[i,2]]
 }
totresdev <- sum(dev[])
for (k in 1:nt) { d[k,k] <- 0 }  # set effects of k vs k to zero
for (c in 1:(nt-1)) {
    for (k in (c+1):nt){
      d[c,k] ~ dnorm(0,.0001)    # priors for all mean treatment effects
    }
  }
# Bucher Inconsistency assessment for loop (1,2,3)
# Indirect estimate
dInd.23 <- d[1,3]-d[1,2]
dInd.12 <- d[1,3]-d[2,3]
dInd.13 <- d[1,2]+d[2,3]
# differences between direct and indirect
diff.23 <- dInd.23-d[2,3]
diff.12 <- dInd.12-d[1,2]
diff.13 <- dInd.13-d[1,3]
# p-values
p.23 <- step(diff.23)
p.12 <- step(diff.12)
p.13 <- step(diff.13)
}                                  # *** PROGRAM ENDS
```

Table 57: Overview of the company's economic evaluation

	Approach	Source / Justification	Location in CS
Model	Markov model with separate health states based on treatment response (defined at a threshold of $50x10^9$/L). Patients remain in an uncontrolled disease state during active treatment. 56 year (lifetime) time horizon with 28-day cycles.	The $50x10^9$/L platelet threshold structure is a standard measure of treatment response in clinical studies, thereby allowing for comparative effectiveness estimates between alternatives.	Section B3.2.2 p80-83
States and events	The model consists of four mutually exclusive health states: (i) Active treatment, (ii) Responder, (iii) No Responder (no treatment), and (iv) Death. Patients initiate treatment and remain in state (i) Active treatment until responder status is determined (time to response is treatment specific - all TPO-RAs 24 weeks). Following (i) Active treatment patients transition into either the (ii) responder state, or (iii) no responder no treatment state. Patients in the (ii) responder state transition into state (iii) no response no treatment, while patients in state (iii) no response no treatment transition back to (i) Active treatment following a bleed or need for rescue therapy. Patients may transition into state (iv) Death from any state.	In clinical practice, platelet count is the most significant prognostic factor of disease severity, treatment response and patient outcomes (e.g. bleeding, rescue therapies, concomitant medication use) The $50x10^9$/L platelet threshold used for defining health states (ii) Responder, (iii) No Responder (no treatment) has also been used in economic models in the identified literature as well as previous NICE appraisals for ITP.	Section B3.2.2 p80-83
Comparators	Avatrombopag in addition to standard of care treatment (including concomitant ITP medication and recue therapies). Eltrombopag (existing NICE-approved TPO-RA) in addition to standard of care treatment. Romiplostim (existing NICE approved TPO-RA) in addition to standard of care treatment. The company assumed that patients could receive three additional lines of subsequent therapy. Second- and third-line	The company anticipates that the population eligible for avatrombopag will be identical to those who currently receive a TPO-RA. Since eltrombopag and romiplostim are the only TPO-RA treatments that represent established clinical management, they are the only relevant comparators in this appraisal. The proportions of therapies administered for each subsequent treatment was informed by market research that included 113 physicians across the EU, and included 20 physicians from the UK.	Section B1.1, p7 Section B3.2.3, p84

	subsequent therapies include a variety of treatment options. Fourth-line subsequent therapy adopts a "watch and wait" strategy.		
Natural History	Time to durable response on TPO-RA treatment was set to 24 weeks. Time to response for non-TPO-RA treatments ranged between 0-24 weeks. Platelet response on any TPO-RA was assumed to be discontinued at a rate of 0.9% per cycle. Platelet response discontinuation rates on any non-TPO-RA ranged between 0.3%-51% per cycle. Treatment duration was set at 109 cycles for all TPO-RA treatments and ranged between 1-364 cycles for non-TPO-RA alternatives.	The 24-week response time for TPO-RA treatments was aligned to the follow-up of the trials included in the NMA (24-26 weeks). Response times for non-TPO-RA treatments are derived from the romiplostim NICE appraisal and other sources [32] Treatment times on TPO-RA was sourced from the lowest mean time on treatment found from fitting log-normal curves onto long-term eltrombopag and romiplostim data (109 cycles eltrombopag, 393 cycles romiplostim) [3]. Non-TPO-RA times on treatment were predominantly sourced from Provan et al (2010) management guidelines [1].	Section B3.3.1; p85-86 Section B3.3.6; p92
Treatment effectiveness	Response rates to TPO-RA treatments are informed via the company's NMA and are as follows: Avatrombopag: 73.16% Eltrombopag: 27.45% Romiplostim: 55.21% Response rates for non-TPO-RA treatments are taken from the eltrombopag appraisal [33]. The model includes three mechanism of benefits from improvements in treatment-effectiveness (response rate): (i) the probability of bleeding; (ii) probability of requiring rescue therapy; and (iv) the probability of requiring concomitant medication.	A NMA was necessary given that evidence comparing avatrombopag with all relevant comparators is not available. Clinical rationale for responding patients to benefit from reductions in the risk of bleeding events, the need for rescue therapies and concomitant medications relative to non-responding patients.	Section B2.8; p43 Section B3.3.1; p 86-87 Section B3.3.6; p92
Adverse events	Treatment associated AEs are differentiated into serious AEs and other AEs. It was assumed all TPO-RAs shared the same risk of serious and other adverse events. Bleeding events are modelled separately. Treatment-specific utility decrements from AEs (serious and other) are applied in the model for one cycle. Bleeds are categorised into minor, outpatient and inpatient events, with inpatient bleeds subdivided into intracranial	The differentiation of bleeding events was consistent with the eltrombopag and romiplostim NICE appraisals [32, 33]. AE rates and non-minor bleeding event rates for each treatment are aligned with the eltrombopag NICE appraisal. Minor bleed rates are aligned to Study 302. Treatment-specific AE utility decrement values are derived from the romiplostim NICE appraisal [32]. The composition of the rescue therapy treatment schedule was	Section B3.3.3.2; p87-88 Section B3.3.3.3; p88-89 Section B3.3.3.4; p89-90 Section B3.3.5; p91

	haemorrhage, gastrointestinal and other serious bleeds. The probability that a patient would require rescue therapy was dependeant on response status. A proportion of rescue therapies were assumed to occur as a result of a bleed.	broadly aligned with the eltrombopag NICE appraisal [33]. The response rates for patients undergoing rescue therapy were based on the chronic liver disease avatrombopag indication submission for platelet use and the eltrombopag NICE appraisal for the other therapies [33].	
Mortality	The model includes 2 separate causes of mortality: all-cause and disease-related/ITP mortality. Separate causes were aligned to general population mortality, disease-related mortality was modelled according to hospitalisations for severe bleeds.	All-cause mortality taken from ONS life tables for average Study 302 age and sex characteristics [51]. Mortality risk from each inpatient bleed type (see adverse events) sourced from Danese et al. (2009) and align to the eltrombopag NICE appraisal [33, 41].	Section B3.3.4; p89-90
Health-related quality of life	Health-related quality of life of patients in the model was dependant on responder status and adverse events (treatment-related and bleeds).	Health related quality of life utility values used in the model were generated using UK general population norm values for average age and sex characteristics, with disutilities for non-response, minor bleed and outpatient bleed applied from a multivariate TOBIT model (using Study 302 EQ-5D data). Disutilities from serious bleeds were sourced from the eltrombopag NICE appraisal [33]. The justification for the company's estimation of utility decrements was to derive HRQoL values from the pivotal avatrombopag Study 302 wherever possible [as recommended in the NICE reference case [29]].	Section B3.4.5; p96-98
Resource utilisation and costs	Resource utilisation and costs in the model related to: treatment acquisition; treatment administration; monitoring; and bleeding. Treatment acquisition costs related to modelled time on treatment and dosages sourced from summary of product characteristics (avatrombopag, eltrombopag), trial data (romiplostim) and guidelines [1, 34, 52, 53]. Romiplostim incurred administration costs equivalent to four weekly clinic attendances in the first model cycle, and 27.7% of those	The company justified avatrombopag and eltrombopag having no administration costs on the basis that both are oral treatments which patients can administer independently at home. Routine follow-up schedule was aligned with the eltrombopag NICE appraisal and sourced relevant unit costs from the NHS schedule of reference costs [31]. Resource and cost requirements associated with each bleeding type have been informed by qualitative research commissioned by the company.	Section B3.5.1; p98-100 Section B3.5.2; p100-103

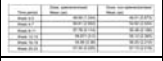
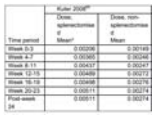
	thereafter. No administration costs were applied for avatrombopag and eltrombopag. Intravenous rescue therapies, Anti-D injections and platelet transplants also incurred administration costs. Patients were assumed to receive regular haematologist consultations, laboratory tests, full blood count and biochemistry assessments (i.e. routine monitoring). Resource and cost implications for each bleeding type was applied in the company model. Minor bleeds were assumed to be self-treated and have no associated costs.		
Discount rates	3.5% discount rate.	NICE Methods Guide	Section 5.2; p165-166
Population and Subgroups	No formal subgroups were presented.	"Subgroup analyses of patients with prior rituximab and splenectomy treatment were not appropriate for this appraisal owing to highly varied use of rituximab by treatment centre and clinical opinion increasingly positioning splenectomy as a later-line treatment once medical interventions are exhausted, respectively."	Section B.1.1; p7
Sensitivity analysis	Deterministic sensitivity analysis was performed on a series of model parameters. Probabilistic sensitivity analysis and scenario analyses were also performed.	NICE reference case [29]	Section B.3.8; p117-126

Table 58: Company base case model input comparison used in appraisals for avatrombopag, eltrombopag [TA 293] and romiplostim [TA 221]

	Avatrombopag [ID3838]		Eltrombopag [TA293] [previously: TA 205]			Romiplostim [TA 221]		
	Base case values	Source	Base case values		Source	Base case values		Source
Patient characteristics								
Age (years)	44.6	Study 302	47.97		RAISE trial	52.2		Kuter 2008 (trial)
Male (%)	37%	Study 302	31%		RAISE trial	35%		Kuter 2008 (trial)
Weight (kg)	82.97	Study 302	74.22		RAISE trial	83.7		Assumption
Body area (m^2)	1.94	Study 302	1.82		RAISE trial	2		Assumption
Post-splenectomy (%)	32.7	Study 302	37 (n.b. results by status)		RAISE trial	Results stratified by status		
Comparators	Eltrombopag, romplostim		Eltrombopag, romplostim, SOC			Romiplostim, SOC		
Response	Durable response		Initial response			Initial response		Systematic review conducted by Amgen for non-romiplostim rates of initial platelet response
Treatment response rates	(24-26 week response)		Non-splenectomised	Splenectomised		Non-splenectomised	Splenectomised	
Avatrombopag	73.16%	Company NMA	N/A	N/A		N/A	N/A	
Eltrombopag	27.45%	Company NMA	76%	80%	RAISE: ≤400 & ≥50x10^9 once during 6-month period	N/A	N/A	
Romiplostim	55.21%	Company NMA	76%	80%	Assumed to be equal to eltrombopag	87.8%	78.6%	Romiplostim phase 3 trials (Kuter 2008)
Rituximab	58.00%	[TA 205]	57.7%	57.7%	[TA221]	57.7%	-	Arnold 2007, Zhou 2008 (average)
Splenectomy	85.00%	Report: [TA 205] Model: Cuker et al (2018)	-	-		-	-	
Watch and rescue	0.00%	[TA 205]	-	-		-	-	

Azathioprine	54.24%	[TA 205]	50.0%	62.8%	[TA221]	50.0%	62.8%	Vianelli 2001, Vesely 2004, Vianelli 2001, Bouroncle 1969
Mycophenolate mofetil	52.76%	[TA 205]	56.52%	44.0%	[TA221]	56.52%	44.0%	Kotb 2005, Hou 2003, Provan 2006
Cyclosporine	54.24%	[TA 205]	50.0%	63.2%	[TA221]	50.0%	63.2%	Kappers-Klunne 2001 Vesely 2004, Zver 2006, Peng 2003
Danazol	49.90%	[TA 205]	45.3%	60.0%	[TA221]	45.3%	60.0%	Maloisel 2004, Vesely 2004
Dapsone	49.02%	[TA 205]	50.0%	46.7%	[TA221]	50.0%	46.7%	Damodar 2005, Godeau 1997, Hernandez 1995, Vesely 2004
Cyclophosphamide	67.06%	[TA 205]	70.0%	61.4%	[TA221]	70.0%	61.4%	ASH guidelines (George 1996), Vesely 2004
Vincristine	62.43%	[TA 205]	67.0% (vinca alkaloids)	53.4% (vinca alkaloids)	[TA221]	67.0% (vinca alkaloids)	53.4% (vinca alkaloids)	ASH guidelines (George 1996), Vesely 2004
Vinblastine	62.43%	[TA 205]			[TA221]			
Rescue therapy response rates			Non-splenectomised	Splenectomised		Non-splenectomised	Splenectomised	
IV immunoglobin (IVIg)	80.35%	[TA 205] (report) [TA 221] (model)	80.5%	78.6%	[TA 221] Estimates from a GSK systematic review and quantitative analysis also available.	80.5%	78.6%	Various IVIg papers
IV steroids	46.00%		46.0%	46.0%		46.0%	46.0%	Unsal 2004, Scaradavou 1997
Anti-D	30.98%		46.0%	0%		46.0%	0%	Assumed same as Anti-D
Dapsone	49.02%	Assumed	-	-		-	-	Not included.
Platelet transfusion	52.00%	ADAPT trials 1 & 2	-	-		-	-	Not included.
Time to respond								
Avatrombopag	24 weeks (6 cycles)	Criteria used in NMA	-			N/A		
Eltrombopag	24 weeks (6 cycles)	Criteria used in NMA	4 weeks (1 cycle)		RAISE (15 days~1 cycle)	N/A		

Romiplostim	24 weeks (6 cycles)			Criteria used in NMA	4 weeks (1 cycle)	Kuter trials (28 days)	4 weeks (1 cycle)	Romiplostim phase 3 trials
Rituximab	8 weeks (2 cycles)			[TA 221]	8 weeks (2 cycles)	[TA 221] –(assumed equal between splenectomised groups) Estimates from a GSK systematic review and quantitative analysis also available.	8 weeks (2 cycles)	Arnold (2007)
Splenectomy	4 weeks (1 cycle)				N/A		N/A	
Azathioprine	16 weeks (4 cycles)				16 weeks (4 cycles)		16 weeks (4 cycles)	Quiquandon 1990
Mycophenolate mofetil	16 weeks (4 cycles)				16 weeks (4 cycles)		16 weeks (4 cycles)	Kotb 2005, Hou 200
Cyclosporine	8 weeks (2 cycles)				8 weeks (2 cycles)		8 weeks (2 cycles)	Emilia 2002
Danazol	16 weeks (4 cycles)				16 weeks (4 cycles)		16 weeks (4 cycles)	Maloisel 200
Dapsone	4 weeks (1 cycle)				4 weeks (1 cycle)		4 weeks (1 cycle)	Godeau 1997
Cyclophosphamide	8 weeks (2 cycles)				8 weeks (2 cycles)		8 weeks (2 cycles)	Cines & Bussel 2005
Vincristine	4 weeks (1 cycle)				4 weeks (1 cycle)		4 weeks (1 cycle)	ASH guidelines (George 1996)
Vinblastine	4 weeks (1 cycle)				4 weeks (1 cycle)		4 weeks (1 cycle)	ASH guidelines (George 1996)
Rescue therapy (IVIg/IV steroids/anti-D/dapsone/platelet transfusion)	0 weeks				0 weeks		0 weeks	Bierling & Godeau 2004, ASH guidelines (George 1996)
Subsequent therapies	2nd	3rd	4th	L.E.K consulting (2020) - Market research on current ITP treatments (n=113 physicians; UK: n=20)				
Eltrombopag	0.00%	0.00%	0.00%		-	[TA221] – with some adjustments Informing subsequent treatments following TPO-RA and standard of care comparator. Rituximab assumed to come prior to TPO-RA in treatment sequencing.	-	Following rosiplostim and the standard of care arm. Amgen UK physician review
Romiplostim	12.50%	19.54%	0.00%		-		N/A	
Rituximab	20.45%	12.64%	0.00%		100% (prior to decision problem)		100% (following romiplostim)	
Splenectomy	10.23%	10.34%	0.00%		-		-	
Watch and rescue	0.00%	0.00%	0.00%		-		-	
Azathioprine	0.00%	0.00%	0.00%		59% (following TPO-RA)		59% (following rituximab)	
Mycophenolate mofetil	34.09%	41.38%	100.00%		37% (following azathioprine)		37% (following rituximab)	
Cyclosporine	2.84%	2.01%	0.00%		4% (following mycophenolate mofetil)		4% (following rituximab)	
Danazol	2.84%	2.01%	0.00%		7% (following cyclosporine)		48% (following immunosuppressants)	

Dapsone	2.84%	2.01%	0.00%		48% (following danazole)		7% (following danazol)	
Cyclophosphamide	2.84%	2.01%	0.00%		0% (following danazole)		2% (following dapsone)	
Vincristine	2.84%	2.01%	0.00%		5% (following cyclophosphamide)		5% (vinca alkaloids)	
Vinblastine	2.84%	2.01%	0.00%		5% (following vincristine)			
Concomitant therapies								
Danazol	5%			Study 302	Not reported or conducted		N/A	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 x 109 /l and received rescue therapy whenever they experienced a bleed that resulted in hospitalisation.
Azathioprine	9%							
Ciclosporin	5%							
Etamsilate	5%							
Dexamethasone	27%							
Phrednisolone	27%							
Treatment dosages								
Active treatment	Dose	Duration (pre response)		Dose	Duration (pre response)			
Avatrombopag	20mg	Daily: 24 weeks	SmPC				N/A	
Eltrombopag	20mg	Daily: 24 weeks	SmPC		Daily	RAISE trial analysis	N/A	
Romiplostim	0.004 mg/kg	Weekly: 24 weeks	Kuter et al (2010)		Weekly	Analysis of Kuter et al (2010)		
Rituximab	375 mg/m^2	Weekly: 4 weeks	Provan et al (2010)	375 mg/m^2	Weekly: 4 weeks	Provan et al (2010)	Not reported.	Treatment doses for comparators were taken from the British National Formulary (BNF)
Azathioprine	1.5 mg/kg	Daily: 4 weeks		1.5 mg/kg	Daily: 4 weeks	TA [221]		
Mycophenolate mofetil	1000mg/kg	x2 daily: 3.5 weeks		1000mg/kg	x2 daily: 3.5 weeks	Provan et al (2010)		
Cyclosporine	5mg/kg	Daily: 4 weeks		5mg/kg	Daily: 4 weeks	TA [221]		
Danazol	200mg	x4 daily: 4 weeks		200mg	x4 daily: 4 weeks			
Dapsone	87.5mg	Daily: 4 weeks		87.5mg	Daily: 4 weeks			
Cyclophosphamide	1.5mg/kg	Daily: 4 weeks		1.5mg/kg	Daily: 4 weeks			

Vincristine	1.5mg	Weekly: 4 weeks		1.5mg	Weekly: 4 weeks	Provan et al (2010)			
Vinblastine	10mg	Weekly: 3 weeks		10mg	Weekly: 3 weeks				
Rescue therapy				Non-splenectomised	Splenectomised		Non-splenectomised	Splenectomised	
Rescue – IVIg	1000mg/kg	1.5 days	Provan et al (2010)	59% 1000mg/kg	64% 1000mg/kg	[TA 221] - Estimates from a GSK systematic review and quantitative analysis also available. (Note dosing for rescue IVIg and Anti- from Provan et al (2010))	59%	64%	Dosages and schedules not reported but sourced from romiplostim phase 3 trials
Rescue – IV steroid	1.25mg	3 days		16% 1.25mg	36% 1.25mg		16%	36%	
Rescue – Anti-D	0.006mg/kg	2 days		25% 0.00625mg/kg	0%		25%	0%	
Rescue – Dapsone	87.5mg	1 day	Assumed	N/A	N/A		N/A	N/A	
Rescue – Platelets transfusion	2	1 day	Assumed	0%	0%		0%	0%	
Concomitant therapies							Dosage	Duration	
Danazol	200mg	x4 daily: 4 weeks	[TA 221]	Not reported or conducted		N/A	200mg	x4 daily: 4 weeks	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 x 109 /l and received rescue therapy whenever they experienced a bleed that resulted in hospitalisation
Azathioprine	1.5 mg/kg	Daily: 4 weeks	[TA 221]				1.5 mg/kg	Daily: 4 weeks	
Ciclosporin	5mg/kg	Daily: 4 weeks	[TA 221]				5mg/kg	Daily: 4 weeks	
Etamsilate	1500mg	Daily: 15 days	"Drug information"				-	-	
Dexamethasone	40	Daily: 3 weeks	Provan et al (2010)				-	-	
Phrednisolone	1.25	Daily: 3 weeks					-	-	
Prednisone	1.25	Daily: 3 weeks					-	-	
Event probabilities									
Time in response				Non-splenectomised	Splenectomised		Non-splenectomised	Splenectomised	

Avatrombopag	108.59 cycles (~434 weeks)		Log-normal curves onto data from Lee et al (2013)	N/A	N/A		N/A	N/A	
Eltrombopag				NR	NR	RAISE/EXTEND	N/A	N/A	
Romiplostim				NR	NR	Assumed equal to eltrombopag	Confidential	Confidential	
Splenectomy	364.48 cycles (~1458 weeks)		Cuker (2018)	-		TA 221] – Estimates from a GSK systematic review and quantitative analysis also available.	-		
Rituximab	18.9 cycles (~ 76 weeks)_		CS: [TA 221] Model: [TA 205]	575 days	575 days		18.9 cycles		
Watch and rescue	0			-	-		-		
Azathioprine	20.3 cycles (82 weeks)			618 days	618 days		20.3 cycles	20.3 cycles	Quiquandon 1990
Mycophenolate mofetil	5.7 cycles (23 weeks)			173 days	173 days		5.7 cycles	5.7 cycles	Hou 2003
Cyclosporine	16.2 cycles (64.8 weeks)			393 days	493 days		16.2 cycles	12.91 cycles	Kappers-Klunne 2001
Danazol	147.35 cycles (590 weeks)			4,426 days	4,485 days		147.35 cycles	145.4 cycles	Various danazol paper
Dapsone	20.3 cycles (81.2 weeks)			618 days	618 days		20.3 cycles	20.3 cycles	Godeau 1997
Cyclophosphamide	27 cycles (108 weeks)			822 days	822 days		27.0 cycles	27.0 cycles	ASH guidelines (George 1996)
Vincristine	1.4 cycles (6 weeks)			43 days	43 days		1.4 cycles	1.4 cycles	ASH guidelines (George 1996)
Vinblastine	1.4 cycles (6 weeks)			43 days	43 days		1.4 cycles	1.4 cycles	ASH guidelines (George 1996)
Bleeds	≥50x10^9/L	<50x10^9/L		≥50x10^9/L	<50x10^9/L		≥50x10^9/L	<50x10^9/L	
Minor bleed	10.0%	17.1%	[TA 205]			[TA221] Estimates from a GSK systematic review and quantitative analysis also available.			Rates and types of bleeding and number of doses of rescue medication for patients under or over 50 x 10^9/l were taken from the
Outpatient bleed	7.1%	45.5%		7.1%	45.5%		7.1%	45.5%	
Inpatient bleed	0.0%	4.3%		0.0%	4.3%		0.0%	4.3%	
Intracranial haemorrhage	0%	19%		0%	19%		0%	19%	
Gastrointestinal	29%	19%		29%	19%		29%	19%	
Other bleed	71%	63%		71%	63%		71%	63%	

									romiplostim phase 3 trials.
Rescue therapy									
Probability of rescue therapy				Non-splenectomised	Splenectomised		Non-splenectomised	Splenectomised	
Responder (≥50x10^9/L)	3.0%		[TA 205]	0%	0%	[TA 221]	0%	0%	Rates and types of bleeding and number of doses of rescue medication for patients under or over 50 x 10^9/l were taken from the romiplostim phase 3 trials.
Non-responder (<50x10^9/L)	22.0%			33%	68%		33%	68%	
Bleed-related	55.6%			-	-		-	-	
Non-bleed	44.4%			-	-		-	-	
Event states:				-	-		-	-	
Responder bleed	1.67%			-	-		-	-	
Responder non-bleed	1.33%			-	-		-	-	
Non-responder bleed	12.22%			-	-		-	-	
Non-responder non-bleed	9.80%			-	-		-	-	
Concomitant medication									
Prob in non-response state	44.9%		Study 302	Not reported or conducted		N/A	Not reported or conducted		N/A
Prob in response state	35.9%		Study 302						
% get a dose reduction | response	16.25% (5.8% total)		Study 302						
% no dose reduction | response	83.75% (30.1% total)		Study 302						
Adverse events	Serious	Other		Serious	Other		Serious	Other	
Avatrombopag	3%	31%	[TA 205]	3%	31%	[TA 221]	N/A	N/A	
Eltrombopag	3%	31%		3%	31%		N/A	N/A	
Romiplostim	3%	31%		3%	31%		3%	31%	Kuter 2008
Rituximab	3%	31%		3%	31%		3.3%	0%	Arnold 2007
Splenectomy	3%	0%		3%	0%		N/A	N/A	
Watch and rescue	15%	24%		15%	24%		N/A	N/A	

Azathioprine	15%	24%		15%	24%		15%	12-36%	Sternthal 2008, Provan 2006, Kappers-Klunne 2001, Zwerner 2007
Mycophenolate mofetil	15%	24%		15%	24%				
Cyclosporine	15%	24%		15%	24%				
Danazol	16%	35%		16%	35%		16%	35%	Maloisel 2004
Dapsone	11%	24%		11%	24%		11%	24%	Godeau 1997, Damodar 2005, Hernandez 1995
Cyclophosphamide	21%	30%		21%	30%		21%	30%	Schiavotto 1993, Facon 1994
Vincristine	21%	30%		21%	30%				
Vinblastine	21%	30%		21%	30%				
Rescue – IVIg	2%	0%		2%	0%		2.1%	0%	Gamunex prescribing information, ASH guidelines
Rescue – IV steroid	3%	70%		3%	70%		3%	70%	NR
Rescue – Anti-D	3%	0%		3%	0%		2.8%	0%	Scaradavou 1997, Aledort 2007
Rescue – Dapsone	11%	24%		11%	24%		11%	24%	Godeau 1997, Damodar 2005, Hernandez 1995
Rescue – Platelets transfusion	0%	0%		0%	0%	Assumption	0%	0%	
HRQoL									
Bleeds	≥50x10^9/L	<50x10^9/L		≥50x10^9/L	<50x10^9/L		≥50x10^9/L	<50x10^9/L	
No bleed	0.800793265	0.760123265	TOBIT model estimates - EQ5D data collected in Study 302	0.86	0.84	Szende (2010)	0.91	0.89	Amgen UK ITP TTO utility study
Minor bleed	0.755833265	0.715163265		0.73	0.73		0.91	0.89	
Outpatient bleed	0.624993265	0.584323265					0.81	0.77	

Intracranial hemorrhage	0.038	0.038	[TA 205]	0.038	0.038		N/A	0.28	
Gastrointestinal bleed	0.45	0.45		0.45	0.45		N/A	0.54	
Other inpatient bleed	0.45	0.45		0.45	0.45		N/A	0.54	
Treatment-related AEs	Serious	Other		Serious	Other		Serious	Other	
Avatrombopag	0.1 (1 cycle)	0.1 (1 cycle)	CS: TA 205 Model: [TA 221]: TPO-RA disutility 0.1 from TA 221 Serious AE disutility values 0.4 TA 221. Rescue therapy disutility of 0.1 assumed (aligns with both previous apparsials).	N/A		[TA 221]	N/A	N/A	"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"
Eltrombopag				0.1 (1 cycle)	0.1 (1 cycle)		N/A	N/A	
Romiplostim							0.1 (1 cycle)	0.1 (1 cycle)	
Rituximab									
Watch and rescue	0 (1 cycle)	0		N/A			N/A		
Splenectomy	0.4 (1 cycle)	0.1 (1 cycle)		N/A			N/A		
Azathioprine				0.4 (1 cycle)	0.1 (1 cycle)		0.4 (1 cycle)	0.1 (1 cycle)	
Mycophenolate mofetil									
Cyclosporine									
Danazol									
Dapsone									
Cyclophosphamide									
Vincristine									
Vinblastine									
Rescue – IVIg	0.1 (1 cycle)			0.1 (1 cycle)			0.1 (1 cycle)		
Rescue – IV steroid									
Rescue – Anti-D									
Rescue – Dapsone									
Rescue – Platelets transfusion									
Mortality									
All-cause mortality	Not reported here.		Life tables (2018-19) from the ONS	Not reported here.		Interim life tables (2007-2009) from the ONS	Not reported here.		UK government actuary department 2006 life tables
Bleeds									
Intracranial haemorrhage	13.2%		Danese (2009)	13.2%		Danese (2009)	Confidential		Confidential
Gastrointestinal bleed	4.6%			4.6%			Confidential		Confidential

Other bleed	1.7%			1.7%		Confidential	Confidential
Costs							
Drugs (exc. PASS)	Pack	Per mg					
Avatrombopag 30 x 20mg	£1920	£2.00	List price			N/A	N/A
Eltrombopag 28 x 50mg	£1540	£1.10	NICE British National Formulary	£1540 (equivalent)	NICE British National Formulary	N/A	N/A
Romiplostim 0.125mg	£241	£1928.00		£241 (equivalent)		£1.93 / mcg (£1,793.04 4-weeks)	
Rituximab 200mg	£314.43	£1.58		£349.26 (equivalent)		£6,300.90 (cycle cost)	NICE British National Formulary + NHS reference costs
Azathioprine 2800mg	£2.57	£0.001		£10.08 (equivalent)		£274.29 (cycle cost)	
Mycophenolate mofetil 25000mg	£6.16	£0.0003		£35.00		£408.71 (cycle cost)	
Cyclosporine 750mg	£18.37	£0.03		£13.80		£302.04 (cycle cost)	
Danazol 11200mg	£36.32	£0.003		£32.76		£287.88 (cycle cost)	
Dapsone 2800mg	£54.78	£0.02		£54.56		£488.12 (cycle cost)	
Cyclophosphamide 5000mg	£139	£0.03		£20.20		£682.16 (cycle cost)	
Vincristine 1mg	£13.47	£13.47		£13.47		£1,082.16 (cycle cost)	
Vinblastine 50mg	£85	£1.70		£65.45		£1,082.16 (cycle cost)	
Rescue – IVIg 1000mg	£50	£0.05		£45		£7,112.74 (cycle cost)	
Rescue – IV steroid 1200mg	£88.81	£0.08		£275.04		£651.90 (cycle cost)	
Rescue – Anti-D 0.3mg	£46.50	£155		£46.50		£5,666.66 (cycle cost)	
Concomitant – Ciclosporin 750mg	£18.37	£0.03		N/A		N/A	
Concomitant – Etamsilate 500mg	£9	£0.02	LloydsPharmacy	N/A		N/A	
Concomitant – Dexamethasone 100mg	£49	£0.49	NICE British National Formulary	N/A		N/A	
Concomitant – Phrednisolone 140mg	£2.41	£0.02		N/A		N/A	
Concomitant – Prednisone 140mg	£2.41	£0.02	Assumed	N/A		N/A	
Administration costs	Cost	Resource		Cost	Resource		
Romiplostim (inpatient administration)	£241.06	SB12Z (chemo 1st visit)	NHS reference cost 2018/19	£204.81	SB12Z (chemo 1st visit)	NHS reference cost 2018/19	Included in cost per cycle (see above)

Romipsotim (home administration)	£0	-		£0	-		[TA626] – MTA		
Initial administration in first model cycle	£964.23	4 clinic visits		£964.23	3 clinic visits				
Long-term administration in next cycles	£267.09	27.7% in clinic per dose	ASH congress abstract 2010 / TA [205]	£226.93	27.7% in clinic per dose	ASH congress abstract 2010			
Vincristine	£241.06	SB12Z (chemo 1st visit)	NHS reference cost 2018/19	£241.06	SB12Z (chemo 1st visit)	NHS reference cost 2018/19			
Vinblastine	£241.06	SB12Z (chemo 1st visit)	NHS reference cost 2018/19	£241.06	SB12Z (chemo 1st visit)	NHS reference cost 2018/19			
Rituximab	£370.68	SB14Z (complex 1st chemo)	NHS reference cost 2018/19	£330.59	SB14Z (complex 1st chemo)	NHS reference cost 2018/19			
Splenectomy	£2750	Private cost	Valereferrals Pricing Guide	-	-	-			
Rescue – IVIg	£195.66	SA45A (injection immune globulin/other)	NHS reference cost 2018/19	£1,235.34	XD34Z (Immunoglobulins band 1)	NHS reference cost 2018/19			
Rescue – IV steroid	£370.68	SB14Z (complex 1st chemo)	NHS reference cost 2018/19	£330.59	SB14Z (complex 1st chemo)	NHS reference cost 2018/19			
Rescue – Anti-D	£195.66	SA45A (injection immune globulin/other)	NHS reference cost 2018/19	£1,235.34	XD34Z (Immunoglobulins band 1)	NHS reference cost 2018/19			
Rescue – Platelets transfusion	£889.66		[TA626] – MTA	£518.51	Code 821 (blood transfusion) + x2 platlet units (£230.393)				
Monitoring costs	Cost	Resource		Cost	Resource		Cost	Resource	
Haematologist consultation	£173.39	1 per month	Costs - NHS reference cost 2018/19 Resource - [TA 205]	£147.53	1 per month	Resource - Assumed Costs - NHS reference cost	£112	2 per month	Resource - trial protocol
Blood test	£2.79	1 per month		£3.00	1 per month		£12 (lab test)	4 per month	Resource - trial protocol
Biochemistry	£1.10	1 per month		£1.00	1 per month			4 per month	
Total cost per 28-day cycle	£163.64	Total		£163.64	Total		£272	Total	

Bleed costs						
Minor bleed	£0.00	Assumed self-treated			£0.00	
Outpatient bleed	£3,134.35 (with rescue) £1,597.00 (without rescue)	L.E.K Consulting on resource utilisation (CS - Table 63) Unit costs (CS – Table 64)	£302.81		£220.00	
Intracranial haemorrhage	£25,698.84 (with rescue) £13,571.33 (without rescue)		£3,451	weighted average over HRG codes AA23A and AA23B	£3,680.00	NHS Reference Costs (cost of HRG A19)
Gastrointestinal	£14,325.35 (with rescue) £4,423.16 (without rescue)		£1,553	Inpatient £1,553 (weighted average over HRG codes FZ38D, FZ38E and FZ38F)	£1,395.00	NHS Reference Costs (cost of HRG F62)
Other bleed	£14,325.35 (with rescue) £4,423.16 (without rescue)		£1,553	HRG code FZ38	£1,718.00	NHS Reference Costs (cost of inpatient bleeding event)
Death due to bleed	£0.00		£0.00	No cost assumed	£0.00	No cost assumed

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Avatrombopag in combination for treating chronic immune thrombocytopenia [ID3838]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 1 December 2021** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 ITC adjusted analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 53 it states: "These continuity adjustments were done externally to the evidence synthesis and, despite the ERG request, at points for clarification, for further details on all adjustments performed to the data used in the ITCs, no explanation was provided to clarify how or why these adjustment values were obtained. The ERG was unable to verify the source, calculus and appropriateness of the continuity adjustments calculated and used by the company."	Removal of the highlighted text on page 53	The information requested was provided to the ERG in response to clarification questions (November 2021).	Not a factual inaccuracy. The ERG was not provided with an explanation for the continuity adjustments for zero cells performed by the company to the ITC data neither in the original submission nor in response to clarification questions.

Issue 2: ERG ITC analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 59 it states:	Sobi believes this statement to be	The ERG conducted their own analysis with traditional continuity correction by	The ERG acknowledges that there is an inherent bias in both the

“The ERG considers that adjustments made by the company will introduce bias favouring the active treatments involved: avatrombopag and romiplostim.”	incorrect.	adding 0.5 to nominators and 1 to denominators. As described by Sweeting et al. 2004 (Stat Med 2004 ;23(9):1351-75. doi:10.1002/sim.1761.), this is the correct approach when the study arms are equal but causes bias in case of 1:2 randomisation. This is because a higher chance of event is assigned to the smaller arm (in this case placebo). As a result, the ERG’s proposed analyses produce point estimates less favourable for AVA and ROM.	company's approach to continuity correction (approximately 0.6 added to the active arm and 0.3 added to the placebo arm) and the ERG’s approach (adding 0.5 to both arms). The ERG considers that both approaches favour the active treatments (avatrombopag in study 302 and romiplostim in Kuter 2008 SPL, respectively). Whilst acknowledging that both approaches introduce bias, the company's chosen continuity correction values provide more favourable ORs to avatrombopag and romiplostim than the ERG approach of adding 0.5. The ERG report has been amended to further clarify this.

Issue 3: Systematic literature searches (economic)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
On page 69 it states: “The ERG considers that the searches undertaken by the company were not as thorough as would be expected for a	Sobi believes this statement to be incorrect.	The searches combined different filters which have been used in previous systematic reviews in this area. Furthermore, the reference lists of	The combining of individual economic evaluation search filters may have increased the sensitivity of the search but only if all terms from each search filter were included. As individual search filters

systematic literature review. In particular, the search filter used to limit the searches to economic evaluations was quite restrictive. The search filter was not referenced; therefore, it was unclear if the filter had been designed and tested for use in highly sensitive search strategies of the type needed for systematic reviews. In addition, the sources searched for unpublished studies were fairly limited, which may have resulted in missed studies."		identified studies were screened to identify any additional studies not captured in the initial searches.	were not referenced in the submission, and only collections of search filters referred to in the response to the points for clarification (ISSG, Cochrane, CADTH), it was not possible for the ERG to check the individual filters used. However, the searches presented in Appendix G of the company submission do not appear to have used a validated search filter or to have included all possible relevant terms for economic evaluations, therefore studies could potentially have been missed. Previously validated search filters to limit retrieval to economic evaluations, such as those developed for the NHS Economic Evaluations Database or those developed by CADTH, would have ensured a more comprehensive search. Both of these filters have been found to identify economic evaluations with a sensitivity of above 90% in MEDLINE and Embase, therefore are suitable for use in a systematic review where it is important to identify all relevant studies. The further checking of references of all included studies reported here may have helped to identify additional relevant studies, however this search method was not

			reported in Appendix G of the company submission or in the company response to the points for clarification.

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
Limited commercially sensitive details related to Study 305 which are not in the public domain have not been redacted as CIC, specifically: • page 15 (Section 1.4 issue 2) page 37 (Section 3.2.1 Study 305)	• CIC redactions have been added to the following passages: **p 15:** (…) *"Study 305 of avatrombopag vs eltrombopag was terminated early due to significant enrolment challenges ([redacted]). The study aimed to recruit [redacted] patients but only [redacted] were randomised when the trial was terminated."* **p 37:** (…) "*Also, protocol amendments included criteria mandating that subjects undergo ([redacted]). The study aimed to recruit [redacted] patients but only [redacted] had been randomised when the*	Details disclosed are commercially sensitive and the relate to a pre-clinical safety finding from rodent disease models. The safety issue was later determined to not be clinically significant in humans.	The CIC markings have been added to the ERG report.

	trial was terminated (one patient was randomised in error and did not receive any study treatment."		
"The ERG base-case ICER is £457,592/QALY for romiplostim compared to avatrombopag. Eltrombopag is dominated when compared to avatrombopag (i.e., higher costs and lower QALYs)" • Page 124	• CIC redactions have been added to the following passages: "The ERG base-case ICER is [redacted] for romiplostim compared to avatrombopag. Eltrombopag is dominated when compared to avatrombopag (i.e., higher costs and lower QALYs).	-	The CIC marking has been added to the ERG report.

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Technical engagement response form

Avatrombopag in combination for treating chronic immune thrombocytopenia [ID3838] As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by the end of **6 April 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Swedish Orphan Biovitrum ('Sobi')
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Sobi has no had no links to, or funding from, the tobacco industry.

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?
Issue 1: The treatment pathway and positioning of avatrombopag relative to rituximab is unclear	Yes, clinician survey on real-world treatment patterns and utilisation in chronic ITP.
Response: Issue 1	
As outlined in the company's core submission (Section B.1.3), TPO-RAs are the current standard of care in England and Wales for patients with ITP who require long-term treatment following initial corticosteroid treatment, and use of rituximab is highly variable between treating physicians, centres and lines of therapy. Rituximab is used as an off-label treatment in patients with ITP and tends to be only used after TPO-RAs. This view is supported by the recent assessment of a NICE committee [TA759] which concluded that rituximab is a treatment option for refractory chronic ITP after TPO-RAs, or if they are not suitable. Avatrombopag will be available as an additional TPO-RA option to other	

NICE-approved therapies, eltrombopag and romiplostim, which have an established position in the ITP treatment pathway relative to rituximab.

Additionally, the company gathered data from 9 expert ITP-treating clinicians who indicated that avatrombopag, if NICE-approved, would be used in the same context as current NICE-approved TPO-RAs (7/9 of respondents agreed, 1 indicated it would 'be part of an individualised patient discussion' and another was 'unable to comment'). Only a small fraction of patients are reportedly receiving alternative options such as rituximab, where use is decreasing in the context of the COVID-19 pandemic. Rituximab was not highlighted by the expert clinicians surveyed to be sequenced equivalently to avatrombopag and other TPO-RAs in the ITP treatment paradigm [1]. These findings are consistent with a recent real-world study of 327 adult ITP patients treated in the UK – broadly representative of the local ITP population – where a majority of patients received TPO-RAs prior to rituximab in the context of the COVID-19 pandemic [2]. The findings also align with the recommendations by the UK ITP Forum on the use of immunosuppressive agents (including rituximab) after TPO-RAs in the context of the COVID-19 pandemic [3].

The company is therefore of the view that, if approved by NICE, avatrombopag will only be considered by clinicians for patients who are already expected to receive either eltrombopag or romiplostim. Avatrombopag is not intended nor expected to displace or otherwise influence the use of non-TPO-RA options (e.g., rituximab) for the treatment of chronic ITP. This is supported by expert clinical opinion obtained by Sobi throughout the development of the submission and response.

Key issue	**Does this response contain new evidence, data or analyses?**

Issue 2: The limited evidence-base for avatrombopag due to recruitment and attrition issues	No
Response: Issue 2	
The company acknowledges that there were challenges in collecting evidence for avatrombopag in a limited number of trials. However, the pivotal Phase III trial provides sufficient robust data to determine key efficacy and safety outcomes relevant to this appraisal. Study 305 was discontinued early due to enrolment challenges based on a preclinical signal which was later found not to affect humans. For this reason, it was not included in generating model results. Study 302 was a pivotal Phase III clinical trial of avatrombopag and is the only study with data appropriate to populate the economic model as it contains robust comparative data on key efficacy and safety outcomes. The company conducted a network meta-analysis (NMA) to provide an indirect comparison of effectiveness of avatrombopag and other TPO-RAs which showed that avatrombopag was at least similar to other TPO-RAs. This finding was consistent with exiting literature, previous NMAs and clinical opinion [4, 5].	
Key issue	**Does this response contain new evidence, data or analyses?**

Issue 3: Exclusion of some TPO-RA trials from the company NMA	Yes, additional NMA analyses with inclusion of previously excluded studies
Response: Issue 3	
Whilst rationale was originally provided in Appendix D.1.1.4 of the company's core submission for the exclusion of the seven TPO-RA comparator trials from the NMA, the company has provided updated NMA results to include these seven trials, as requested in the ERG report. A feasibility analysis revealed that the inclusion of previously excluded studies does not modify the results of the NMA regarding the odds for durable platelet response and odds for the reduction of concomitant therapy, since these outcomes were not assessed in those studies. Additional information was identified for four previously analysed outcomes including: • Need for rescue therapy (2 RCTs) • Any bleeding events (6 RCTs) • Bleeding events WHO 2–4 (1 RCT) • Any adverse events (4 RCTs)	

The estimates were extracted from the studies and the NMA was rerun for the outcomes listed above using previously described methodology.

As shown in full as additional evidence in the document 'Additional NMA analyses with inclusion of previous excluded studies', the results of the additional studies do not impact the cost-effectiveness results or alter the conclusion of the NMA submitted as part of the core submission.

Key issue	**Does this response contain new evidence, data or analyses?**
Issue 4: The company NMA estimates of comparative effectiveness between TPO-RAs	Yes, updated continuity correction analyses for NMA estimates

Response: Issue 4

We acknowledge that the ERG has concerns about the company's NMA for the primary efficacy outcome of durable platelet response used in the cost-effectiveness analysis. The company has sought to respond to each concern in turn and, where appropriate, has revised its base case analysis accordingly.

The company would also like to note that the discussion below serves to highlight the uncertainty associated with the indirect comparison between TPO-RAs. In clinical practice, they are likely to provide similar outcomes, although avatrombopag has the advantages of being an additional oral option, having increased dosing flexibility and lack of dietary restriction, which may improve

disease management and clinical outcomes [6]. This view is supported by recent findings from the European Thrombopoietin-Receptor Agonist Patient experience (TRAPeze) survey, which found that UK patients prioritised method of administration (odds ratio (OR) 5.6, 95% confidence interval (CI) 3.2–10.1) and drug-food interactions (OR 3.2, 95% CI 1.8–5.7) when indicating a treatment preference regarding TPO-RAs [6]. Consequently, treatment with avatrombopag over eltrombopag and romiplostim may incrementally improve patient quality of life, according to the authors [6].

1. *ERG concern: the NMA results for avatrombopag vs. placebo (common comparator) lack face validity with respect to the trial results from Study 302 (i.e., odds ratio reported from NMA for avatrombopag vs. placebo is 102.80 [95% CrI: 3.87 - 2,796,449] compared to the study-specific odds ratio of 18.72 [95% CI: 1.02 - 340]).*

The company questions the assertion that the company's reported NMA result lacks 'face validity' since we do not consider an odds ratio of 18.72 [95% CI: 1.02 - 340]) as a credible estimate of avatrombopag efficacy. The ERG report refers to an odds ratio of 18.72 as 'study-specific' (page 53, Table 12, Table 18), which we consider as not appropriate, and not supported by any analyses reported in Study 302. There were 11 and 0 events observed in AVA and PLB groups of Study 302 (n/N = 11/32 vs 0/17), which does not allow an OR calculation due to the division by zero. Therefore, 18.72 is an estimate of OR with the traditionally used 0.5 continuity correction. This approach is highly uncertain because it adds a greater chance to the smaller arm (i.e., placebo) and it is highly uncertain as to what would be the effect in the placebo arm if the study recruited a much larger number of patients.

The limitations of using 0.5 correction adopted by ERG are described by the Cochrane-Handbook section 16.9.2:

"Whilst the fixed correction meets the objective of avoiding computational errors, it usually has the undesirable effect of biasing study estimates towards no difference and overestimating variances of study estimates (consequently down-weighting inappropriately their contribution to the meta-analysis). Where the sizes of the study arms are unequal (which occurs more commonly in non-randomized studies than randomized trials), they will introduce a directional bias in the treatment effect. Alternative non-fixed zero-cell corrections have been explored by Sweeting et al., including a correction proportional to the reciprocal of the size of the contrasting study arm, which they found preferable to the fixed 0.5 correction when arm sizes were not balanced [7]."

To illustrate the problem highlighted by Sweeting *et al* in this case, the odds ratio of 18.72 was calculated with the assumption that the probability of response in the placebo group of Study 302 was 3% despite there being virtually no events observed (before correction: 0/17 => after correction 0.5/18 = 3%).

We emphasise that the 0.5 correction is termed 'standard' to reflect that the approach is most simple and frequently used. This approach is however not free from potential bias and therefore the estimates of odds ratio calculated with this method should not be considered as gold standard. To summarise, we would like to highlight that the value of 18.72 was calculated with strong assumptions and is likely biased since the correction was used for a study randomised with 1:2 ratio. Therefore:

- 18.72 should not be referred to as a 'study-specific' outcome.
- 18.72 should not be considered as an unbiased estimate of the odds ratio for the comparison AVA vs PLC. It is therefore inappropriate to use it for the validation of credibility of the results of indirect comparison as was done in the section 3.5.1.3 of the ERG report.

- A frequentist approach with 0.5 correction can only be considered as one of several sensitivity analyses to estimate the uncertainty of the true effect.

2. *ERG concern: the appropriateness of the continuity corrections used in the NMA to correct for the presence of zero events in study arms of the trials (Study 302 for avatrombopag and Kuter 2008 SPL for romiplostim* [8]*).*

We used zero correction proportional to the sample size of the respective group, which reduces the risk of directional bias since all studies with zero cells were randomised in a 1:2 ratio as proposed by Sweeting *et al.* 2004 [7].

As presented in Table i below, in all studies which required continuity correction, patients were allocated to respective arms in a 1:2 ratio, which indicates that 0.5 correction was not appropriate in this case. As described in the literature (Sweeting *et al.* 2004 [7], the method of 0.5 correction adopted by the ERG may be inappropriate for studies with unequal groups, since it introduces directional bias.

Table i. Continuity correction of studies

Study	**Binary outcomes**						
	Treatment	**Durable response**			**Reduction in the use of concomitant ITP medication**		
		Event rate (extracted) n / N (%)	**Event rate (used in ITC) n / N (%)**	**OR* (95% CI)**	**Event rate (extracted) n / N (%)**	**Event rate (used in ITC) n / N (%)**	**OR (95% CrI)**
Study 302	AVA	**11 / 32 (34.38)**	**11.604 / 32 (36.26)**	18.72	**5 / 15 (33.33)**	**5.577 / 15 (37.18)**	7.86 (0.38, 163.88)

	PLC	**0 / 17 (0.00)**	**0.321 / 17 (0.02)**	(1.02, 340.20)	**0 / 7 (0.00)**	**0.269 / 7 (0.04)**	
RAISE	ELT	Observed: 57 / 95 (60.00) ITT: 57 / 135 (42.22)	Observed: 57 / 95 (60.00) ITT: 57 / 135 (42.22)	Observed: 13.13 (4.34, 39.74) ITT: 10.60 (3.65, 30.81)	37 / 63 (58.73)	37 / 63 (58.7)	2.99 (1.25, 7.15)
	PLC	Observed: 4 / 39 (10.26) ITT: 4 / 62 (6.45)	Observed: 4 / 39 (10.26) ITT: 4 / 62 (6.45)		10 / 31 (32.25)	10 / 31 (32.3)	
Kuter 2008 SPL	ROM	**16 / 42 (38.10)**	**16.627 / 42 (39.59)**	26.77 (1.52, 472.10)	12 / 12 (100.00)	12 / 12 (100.00)	91.67 (3.28, 2,565.44)
	PLC	**0 / 21 (0.00)**	**0.313 / 21 (0.01)**		1 / 6 (16.67)	1 / 6 (16.67)	
Kuter 2008 non-SPL	ROM	25 / 41 (60.98)	25 / 41 (60.98)	31.25 (3.82, 255.70)	8 / 11 (72.72)	8 / 11 (72.72)	2.67 (0.48, 14.70)
	PLC	1 / 21 (4.76)	1 / 21 (4.76)		5 / 10 (50.00)	5 / 10 (50.00)	
FIT 1	FOS	**9 / 51 (17.65)**	**9.638 / 51 (18.90)**	11.40 (0.64, 204.19)	----------	----------	----------
	PLC	**0 / 25 (0.00)**	**0.313 / 25 (0.01)**		----------	----------	----------
FIT 2	FOS	9 / 50 (18.00)	9 / 50 (18.00)	5.05 (0.60, 42.34)	----------	----------	----------
	PLC	1 / 24 (4.17)	1 / 24 (4.17)		----------	----------	----------

Abbreviations: AVA, avatrombopag; ELT, eltrombopag; FOS, fostamatinib; PLC, placebo; ROM, romiplostim; CrI, credible interval; OR, odds ratio

3. *ERG concern: response outcomes for the pivotal study of eltrombopag (RAISE) were estimated for the observed population, whereas for all other studies included in the NMA the ITT population was used.*

The company submission was conducted based on best-available data reported in the respective trials, which resulted in the discrepancy highlighted.

Nevertheless, the comparison of the results of both analyses (as reported vs ITT) indicated that the company analysis was conservative and presented less favourable estimates than the analysis conducted by the ERG. Therefore, the company suggests this issue should not be considered a major concern for decision making.

4. *ERG concern: The appropriateness of the inclusion of fostamatinib trials in the NMA*

Fostamatinib studies were included in the network to help the estimation of between-study heterogeneity for the random-effect model.

The company would like to highlight that inclusion of fostamatinib trials had no impact on the results of the fixed-effect NMAs, which was confirmed by the ERG (star-like networks), and that the ERG agreed that fixed-effect models represent a better fit than random effect-models.

Since the ERG acknowledged that fostamatinib trials have no impact on fixed-effect NMAs, and that fixed-effect analyses are relevant, the company suggests this issue should not be considered a major concern for decision making.

5. ERG concern: Heterogeneity in placebo response rates across the trials included in the NMA.

The company appreciate that the ERG understands the problem arising from the low availability of scientific evidence:

"The placebo effect and differences in placebo responses identified may have contributed to high between-study heterogeneity, which can be a source of bias when comparing treatment effects. However, due to the sparse nature of the network, this between-study heterogeneity cannot be estimated. (Section 3.4.3)"

The company wish to highlight that 3 out of 6 studies reported zero events in their control arms (Table ii). Therefore, any attempts of adjustment for baseline risk would require additional assumptions and continuity corrections for calculation purposes leading to reduced credibility.

Table ii. Event rates reported in study control arms

Study	Treatment	Event rate n/N (%)
Study 302	PLC	0/17 (0.00%)
RAISE	PLC	4/39 (10.26%)
Kuter 2008 spl.	PLC	0/21 (0.00%)
Kuter 2008 non-spl.	PLC	1/21 (4.76%)
FIT 1	PLC	0/25 (0.00%)
FIT 2	PLC	1/24 (4.17%)

6. *ERG concern: the ERG has undertaken additional analyses to correct the issues identified in the company's NMA for the outcome of durable platelet response. These estimates suggest that romiplostim is expected to be the most effective treatment (odds ratio of 29.61 [95% CI: 5.42 - 161.58] for romiplostim vs. placebo), followed by avatrombopag (odds ratio of 18.72 [95% CI: 1.03 - 340.54] for avatrombopag vs. placebo), and then eltrombopag (odds ratio of 10.60 [95% CI: 3.64 – 30.87] for eltrombopag vs. placebo).*

The results of the analyses conducted by the ERG are associated with important limitations, predominantly due to inadequate fixed 0.5 continuity corrections, which causes directional bias. Therefore, the company suggests that the analysis conducted by the ERG should be considered as a sensitivity analysis to estimate uncertainty of the effect.

7. *ERG concern*: *Analysis with frequentist approach and 0.5 correction. The ERG considered Bayesian NMA as a suboptimal method based on the fact that there was not ideal convergence of the Markov chains. This can be explained with very low number of events in placebo arms which caused the problem for the estimation of the effects. Finally, the ERG recommended conducting a frequentist NMA with zero correction.*

In this particular case, the use of a frequentist approach as additional sensitivity analysis is reasonable, although even this approach is prone to be biased in the presence of studies with zero cells and imbalanced arms, as demonstrated by simulations conducted by Sweeting *et al.* 2004. Furthermore, the ERG applied the 0.5 continuity correction, which was demonstrated to be highly inappropriate for studies with zero cells. As a result, the estimates became unfavourable for avatrombopag and promoted romiplostim and, to a lower extent, eltrombopag.

In the light of these limitations, we propose a third sensitivity analysis for durable platelet response, assuming a continuity correction proportional to the sample size, which seems to be more appropriate given the findings presented by Sweeting *et al*. 2004 (Table iii). According to this approach, the odds ratio for the comparison between ROM vs AVA is 1.22 instead of 1.58 in the ERG's approach.

Table iii. Continuity correction comparison

ERG's approach with 0.5 continuity correction						
	n + 0.5	**N + 1**	**(%)**	**OR vs PLC**	**OR vs PLC (pooled)**	**OR ROM vs AVA**
Study 302	11.5	33	35%	**18.72**	**18.72**	**1.58**
	0.5	18	3%			
Kuter 2008 spl.	16.5	43	38%	**26.77**	**29.61**	
	0.5	22	2%			
Kuter 2008 non-spl.	25	41	61%	**31.25**		
	1	21	5%			
Novel approach with continuity correction proportional to sample size						
	n_cont_corr	**N**	**(%_cont_corr)**	**OR vs PLC**	**OR vs PLC (pooled)**	**OR ROM vs AVA**
Study 302	11.65	32	36%	**27.49**	**27.49**	**1.22**
	0.35	17	2%			
Kuter 2008 spl.	16.67	42	40%	**40.79**	**33.56**	
	0.33	21	2%			

Kuter 2008 non-spl.	25	41	61%	**31.25**
	1	21	5%	

Abbreviations: AVA, avatrombopag; ROM, romiplostim; OR, odds ratio

Conclusion

When interpreting the results of the ERG's and this additional third analysis, it should be considered that chronic ITP is a rare condition for which there are a limited number of quality clinical trials. The identified studies enrolled relatively small samples, resulting in limited statistical power, and thus limited credibility of comparisons. Durable platelet response was either not observed in placebo groups or was reported only in single individuals. This may confirm the efficacy of the assessed drugs but also is a significant uncertainty for indirect comparisons, since the true effect of placebo, which is the common comparator, is difficult to estimate. Moreover, recent studies encountered a problem of premature discontinuation of participants from the placebo arms, who were allowed to receive active therapy in clinical practice. All of these limitations increase uncertainty of the estimates reported in the respective studies and uncertainty of the indirect comparison, which is also a typical problem for the assessment of treatments used in rare diseases.

The range of uncertainty in this particular analysis can be illustrated with a range of estimates for the comparison between avatrombopag and romiplostim regarding durable response from various sensitivity analyses. Depending on the methodology (Bayesian or frequentist approach) and approach to zero correction (0.5 or proportional to sample size) the estimates of the odds

ratio range from 53% higher chance of response in favour of avatrombopag to 58% higher chance in favour of romiplostim (Table iv).

Table iv. Summary of model approaches

Analysis	Odds ratio for the comparison ROM vs AVA ($OR_{ROM\ vs\ PLC}$ / $OR_{AVA\ vs\ PLC}$ = $OR_{ROM\ vs\ AVA}$)	Interpretation
Bayesian network with CC proportional to sample size	45.71/96.96 = 0.47	ROM associated with lower chance for durable response
Bayesian network with 0.5 CC and observed data (ERG)	38.21/37.82 = 1.01	The same efficacy of ROM and AVA
Bayesian network with 0.5 CC and ITT data (ERG)	38.45/39.78= 0.96	Comparable efficacy of ROM and AVA
Frequentist NMA with 0.5 CC (ERG)	29.61/18.72 = 1.58	ROM associated with higher chance for durable response
Frequentist NMA with CC proportional to sample size	33.56/27.49 = 1.22	ROM associated with slightly higher chance for durable response

Results with such high uncertainty should be interpreted with caution and basing the inference only on the results of one-way sensitivity analyses may not be appropriate. Therefore, in such situations it is necessary to confront the results with other related outcomes. Importantly, the analysis of the incidence of any bleeds indicates that among all active therapies avatrombopag was

associated with the lowest incidence of any bleeds, which was nearly 3 times lower compared with romiplostim (0.34 vs 0.90) and eltrombopag (0.34 vs 0.89). The rate of clinically significant bleeding events was comparable between treatments and the odds of the reduction in the use of concomitant therapies was numerically highest for avatrombopag compared with other therapies in all sensitivity analyses. This overall picture demonstrates the uncertainty with regard to the results for durable platelet response since some of the outcomes, such as incidence of any bleeds, would be expected to be surrogate outcomes for durable platelet response. To summarise, the overall results shown in the NMA indicate that avatrombopag may be at least as effective as other therapies used in patients with ITP, however the oral mode of administration and lack of dietary restrictions may overcome potential compliance challenges that can adversely impact efficacy outcomes of alternative TPO-RAs.

Key issue	**Does this response contain new evidence, data or analyses?**
Issue 5: Time to treatment response in the model is longer that that observed in clinical practice	No
Response: Issue 5	
The company accepts the issues highlighted by the ERG and has added the ERG's approach into the company's base case.	

Key issue	Does this response contain new evidence, data or analyses?
Issue 6: Model design is limited to pairwise comparisons only	No
Response: Issue 6	
The company acknowledges the request to have functionality that permits a simultaneous comparison of cost-effectiveness results for multiple alternative treatment strategies and enables a fully incremental analysis. We consider this issue to have been addressed by the ERG in their preferred version of the model. The company has also used this version of the model in its revised base case cost-effectiveness results.	
Key issue	**Does this response contain new evidence, data or analyses?**
Issue 7: Mixed treatment sequence cannot determine optimum positioning for AVA amongst TPO-RAs	Yes, clinician survey on real-world treatment patterns and utilisation in chronic ITP
Response: Issue 7	

The company understands the reasons for the ERG suggesting the potential inclusion of cost-effectiveness results under various treatment sequences. However, the company asserts that treatment sequencing is likely not considered to be plausible from a clinical perspective or in the context of NICE decision-making for this indication.

Firstly, evidence provided by the company alongside the wider literature and clinical opinion suggests similar efficacy and safety between avatrombopag and the other TPO-RAs. It is also not possible, or appropriate, for the company to determine the order in which TPO-RAs may be prescribed in practice. Therefore, modelling the TPO-RAs sequentially should be understood as not appropriate or feasible. Furthermore, there are limited differences in long-term treatment duration between avatrombopag, eltrombopag and romiplostim, as indicated by expert clinician survey results and addressed separately in Issue 8. Therefore, modelling various treatment sequences is unlikely to yield cost-effectiveness results which are different to the company base case. This is supported by the exploratory analysis undertaken by the ERG which suggested various TPO-RA treatment sequences had a minimal impact on the cost-effectiveness results.

Secondly, avatrombopag in clinical practice will be considered for use in patients who were already judged to be suitable candidates for treatment with an alternative TPO-RA (i.e., in the same ITP treatment line as the other available TPO-RAs). This is consistent with the expert clinician survey results where the majority (7/9) of respondents agreed that, were avatrombopag available, they would use it in the same ITP treatment line as the other available TPO-RAs, while one further responder elaborated to say that they would offer avatrombopag in the same line as other TPO-RAs as part of an individualised patient

discussion [1]. This means comparing a treatment sequence with sequential TPO-RAs and non-TPO-RA options is not appropriate for this appraisal.	
Key issue	**Does this response contain new evidence, data or analyses?**
Issue 8: Non-TPO-RA dosages in the model are outdated	No
Response: Issue 8	
The company accepts the issues highlighted by the ERG and has revised them into the updated base case analysis. It is notable that the updated dosing assumptions for non-TPO-RA treatments in ERG scenario 4 have a negligible impact on the cost-effectiveness results.	
Key issue	**Does this response contain new evidence, data or analyses?**
Issue 9: Different definitions of response for TPO-RAs and non-TPO-RAs	No
Response: Issue 9	

A number of treatments may be used in the clinical pathway for patients that do not adequately respond, or are contraindicated to, TPO-RAs. These include but are not limited to, steroids, rituximab, cytotoxic agents, and fostamatinib. Except for fostamatinib, which is not NICE-approved, all of these listed treatments are currently unlicensed in England and Wales for the treatment of ITP, and therefore comparison on treatment response is hampered by a lack of published evidence.

Fostamatinib and all three TPO-RA ITP licensing studies explored very similar definitions of durable platelet response as an endpoint, involving a platelet response above 50×10^9/L for ≥6 of the last 8 weeks of treatment. Unfortunately for other therapeutic options, the company was unable to match the definition of durable platelet response given the lack of available data in an analogous population of ITP patients.

Key issue	**Does this response contain new evidence, data or analyses?**
Issue 10: Long term treatment duration of TPO-RAs	Yes, clinician survey on real-world treatment patterns and utilisation in chronic ITP
Response: Issue 10	
Data were gathered from 9 expert ITP-treating clinicians in the UK providing estimates on the long-term treatment duration and discontinuation rates with existing TPO-RA treatments. This data suggested limited differences between eltrombopag and romiplostim in clinical practice. Avatrombopag and eltrombopag are both administered as oral treatments and therefore we	

expect these treatments to have a similar treatment duration. This is a conservative assumption considering avatrombopag has a more flexible dosing schedule and does not require food restrictions or hepatoxicity monitoring which may facilitate improved long-term treatment adherence.

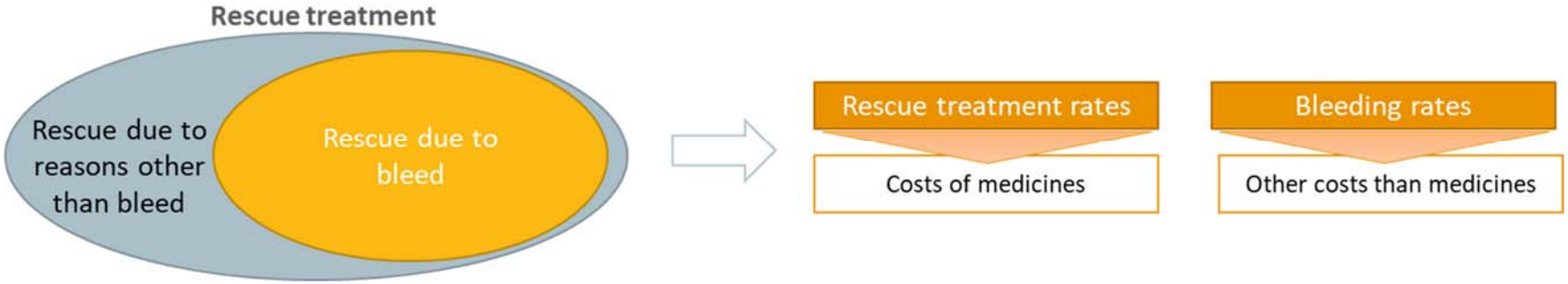
The company assert that it is plausible to assume a similar long-term durability of treatment response between the TPO-RA treatments. Consistent with this assumption, 66.7% (6/9) of the expert clinician survey responders expected that avatrombopag would offer at least a comparable or longer average duration of response for ITP patients on stable treatment than the other available TPO-RAs, while none of the responders anticipated that avatrombopag would offer a shorter average duration of response versus other available TPO-RAs. Therefore, the assumptions which underpin ERG scenario 6b are not considered to be accurate and should be disregarded.

Key issue	**Does this response contain new evidence, data or analyses?**
Issues 11 and 16: Approach to costing bleeding and rescue therapy events	Yes, costs of bleeds (Table vi)
Response: Issues 11 and 16	

The company recognises the concerns raised by the ERG in relation to the costs and configuration of bleeds and rescue therapy events used in the model. We have sought to clarify the rationale behind our approach taken to modelling. We also recognise limitations in some of the data sources used for bleeding costs and have accordingly updated our base case analysis.

Rescue treatment for ITP patients is needed when a bleed occurs. However, there are also other reasons for using rescue therapy in patients that need a rapid platelet response. For example, in patients with extremely low platelet counts (e.g., $<20\times10^9$/L), or clinical signs and symptoms suggesting a potential bleed, or patients presenting with impaired health-related quality of life. The company maintains that these additional reasons for using rescue therapy should be included within the model. (Figure i)

Figure i. Relation between rescue treatment rates and bleeding rates



In relation to ERG concerns raised surrounding the rates of rescue therapy used in the company's model, only three sources have been identified for rates of the need for rescue therapy (Table v):

- Eltrombopag NICE submission
- Core phase of AVA study 302
- Core + extension phase of AVA study 302

A total of 9/49 (18.4%) patients required rescue therapy during Study 302. Therefore, inclusion of this data in the model would be highly uncertain (as health state probabilities would be derived from a low number of events). Moreover, in the eltrombopag submission NICE concluded that using higher rates of rescue medication was more appropriate. Therefore, these rates were considered as validated by NICE and used in the company base case.

Table v. Proportion of patients who need rescue therapy by response status (due to bleed and other reasons)

	Platelets ≥50x10^9/L	Platelets <50x10^9/L	Source
Rescue therapy rate - base case	3.0%	22.0%	Eltrombopag NICE submission
Rescue therapy rate - option 1	4.1%	6.1%	Study 302, Core
Rescue therapy rate - option 2	3.9%	13.2%	Study 302, Core + Extension

Using a new approach to modelling rescue therapy was driven by an improved clinical understanding of the impact of ITP, feedback from an Advisory Board [4], and the availability of new data for costs of bleeds. These costs were obtained from commissioned market research, which was conducted by an independent agency, in order to inform understanding and provide data on the current treatment of ITP across Europe and the UK. This included a survey as well as structured interviews with 113 physicians across the EU, and included 20 physicians from the UK [9]. Resource use figures from this research have been combined with UK unit costs to provide a cost of managing bleeding events for both outpatient and inpatient bleeds, including life threatening (intracranial haemorrhage) bleeds. Such detailed information was not available at the time of previous NICE appraisals in ITP, therefore only NHS reference costs could have been considered, and modelled, at that time. The research conducted suggests that in clinical practice there are many different costs related to the treatment of bleeds that are incurred, such as the costs of ER admission and use of ICU beds. These costs go beyond the NHS reference costs only and were considered more appropriate to be used in the company submission as they better reflect clinical practice. This approach was validated by two external health economists and a consultant haematologist as part of an Advisory Board [4].

We recognise that the costs obtained from the market research are significantly higher than NHS tariffs, however, even considering them as overestimated, the costs outside of the tariff should not be fully ignored. Therefore, in the revised base case we suggest using average costs of bleeds between the NHS tariff and market research data (Table vi).

Table vi: Costs of bleeds

Type of bleed	Company submission	ERG base case	Revised company base case
Minor bleed	£0	£0	£0
Outpatient bleed	£3,134	£460	£1,797
Intracranial haemorrhage	£25,699	£4,690	£15,194
Gastrointestinal bleeds	£14,325	£3,092	£8,709
Other inpatient bleed	£14,325	£2,890	£8,608

It should be noted that the cost of bleeds obtained from the market research only included rescue therapy that was used due to bleeds and was accounted for in the model separately. Applying a new approach to bleed and rescue costs was intended to allow for use of the new cost data without double counting of the cost of rescue therapies. We believe this is the most appropriate approach. It should be noted that the approach used in previous appraisals [TA293 and TA221] is also implemented in the model. In this scenario the costs of medicines have been excluded from the costs of bleeding management. This scenario was not presented in the company submission; however, its results are consistent with the company base case. Instead, in the company

submission, a scenario where no rescue therapy for causes other than bleeds has been considered. This is the most conservative approach to rescue therapies with inclusion of the most recent data from market research. Despite the conservative character of this scenario, its results are consistent with the company base case.

Key issue	**Does this response contain new evidence, data or analyses?**
Issue 12: Mortality risks associated with ITP	No

Response: Issue 12
The company accepts that there is uncertainty and a paucity of data around long-term survival in ITP patients. This uncertainty is reflected in previous ITP TAs applying a variety of mortality hazard ratios. Nevertheless, clinical opinion suggests that for treated patients there is no excess morbidity. This is in alignment with the views already provided by the UK ITP Forum within this appraisal, as stated in the company submission: *"Mortality attributed to ITP or its treatments is caused by fatal bleeding events or infection associated with immunosuppressive agents. Since avatrombopag does not suppress the immune system, responding patients are at reduced risk of fatal events. Fatal events are rare and it is unlikely that a study will ever be sufficiently powered to detect a difference in survival between treatment and placebo or standard of care arms. ITP is thought to have a heterogeneous pathogenesis, not all patients respond to current SOC and as an additional effective medical therapy, avatrombopag has the potential to save lives."*

It should be further noted that mortality is not a significant driver of the cost-effectiveness results given the data available. This is based on the deterministic and probabilistic sensitivity analyses from the core evidence submission (section B.3.8) and scenarios 7a-7d as per page 22 in the ERG report, all of which provide results which are consistent with the company base case (i.e., dominance).	
Key issue	**Does this response contain new evidence, data or analyses?**
Issue 13: Health-related quality of life utility values used in the model	No
Response: Issue 13	
The company accepts the issue highlighted by the ERG involving the need to adjust the utility values by age over time in the model. The company has added the ERG changes into its updated base case analysis. The company notes that the adjusted utility values have a negligible impact on the cost-effectiveness results with avatrombopag remaining dominant (more effective and less costly) to both eltrombopag and romiplostim.	
Key issue	**Does this response contain new evidence, data or analyses?**

Issue 14: Overestimation of romiplostim administration costs	No
Response: Issue 14	
The company accepts the issues highlighted by the ERG and has added the ERG changes into its revised base case. In ERG scenarios 9a-9d, the revised assumptions had only a minor impact on the cost-effectiveness results between avatrombopag and romiplostim, with results consistent to the base case in the company submission.	
Key issue	**Does this response contain new evidence, data or analyses?**
Issue 15: Overestimation of romiplostim dosing	No
Response: Issue 15	
The company accepts the issue highlighted by the ERG around the dosing assumptions for romiplostim and has added it into its updated base case analysis. In ERG scenarios 10a and 10b, the revised assumptions had only a minor impact on the cost-effectiveness results between avatrombopag and romiplostim, with results consistent to the base case in the company core submission.	

Key issue	Does this response contain new evidence, data or analyses?
Issue 16: Approach to costing bleeding and rescue therapy events in the model	Yes, costs of bleeds (Table vi)
Response: Issue 16	
Combined with response to issue 11 (above)	

References

1. Sobi. Clinician survey on real-world treatment patterns and utilisation in chronic ITP. Data on file.2022.
2. Rampotas A, Watson E, Burton K, Hill QA, Pavord S. A real-world study of immune thrombocytopenia management during the COVID-19 pandemic in the UK. British Journal of Haematology. 2022;196(2):351-355.
3. Pavord S, Thachil J, Hunt BJ, Murphy M, Lowe G, Laffan M, et al. Practical guidance for the management of adults with immune thrombocytopenia during the COVID-19 pandemic. Br J Haematol. 2020;189(6):1038-1043.
4. Sobi. Sobi ITP UK advisory board meeting. Data on file. 2020.
5. Zhang J, Liang Y, Ai Y, Li X, Xie J, Li Y, et al. Eltrombopag versus romiplostim in treatment of adult patients with immune thrombocytopenia: A systematic review incorporating an indirect-comparison meta-analysis. PLOS ONE. 2018;13(6):e0198504.
6. McDonald V, Newland A, Morgan M, Wilson K, Nazir J, Maguire P, et al. Patient preferences and experiences regarding thrombopoietin-receptor agonists for immune thrombocytopenia in the United Kingdom and Ireland (TRAPeze UK & IE study). Hematology (Amsterdam, Netherlands). 2021;26(1):799-808.
7. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Statistics in medicine. 2004;23(9):1351-1375.
8. 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. Lancet (London, England). 2008;371(9610):395-403.
9. L.E.K. consulting. ITP epidemiology and treatment paradigm review. Data on file; 2020.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
NA	NA	NA	NA

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Issue 4: Comparative effectiveness estimates from the NMA for durable platelet response	Including the following estimates of ORs for durable platelet response: 1.58 for comparison avatrombopag vs romiplostim and 0.57 for comparison avatrombopag vs eltrombopag.	Including the following estimates of ORs for durable platelet response: 1.22 for comparison avatrombopag vs romiplostim and 0.29 for comparison avatrombopag vs eltrombopag.	For technical engagement, the company has used and presented the ERG's version of the model with 'ERG settings' (i.e. accepted the changes to the company's original base case). The impact of including the company's approach to issue 4 relative to the ERG's base case is detailed: ***commercial in confidence information removed***

	ERG base case ICER				
	Costs	QALYs	Inc. cost	Inc. QALY	ICER
Avatrombopag	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eltrombopag	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Romiplostim	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

<table>
<tr>
<td>Issue 16: Approach to costing bleeding and recue therapy events in the model</td>
<td>Company submission cost of bleeds listed in Table 4.</td>
<td>Using average costs of bleeds between the NHS tariff and study data as listed in Table 4.</td>
<td>For technical engagement, the company has used and presented the ERG's version of the model with 'ERG settings' (i.e. accepted the changes to the company's original base case). The impact of including the company's approach to issue 16 relative to the ERG's base case is detailed: commercial in confidence information removed
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<tr><td></td><td colspan="5">ERG base case ICER</td></tr>
<tr><td></td><td>Costs</td><td>QALYs</td><td>Inc. cost</td><td>Inc. QALY</td><td>ICER</td></tr>
<tr><td>Avatrombopag</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Eltrombopag</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Romiplostim</td><td></td><td></td><td></td><td></td><td></td></tr>
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<tr>
<td>Company's base case following technical engagement (or revised base case)</td>
<td>Incremental QALYs: [QQQ]</td>
<td>Incremental costs: [£££]</td>
<td>For technical engagement, the company has used and presented the ERG's version of the model with 'ERG settings' (i.e. accepted the changes to the company's original base case), and has only altered inputs in relation to issues 3 (including TPO-RA trials in NMA), 4 (NMA estimates of comparative effectiveness between TPO-RAs) and 16 (approach to costing bleeding and rescue therapy). The impact of change to issue 3 is not detailed in this table (i.e. Table 4) as it did not alter the cost-effectiveness analysis.

The final company base case is presented: commercial in confidence information removed
<table>
<tr><td></td><td colspan="5">ERG base case ICER</td></tr>
<tr><td></td><td>Costs</td><td>QALYs</td><td>Inc. cost</td><td>Inc. QALY</td><td>ICER</td></tr>
<tr><td>Avatrombopag</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Eltrombopag</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Romiplostim</td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
</td>
</tr>
</table>

Sensitivity analyses around revised base case

N/A

Creativ Ceutical
The enlightened decision

Network meta-analysis of efficacy and safety of avatrombopag versus comparators in adult patients with chronic immune thrombocytopenia who have had an insufficient response to a previous treatment

Additional analyses

Date: 06-04-2022

1. Table of contents

2. List of tables

3. List of figures

4. Abbreviations

AEs	Adverse events
AVA	Avatrombopag
ELT	Eltrombopag
FOS	Fostamatinib
IRR	Incidence rate ratio
ITP	Immune thrombocytopenia
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
PLC	Placebo
Pts	Patients
RCT	Randomised controlled trial
ROM	Romiplostim
RR	Relative risk
SoC	Standard of care

5. Feasibility assessment of additional analyses

Table 1 presents available outcomes in both studies that were previously included in the NMA and studies that were considered not relevant. The feasibility analysis revealed that the inclusion of previously excluded studies does not modify the results of NMA regarding the odds for durable platelet response and odds for the reduction of concomitant therapy, since these outcomes were not assessed in those studies. Additional information were identified for four previously analyses outcomes including:

- Need for rescue therapy (2 RCTs)
- Any bleeding events (6 RCTs)
- Bleeding events WHO 2-4 (1 RCT)
- Any adverse events (4 RCTs)

The estimates were extracted from the studies and NMA was rerun for the outcomes listed above using previously described methodology.

Table 1 Outcomes reported in the included studies

	Study	Durable response	Need for rescue therapy	Reduction in the use of concomitant therapy	Bleeding events WHO grade 1-4	Bleeding events WHO grade 2-4	Adverse events
Studies included in the recent NMA							
Studies previously included	Study 302[1]	✓	✓	✓	✓	✓	✓
	Study 305 (NCT01433978)	NR	NR	NR	✓	✓	✓
	RAISE[2]	✓	✓	✓	✓	✓	✓
	Kuter 2008 spl[3]	✓	✓	✓	NR	✓	NR
	Kuter 2008 non-spl[3]	✓	✓	✓	NR	✓	NR
	Kuter 2008 spl & non-spl[3]	NR	NR	NR	✓	NR	✓
	FIT 1[4]	✓	NR	NR	NR	NR	NR
	FIT 2[4]	✓	NR	NR	NR	NR	NR
	FIT 1 & FIT 2[4]	NR	✓	NR	✓	✓	✓
Studies excluded from the recent NMA							
Studies previously excluded	Tomiyama[5]	NR	NR	NR	NR	NR	✓
	Yang 2016[6]	NR	✓	NR	✓	✓	✓
	Bussel 2007[7]	NR	NR	NR	✓	NR	✓
	Bussel 2009[8]	NR	NR	NR	✓	NR	✓
	Shirasugi 2011[9]	NR	✓	NR	✓	NR	✓
	Huang 2018[10]	NR	✓	NR	✓	NR	NR
	Kuter 2010[11]	NR	NR	NR	✓	✓	NR

6. NMA Results

Fixed- and random-effect model NMA was run for each outcome. The best-fitting model was selected based on parsimony and lower DIC value. Fixed-effect model was preferred over random-effect since it contains lower number of estimable parameters. Random effect-model could be selected only if presented with DIC lower by 5 points compared with fixed effect model.

For all 4 NMAs, which rerun following the inclusion of previously excluded studies, fixed effect models were considered more appropriate based on lower DIC value (Table 2).

The details regarding input data, calculation of the incidence rates and incidence rate rations as well as the results of the NMAs are presented in the subsequent sections. The results for random-effect model NMAs are presented in Appendix 1: Results of random-effect models.

Table 2 Model fitting data for the updated NMAs

Endpoint	Fixed-effect model			Random-effect model			
	$\overline{D}_{res}$	pD	DIC	$\overline{D}_{res}$	pD	DIC	SD (95% CrI)
Any bleeding	14.129	5.019	**19.148**	9.939	8.022	17.961	0.49 (0.04, 1.35)
Bleeding events WHO 2-4 grade	11.877	5.012	**16.890**	12.386	6.247	18.633	0.76 (0.02, 3.29)
Need for rescue therapy	12.772	4.001	**16.774**	12.266	5.787	18.053	0.61 (0.02, 2.30)
Any AE	3.407	4.002	**7.409**	3.258	5.853	9.111	0.21 (0.006, 0.70)

6.1.1. Any bleeding events (estimated incidence)

6.1.1.1. Overall information and input data

Table 3. Summary of the data for the NMA for the proportion of patients with any bleed

Characteristic		Value
Number of studies		11
Number of treatment regimens		6
Number of patients		1170
DIC	Fixed-effects model	**19.148**
	Random-effects model	17.961

Table 4. Input data for the NMA of proportion of patients with any bleed (grade 1-4 WHO)

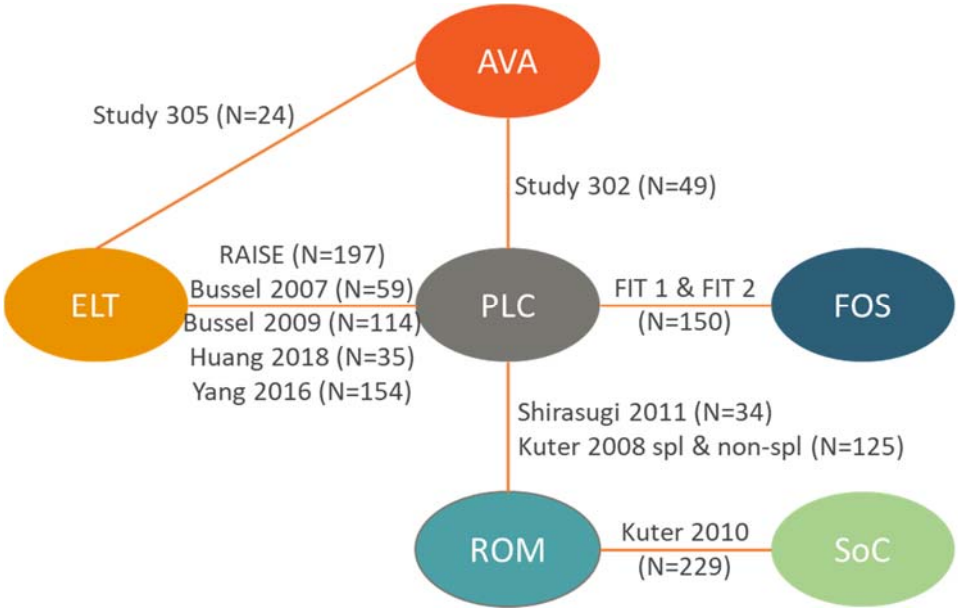
Study	Treatment	Event rate n/N (%)	RR [95%CI]	Mean exposure [years]	Total pts-years	Incidence rate [/pts-yrs.]	IRR [95%CI]
Study 302	AVA	14/32 (43.8%)	0.83 [0.46, 1.5]	0.44	14.02	0.9986	0.32 [0.14, 0.75]
	PLC	9/17 (52.9%)		0.17	2.92	3.0789	
Study 305	AVA	6/13 (46.2%)	0.56 [0.29, 1.08]	0.30	3.62	1.6596	0.41 [0.15, 1.16]
	ELT	9/11 (81.8%)		0.20	2.23	4.0345	
RAISE	ELT	106/135 (78.5%)	0.87 [0.77, 0.98]	0.43	58.62	1.8084	0.9 [0.65, 1.24]
	PLC	56/62 (90.3%)		0.45	27.86	2.0103	
Bussel 2009	ELT	7/76 (9.2%)	0.7 [0.24, 2.06]	0.10	7.30	0.9593	0.75 [0.24, 2.36]
	PLC	5/38 (13.2%)		0.10	3.90	1.2804	
Huang 2018	ELT	0/17 (0%)	0.11 [0.01, 2.04]	0.11	1.90	0.0000	0.12 [0.01, 2.27]*
	PLC	4/18 (22.2%)		0.12	2.08	1.9259	
Bussel 2007	ELT	2/30 (6.7%)	0.48 [0.1, 2.44]	0.09	2.64	0.7573	0.55 [0.10, 3.02]
	PLC	4/29 (13.8%)		0.10	2.92	1.3681	
Yang 2016	ELT	N=104	NA	NA	NA	NA	0.28 [0.13, 0.59][a]
	PLC	N=50	NA	NA	NA	NA	
FIT 1 & FIT 2	FOS	28/101 (27.7%)	0.8 [0.49, 1.31]	0.25	25.12	1.1145	0.5 [0.27, 0.91]
	PLC	17/49 (34.7%)		0.16	7.60	2.2366	
Kuter 2010	ROM	80/154 (51.9%)	0.97 [0.75, 1.26]	NA	NA	3.56[b]	0.71 [0.58, 0.87]
	SoC	40/75 (53.3%)		NA	NA	5.02[b]	
Shirasugi 2011	ROM	16/22 (72.7%)	0.73 [0.56, 0.94]	0.23	5.08	3.1515	0.72 [0.34, 1.52]
	PLC	12/12 (100%)		0.23	2.75	4.3697	
Kuter 2008 spl & non-spl	ROM	45/84 (53.6%)	0.88 [0.64, 1.2]	0.67	56.41	0.7978	0.85 [0.52, 1.38]
	PLC	25/41 (61%)		0.65	26.62	0.9393	

RR – relative risk; IRR – incidence rate ratio *correction for zero events applied; NA – not applicable

[a] – value reported in the publication as generalized linear mixed model with a Logit canonical link function for repeated binary data, allowing for baseline dichotomized WHO bleeding grade, use of ITP medication at baseline, splenectomy, baseline platelet count ≤15 × 109/l, and treatment as fixed effects and patient treated as a random effect

[b] – rates reported in the publication

Figure 1. Network of evidence for proportion of patients with any bleed



6.1.1.2. NMA results

Figure 2. Forest plot for the incidence rate ratio for comparison AVA vs comparators regarding any bleed – fixed effect model

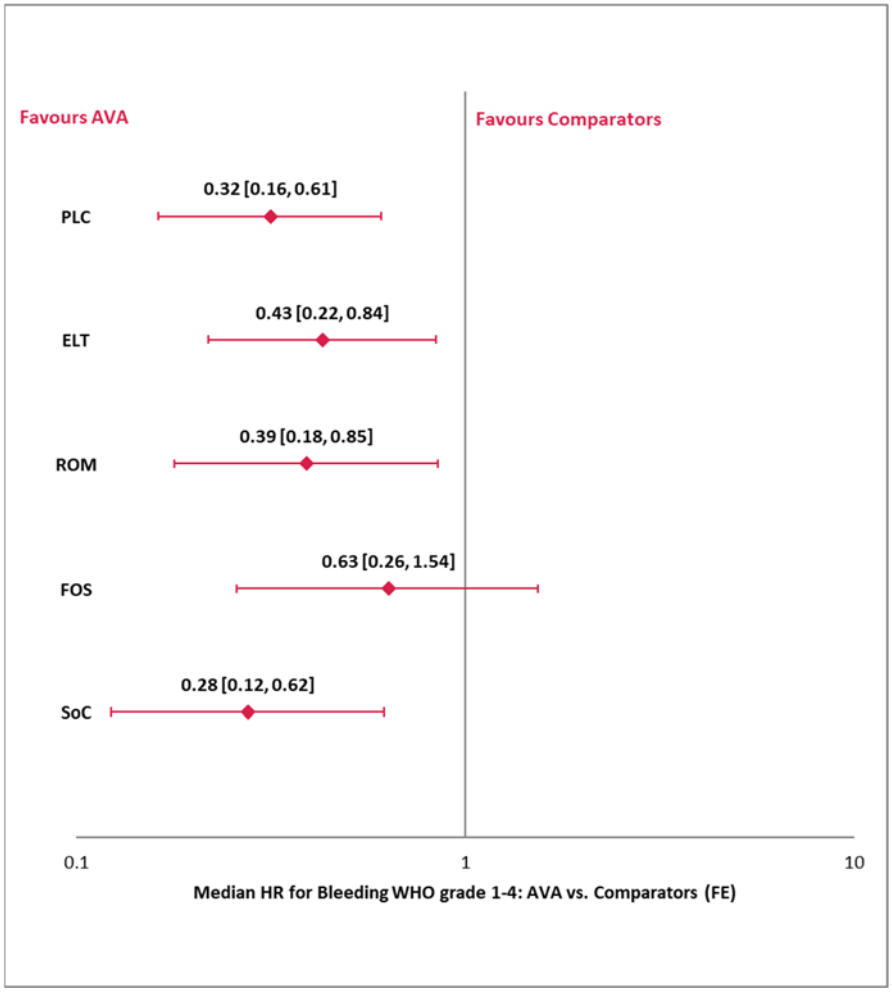


Table 5. Incidence rate ratios for any bleed – fixed effect model

	IRR for all comparisons (FE model)						Probability of being best	SUCRA	Probability AVA being better than comparator
	vs. PLC	vs. AVA	vs. ELT	vs. ROM	vs. FOS	vs. SoC			
PLC	PLC	**3.17 [1.64, 6.14]**	**1.36 [1.03, 1.80]**	1.24 [0.82, 1.87]	**2.01 [1.10, 3.67]**	0.88 [0.55, 1.39]	0%	18%	100%
AVA	**0.32 [0.16, 0.61]**	AVA	**0.43 [0.22, 0.84]**	**0.39 [0.18, 0.85]**	0.63 [0.26, 1.54]	**0.28 [0.12, 0.62]**	84%	97%	-
ELT	**0.73 [0.56, 0.97]**	**2.32 [1.19, 4.56]**	ELT	0.91 [0.55, 1.50]	1.48 [0.76, 2.87]	0.64 [0.38, 1.10]	0%	54%	99%
ROM	0.81 [0.54, 1.22]	**2.56 [1.17, 5.59]**	1.10 [0.67, 1.81]	ROM	1.63 [0.78, 3.37]	**0.71 [0.58, 0.87]**	0%	46%	99%
FOS	**0.50 [0.27, 0.91]**	1.58 [0.65, 3.86]	0.68 [0.35, 1.32]	0.62 [0.30, 1.28]	FOS	**0.44 [0.20, 0.93]**	16%	78%	84%
SoC	1.14 [0.72, 1.81]	**3.61 [1.61, 8.10]**	1.55 [0.91, 2.65]	**1.41 [1.15, 1.73]**	**2.29 [1.07, 4.88]**	SoC	0%	7%	100%

Significant results were reported in bold

6.1.1.3. Analysis of consistency

Analysis of consistency within the closed loop AVA-PLC-ELT was conducted using modified Bucher's method as outlined in the NICE DSU TSD 4 (http://nicedsu.org.uk/wp-content/uploads/2016/03/TSD4-Inconsistency.final_.15April2014.pdf) according to the following schedule:

1. Studies comparing ELT vs PLC were meta-analysed using random-effect model (Figure 3).
2. Bucher's indirect comparison was conducted between estimates from Study 302 and the outcomes of step 1. (Table 6)
3. The consistency between a head-to-head study comparing AVA and ELT (Study 305) and the indirect estimates was assessed using heterogeneity test (Figure 4)

The analysis of consistency revealed no heterogeneity (I^2 = 0%) between direct (Study 305) and indirect estimates for the comparison between AVA vs ELT, which indicates that there is no evidence for inconsistency in this loop of the network.

Figure 3. Forest plot for the pairwise meta-analysis of studies comparing ELT vs PLC

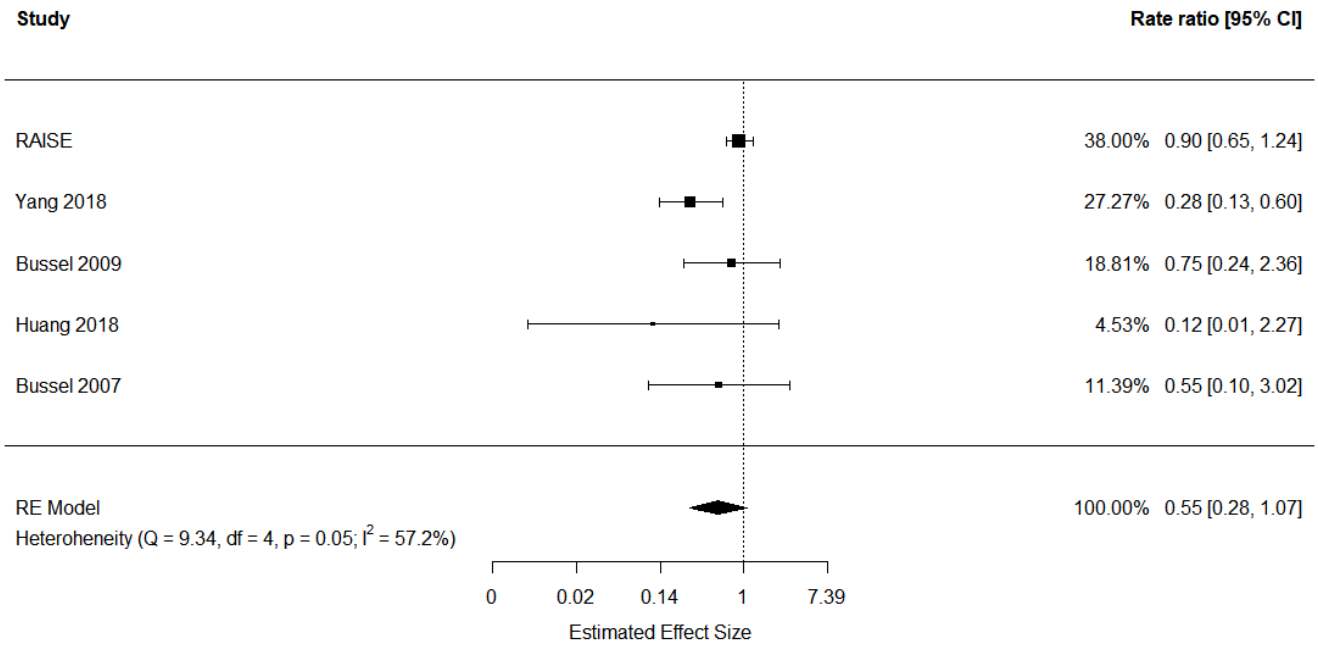
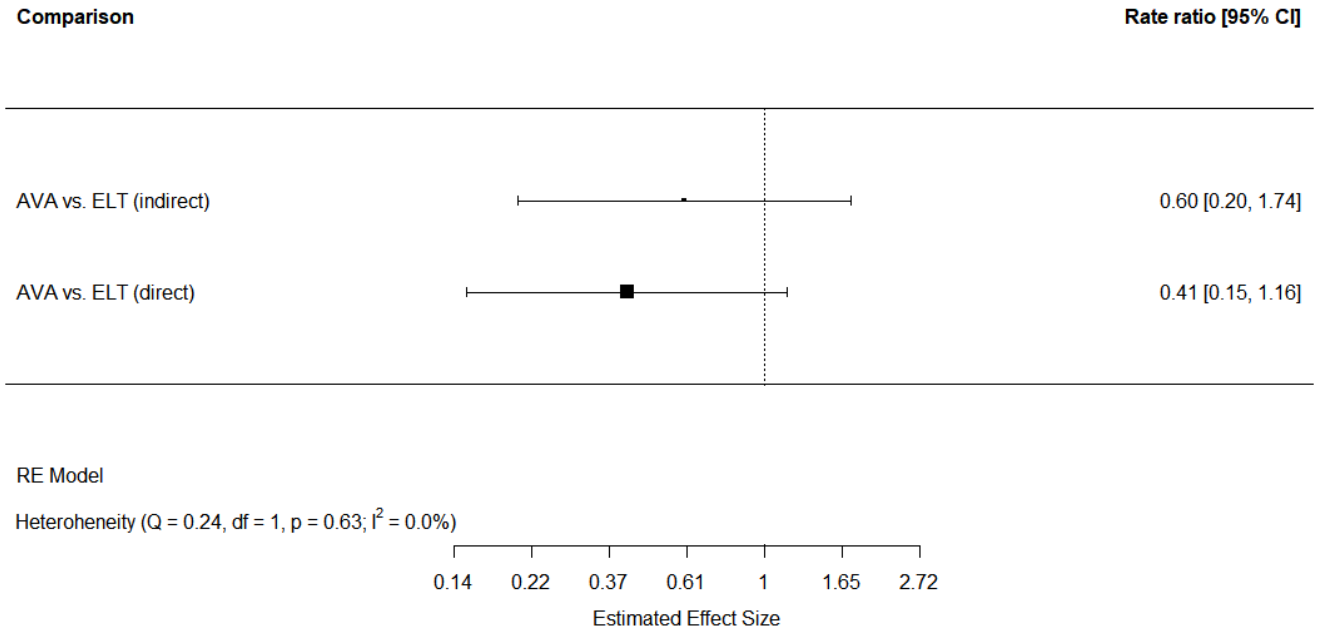


Table 6 Indirect comparison AVA vs. ELT

AVA vs. PLC (Study 302)	ELT vs. PLC (Pairwise MA – RE model)	AVA vs. ELT (Bucher's method)
0.32 [0.14, 0.75]	0.55 [0.28, 1.07]	**0.60 [0.20, 1.74]**

Figure 4. Analysis of consistency between direct and indirect evidence for the comparison between AVA and ELT.



6.1.2. Bleeding events WHO grade 2-4 (estimated incidence)

6.1.2.1. Overall information and input data

Table 7. Summary of the data for the NMA for the proportion of patients with bleed WHO grade 2-4

Characteristic		Value
Number of studies		8
Number of treatment regimens		6
Number of patients		928
DIC	Fixed-effects model	**16.890**
	Random-effects model	18.633

Table 8. Input data for the NMA of proportion of patients with bleed WHO grade 2-4

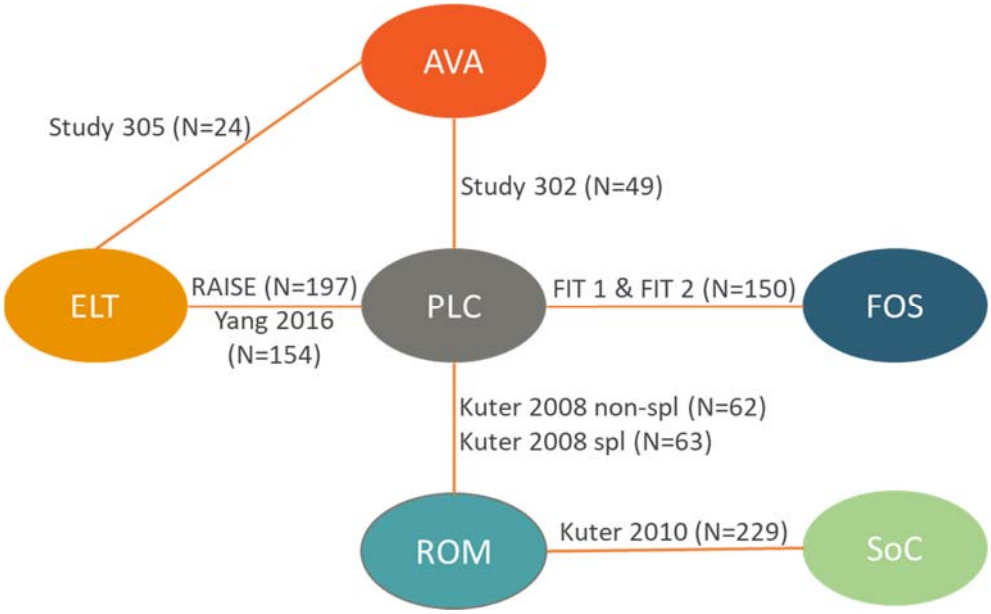
Study	Treatment	Event rate n/N (%)	RR [95%CI]	Mean exposure	Total pts-years	Incidence rate [/pts-yrs.]	IRR [95%CI]
Study 302	AVA	3/32 (9.4%)	5.59 [0.18, 173.05]	0.44	14.02	0.0053	4.63 [0.04, 575.58]*
	PLC	0/17 (0.0%)		0.17	2.92	0.0011	
Study 305	AVA	4/13 (30.8%)	0.85 [0.27, 2.62]	0.30	3.62	1.1064	0.62 [0.15, 2.47]
	ELT	4/11 (36.4%)		0.20	2.23	1.7931	
RAISE	ELT	44/135 (32.6%)	0.63 [0.45, 0.89]	0.43	58.62	0.7506	0.65 [0.41, 1.03]
	PLC	32/62 (51.6%)		0.45	27.86	1.1488	
Yang 2016	ELT	N=104	NA	NA	NA	NA	0.59 [0.21, 1.64][a]
	PLC	N=50	NA	NA	NA	NA	
FIT 1 & FIT 2	FOS	10/101 (9.9%)	0.61 [0.26, 1.44]	0.25	25.12	0.3981	0.38 [0.15, 0.96]
	PLC	8/49 (16.3%)		0.16	7.60	1.0525	
Kuter 2008 spl	ROM	9/42 (21.4%)	0.56 [0.25, 1.25]	0.68	28.38	0.3171	0.55 [0.21, 1.42]
	PLC	8/21 (38.1%)		0.66	13.83	0.5783	
Kuter 2008 non-spl	ROM	4/42 (9.5%)	0.32 [0.1, 1]	0.68	28.36	0.1410	0.29 [0.08, 1.04]
	PLC	6/20 (30.0%)		0.62	12.48	0.4807	
Kuter 2010	ROM	20/154 (13%)	0.75 [0.39, 1.42]	NA	NA	0.47[b]	0.68 [0.39, 1.20]
	SoC	13/75 (17.3%)		NA	NA	0.69[b]	

RR – relative risk; IRR – incidence rate ratio *correction for zero events applied; NA – not applicable

[a] – value reported in the publication as generalized linear mixed model with a Logit canonical link function for repeated binary data, allowing for baseline dichotomized WHO bleeding grade, use of ITP medication at baseline, splenectomy, baseline platelet count ≤15 × 109/l, and treatment as fixed effects and patient treated as a random effect

[b] - reported in the publication

Figure 5. Network of evidence for proportion of patients with bleed WHO grade 2-4



6.1.2.2. NMA results

Figure 6. Forest plot for proportion of patients with bleed WHO grade 2-4, avatrombopag vs comparators – fixed effect model

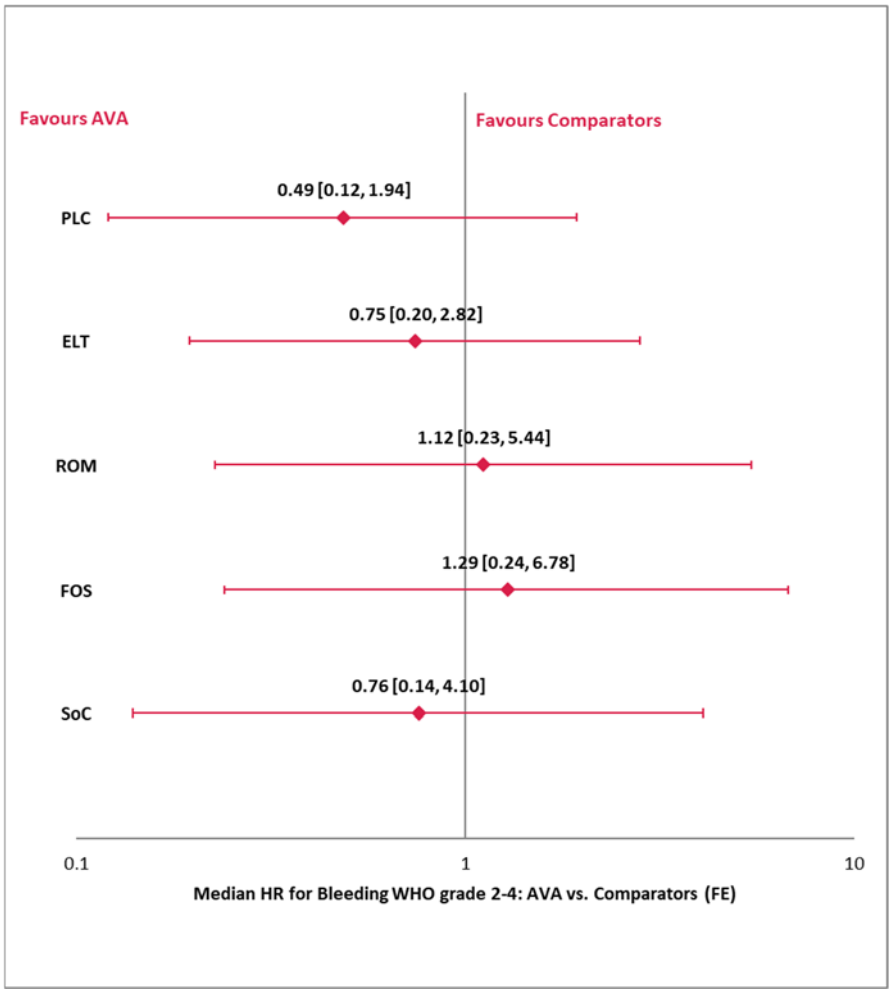


Table 9. Incidence rate ratios for bleeding events WHO grade 2-4 – fixed effect model

	IRR for all comparisons (FE model)						Probability of being best	SUCRA	Probability AVA being better than comparator
	vs. PLC	vs. AVA	vs. ELT	vs. ROM	vs. FOS	vs. SoC			
PLC	PLC	2.05 [0.52, 8.26]	**1.53 [1.01, 2.32]**	**2.29 [1.07, 4.92]**	**2.65 [1.05, 6.72]**	1.56 [0.60, 4.04]	0%	8%	85%
AVA	0.49 [0.12, 1.94]	AVA	0.75 [0.20, 2.82]	1.12 [0.23, 5.44]	1.29 [0.24, 6.78]	0.76 [0.14, 4.10]	29%	59%	-
ELT	**0.65 [0.43, 0.99]**	1.34 [0.35, 5.11]	ELT	1.50 [0.63, 3.57]	1.73 [0.63, 4.79]	1.02 [0.36, 2.89]	1%	42%	67%
ROM	**0.44 [0.20, 0.94]**	0.90 [0.18, 4.39]	0.67 [0.28, 1.59]	ROM	1.16 [0.35, 3.86]	0.68 [0.39, 1.21]	24%	73%	45%
FOS	**0.38 [0.15, 0.95]**	0.77 [0.15, 4.14]	0.58 [0.21, 1.60]	0.86 [0.26, 2.88]	FOS	0.59 [0.16, 2.23]	42%	77%	38%
SoC	0.64 [0.25, 1.67]	1.32 [0.24, 7.14]	0.98 [0.35, 2.78]	1.47 [0.83, 2.59]	1.70 [0.45, 6.44]	SoC	3%	40%	63%

Significant results were reported in bold

6.1.2.3. Analysis of consistency

Analysis of consistency within the closed loop AVA-PLC-ELT was conducted using modified Bucher's method as outlined in the NICE DSU TSD 4 (http://nicedsu.org.uk/wp-content/uploads/2016/03/TSD4-Inconsistency.final_.15April2014.pdf) according to the following schedule:

1. Studies comparing ELT vs PLC were meta-analysed using random-effect model (Figure 7).
2. Bucher's indirect comparison was conducted between estimates from Study 302 and the outcomes of step 1. (Table 10)
3. The consistency between a head-to-head study comparing AVA and ELT (Study 305) and the indirect estimates was assessed using heterogeneity test (Figure 8)

The analysis of consistency revealed no heterogeneity (I^2 = 0%) between direct (Study 305) and indirect estimates for the comparison between AVA vs ELT, which indicates that there is no evidence for inconsistency in this loop of the network.

Figure 7. Forest plot for the pairwise meta-analysis of studies comparing ELT vs PLC

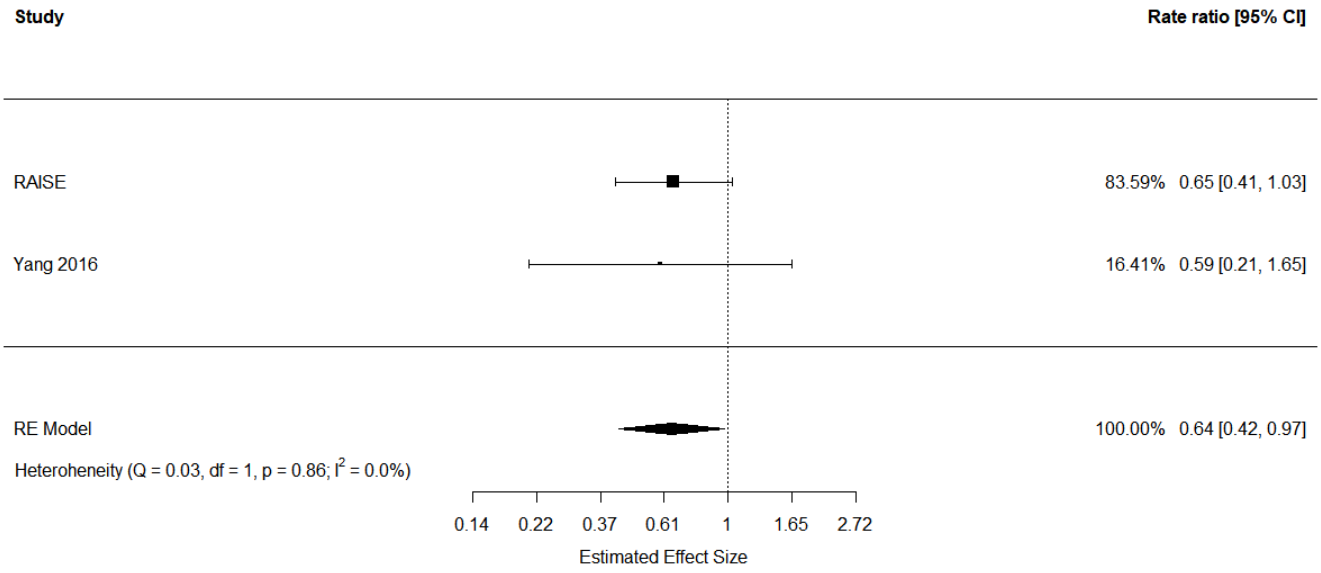


Table 10 Indirect comparison AVA vs. ELT

AVA vs. PLC (Study 302)	ELT vs. PLC (Pairwise MA – RE model)	AVA vs. ELT (Bucher's method)
4.63 [0.04, 575.58]	0.64 [0.42, 0.97]	**7.20 [0.06, 911.60]**

Figure 8. Analysis of consistency between direct and indirect evidence for the comparison between AVA and ELT.

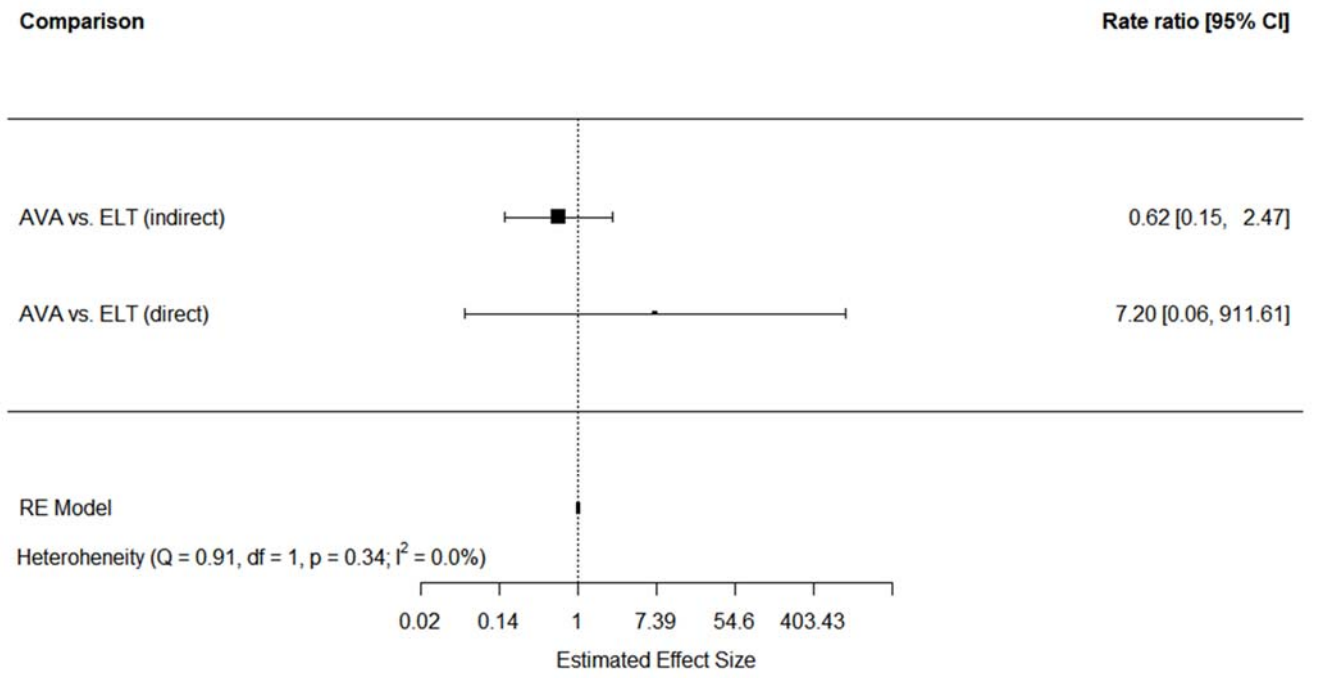


Table 11 Indirect comparison AVA vs. ELT

AVA vs. PLC (Study 302)	ELT vs. PLC (Pairwise MA – RE model)	AVA vs. ELT (Bucher's method)
4.63 [0.04, 575.58]	0.64 [0.42, 0.97]	**7.20 [0.06, 911.94]**

Table 12 Analysis of consistency for the comparison AVA vs. ELT

Study	RR	Lower CI 95%	Upper CI 95%
Study 305	0.62	0.15	2.47
Indirect comparison	7.20	0.06	911.94
Total (FE)	0.74	0.20	2.82
Total (RE)	0.74	0.20	2.82

Q = 0.91, p=0.339, I^2=0%

6.1.3. Need for rescue therapy

6.1.3.1. Overall information and input data

Table 13. Summary of the data for the NMA for the proportion of patients with need for rescue therapy

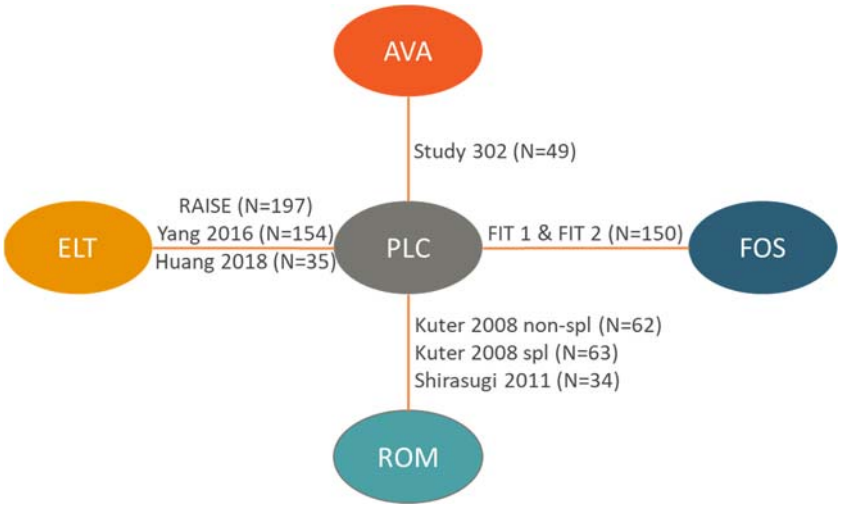
Characteristic		Value
Number of studies		8
Number of treatment regimens		5
Number of patients		744
DIC	Fixed-effects model	**16.774**
	Random-effects model	18.053

Table 14. Input data for the NMA of the estimated incidence of need for rescue therapy

Study	Treatment	Event rate n/N (%)	RR [95%CI]	Mean exposure [years]	Total pts-years	Incidence rate [/pts-yrs.]	IRR [95%CI]
Study 302	AVA	7/32 (21.9%)	1.86 [0.43, 7.98]	0.44	14.02	0.4993	0.73 [0.15, 3.51]
	PLC	2/17 (11.8%)		0.17	2.92	0.6842	
RAISE	ELT	24/135 (17.8%)	0.44 [0.27, 0.71]	0.46	61.57	0.3898	0.46 [0.26, 0.8]
	PLC	25/62 (40.3%)		0.47	29.22	0.8557	
Yang 2016	ELT	9/104 (8.7%)	0.25 [0.12, 0.53]	0.11	11.83	0.7611	0.26 [0.11, 0.58]
	PLC	17/50 (34%)		0.11	5.73	2.9690	
Huang 2018	ELT	0/17 (0%)	0.06 [0, 1.01]	0.11	1.90	0.0000	0.06 [0, 1.13]*
	PLC	8/18 (44.4%)		0.12	2.08	3.8519	
FIT 1 & FIT 2	FOS	27/101 (26.7%)	0.6 [0.38, 0.93]	0.25	25.12	1.0747	0.37 [0.21, 0.65]
	PLC	22/49 (44.9%)		0.16	7.60	2.8944	
Kuter 2008 spl	ROM	11/42 (26.2%)	0.46 [0.24, 0.86]	0.68	28.38	0.3876	0.45 [0.2, 1.01]
	PLC	12/21 (57.1%)		0.66	13.83	0.8674	
Kuter 2008 non-spl	ROM	7/41 (17.1%)	0.28 [0.13, 0.59]	0.68	27.69	0.2528	0.25 [0.1, 0.64]
	PLC	13/21 (61.9%)		0.62	13.11	0.9920	
Shirasugi 2011	ROM	2/22 (9.1%)	0.55 [0.09, 3.4]	0.23	5.08	0.3939	0.54 [0.08, 3.84]
	PLC	2/12 (16.7%)		0.23	2.75	0.7283	

RR – relative risk; IRR – incidence rate ratio *correction for zero events applied

Figure 9. Network of evidence for the incidence of need for rescue therapy



6.1.3.2. NMA results

Figure 10. Forest plot for the incidence rate ratio for comparison AVA vs comparators regarding need for rescue therapy – fixed effect model

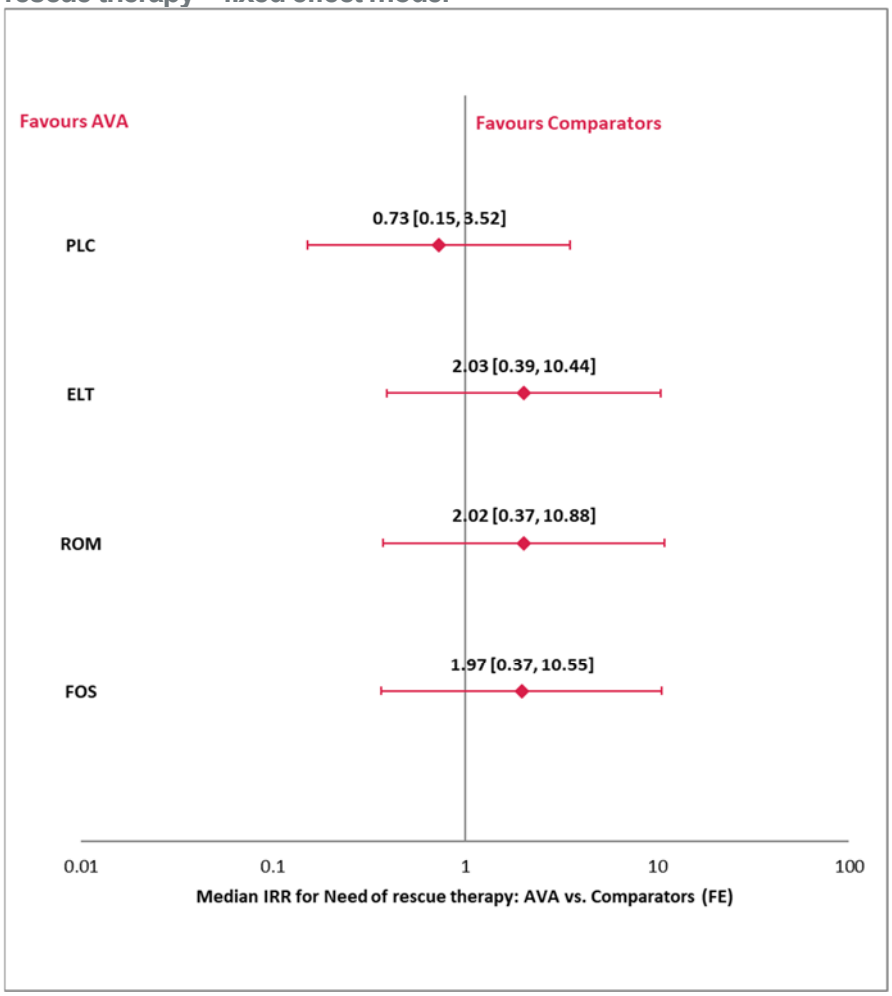


Table 15. Incidence rate ratios and rankings for need for rescue therapy – fixed effect model

	IRR for all comparisons (FE model)					Probability of being best	SUCRA	Probability AVA being better than comparator
	vs. PLC	vs. AVA	vs. ELT	vs. ROM	vs. FOS			
PLC	PLC	1.36 [0.28, 6.60]	**2.76 [1.76, 4.36]**	**2.76 [1.54, 4.94]**	**2.69 [1.53, 4.72]**	0%	9%	65%
AVA	0.73 [0.15, 3.52]	AVA	2.03 [0.39, 10.44]	2.02 [0.37, 10.88]	1.97 [0.37, 10.55]	13%	32%	-
ELT	**0.36 [0.23, 0.57]**	0.49 [0.10, 2.55]	ELT	1.00 [0.48, 2.10]	0.98 [0.47, 2.01]	28%	71%	20%
ROM	**0.36 [0.20, 0.65]**	0.50 [0.09, 2.67]	1.00 [0.48, 2.10]	ROM	0.98 [0.43, 2.19]	31%	70%	21%
FOS	**0.37 [0.21, 0.65]**	0.51 [0.09, 2.72]	1.03 [0.50, 2.11]	1.02 [0.46, 2.30]	FOS	27%	68%	21%

Significant results were reported in bold

6.1.4. Adverse events

6.1.4.1. Overall information and input data

Table 16. Summary of the data for the NMA for the proportion of patients with adverse events

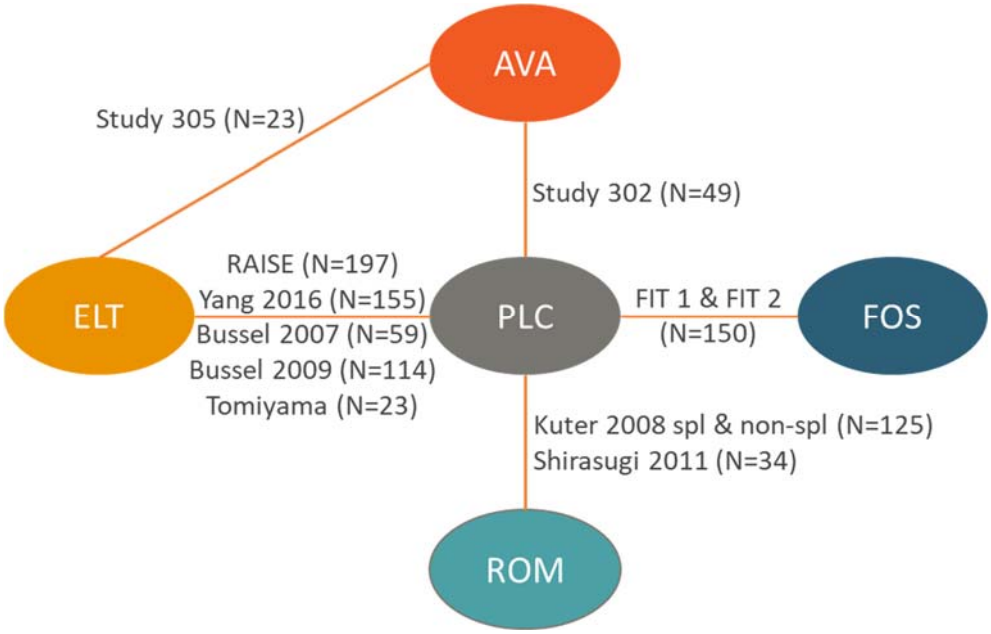
Characteristic		Value
Number of studies		10
Number of treatment regimens		5
Number of patients		928
DIC	Fixed-effects model	**7.409**
	Random-effects model	9.111

Table 17. Input data for the NMA of the estimated incidence of any adverse event

Study	Treatment	Event rate n/N (%)	RR [95%CI]	Mean exposure [years]	Total pts-years	Incidence rate [/pts-yrs.]	IRR [95%CI]
Study 302	AVA	31/32 (96.9%)	1.65 [1.1, 2.46]	0.44	14.02	2.2112	0.65 [0.32, 1.32]
	PLC	10/17 (58.8%)		0.17	2.92	3.4211	
Study 305	AVA	11/12 (91.7%)	0.92 [0.77, 1.09]	0.30	3.62	3.0426	0.62 [0.27, 1.42]
	ELT	11/11 (100.0%)		0.20	2.23	4.9310	
RAISE	ELT	118/135 (87.4%)	0.95 [0.86, 1.05]	0.46	61.57	1.9165	0.98 [0.72, 1.35]
	PLC	56/61 (91.8%)		0.47	28.74	1.9482	
Tomiyama	ELT	11/15 (73.3%)	2.93 [0.85, 10.12]	0.12	1.73	6.3556	2.93 [0.65, 13.23]
	PLC	2/8 (25%)		0.12	0.92	2.1667	
Yang 2016	ELT	66/104 (63.5%)	0.95 [0.75, 1.21]	0.15	15.69	4.2059	0.95 [0.63, 1.44]
	PLC	34/51 (66.7%)		0.15	7.69	4.4200	
Bussel 2007	ELT	14/30 (46.7%)	0.80 [0.49, 1.30]	0.09	2.64	5.3012	0.91 [0.45, 1.85]
	PLC	17/29 (58.6%)		0.10	2.92	5.8145	
Bussel 2009	ELT	45/76 (59.2%)	1.61 [1.02, 2.54]	0.10	7.30	6.1667	1.72 [0.94, 3.13]
	PLC	14/38 (36.8%)		0.10	3.90	3.5852	
FIT 1 & FIT 2	FOS	85/102 (83.3%)	1.11 [0.92, 1.34]	0.25	25.37	3.3503	0.69 [0.47, 1.02]
	PLC	36/48 (75.0%)		0.16	7.45	4.8350	
Kuter 2008 spl & non-spl	ROM	84/84 (100.0%)	1.05 [0.98, 1.13]	0.67	56.41	1.4892	1.02 [0.70, 1.49]
	PLC	39/41 (95.1%)		0.65	26.62	1.4653	
Shirasugi 2011	ROM	20/22 (90.9%)	0.99 [0.80, 1.23]	0.23	5.08	3.9394	0.98 [0.47, 2.05]
	PLC	11/12 (91.7%)		0.23	2.75	4.0056	

RR – relative risk; IRR – incidence rate ratio

Figure 11. Network of evidence for the incidence of any adverse event



Inconsistency analysis with Bucher's method was not feasible for the outcome 'need for rescue therapy' because there were no closed loops in the network of evidence.

6.1.4.2. NMA results

Figure 12. Forest plot for the incidence rate ratio for comparison AVA vs comparators regarding any adverse event – fixed effect model

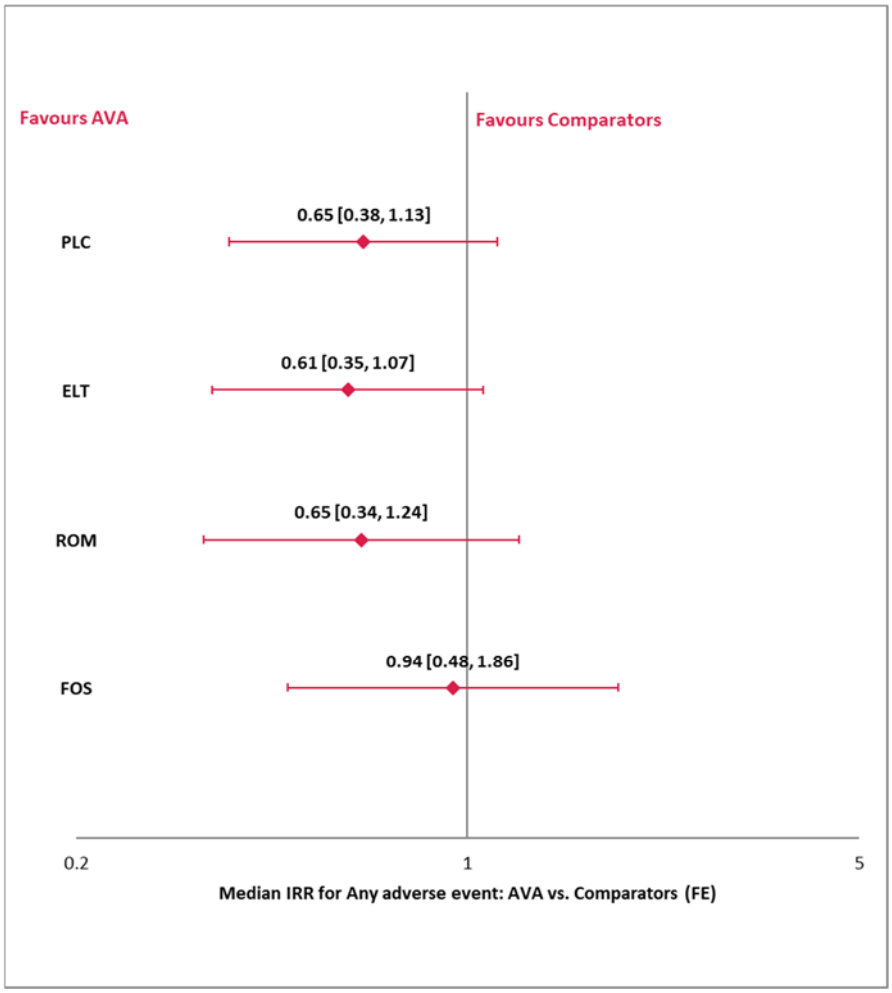


Table 18. Incidence rate ratios and rankings for any adverse event – fixed effect model

	IRR for all comparisons (FE model)					Probability of being best	SUCRA	Probability AVA being better than comparator
	vs. PLC	vs. AVA	vs. ELT	vs. ROM	vs. FOS			
PLC	PLC	1.53 [0.89, 2.66]	0.94 [0.76, 1.16]	0.99 [0.71, 1.39]	1.44 [0.98, 2.13]	0%	33%	94%
AVA	0.65 [0.38, 1.13]	AVA	0.61 [0.35, 1.07]	0.65 [0.34, 1.24]	0.94 [0.48, 1.86]	56%	84%	-
ELT	1.07 [0.86, 1.32]	1.63 [0.94, 2.86]	ELT	1.06 [0.71, 1.58]	1.54 [0.99, 2.40]	0%	19%	96%
ROM	1.01 [0.72, 1.41]	1.55 [0.81, 2.96]	0.95 [0.63, 1.41]	ROM	1.46 [0.87, 2.43]	2%	31%	91%
FOS	0.69 [0.47, 1.02]	1.06 [0.54, 2.09]	0.65 [0.42, 1.01]	0.69 [0.41, 1.15]	FOS	42%	82%	57%

Significant results were reported in bold

6.1.4.3. Analysis of consistency

Analysis of consistency within the closed loop AVA-PLC-ELT was conducted using modified Bucher's method as outlined in the NICE DSU TSD 4 (http://nicedsu.org.uk/wp-content/uploads/2016/03/TSD4-Inconsistency.final_.15April2014.pdf) according to the following schedule:

1. Studies comparing ELT vs PLC were meta-analysed using random-effect model (Figure 13).
2. Bucher's indirect comparison was conducted between estimates from Study 302 and the outcomes of step 1. (Table 19)
3. The consistency between a head-to-head study comparing AVA and ELT (Study 305) and the indirect estimates was assessed using heterogeneity test (Figure 14)

The analysis of consistency revealed no heterogeneity (I^2 = 0%) between direct (Study 305) and indirect estimates for the comparison between AVA vs ELT, which indicates that there is no evidence for inconsistency in this loop of the network.

Figure 13. Forest plot for the pairwise meta-analysis of studies comparing ELT vs PLC

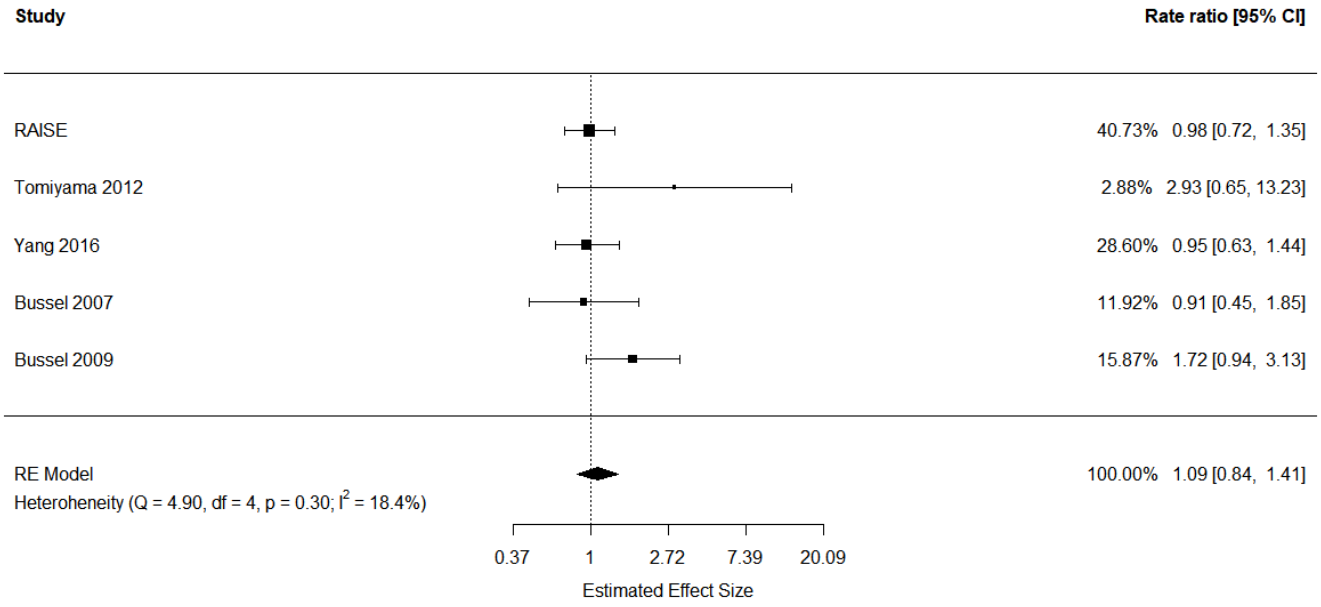
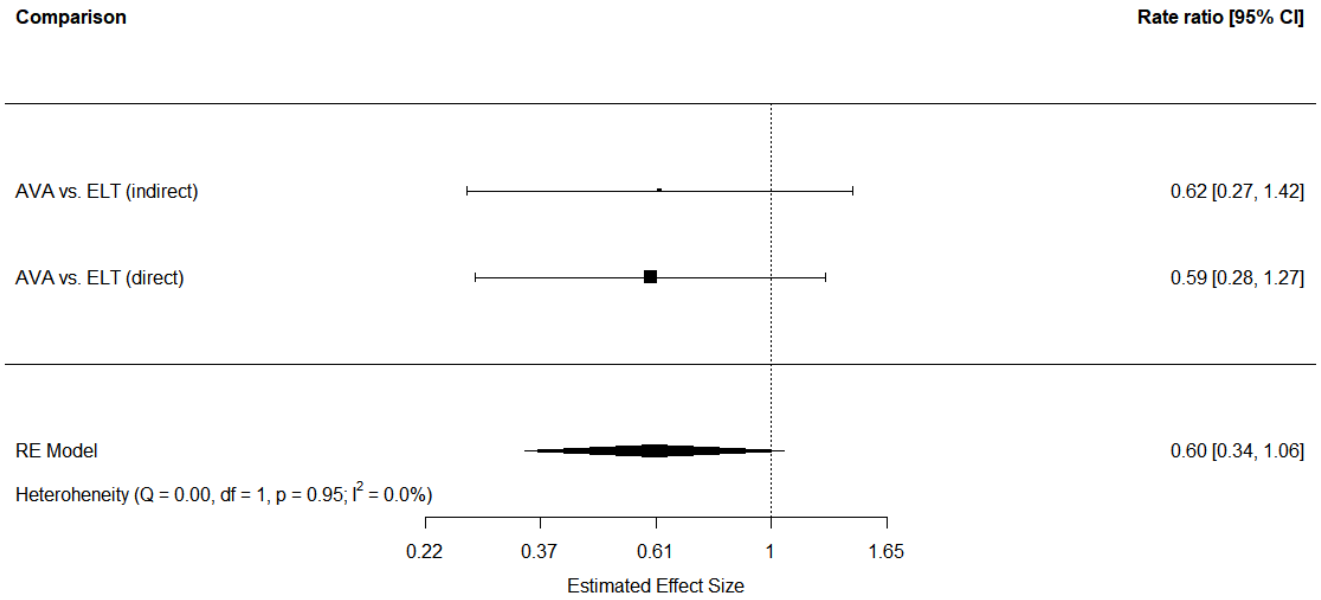


Table 19 Indirect comparison AVA vs. ELT

AVA vs. PLC (Study 302)	ELT vs. PLC (Pairwise MA – RE model)	AVA vs. ELT (Bucher's method)
0.65 [0.32, 1.32]	1.09 [0.84, 1.41]	**0.59 [0.28, 1.27]**

Figure 14. Analysis of consistency between direct and indirect evidence for the comparison between AVA and ELT.



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8. Appendix 1: Results of random-effect models

8.1. Incidence of any bleeding events

Table 20. Incidence rate ratios and rankings for any bleed – random effect model

	IRR for all comparisons (RE model)						Probability of being best	SUCRA	Probability AVA being better than comparator
	vs. PLC	vs. AVA	vs. ELT	vs. ROM	vs. FOS	vs. SoC			
PLC	PLC	**3.46 [1.21, 10.98]**	1.64 [0.92, 3.64]	1.25 [0.48, 3.28]	2.00 [0.53, 7.68]	0.89 [0.19, 4.30]	0%	21%	99%
AVA	**0.29 [0.09, 0.83]**	AVA	0.47 [0.16, 1.53]	0.36 [0.08, 1.49]	0.58 [0.10, 3.15]	0.26 [0.04, 1.64]	72%	91%	-
ELT	0.61 [0.27, 1.09]	2.11 [0.65, 6.14]	ELT	0.77 [0.21, 2.23]	1.23 [0.24, 4.91]	0.55 [0.09, 2.68]	3%	59%	92%
ROM	0.80 [0.31, 2.07]	2.76 [0.67, 12.28]	1.31 [0.45, 4.69]	ROM	1.60 [0.31, 8.34]	0.71 [0.21, 2.47]	2%	42%	94%
FOS	0.50 [0.13, 1.89]	1.73 [0.32, 10.12]	0.81 [0.20, 4.12]	0.63 [0.12, 3.25]	FOS	0.44 [0.06, 3.52]	20%	67%	78%
SoC	1.13 [0.23, 5.34]	3.89 [0.61, 27.15]	1.83 [0.37, 11.31]	1.41 [0.40, 4.83]	2.27 [0.28, 17.26]	SoC	3%	20%	94%

Significant results were reported in bold

8.2. Incidence of bleeding events WHO grade 2-4

Table 21. Incidence rate ratios and rankings for bleeding events WHO grade 2-4 – random effect model

	IRR for all comparisons (RE model)						Probability of being best	SUCRA	Probability AVA being better than comparator
	vs. PLC	vs. AVA	vs. ELT	vs. ROM	vs. FOS	vs. SoC			
PLC	PLC	1.73 [0.09, 16.12]	1.48 [0.24, 6.12]	2.34 [0.42, 15.25]	2.63 [0.24, 30.58]	1.61 [0.09, 33.70]	0%	20%	71%
AVA	0.58 [0.06, 11.36]	AVA	0.84 [0.10, 10.80]	1.34 [0.10, 50.23]	1.51 [0.07, 88.31]	0.91 [0.03, 78.29]	22%	52%	-
ELT	0.68 [0.16, 4.16]	1.19 [0.09, 10.05]	ELT	1.58 [0.19, 23.69]	1.78 [0.12, 42.96]	1.08 [0.05, 42.29]	4%	44%	58%
ROM	0.43 [0.07, 2.38]	0.75 [0.02, 10.39]	0.63 [0.04, 5.35]	ROM	1.14 [0.05, 22.24]	0.69 [0.07, 7.39]	22%	69%	40%
FOS	0.38 [0.03, 4.16]	0.66 [0.01, 14.56]	0.56 [0.02, 8.53]	0.88 [0.04, 19.81]	FOS	0.61 [0.01, 29.79]	38%	70%	37%
SoC	0.62 [0.03, 11.34]	1.10 [0.01, 31.76]	0.92 [0.02, 20.66]	1.46 [0.14, 15.24]	1.65 [0.03, 70.63]	SoC	13%	46%	53%

Significant results were reported in bold

8.3. Incidence of need for rescue therapy

Table 22 Incidence rate ratios for need for rescue therapy - random effect model

	IRR for all comparisons (RE model)					Probability of being best	SUCRA	Probability AVA being better than comparator
	vs. PLC	vs. AVA	vs. ELT	vs. ROM	vs. FOS			
PLC	PLC	1.35 [0.15, 12.76]	**3.06 [1.16, 12.95]**	2.72 [0.81, 8.37]	2.69 [0.44, 16.34]	0%	13%	62%
AVA	0.74 [0.08, 6.81]	AVA	2.33 [0.22, 34.52]	2.00 [0.15, 23.80]	1.98 [0.12, 33.10]	13%	34%	-
ELT	**0.33 [0.08, 0.86]**	0.43 [0.03, 4.65]	ELT	0.88 [0.12, 3.67]	0.88 [0.08, 6.15]	35%	73%	22%
ROM	0.37 [0.12, 1.24]	0.50 [0.04, 6.56]	1.13 [0.27, 8.01]	ROM	0.99 [0.12, 8.68]	24%	65%	26%
FOS	0.37 [0.06, 2.29]	0.51 [0.03, 8.57]	1.13 [0.16, 13.20]	1.01 [0.12, 8.45]	FOS	28%	64%	27%

8.4. Incidence of adverse event

Table 23 Incidence rate ratios for adverse events - random effect model

	IRR for all comparisons (RE model)					Probability of being best	SUCRA	Probability AVA being better than comparator
	vs. PLC	vs. AVA	vs. ELT	vs. ROM	vs. FOS			
PLC	PLC	1.51 [0.76, 2.95]	0.91 [0.61, 1.24]	1.00 [0.59, 1.71]	1.44 [0.74, 2.86]	1%	36%	89%
AVA	0.66 [0.34, 1.31]	AVA	0.60 [0.30, 1.18]	0.66 [0.28, 1.59]	0.95 [0.38, 2.53]	51%	81%	-
ELT	1.09 [0.81, 1.63]	1.67 [0.85, 3.35]	ELT	1.09 [0.61, 2.16]	1.58 [0.78, 3.56]	0%	19%	94%
ROM	1.00 [0.59, 1.70]	1.52 [0.63, 3.60]	0.91 [0.46, 1.65]	ROM	1.45 [0.62, 3.43]	5%	36%	85%
FOS	0.69 [0.35, 1.35]	1.05 [0.40, 2.64]	0.63 [0.28, 1.29]	0.69 [0.29, 1.62]	FOS	42%	78%	54%

Clinician survey on real-world treatment patterns and utilisation in chronic ITP

1. Background

To address select uncertainties identified by the Evidence Review Group during the NICE appraisal of avatrombopag [GID-TA10738], the company prepared a clinical expert survey comprising several questions [*Appendix B*] aimed at understanding their real-world experience of management of primary chronic ITP, including: their approach to first-line therapy selection; sequencing of subsequent lines of therapies; rescue therapy utilisation, and; duration of response for TPO-RAs in the context of chronic disease. Where relevant, clinicians were requested to discriminate further between members of the TPO-RA class (I.e. avatrombopag, romiplostim, and eltrombopag), particularly as this is relevant to anticipated duration of treatment and/or platelet response.

2. Summary of results

2.1 Clinical experience

A total of 10 clinical experts were invited to participate in the survey, of which 9 responded prior to the survey closure [*Appendix A*]. 100% (9/9) of respondents were Consultant Haematologists and ITP clinical leads at centres meeting the ITP specialist centre criteria set out by the UK ITP forum, with a mean of 20 years (range: 7-40 years) of reported experience in treating ITP patients. 1/9 experts (11%) reported direct (positive) clinical experience of using avatrombopag in chronic ITP, outside of the clinical trial setting.

2.2 Treatment selection

The clinical experts were asked to provide their approach to first-line treatment of ITP. 7/9 (78%) of respondents would consider steroids or IVIg; 1/9 (11%) would consider only corticosteroids, and 1/9 (11%) would consider *only* a TPO-RA. 2/9 (22%) of clinical experts also indicated that they consider using a TPO-RAs in the first-line setting during the COVID-19 pandemic, which reflects interim NHSE COVID-19 commissioning guidance.[1]

[1] NHS England (2022) Interim Clinical Commissioning Policy: Thrombopoietin receptor agonists as first line therapy for new or relapsed immune thrombocytopenia in adults and children over the age of 1 year during the COVID-19 pandemic. Available at <https://www.england.nhs.uk/coronavirus/publication/interim-clinical-commissioning-policy-thrombopoietin-receptor-agonists-as-first-line-therapy-for-new-or-relapsed-immune-thrombocytopenia-in-adults-and-children-over-the-age-of-1-year/>

When the clinical experts were asked to indicate where they would use avatrombopag if available, 8/9 (89%) of respondents indicated that they would use avatrombopag in the same treatment line as other available TPO-RAs, with one of these experts qualifying that the decision would be as part of an individualised patient discussion. The clinical experts cited several reasons for this decision, including provision of reliable randomised controlled trial (RCT) data for avatrombopag in ITP and perceived advantages over other TPO-RAs including a lack of dietary restrictions, oral mode of administration and similar effectiveness. One expert indicated that they were unsure/unable to comment at this stage.

2.3 Treatment duration

The clinical experts reported varying experiences with regards to average duration of treatment response for chronic ITP patients on stable treatment with TPO-RAs, which ranged from "weeks/months" to "2.5 years". 2/9 (22%) of the clinical experts noted that a minority of responders achieve a stable response and are able to discontinue treatment, with consistent estimates of "20-30%" and "25%" of patients reported to meet this criterion by the pair of experts. Conversely, another 2/9 (22%) of clinical experts noted that the same group of patients may lose their response to any given TPO-RA, with one clinician citing this to be as many as 40% of responders in their experience. Nevertheless, despite varying experiences in observed duration of treatment with currently available TPO-RAs, 6/9 (67%) of experts expected a similar or longer duration of treatment for patients treated with avatrombopag as compared to alternative TPO-RAs. The remaining 3/9 (33%) of experts reported that they were unsure or unable to comment.

2.3 Use of rescue therapy

When exploring the experts' frequency of rescue intervention utilisation in chronic ITP patients, the clinical experts estimated a comparatively lower mean rescue therapy requirement of just 7.8% of patients (range: 0-30%) with an average platelet count of at least $50x10^9$/L. For patients with a platelet count of less than $50x10^9$/L, the experts reported a comparatively higher mean rescue requirement in 36.9% (range: 5-90%) of patients.

In response to further questioning on patients that require rescue therapy, only 8 clinicians responded, and several were unable to provide numerical estimates on the percentage of patients treated with each rescue interventions. Nevertheless, the responses show that IVIg and corticosteroids are predominately used, with platelet

transfusions reserved for patients with high bleeding risk or requiring urgent invasive procedures:

1. Intravenous immune globulin (IVIg)

   Responses: Range: 30-65% [*30%, 50%, 65%, 'only if urgent platelet rise needed', 70/80%, 30%, 'if bleeding risk', 'use dependent on co-morbidities'*]

2. Corticosteroids

   Responses: Range: 0-100% [*70%, 90%, 30%, 100%, 'until the start of the pandemic – now use TPO first line', 'use dependent on co-morbidities', 20%, 'depends on previous responses', 90%]*

3. Anti-D immunoglobulin (Anti-D)

   Responses: 0% [*all 8 respondents*]

4. Dapsone

   Responses: Range: 0-5% [*0% - 7 respondents, 5% - 1 respondent*]

5. Platelet transfusion

   Responses: Range: 0-30% [*0% <5%, 30%, '20% for immediate surgery or as a short term bridge', 'very occasionally if marked bleeding symptoms and/or need urgent invasive procedure', 'only if bleeding', 'only if no response to rescue therapy', 'if there is a bleeding risk']*

6. Other

   Responses: Mycophenolate, 5% TPO (eltrombopag)

Appendix A – Name and treating centre of respondents

Consultant name	ITP Clinical Centre/Trust
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Appendix B – Survey questions

1. About you:

a. What is your name?

b. Are you a Consultant Haematologist?

c. At which ITP Centre(s) do you treat ITP patients?

d. How many years have you treated ITP patients?

e. Do you have clinical experience of treating with Doptelet (avatrobopag) (e.g. as part of a trial)?

2. ITP treatment pathway

a. What are typically the first-line treatment(s) you would select for ITP patients requiring medical intervention?

- Corticosteroids
- Intravenous immunoglobulins
- Other (*free text box*)

b. If Doptelet (avatrobopag) was available, would you use/substitute it in the same treatment line for other available thrombopoietin receptor agonist (TPO-RAs)

- Yes
- No
- Unsure / unable to comment

Please provide further comment as appropriate [*free text box*]

3. Long-term treatment duration

a. What is the average length of treatment response for chronic ITP patients on stable treatment with the following TPO-RA interventions?

- Eltrombopag
- Romiplostim

b. If Doptelet (avatrombopag) was available, how would you expect it to compare with eltrombopag and romiplostim in terms of the average length of treatment response for patients on stable treatment?

- A similar duration
- Longer
- Shorter
- Unsure / unable to comment

Please provide further comment as appropriate [*free text box*]

4. Rescue therapy

a. Please provide an estimate of the percentage of chronic ITP patients requiring rescue therapy:

- With a platelet count $\geq 50\times10^9$/L
- With a platelet count $<50\times10^9$/L

Please provide further comment as appropriate [*free text box*]

b. For chronic ITP patients treated with a rescue therapy, please estimate the percentage of these patients you treat with the following rescue interventions:

- IVIg
- Corticosteroids
- Anti-D
- Dapsone
- Platelet transfusion
- Other [free text box]

Please provide further comment as appropriate [*free text box*]

5. Comments

If you have any further comments, please provide them here.

[free text box]

ENDS

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Avatrombopag in combination for treating chronic immune thrombocytopenia [ID3838]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Clinical expert statement

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **<<insert deadline>>**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Clinical expert statement

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating chronic immune thrombocytopenia and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	[redacted]
2. Name of organisation	[redacted]
3. Job title or position	[redacted]
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with chronic immune thrombocytopenia? ☐ A specialist in the clinical evidence base for chronic immune thrombocytopenia or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it (**UK ITP Forum submission**) ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
8. What is the main aim of treatment for chronic immune thrombocytopenia?	Treatment needs to be individualised to the patient. However generally, treatment aims to prevent severe bleeding episodes, and this is usually achieved

(For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	by maintaining a platelet count above 30.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	As per the international consensus, an increase in platelet count to greater than 30, double baseline and an absence of bleeding (PMID: 19005182).
10. In your view, is there an unmet need for patients and healthcare professionals in chronic immune thrombocytopenia?	Yes, not all patients respond or tolerate currently available therapies
11. How is chronic immune thrombocytopenia currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Adult patients with ITP requiring initial treatment will usually receive corticosteroids and/or intravenous immunoglobulins. Patients subsequently requiring treatment will typically receive a thrombopoietin receptor agonist (TPO RA) i.e. romiplostim or eltrombopag. Alternative treatment options include rituximab, mycophenolate or azathioprine. Due to different efficacy and side effect profiles, the choice of medical therapy is individualised. Evidence from the adult UK ITP registry showed that the use of surgical splenectomy to treat ITP is in decline (EHA 2019 PF691 Splenectomy in immune thrombocytopenia: do changing treatment patterns for ITP affect outcomes? Data from the UK ITP Registry). There are currently no UK specific guidelines. The British Society of Haematology previously signposted clinicians to the first international consensus guideline (2010 PMID: 19846889) and practice in the UK has been broadly in line with that. The international consensus guideline was updated in 2019 (PMID: 31770441). ITP is a rare condition with relatively little high grade evidence. The guideline is therefore permissive for the selection of second and third line therapies and clinicians will typically make individualised decisions about these treatments in partnership with their patients. Avatrombopag is listed

	in these guidelines as a second line medical therapy with relatively robust evidence (alongside romiplostim, eltrombopag, fostamatinib and rituximab). At the current time, fostamatinib has not been approved by NICE and is not routinely available in England. Since onset of the COVID-19 pandemic, there has been a greater focus on non-immunosuppressive treatment options (such as TPO RA), due to the association between immunosuppression and worse outcome following COVID-19 infection, and TPO RA would now be most commonly considered second line. Patients not responding or tolerating one TPO RA will often have a trial of an alternative TPO RA, with a reasonable chance of success. Introducing Avatrombopag as a third TPO RA within its licence indication "ITP in adults refractory to other treatments (e.g. corticosteroids, immunoglobulins)" is likely to result in its use second line, similar to currently prescribed TPO RA drugs.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	ITP is a condition managed by haematologists in secondary care. Prescribing would be limited to this setting. This is an oral drug and no additional investment would be needed to introduce the technology. Resource use will not increase with this treatment. An alternative TPO RA romiplostim is a subcutaneous injection weekly that requires some day unit support to deliver (and/or train patients to self-administer). Hence a reduction in romiplostim use could result in some reduction in resource needs if patients took an oral treatment instead.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life	The introduction of a further effective non-immunosuppressive agent has the potential to increase length of life, although this will be difficult to prove in a trial setting due to rarity of ITP and also of fatal bleeding events. Additionally, the excess mortality observed in ITP patients vs. the general population, is as much

more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	related to infection as it is to bleeding (PMID 21263148, PMID 11313240) and therefore the successful reduction of concomitant steroids, and avoidance of alternative immunosuppressive treatments, could translate to lower mortality through infection as well as avoidance of bleeding. There is little formal data published on HRQoL in studies of avatrombopag for ITP. It could be anticipated that HRQoL gains may be achieved over alternative TPO RA as this treatment offers the convenience of oral therapy without dietary restrictions. HRQoL gains could also occur in patients able to reduce or stop concomitant medications with known adverse effects, such as corticosteroids.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No clear subgroups. There remains uncertainty over whether TPO RA class is associated with greater thrombosis risk (PMID: 35007700). Hence alternative treatments may be more appropriate in those with the highest perceived thrombotic risk, but individual thrombotic risk also needs to be balanced against other differences such as efficacy, need for anticoagulation & infection risk when deciding on the best treatment option for an individual patient.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Easier. Unlike eltrombopag, no dietary restrictions for the patient Unlike romiplostim, no subcutaneous injections or training or day unit time required Unlike rituximab, no day unit infusions. If patient responds then reduction in concomitant medications such as steroids (as per real world study PMID: 35179784)
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Starting treatment would be informed by the treatment goals described above, TPO RA would be stopped for intolerance or treatment failure (failure to respond

	after patient has received the maximum dose for 4 weeks). Drug would also be tapered and ultimately stopped if platelet count remained above the target range of 50-150 as per SPC. Otherwise treatment would be long term maintenance, although real world and trial data of other TPO RA suggest that some patients with platelet counts in the range 50-150 can be successfully tapered and stopped after a period of time, and still maintain their platelet count.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Limited data available for avatrombopag. HRQoL tools specific to ITP are available, while some general scales have been validated for use in ITP (PMID: 30568522). Trial is against placebo and will not capture the benefits over alternative TPO RA (oral, no dietary restrictions).
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	There are some clear advantages from a patient perspective. Particularly lack of the dietary restrictions required for eltrombopag, which can be forgotten or confused by older patients who take calcium or dairy products that reduce absorption of eltrombopag, leading to breakthrough thrombocytopenia.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Most commentators have considered avatrombopag safe and well tolerated in patients with chronic ITP e.g. PMID: 34815110. In meta-analysis, No statistically significant differences were observed for AEs avatrombopag compared to placebo, with the caveat that these studies were not powered for safety considerations (PMID: 33934279). The most common TEAEs reported in the phase III study were: headache, contusion, upper respiratory tract infection, arthralgia, epistaxis, fatigue,

	gingival bleeding and petechiae. The bleeding symptoms and fatigue are likely to be explained by the underlying condition. Headache was reported in other TPO RA studies and is seldom an issue in real world practice. Overall, 9/128 patients had a thromboembolic event, a rate that appears similar to that reported in long term studies of other TPO RA.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes. However the criteria for response in TPO RA clinical trials have used more stringent end points to define response, that would be used in the real world, when a platelet count greater than 30 without clinical bleeding could still be judged successful. Hence, in real world practice, the number of patients considered to be treatment responders, may be higher.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	PMID: 33934279. Network meta-analysis of avatrombopag PMID: 35179784. Real world study of avatrombopag (see Q23)
22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA759]?	PMID: 35149911. Network meta-analysis of 19 ITP treatments. PMID: 33251910. Phase III study of eltrombopag in China
23. How do data on real-world experience compare with the trial data?	PMID: 35179784. Retrospective multicentre study of 44 patients switching from alternative TPO RA to avatrombopag. 41/44 (93%) achieved a platelet count >50 with 57% able to discontinue concomitant medications including steroids. This suggests that in real world usage, treatment will be at least as effective as demonstrated in the phase III trial.
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any	No

potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Positioning of rituximab in the treatment pathway The treatment pathway and positioning of avatrombopag relative to non-thrombopoietin receptor agonists (TPO-RAs) such as rituximab. At what point in the treatment pathway would you expect patients to have avatrombopag? How non-TPO-RAs such as	As outlined above, the TPO RA class, including avatrombopag would most likely to be considered second line and before immunosuppressive options such as rituximab. This position being somewhat consolidated in the COVID era. The individualised patient decision continues to be emphasised in guidelines. Patient preference, activities, work plan and perceived burden of treatment may influence the decision. Younger women have been observed to have better responses to rituximab, and reproductive plans may influence decision making. TPO RA class has not been proven to represent a greater risk of TE events, but perceived TE risk may also influence treatment selection.

rituximab are currently used in practice for treating the condition? If recommended, would avatrombopag be offered as an alternative option to non-TPO-RAs such as rituximab, or be used before or after rituximab?	
Limited evidence base for avatrombopag due to recruitment and attrition issues Both two main avatrombopag trials had issues with their methodology, with limited evidence on avatrombopag's treatment effect relative to the placebo or eltrombopag. The ERG has highlighted that no alternative data exist. Is this the case? Are you aware of other evidence on the comparative effectiveness of avatrombopag relative to the placebo or	Please see Q21

eltrombopag?	
Exclusion of some TPO-RA trials from the NMAs in the company's submission The company excluded 7 TPO-RA comparator trials from their network meta-analysis (NMA), which assessed the treatment effect of avatrombopag relative to other treatments currently in use as well as the placebo. These were due to treatment durations, initial TPO-RA doses, and population ethnicity. The ERG disagreed with these exclusions. Do you consider excluding these TPO-RA trials from the NMA appropriate based on how TPO-RA treatments are used in practice? Do you agree that including these TPO-RA comparator trials in the NMAs could contribute to data on more clinically important	I largely agree with the ERG assessment. My comments are the same as the ITP forum, copied below. Obviously, any TPO RA cost comparison should fairly reflect the ethnic background of patients in the UK, since the lower starting dose of eltrombopag is only used in those of certain Asian background. However we think that the ERG is well aware of this and looks to include relevant endpoints such as bleeding events from these studies, which seems reasonable. We also agree that the real world starting dose of romiplostim is more typically 3 mcg/kg, as demonstrated in a published review of practice by the UK ITP Forum (PMID 27879997). Although largely reflecting most patients who will respond to treatment, It is possible that studies of <9 weeks may underestimate the response rate. SPC states treatment failure is no response after 4 weeks at maximum dose, and it can take time to titrate dose with romiplostim (dose range 1-10 mcg/kg)

outcomes such as bleeding?	
Modelled time to treatment response The company assumes that patients would wait a full 24 weeks to determine a 'non-response' to TPO-RA treatment (avatrombopag, eltrombopag, romiplostim) in its model. The ERG considered this timeframe should be within 8 weeks rather than 24 weeks. In your opinion, which timeframe reflects the clinical practice more closely? How long would patients stay on a TPO-RA treatment such as avatrombopag despite the lack of response of the condition to the treatment in practice?	A failure to respond to TPO RA after 4 weeks at maximum dose would represent a treatment failure. For real world prescribing, I think 8-10 weeks for avatrombopag and eltrombopag, 12-16 weeks for romiplostim (there are more dose increments before reaching maximum dose). As discussed, what constitutes a clinically meaningful treatment response in the real world may include a platelet count between 30 and 50.
Modelled treatment sequences and stopping TPO-RAs The company has not	As stated, there remains some uncertainty over the relative effectiveness of the three TPO RA discussed. In practice, all three TPO RA appear to have good response rates in clinical practice compared to immunosuppressive treatments. If there were no funding restrictions, the advantages of

used the modelled treatment sequences to determine the most efficient use and positioning of avatrombopag among the TPO-RAs. This analysis requires additional evidence on the comparative effectiveness between avatrombopag, eltrombopag and romiplostim, and the duration of each treatment. What would be the positioning of avatrombopag among TPO-RAs in terms of sequence of treatments in practice? Do patients stay on TPO-RAs for the same duration in the long term?	no dietary restriction and oral delivery would make it likely that avatrombopag would be sequenced ahead of eltrombopag and romiplostim. The duration of treatment is likely to be broadly similar between TPO RA.
Modelled treatment response rates for TPO-RAs and non-TPO-RAs Treatment response estimates for first and subsequent lines of therapy in the model are	For non TPO RA studies, the most clinically relevant definition of a platelet response is >30, double baseline and absence of bleeding. This is based on an international consensus (PMID: 19005182). How long the condition takes to respond to the non-TPO RA treatment will depend on the treatment. For example response to rituximab can occur within 3-6 weeks but also later responses after 3-4 months have been reported. Initial response rates of 60-80% are reported for rituximab (PMID: 31770441).

based on different definitions of 'response' for TPO-RAs and non-TPO-RAs. A response for TPO-RAs was defined as durable platelet count, whereas the definition for treatment response for non-TPO-RAs is unclear. How would a treatment response to non-TPO-RAs be defined in practice? How long it takes the condition to respond to non-TPO-RAs? And what is the proportion of patients respond to non-TPO-RAs?	Generally, it will take longer to response to rituximab and oral immunosuppression compared to TPO RA.
Long-term treatment duration The long-term durability of treatment response on TPO-RA treatment was assumed to be an average of 436 weeks/8.4 years over a patient's lifetime. The ERG considered that the	Most patients who discontinue TPO RA for reasons of treatment failure (e.g. platelet swings, non response) or side effects, are likely to do so in the first year. Those with stable responses lasting for longer than this, are quite likely to be stable on drug over the longer term. Some patients are able to discontinue drug and maintain their platelet count after careful tapering. Perhaps around 1 in 8 in my experience, but studies vary. Since eltrombopag and romiplostim differ in delivery (oral vs SC), dosing range, dietary restrictions (eltrombopag) and side effect profile, it would be reasonable to think that long term compliance/tolerance may differ, however I have patients who have been stable for over a decade on

long-term discontinuation rates of different TPO-RAs are likely to be different. And even the treatment durations/discontinuation rates are identical among TPO-RAs, the actual mean estimate would have an impact on the model results. Would patients stay on TPO-RAs for the same length of time after an initial response of their condition in your opinion? How long would patients be expected to stay on different TPO-RA treatments? What would be the range of treatment duration of TPO-RA treatments in the long term in your opinion?	both drugs and that difference does not seem to be very marked.
Rates of rescue therapy The rates of rescue therapy for responders	Most patients who receive a second or greater line of treatment will receive rescue therapy initially, while waiting for that treatment to work. That rescue therapy is most commonly steroids (sometimes IVIg), that is then tapered and stopped as the platelet count rises. For non responding patients, during the time that is being given to decide if the line of treatment is effective or not, the rescue might

Clinical expert statement

and non-responders to treatment are uncertain in the company's model. The company used 3% for responders and 22% for non-responders per model cycle, respectively. The ERG is unable to validate the rates reported by the company. Usually how many patients whose condition responds to the treatments would need a rescue therapy? And how many whose condition does not respond to the treatments would need a rescue therapy?	continue (e.g. steroid) or need to be re-introduced. In responders, they are likely to have had initial rescue at the beginning of treatment, but once the response is achieved, they are unlikely to require rescue treatment at all. That said, those on TPO RA for a long time may experience a temporary breakthrough drop in platelets, for example triggered by an infection and require an additional rescue therapy e.g. low dose steroid, that can be tapered and stopped.
Mortality risks associated with immune thrombocytopenia (ITP). The company only considered fatal bleeds for disease-related mortality. There is	In a population-based study, patients with chronic ITP had a twofold increase in mortality compared with the age and gender-matched general population (5-year mortality 24% vs. 14%) (Norgaard et al, 2011) even when controlled for co-morbidity. Norgaard et al (2011) explored the causes of this excess mortality, finding that 5-year cause-specific mortality was significantly higher for infection (4.2% vs. 0.7%), haemorrhage (2.5% vs. 0.3%) and subsequent development of haematological malignancy (3.3% vs. 0.4%). PMID 21263148

considerable uncertainty surrounding the long-term survival of ITP patients. Besides fatal bleeding, what other mortality risks affect patients with chronic ITP in the long term?	
Administration costs for romiplostim The ERG has main concerns with the company's assumptions on the administration costs for romiplostim. The company assumed that: the first 4 romiplostim administrations are costed within a clinical setting; and 27.7% of long-term patients administrating romiplostim in a clinic setting. The ERG assumed that: all patients receive their first dose in a clinical setting; and 27% thereafter (as opposed to the first 4 doses received in a clinical	The company may be closer on this one. It is likely that most patients (>50%) during the titration phase e.g. weeks 1-10 will be attending weekly or every 2 weeks to the day unit for blood count check and having romiplostim dosed and then administered by day unit staff. In treatment responders receiving a prescription for 4 weeks, who do not require a blood count check and not wanting to attend the day unit, the majority (>50%) will administer or have a carer administer at home. But I still have a number of often older patients on long term romiplostim, that attend weekly for staff to give their romiplostim as they are unwilling or unable to give or have a family member give at home. Difficult to know the exact figures without a clinical audit.

setting) or, 12.5% of patients received romiplostim in a clinical setting after their first clinical visit. And the clinical administration costs for romiplostim is the same as clinical haematology outpatient visit (£165.57) as opposed to £241.06. Between the company and ERG's scenarios, which reflect the clinical practice more closely in your opinion? How romiplostim is administered in practice in terms of the proportion of patients having their first dose(s) in a clinical setting; and the proportion of patients receiving it in a clinical setting thereafter?	
Are there any important issues that have been missed in the ERG report?	No

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Avatrombopag appears effective and well tolerated and would be a welcome addition to available TPO RAs
It would be likely to be used most frequently, but not invariably, before immunosuppressive treatments
It has some advantages over alternative TPO RAs, with greater convenience as an oral treatment with no dietary restrictions, and does not cause liver upset.
Clinical trial data is somewhat sparse for comparison to alternative TPO RA, and further studies and real world data, including HRQoL data, would be useful.
Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Avatrombopag in combination for treating chronic immune thrombocytopenia [ID3838]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by the end of **6 April 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	UK ITP Forum
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No links**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
The treatment pathway and positioning of avatrombopag relative to rituximab is unclear.	Yes	Our view would be similar to the ERG. During the COVID pandemic, there has been a focus on avoiding immunosuppression, since high dose steroids, rituximab and mycophenolate have been shown to be risk factors for a more severe outcome if the patient develops a COVID 19 infection. Since the TPO RA class is not immunosuppressive, there is a greater focus on this type of treatment. Indeed an interim commissioning statement from NHS England recognises that this class of treatment may be considered first line for ITP with the same reasoning (steroids being standard first line treatment). https://www.england.nhs.uk/coronavirus/documents/interim-clinical-commissioning-policy-thrombopoietin-receptor-agonists-as-first-line-therapy-for-new-or-relapsed-immune-thrombocytopenia-in-adults-and-children-over-the-age-of-1-year-during-the-covid/ There may however be circumstances in which it would be considered more appropriate for an individual patient to receive rituximab ahead of considering avatrombopag, for example if there were particular concerns over thrombosis risk.
The limited evidence-base for avatrombopag due to recruitment	No	No known additional evidence available

and attrition issues		
Exclusion of some TPO-RA trials from the NMAs in the company's submission	Yes	Obviously, any TPO RA cost comparison should fairly reflect the ethnic background of patients in the UK, since the lower starting dose of eltrombopag is only used in those of certain Asian background. However we think that the ERG is well aware of this and looks to include relevant endpoints such as bleeding events from these studies, which seems reasonable. We also agree that the real world starting dose of romiplostim is more typically 3 mcg/kg, as demonstrated in a published review of practice by the UK ITP Forum (PMID 27879997). Although largely reflecting most patients who will respond to treatment, It is possible that studies of <9 weeks may underestimate the response rate. SPC states treatment failure is no response after 4 weeks at maximum dose, and it can take time to titrate dose with romiplostim (dose range 1-10 mcg/kg)
The company estimates of comparative effectiveness between TPO-RAs for the outcome of durable platelet response	No	No comments on the ERG analysis. No known additional data on durable platelet response.
The modelled time to treatment response. In clinical practice TPO-RA treatment duration is likely below 24-weeks for patients not responding to treatment.	No	Agree with shorter (8 week) evaluation for Eltrombopag and Avatrombopag proposed by ERG, but as discussed above, it is likely to take longer with Romiplostim. Even if starting at 3 mcg/kg, there are 7 dose increases to reach maximum dose, + 4 weeks at maximum dose to establish treatment failure.
The composition of subsequent treatments in the model only allows pairwise comparisons of treatment strategies.	No	No comments
The company's mixed treatment sequencing approach cannot determine the optimum position for avatrombopag among TPO-RAs.	No	No known additional evidence

Source to inform dosages for non-TPO-RAs is outdated.	No	Agree with ERG, Provan 2019 is the more up to date reference.
Different definitions of response for TPO-RAs and non-TPO-RAs	Yes	The most clinically relevant definition of a platelet response is >30, double baseline and absence of bleeding. This is based on an international consensus (PMID: 19005182). The higher threshold of 50 used in TPO RA studies is why non TPO RA studies often report higher response rates. The single vs sustained platelet count response requirements are the second reason for differences since most studies measure response as time until loss of response. Hence the response rates as defined in the clinical trials of TPO RA are lower than what we would consider a real world response to these treatments.
The long-term treatment duration of TPO-RAs	Yes	Given that eltrombopag and romiplostim differ in delivery (oral vs SC), dosing range, dietary restrictions (eltrombopag) and side effect profile, it would be reasonable to think that long term compliance/tolerance may differ. Avatrombopag LT FU study: PMID 33586606. LT FU data on other TPO RA: it may be possible to seek real world data on duration of therapy from the UK ITP registry.
Proportion of patients receiving rescue therapy	No	It is the experience of the forum that patients on TPO RA will on occasion lose platelet count control transiently (e.g. associated with an acute intection) and this may require additional treatment such as a short course of steroids. However we are not aware of an evidence base.
The longer-term mortality risks associated with ITP	Yes	Please also see publications PMID: 30933417, 29978544, 32320469,
Health-related quality of life utility values used in the model	No	No comment
Overestimation of administration costs for romiplostim	No	This is probably not an overestimate. It is likely that most patients (>50%) during the titration phase e.g. weeks 1-10 will be attending weekly to the day unit for blood count check and having romiplostim dosed and then administered by day unit staff. In treatment responders receiving a prescription for 4 weeks, who do not require a blood count check and not wanting to attend the day unit, the majority (>50%) will administer or have a carer administer at home. A clinical practice audit could help

		clarify this if appropriate.
Overestimation of treatment acquisition costs for romiplostim	No	No comment
Approach to costing bleeding and rescue therapy events in the model	No	It is difficult to ascertain from Table 32, which treatments would be used for rescue in these models. We would comment that it is highly likely that for organ/gastrointestinal or intracranial bleeding, the patient would receive IVIg 1 g/kg as acute rescue treatment and this is an expensive treatment with limited availability (PMID 33093181).

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

Single Technology Appraisal (STA)

Avatrombopag in combination for treating chronic immune thrombocytopenia [ID3838]

ERG addendum: review of company's response to technical engagement

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Rider on responsibility for report

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

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in [redacted], all academic-in-confidence (AIC) data are highlighted in [redacted].

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1 OVERVIEW

This addendum to the Evidence Review Group (ERG) report presents the ERG's critique of the additional evidence provided by the company in their response to a number of key issues that were raised by the ERG in its report, which were discussed at technical engagement.

The technical engagement covered 16 key issues for consideration. The company's response to technical engagement indicated that they accepted the ERG's judgement on some aspects of Issues 1, 2, 7, 9, 10 and 12; agreed with the ERG on issues 3, 5, 6, 8, 12, 13, 14 and 15; but disagreed with the ERG on issues 4, 11 and 16. Table 1 summarises the issues and whether the ERG considers them resolved, unresolved, and their remaining uncertainty. The ERG critique to the company's response for the unresolved issues, partially resolved issues and the company's additional NMA analyses is presented in Section 2. The results of the company and ERG's updated analysis are presented in Section 3.

Table 1: Summary of the key issues

Issue		**Resolved?**
1	The treatment pathway and positioning of avatrombopag relative to rituximab is unclear.	Partially resolved with uncertainty remaining
2	The limited evidence-base for avatrombopag due to recruitment and attrition issues	Unresolved
3	Exclusion of some TPO-RA trials from the NMAs in the company's submission	Resolved
4	The company estimates of comparative effectiveness between TPO-RAs for the outcome of durable platelet response	Unresolved
5	The modelled time to treatment response. In clinical practice TPO-RA treatment duration is likely to be below 24-weeks for patients not responding to treatment.	Partially resolved with uncertainty remaining
6	The composition of subsequent treatments in the model only allows pairwise comparisons of treatment strategies.	Resolved
7	The company's mixed treatment sequencing approach cannot determine the optimum position for avatrombopag among TPO-RAs.	Unresolved
8	Source to inform dosages for non-TPO-RAs is outdated.	Resolved
9	Different definitions of response for TPO-RAs and non-TPO-RAs	Unresolved
10	The long-term treatment duration of TPO-RAs	Unresolved
11	Proportion of patients receiving rescue therapy	Unresolved
12	The longer-term mortality risks associated with ITP	Resolved
13	Health-related quality of life utility values used in the model	Resolved
14	Overestimation of administration costs for romiplostim	Resolved
15	Overestimation of treatment acquisition costs for romiplostim	Resolved
16	Approach to costing bleeding and recue therapy events in the model	Unresolved

2 DESCRIPTION AND CRITIQUE OF ADDITIONAL EVIDENCE

2.1 Issue 1: The treatment pathway and positioning of avatrombopag relative to rituximab is unclear

Rituximab is listed as a relevant comparator in the NICE scope. The ERG's clinical adviser described variation in the use of rituximab, both across the NHS and over time. Prior to the COVID-19 pandemic, rituximab was increasingly being used before TPO-RAs. The pandemic changed treatment preferences due to the immune suppression rituximab can cause and TPO-RAs are now being used prior to rituximab. It is unclear whether this will change again. The ERG has identified this as a potential issue as it is uncertain whether rituximab should be considered a relevant comparator.

The ERG considers the company's position that eltrombopag and romiplostim are the most relevant comparators to be reasonable, but recognises that there is uncertainty about the positioning of rituximab in the treatment pathway. In its technical engagement response, the company presented new evidence in the form of a UK clinician survey (n=9) on real-world treatment patterns and utilisation.

The ERG's response

The ERG considers that this new evidence adds little to clarify this issue since rituximab was not mentioned, neither in the survey questions nor in the report document (i.e. the nine clinicians were not explicitly asked about their use of rituximab).

2.2 Issue 2: The limited evidence-base for avatrombopag due to recruitment and attrition issues

Both of the two main avatrombopag trials had methodological limitations. Study 302 was small (n=49) and had an important imbalance in missing outcome data due to lack of efficacy in the placebo group (only one placebo patient completed the trial). Study 305 of avatrombopag vs eltrombopag was terminated early due to significant enrolment challenges and its results were not used in the economic model. The study aimed to recruit [redacted] patients but only [redacted] were randomised when the trial was terminated.

The ERG's main concern with the trial limitations was their impact on uncertainty when estimating the durable platelet response rate in the placebo group. Nearly all the event (numerator) data were derived from non-responder imputation, rather than actual trial data, because only one placebo patient completed the trial. This consequently led to uncertainty surrounding the company NMA estimates of comparative effectiveness between TPO-RAs (see key issue 4). This issue therefore adds uncertainty to the cost-effectiveness estimates. Although the company acknowledges that there were challenges in

collecting trial evidence for avatrombopag it also states that study 302 contains "robust comparative data on key efficacy and safety outcomes".

The ERG's response

The ERG does not agree that study 302 provides sufficient robust data to determine key efficacy and safety outcomes for the reasons previously stated.

2.3 Issue 3: Exclusion of some TPO-RA trials from the NMAs in the company's submission

The company excluded seven TPO-RA comparator trials from their NMAs, despite these trials being included in their systematic review. The ERG and their clinical adviser reviewed these decisions and disagreed with the company's reasons for excluding these trials. This was potentially important for four outcomes, especially the clinically-important outcomes bleeding events grade 1-4 and adverse events since, respectively, six and five trials were excluded from the NMAs of these outcomes. In its technical engagement response, the company presented additional NMA analyses which included all the previously excluded studies.

The ERG's critique

For the romiplostim study by Kuter 2008 the ERG notes a small difference in the incidence rate ratio between the ERG-calculated value (0.89, based on the company's response to clarification question A18 (see Table 14 of the ERG report), and the value used in the company's new NMA (0.85) for the outcome proportion of patients with any bleed.

The company selected fixed effect NMA models over random effects models based on the DIC. The ERG considers this appropriate. Values for $\overline{D}_{res}$ are provided but it is unclear whether this is the residual deviance to which the number of data points can be compared to. Therefore, the ERG was unable to evaluate whether the models fitted the data well.

Inconsistency was checked for networks with closed loops using the Bucher method according to the NIICE DSU TSD4.[1] The company chose to pool some of the evidence feeding into the direct vs indirect evidence comparisons using a random effects model. Since the fixed effect model was selected for the NMA, the same model should have been used for the inconsistency checks. In addition, the Bucher method is not recommended when random effects models are used to synthesise part of the evidence in the loop (section 7.3.1.4 of Dias et al.[2] and Ades et al.[3]). However, given that overall there was little heterogeneity, the conclusion that there was no evidence of inconsistency is unlikely to change if a fixed effect model was used instead. The ERG is therefore satisfied that there is no evidence of inconsistency in the networks presented.

The ERG compared the results of the new NMAs with those of the original NMAs and agree with the company that the additional data do not meaningfully alter the effect estimates for the four outcomes with new data.

2.4 Issue 4: The company's estimates of comparative effectiveness between TPO-RAs for the outcome of durable platelet response

2.4.1 Background

The ERG report highlighted a number of major concerns about the company's NMA for the primary effectiveness outcome of durable platelet response, which is the key efficacy outcome used to inform the cost-effectiveness analysis. In the company's submission, the base case NMA results for durable platelet response showed that avatrombopag had the highest response rates compared to eltrombopag and romiplostim, with avatrombopag having a large point estimate, with significant uncertainty, when compared to placebo (odds ratio (OR) of 102.80, with 95% CrI: 3.87 - 2,796,449). The NMA was conducted within a Bayesian framework using a fixed-effect model. Three of the studies (Study 302, Kuter et al 2008 SPL and study FIT1) in the NMA for this outcome had zero events reported in their placebo arms, due to imbalanced discontinuation from the placebo arm of Study 302 and low sample sizes across the studies. To address this fact, the company added an adjustment value (continuity correction) to the number of durable response events. The company appeared to use different adjustment values across treatment arms within a study and also across studies. The ERG also noted that the company adjusted the number of response events but did not perform an adjustment to the number of 'no events' or equivalently, to the total number of participants in each treatment arm. These continuity adjustments appeared to be undertaken externally to the evidence synthesis and then incorporated into the NMA. Despite the ERG's request at points for clarification for full details on all adjustments performed to the data used in the indirect treatment comparisons, no explanation was provided to clarify how or why the selected adjustment values used in the company's NMA were chosen. Therefore, the ERG was unable to verify the source, calculus and appropriateness of the continuity correction adjustments used in the company's NMA.

The following concerns were listed in the ERG report regarding the company's NMA for the primary efficacy outcome of durable platelet response used in the cost-effectiveness analysis:

- ERG concern 1: The NMA results for avatrombopag vs. placebo (common comparator) lack face validity with respect to the trial results from Study 302 (i.e., odds ratio reported from NMA for avatrombopag vs. placebo is 102.80 [95% CrI: 3.87 - 2,796,449] compared to the study-specific odds ratio of 18.72 [95% CI: 1.02 - 340]);

- ERG concern 2: The appropriateness of the continuity corrections used in the NMA to correct for the presence of zero events in study arms of the trials (Study 302 for avatrombopag and Kuter 2008 SPL for romiplostim);
- ERG concern 3: Response outcomes for the pivotal study of eltrombopag (RAISE) were estimated for the observed population, whereas for all other studies included in the NMA the ITT population was used;
- ERG concern 4: The appropriateness of the inclusion of fostamatinib trials in the NMA;
- ERG concern 5: Heterogeneity in placebo response rates across the trials included in the NMA.

2.4.2 The ERG's position

Whilst acknowledging that any zero-cell adjustments will inherently introduce bias into the NMA results, the ERG considered that, without any information on how the adjustment values used by the company were obtained, these values were as arbitrary as the standard continuity correction of 0.5 typically reported in the literature to correct for zero events.[4] The ERG also considered it more appropriate to use the ITT data for all trials, instead of the company's approach of using the observed data for the RAISE trial and the ITT population data for the remaining studies. Moreover, the ERG used frequentist inference, instead of Bayesian, to estimate the relative effects in the NMA, so that the potential influence of the flat prior distributions where there is very limited evidence was discarded and only the trial data considered.

The ERG's base case NMA estimates (based on a frequentist model with continuity correction of 0.5 applied to both events and non-events, and with ITT data used for all trials) suggested that romiplostim is expected to be the most effective treatment (OR of 29.61 [95% CI: 5.42 - 161.58] for romiplostim vs. placebo), followed by avatrombopag (odds ratio of 18.72 [95% CI: 1.03 - 340.54] for avatrombopag vs. placebo), and then eltrombopag (odds ratio of 10.60 [95% CI: 3.64 – 30.87] for eltrombopag vs. placebo).

2.4.3 The company's response

The company acknowledged the ERG concerns around their NMA results for the primary efficacy outcome of durable platelet response used in the cost-effectiveness analysis, highlighting the uncertainty associated with the indirect comparisons between TPO-RAs. At technical engagement, the company addressed each of the ERG concerns in turn and as follows:

- ERG concern 1: the company stated that the OR of 18.72 [95% CI: 1.02 - 340] used in the ERG's base case is not a credible estimate of avatrombopag's efficacy *vs* placebo. Referring to the Cochrane Handbook[5] and Sweeting et al.,[6] the company considers the ERG's approach

of using the 'standard' continuity correction value of 0.5 for zero-events as likely to introduce bias since all studies with zero cells were randomised in a 1:2 ratio. The company considered that, under this adjustment, the probability of response in the placebo group of Study 302 would be of 3% despite no events observed.

- ERG concern 2: As per concern 1 and based on the company's interpretation of Sweeting et al.,[6] the company considered that the ERG's method of 0.5 correction of zero cells as highly inappropriate for studies with unequal randomisation since it introduces directional bias.
- ERG concern 3: The company stated that their original submission was based on the best-available data reported in the respective trials, resulting in the discrepancies highlighted by the ERG. The company indicated that their analysis was conservative and presented less favourable estimates than the analysis conducted by the ERG.
- ERG concern 4: The company agreed that fostamatinib trials have no impact on fixed-effect NMA results.
- ERG concern 5: The company highlighted that 3 out of 6 studies used in the durable platelet response NMA reported zero events in their placebo arms. The company presented the observed event rates in the placebo arms of each of these studies, with an appreciation of the existing heterogeneity in placebo responses.
- Further comments from the company on the ERG additional analysis:
    - The company considered the use by the ERG of a frequentist approach to the estimation of relative treatment effects to be reasonable but the use of the default 0.5 continuity correction to the zero cell studies should only be considered as a sensitivity analysis;
    - The company proposed a continuity correction proportional to the sample size, based on their interpretation of the Sweeting et al.[6] However, this continuity correction was applied only to the events, with no adjustment to the total number of participants in each study arm as would be implied by adding the same adjustment to the no events cell as well. The results now proposed by the company are presented in Table 2, together with the company's original NMA results and the ERG's base case NMA results for completeness.

Table 2 Relative effectiveness results for the primary outcome on durable platelet response.

Comparator *vs* placebo	Outcome: Durable platelet response		
	Company's submission NMA results (Bayesian fixed-effects model, CC values unexplained and applied to events only)	**ERG base case NMA results (Frequentist fixed-effects model, CC of 0.5 applied to both events and no events and with ITT RAISE data)**	**Company's revised NMA results (derived directly from studies, CC proportional to sample size and applied to events only) ***
	Odds Ratio (95% CrI)	Odds Ratio, (95% CI)	Odds Ratio
Avatrombopag	102.80 (3.87, 2,796,448.5)	18.72 (1.03, 340.54)	27.49
Eltrombopag	14.27 (5.14, 53.73)	10.60 (3.64, 30.87)	10.60
Romiplostim	46.49 (9.12, 670.61)	29.61 (5.42, 161.58)	33.56
Romiplostim *vs* Avatrombopag	0.46 (0.00, 30.02)	1.58 (0.05, 45.57)	1.22

Abbreviations: CC= continuity correction, CrI= credible interval, CI= confidence interval. * Note that no confidence intervals were provided by the company for any of the calculated ORs.

2.4.4 The ERG's critique

As highlighted in the ERG report, a number of important limitations were identified in the NMAs presented by the company in their original submission. As mentioned in section 3.4.1 of the ERG report, in the company's submission in the NMA for durable platelet response, a continuity correction value was added to the studies with zero-cells, for which no detail was provided. This adjustment was applied only to the events in the treatment and placebo arms. The ERG base case NMA results used a continuity correction of 0.5 affecting both 'events' and 'no events' in the treatment and placebo arms (consequently 1 is added to the number of participants in each trial arm). At response to technical engagement the company proposed new continuity correction values that are proportional to the sample size.[6] However, as per the company submission, the new continuity corrections proposed by the company were applied only to the events in the treatment and placebo arms, making no correction for 'no events' and therefore not adjusting the total number of participants in each study arm. The ERG has reservations about the approach being proposed by the company.

Use of continuity corrections for event only vs. event + no event

The company performed adjustments to durable platelet response events, but did not perform any adjustment to the 'no events' cell. It is common practice to adjust both 'events' and 'no events' in the treatment and placebo arms when performing zero-cells corrections, and this is also advocated by Sweeting et al.[6] The ERG believes that the company's approach is inappropriate as it intrinsically alters the number of participants experiencing 'no events', taking these away from the total number of participants in each arm, and thus, altering the relative effect estimates that may be derived. The adjustment for both 'events' and 'no events' is advocated by both the Cochrane Handbook (section

10.4.4.1)[5] and Sweeting et al. (Tables 1 and 3),[6] indicating that the addition of the chosen adjustments should be made to all cells of a 2×2 table where the zero-cells problems occur.

Using study 302 as an example, Table 3 below presents the 2x2 table for this study and portrays the impact of different continuity correction approaches on 'events', 'no events' and total participant numbers in each treatment arm, and ultimately on the odds ratio for avatrombopag vs. placebo. Approach 1 relates to the case where no continuity correction of zero-cells is performed, which does not permit the calculation of the odds ratio. Approach 2 relates to the ERG's base case where a continuity correction of 0.5 is applied to both the 'events' and 'no events' (all cells), resulting in an odds ratio of 18.72 for avatrombopag vs placebo. Note that the 'no events' increased by the same amount as the 'event' cells, as indicated by the Cochrane Handbook[5] and Sweeting et al.,[6] which has implications for the total number of individuals in each arm. Note also that the placebo event rate under this approach is 2.8% (=0.5/18), which is below the event rate observed in the placebo arms of the other relevant trials with no zero-cells included in the NMA (4.8% in Kuter et al. 2008 Non-SPL; and 10.3% in the RAISE study). Approach 3 is the company's revised approach in response to technical engagement, where the continuity corrections are derived according to the proportion of individuals in each treatment group, i.e., an adjustment of 0.35 to placebo events and 0.65 to avatrombopag events. In this approach the total number of individuals in each arm was not adjusted to account for the increment in 'events' due to the correction, implying a reduction of the 'no event' rate. The ERG considers the approach presented by the company unsuitable. Finally, the ERG has corrected the company's proposed approach – see Approach 4 – by also adjusting the 'no events' cell in each arm by the same amount as the 'events' cell, reducing the estimated odds ratio for avatrombopag vs placebo from 27.49 to 26.91.

Table 3 The impact of different continuity correction values and approaches on the odds ratio for avatrombopag vs placebo in Study 302.

Study 302: durable platelet response	Events	No events	Total
1. No adjustment			
Avatrombopag	11	21	32
Placebo	0	17	17
Total	11	38	49
			OR Ava vs Pla = (11/21) / (0/17) = undefined
2. Continuity correction of 0.5 to events and no events (all cells) as in ERG base case			
Avatrombopag	11.5	21.5	33
Placebo	0.5	17.5	18
Total	12	39	51
			OR Ava vs Pla = (11.5/21.5) / (0.5/17.5) = 18.72 (95% CI: 1.03, 340.54)

Study 302: durable platelet response	Events	No events	Total
3. Continuity correction in the company's revised analysis of 0.35 (=17/(32+17)) to placebo events and 0.65 (=32/(32+17)) to avatrombopag events			
Avatrombopag	11.65	32-11.65 = 20.35	32
Placebo	0.35	17-0.35 = 16.65	17
Total	12	37	49
		OR Ava vs Pla = (11.65/20.35) / (0.35/16.65) = 27.49 (95% CI: 0.88, 855.90)	
4. ERG corrected continuity correction of 0.35 to placebo events and no events and 0.65 to avatrombopag events and no events			
Avatrombopag	11.65	21.65	33.30
Placebo	0.35	17.35	17.70
Total	12	39	51
		OR Ava vs Pla = (11.65/21.65) / (0.35/17.35) = 26.91 (95% CI: 0.87, 835.27)	

Appropriate continuity correction values

As discussed in the ERG report, section 3.4.3, the ERG considers the company's continuity correction values to be equally as arbitrary as the continuity correction of 0.5 typically used in the literature. The ERG appreciates and agrees with Sweeting et al.[6] that, when presented with unbalanced numbers of trial participants in each arm, a correction of 0.5 may underperform and lead to misleading estimates of the odds ratio. It is the understanding of the ERG that Sweeting et al.[6] does not explicitly advocate an adjustment based on the proportion of individuals in each arm as undertaken by the company. Instead, one of Sweeting et al.[6] suggestions is the use of the reciprocal of the opposite treatment arm size to address the imbalance issue (section 3.2, page 1357/58), whilst acknowledging that other constants may also be considered. The ERG acknowledges that Sweeting et al.[6] suggestions to use of the reciprocal of the opposite treatment arm size is not ideal when dealing with small trials such as the ones included in the NMA for durable platelet response and the company's chosen correction values can be considered to be within the broad category of reasonable constants.[6] However, Sweeting et al.[6] is clear in its conclusions that sensitivity analysis using several continuity correction factors should be performed as routine practice. The ERG fully agrees with these conclusions.

The different continuity correction values shown in Table 3 for Study 302 and applied to both events and no events (Approaches 2 and 4) varied from 0.35 to 0.5 in the placebo arm and from 0.5 to 0.65 in the treatment arm. These corrections implied different odds ratio point estimates for avatrombopag vs placebo of 18.72 and 26.91 for Approaches 2 and 4, respectively, which demonstrates how impactful the chosen correction values may have on the estimates of relative treatment effect.

Addressing the company's comments to ERG concerns 3 to 5

ERG concern 3: The ERG notes that data from the observed population of the RAISE trial was included in the company's NMA, whereas data for the ITT population was used for the other studies. The ERG has not changed its position that data from the ITT population should be used across all studies included in the NMA.

ERG concern 4: The ERG considers that, given the star-shaped structure of the NMA for the durable platelet response outcome, the inclusion of the two fostamatinib trials has no impact on the fixed-effect model results and, therefore, does not need to be included in the analysis.

ERG concern 5: As discussed in Section 3.3 of the ERG report, heterogeneity in placebo response rates was identified. The ERG appreciates that in sparse networks, such as the one presented for the outcome of durable platelet response, limited adjustments can be achieved. The ERG considers that the placebo effect and differences in placebo responses identified may have contributed to high between-study heterogeneity, which can be a source of bias when comparing treatment effects. However, due to the sparse nature of the network, this between-study heterogeneity cannot be estimated.

Addressing the company's comments to the ERG's additional analysis

The ERG considers a frequentist (instead of a Bayesian) approach to be best suited to perform the estimation of pooled relative effects for durable platelet response. The use of a frequentist approach avoids the potential additional uncertainty brought by flat prior distributions when data are very sparse. The company's concern that the frequentist approach is prone to bias in the presence of studies with zero cells and imbalanced arms, relates to the usual continuity correction of 0.5 which is added by default in most frequentist meta-analysis software which has an additional bias when compared to the exact likelihood approach (with no continuity correction) typically used by Bayesian software. However, this concern does not apply when an adjustment to zero cells is needed for both Bayesian and frequentist approaches, as is the case for the NMA of durable platelet response.

As highlighted in the ERG report, the ERG acknowledges that any zero-cell adjustments will inherently introduce bias to the NMA pooled results. The ERG considers the company's approach of adjusting 'events' only, without making any adjustment to 'no events' inappropriate. This approach has no support in the relevant evidence synthesis methods literature. This was corrected by the ERG and presented as a scenario analysis.

The NMA for the outcome of durable platelet response presented an extreme scenario where several trials have zero-cells, many trials are small, most contrasts of interest are only informed by one trial, and the network is star-shaped, meaning there is no additional indirect evidence to strengthen the relative effect estimates where a zero-cell is present. Under these circumstances it is inevitable that in

a Bayesian framework the model will be numerically unstable and it either fails to converge and no treatment effects are estimated, or converges to posterior distributions with very high standard deviations for relative treatment effect estimates of interest. Under these circumstances, and acknowledging that the 0.5 continuity correction has been widely used in the evidence synthesis literature, section 6.3 of the NICE DSU TSD 2[4] cites Sweeting et al.[6] and indicates that "*One solution is to revert to the practice of adding 1 to the denominator and 0.5 to the numerator, …*", supporting the use of a 0.5 continuity correction. Nonetheless, the ERG agrees with the findings by Sweeting et al.[6] that, in the presence of unbalanced trials in terms of participants in each arm, a correction of 0.5 may not be optimal. The ERG considers the adjustment values used by the company in response to technical engagement, based on the proportion of participants in each trial arm, to be equally as arbitrary as the 0.5 continuity correction value. The ERG agrees with Sweeting et al.[6] conclusions that sensitivity analysis using several methods and continuity correction factors should be performed as routine practice. Therefore, an additional scenario using the company's corrected approach is presented.

2.4.5 Conclusion

The ERG maintains its base case assumptions using pooled estimates of comparative effectiveness for durable platelet response from the ERG's frequentist fixed-effect NMA for avatrombopag, eltrombopag, romiplostim and placebo, with 0.5 continuity correction applied to both 'events' and 'no events' (Table 41, page 113 of the ERG report) of studies with zero cells.

Acknowledging the limited evidence-base for avatrombopag due to recruitment and attrition issues (Issue 2), the ERG considers that the recommendations by Sweeting et al.[6] that sensitivity analysis using several methods and continuity correction factors should be performed as very relevant here. Therefore, in order to evaluate the impact of different continuity correction values on the comparative effectiveness for the outcome of durable platelet response for avatrombopag, eltrombopag, and romiplostim, the ERG presents a sensitivity analysis using the ERG's corrected version of the company's approach; this corresponds to Approach 4 in Table 3, based on a continuity correction according to the proportion of patients in each study arm. Both the ERG's base case NMA results (using the 0.5 continuity correction) and the ERG's sensitivity analysis are presented in Table 4.

Table 4 The results of the ERG's base-case and sensitivity analysis for the relative effectiveness estimates for the primary outcome of durable platelet response.

Comparator *vs* placebo,	**Outcome: Durable platelet response** Odds Ratio, (95% CI)	
	ERG base case NMA results (Frequentist fixed-effects model, CC of 0.5 applied to both events and no events and with ITT RAISE data)	**ERG sensitivity analysis NMA results (Frequentist fixed-effects model, CC according to the proportion of participants in each study arm applied to both events and no events and with ITT RAISE data)**

Avatrombopag	18.72 (1.03, 340.54)	26.91 (0.87, 835.27)
Eltrombopag	10.60 (3.64, 30.87)	10.60 (3.64, 30.87)
Romiplostim	29.61 (5.42, 161.58)	33.39 (5.52, 201.98)
Romiplostim *vs* Avatrombopag	1.58 (0.05, 45.57)	1.24 (0.03, 59.99)

Abbreviations: CC= continuity correction, CrI= credible interval, CI= confidence interval.

2.5 Issue 5: The modelled time to treatment response. In clinical practice TPO-RA treatment duration is likely to be below 24-weeks for patients not responding to treatment

The company's model assumes that patients wait a full 24 weeks to assess non-response to TPO-RA treatment (avatrombopag, eltrombopag or romiplostim). The product SmPCs for the TPO-RAs all stipulate stopping treatment if response is not achieved within a short time window after establishment of maximum dose. The ERG considers non-response to treatment with a TPO-RA to be observed within clinical practice within a timeframe of around 8 weeks rather than 24 weeks as used in the company's model. A timeframe of 8 weeks to assess non-response to TPO-RAs in first-line treatment would also be consistent with the modelled timeframe of 8 weeks used to assess non-response in subsequent lines of therapy. Furthermore, the ERG considers there to be little evidence of a specific time-to-response effect in Study 302 to suggest that TPO-RAs warrant a longer 24-week timeframe to assess response to treatment. Extending treatment for non-responders by a further 16 weeks (from 8 to 24 weeks) will increase costs but it does not appear to meaningfully increase response to treatment; however, the latter cannot be assessed using the durable platelet response definition as used in the model as this refers to at least 6 weekly platelet counts $\geq 50 \times 10^9$/L in the final 8 weeks of a 24-26-week study.

In response to technical engagement, the company accepts the issues highlighted by the ERG and no new evidence, data or analyses have been presented.

2.6 Issue 7: The company's mixed treatment sequencing approach cannot determine the optimum position for avatrombopag among TPO-RAs

The mixed treatment approach used by the company is very pragmatic and an oversimplification of modelling treatment sequences. A more appropriate approach would involve a comprehensive assessment of fixed treatment sequences, which are then weighted by the percentage of patients in UK clinical practice that are likely to follow each treatment pathway, in order to reflect the variability in treatment options in practice. Importantly, the company has not used the treatment sequencing to determine the most efficient use and positioning of avatrombopag among the TPO-RAs (and non-

TPO-RAs). The most cost-effective treatment sequence will depend on the response rates of the alternative TPO-RAs and the time spent between treatments as non-responders, as well as the treatment costs where it might be anticipated that it is more cost-effective to start treatment with cheaper therapies before progressing to more expensive options.

In response to technical engagement, the company asserts that treatment sequencing is not likely to be considered plausible from a clinical perspective for this indication on two grounds: (1) similar efficacy and safety between avatrombopag and the other TPO-RAs and limited differences in long-term treatment duration between avatrombopag, eltrombopag, and romiplostim; and (2) avatrombopag will be considered for use in clinical practice in patients who are already judged to be suitable candidates for treatment with an alternative TPO-RA.

The ERG's response

The ERG accepts that it is unclear whether a cost-effectiveness analysis comparing treatment sequences is an appropriate approach to the decision problem because it is not directly defined in the NICE scope. However, the two reasons presented by the company for not comparing a treatment sequence with alternative TPO-RAs are not supported by evidence. Firstly, avatrombopag, eltrombopag and romiplostim have not been shown to have similar comparative efficacy, safety and long-term treatment duration. It is clear from the individual clinical trial results for each of the TPO-RAs vs. placebo for the primary outcome of durable platelet response that a difference between the TPO-RAs does exist. In response to issue 4, the results of the NMA for the primary outcome suggests that romiplostim is expected to be the most effective treatment, followed by avatrombopag and then eltrombopag. In terms of long-term treatment duration, in response to issue 10, the company provided evidence from 9 expert ITP-treating clinicians in the UK that indicated that [redacted]. The ERG acknowledges that less dietary restrictions and hepatoxicity monitoring associated with avatrombopag may increase longer term adherence to treatment; however, a difference in mean time on treatment between TPO-RAs (eltrombopag and romiplostim) has been demonstrated previously: Lee et al.[7] showed a notable difference in long-term discontinuation rates of 109 cycles for eltrombopag and 393 cycles for romiplostim. Secondly, the ERG does not dispute the fact that avatrombopag is likely to be used in patients who are already judged to be suitable candidates for treatment with an alternative TPO-RA, but from a NICE decision-making perspective, it might be anticipated that clinical practice would start treatment with cheaper, effective, TPO-RAs before progressing to more expensive options.

Additional evidence on the comparative effectiveness between avatrombopag, eltrombopag, and romiplostim and the duration of each treatment (long-term discontinuation rates) is required to assess the most efficient use and positioning of avatrombopag among the TPO-RAs.

2.7 Issue 9: Different definitions of response for TPO-RAs and non-TPO-RAs

The estimates of treatment response for first and subsequent lines of therapy used in the model are based on different definitions of treatment response for TPO-RAs and non-TPO-RAs. At first-line (TPO-RAs), the definition of response is durable platelet count, while for subsequent lines of therapy, not involving a TPO-RA, an alternative definition of response is used (likely to be a single point in time rather than sustained response over a fixed time period). The ERG notes that this results in very high response rates for non-TPO-RAs in subsequent lines of treatment compared to response rates from first-line TPO-RA. In addition, the treatment response estimates used in the model for subsequent lines of therapy (mixed treatment strategy) are based on a mixed treatment response definition because subsequent lines of therapy include a mix of both TPO-RAs and non-TPO-RAs.

In response to technical engagement, the company indicated that they were unable to match the definition of durable platelet response given the lack of available data in an analogous population of ITP patients and no new evidence, data or analyses were presented.

2.8 Issue 10: The long-term treatment duration of TPO-RAs

The longer-term durability of treatment response on TPO-RA treatment (avatrombopag, eltrombopag or romiplostim) is uncertain. In the company's model, a constant discontinuation rate of 0.9% per 4-week model cycle was assumed for all the TPO-RAs. This estimate was based on the lowest of the mean times on treatment of 109 cycles for eltrombopag (436 weeks or 8.4 years over a patients' lifetime) and 393 cycles for romiplostim reported in Lee et al.[7] The difference in mean time on treatment for eltrombopag and romiplostim suggests that there could be a notable difference in long-term discontinuation rates between the TPO-RAs.

In response to technical engagement, the company asserts that it is plausible to assume a similar long-term durability of treatment response between the TPO-RA treatments. To support this, the company provided evidence from a clinician survey that indicated that [redacted].

The ERG's response

The ERG notes that even if the treatment duration is assumed to be identical between the TPO-RA treatments, the actual mean estimate used in the model (for example, 109 cycles vs. 393 cycles) will

have an impact on the cost-effectiveness of avatrombopag relative to eltrombopag and romiplostim. This is because the higher the treatment response rate between the alternative TPO-RAs, the longer (greater mean time on treatment) or shorter (lower mean time on treatment) this response is maintained over time, which impacts the time to the 'no treatment no response' health state that incurs an elevated risk of bleeding (and associated high costs of hospitalisation and mortality) and need for rescue therapy. Lower discontinuation rates for a more effective treatment will only result in improved cost-effectiveness when the movement to the 'no treatment no response' health state occurs late enough in time so that the elevated risk of severe bleeding events and need for rescue therapy are significantly discounted, and the next subsequent line of therapy is less cost-effective than the TPO-RA.

Evidence on the long-term treatment duration for initial responders to TPO-RAs is required to resolve this uncertainty.

2.9 Issue 11: Proportion of patients receiving rescue therapy

The ERG had two main concerns with the rates of rescue therapy used in the model:

1) The rates used in the company's model of 3% and 22% per model cycle for responders and non-responders, respectively, are reported to be based on TA293[8] (eltrombopag); however, the ERG was unable to validate the rates reported as the source used in TA293 is unclear.
2) The company stratified rescue therapy into two attributable causes: bleeding and non-bleeding events. Rates for each of the attributable causes were informed by nine patients from Study 302 and are therefore highly uncertain.

In response to technical engagement, the company indicated that a total of 9 out of 49 patients required rescue therapy during Study 302 and inclusion of this data in the model would be highly uncertain. Moreover, in the eltrombopag submission (TA293), NICE concluded that using higher rates of rescue therapy was more appropriate. Therefore, the company considered these to be validated by NICE.

The ERG's response

The ERG does not consider that the company's response addresses the two main concerns raised by the ERG. The company have not explored the source of the rates of rescue therapy used in the previous NICE submission for TA293. The company have also indicated that the rates of rescue therapy from Study 302 are highly uncertain but they have not provided justification for using these uncertain estimates to stratify rescue therapy use into bleed events (44%, based on only 4 out of 9 patients) and non-bleed events (56%).

2.10 Issue 16: Approach to costing bleeding and recue therapy events in the model

The ERG had three main concerns with the approach used by the company for costing bleeding and rescue therapy events in the model:

(i) The rates of rescue therapy for responders and non-responders are uncertain and the estimates used by the company could not be verified by the ERG from their original source [i.e., the source of the estimates used in TA293[8] are unclear] (see Issue 11).

(ii) Bleed-related rescue therapy event probabilities and associated costs are assumed to be nested within those for bleeding events. The ERG believes that this approach by the company complicates the interpretation of bleed and rescue costs and represents a significant departure from the approach used in previous appraisals [TA293[8] and TA221[9]].

(iii) the bleed costs applied in the model are derived from a paradigm review commissioned by the company, with markedly higher costs compared to NHS reference costs and those applied in previous appraisals [TA293[8] and TA221[9]].

In response to technical engagement, the company acknowledged the limitations in some of the data sources used for bleeding costs, but justified their overall approach based on having improved understanding of the impact of ITP since the previous technology appraisals, feedback from an Advisory Board, and new market research data. The company's response to the rates of rescue therapy (point (i)) is detailed in Issue 11. Regarding the reconfiguration of event costs (point (ii)), the company reports that this was to allow for the use of the new market research data without double counting the cost of rescue therapies. The company also justified the collection and application of new data on the costs of bleed events (point (iii)) on the basis that many different bleed-related costs are beyond the scope of NHS reference costs such as the costs of ER admission and use of ICU beds.

In response to technical engagement the company adopts a middle-ground scenario for its revised base-case analysis, which uses the average costs of bleeds between the NHS reference cost tariff (used in the ERG's base-case) and the market research values (company's submission) combined with independent rescue therapy costs (derived via contemporary drug prices for rescue therapy treatment usage from the eltrombopag NICE submission).

The ERG's response

The company have not addressed the concerns raised by the ERG. The company's justification for requiring new market research data to inform bleed-related event costs (i.e., that there are relevant costs that fall outside of the NHS tariffs) has not been evidenced. As acknowledged by the company, the bleed-related costs used in the company's submission are extremely high compared to NHS reference cost tariffs. However, the company have not indicated which specific costs for bleeding events are excluded from NHS reference costs, and how the mid-point between NHS and market

research values appropriately captures alleged omissions. In addition, the methodology used in the company's market research approach to determine event-related resource use is not provided and therefore cannot be validated.

In summary, the ERG has not received any new evidence to suggest that the company's revised approach to costing bleed and rescue therapy events improves upon the approach used in previous technology appraisals (i.e., rescue medication costs derived from pivotal study data, with the addition of NHS reference costs in the event that rescue therapy was related to a bleed event).

3 RESULTS

3.1 Company analysis

3.1.1 Modelling assumptions

In response to the issues noted by the ERG and following technical engagement, the company updated their base case cost-effectiveness analysis and provided revised base-case results. The following ERG-preferred assumptions are incorporated within the company's revised model:

- Issue 6: Fully incremental comparison of alternative treatment strategies (ERG Scenario 2 in ERG report).
- Issue 8: Using updated guidance to inform dosages for non-TPO-RAs in the model (ERG Scenario 4 in ERG report).
- Issue 13: Health-related quality of life utility values are adjusted by age over time (ERG Scenario 8 in ERG report).
- Issue 14: Administration costs for romiplostim (ERG Scenario 9d in ERG report).
- Issue 15: Romiplostim dosing costs (ERG Scenario 10a in ERG report).

The company have provided alternative estimates for the following assumptions, which differ from the ERG's preferred assumptions (ERG Scenarios 4 and 11 in ERG report) and the company's original base-case:

- Issue 4: Comparative effectiveness estimates from the NMA for durable platelet response. The company have presented revised estimates for the odds ratio of avatrombopag vs. placebo and romiplostim vs. placebo, based on a continuity correction adjustment for zero-event cells according to the proportion of individuals in each treatment group. Note that the company's revised estimates are based on data from the ITT population for all studies included in the NMA, which is in line with the ERG's base-case assumption.
- Issues 11 and 16: Approach to costing bleeding and rescue therapy events in the model.

The company have used average costs of bleeds between the NHS reference cost tariff and new market research data (see Table vi of company's response to technical engagement).

3.1.2 Company's cost-effectiveness results

Table 5 shows the deterministic cost-effectiveness results for the company's revised base-case analysis following technical engagement.

Table 5 Company's revised base-case results following technical engagement.

Changes made in response to technical engagement	Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Issue 4	**Revised comparative effectiveness estimates for durable platelet response based on data adjustments to zero-event cells (events only) according to the proportion of individuals in each treatment group**					
	ELT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	AVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Issues 11 and 16	**Revised costs of bleeding and rescue therapy events using the average costs of bleeds between the NHS reference cost tariff and new market research data and the addition of independent rescue therapy costs (derived from eltrombopag NICE submission)**					
	AVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ELT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company revised base-case	**Company's revised base-case results incorporating changes made to issues 4, 11 and 16 (and accepting the ERG's preferred assumptions for all other issues)**					
	AVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ELT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AVA, avatrombopag; ELT, eltrombopag; ROM, romiplostim

3.2 ERG analysis

The ERG's preferred assumptions and base-case results remain, as per the ERG report. The ERG has undertaken an additional sensitivity analysis to assess the impact of the alternative continuity correction approach proposed by the company in relation to issue 4. In this sensitivity analysis, the ERG applies the comparative effectiveness estimates from the NMA for durable platelet response from Table 4 (ERG sensitivity analysis NMA results).

Table 6 shows the results of the ERG's sensitivity analysis following technical engagement.

Table 6 Results of ERG sensitivity analysis following technical engagement

	Treatment	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
ERG base-case	**ERG preferred assumptions (including continuity correction of 0.5, for events and no events, for issue 4 and NHS reference cost tariffs for issues 11 and 16)**					
	AVA	[redacted]	[redacted]			
	ELT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG sensitivity analysis	**ERG preferred assumptions but with an alternative continuity correction to zero-event cells (events and no events) according to the proportion of individuals in each treatment group (issue 4)**					
	ELT	[redacted]	[redacted]			
	AVA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ROM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AVA, avatrombopag; ELT, eltrombopag; ROM, romiplostim

The ERG refers the committee to the addendum with the company's revised base case results and ERG sensitivity analysis with confidential prices included for the comparators.

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