Avatrombopag for chronic immune thrombocytopenia

For public – redacted

Technology appraisal committee B [09 June 2022]

Chair: Charles Crawley

Lead team: Iolo Doull, Nigel Westwood, Peter Wheatley Price

Evidence assessment group: CRD and CHE Technology Assessment Group

Technical team: Emily Leckenby, Rebecca Thomas, Yelan Guo, Henry Edwards

Company: Swedish Orphan Biovitrum Ltd

NICE

Key issues

Partially resolved
Unresolved
Unknown impact
Small impact
Large impact

Decision problem

- **Positioning of rituximab in the treatment pathway**
  - Is rituximab a relevant comparator for avatrombopag?
  - What are the most appropriate comparators for avatrombopag?

Clinical effectiveness

- **Limited evidence base for avatrombopag due to recruitment and attrition issues**
  - What is the committee's view on the evidence from Study 302?
  - Is it appropriate to use data from Study 302 to determine key efficacy and safety outcomes?

- **Comparative effectiveness estimates from NMA for durable platelet response**
  - Is baseline platelet count a treatment effect modifier?
  - Which correction method used in the NMA is preferred?
  - Are the TPO-RAs considered to have similar effectiveness according to the NMAs?

NICE

Abbreviations: NMA: network meta-analysis; TPO-RA: thrombopoietin receptor agonist

Key issues

Cost effectiveness

- **Modelled time to treatment response**
  - Is 24-week timeframe for assessing non-response in model appropriate?

- **Modelled treatment sequences**
  - What is committee's view on modelling treatment sequencing of TPO-RAs?
  - Is modelling treatment sequencing informative for decision making?

- **Modelled treatment response rates for TPO-RAs and non-TPO-RAs**
  - Is it appropriate to define response to treatment differently between TPO-RAs and non-TPO-RAs in model?

- **Long-term treatment duration**
  - Is the assumption that treatment duration is the same between TPO-RAs appropriate?
  - Is 109 cycles (4-week per cycle) a reasonable estimate for treatment duration?

- **Costs of bleeds and rescue therapy events used in model**
  - What is the committee's view on the company's approach to costing bleed events and rescue therapy? Is it appropriate?

Partially resolved
Unresolved
Unknown impact
Small impact
Large impact

Abbreviations: NMA: network meta-analysis; TPO-RA: thrombopoietin receptor agonist

Background on chronic immune thrombocytopenia

A rare autoimmune disorder characterised by increased platelet destruction

Definition

- Immune thrombocytopenia (ITP): platelet count lower than 100 x 10^9/L (Kayal et al., 2014) caused by abnormally high platelet destruction and impaired platelet production with normal bone marrow, in absence of other causes of thrombocytopenia

Epidemiology

- EMA recognises ITP as a rare condition; 3,000 to 4,000 UK adults estimated to have ITP at any one time
- Prevalence higher in females (Bennett et al., 2011) and patients over age 50 (Segal and Powe, 2006).
- Majority of diagnosed cases in adults progress to chronic disease

Symptoms and prognosis

- Fatigue, purpura, spontaneous bruising and regular bleeding episodes
  - Episodes can range from minor bleeds to severe, life-threatening haemorrhages
- People with ITP also experience anxiety and fear about maintaining their platelet levels
- Maintaining platelet count at ≥ 50 x 10^9/L (Rodeghiero, 2009) prevents clinically significant bleeding

Diagnosis and classification

- Diagnosis is based on excluding other possible causes of symptoms
- Treatment for ITP is usually required when platelet count is below 30 x 10^9 per litre (Neunert et al., 2019)

NICE **Abbreviations**: ITP: immune thrombocytopenia

Avatrombopag (Doptelet, Swedish Orphan Biovitrum AB)

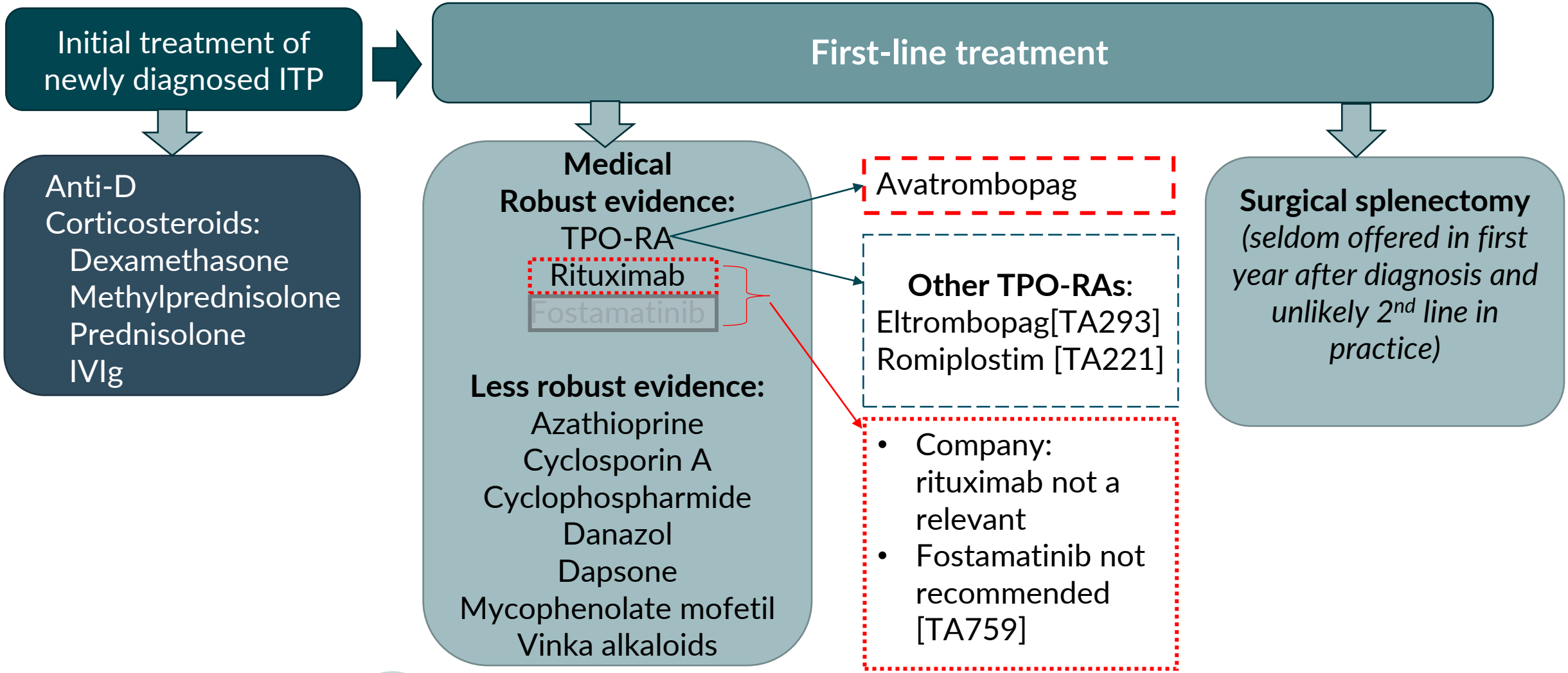
Table 1 Avatrombopag details

<table>
<tr><td>Marketing authorisation</td><td>• Approved for “treatment of primary chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g. corticosteroids or immunoglobulins)
• EMA approved; granted January 2021</td></tr>
<tr><td>Mechanism of action</td><td>• TPO-RA that stimulates proliferation and differentiation of megakaryocytes from haemopoietic stem and progenitor cells; increases platelet production</td></tr>
<tr><td>Administration</td><td>• Oral: 20mg film coated tablet to be taken orally before, during or after food depending on individual patient platelet count
• Maintenance dose varies between 20mg weekly and 40mg daily
<table>
<tr><td>Dose level 1 = 20mg once weekly</td><td>Dose level 4 (initial dose) = 20mg once daily</td></tr>
<tr><td>Dose level 2 = 20mg twice weekly
40mg once weekly</td><td>Dose level 5 = 40mg thrice weekly, 20mg on remaining 4 days</td></tr>
<tr><td>Dose level 3 = 20mg thrice weekly</td><td>Dose level 6 = 40mg once daily</td></tr>
</table>
Discontinue avatrombopag if:
• platelet count does not increase to ≥ 50 x 10^9/L after 4 weeks of dosing at maximum dose of 40mg once daily;
• platelet count greater than 250 x 10^9/L after 2 weeks of dosing at 20 mg once weekly</td></tr>
<tr><td>Price</td><td>• 10x20mg tablets: £640; 15x20mg tablets: £960
• 30x20mg tablets: anticipated price, £1,920
• Subject to confidential patient access scheme
Annual cost of treatment (assuming 20mg daily): £21,983</td></tr>
</table>

Abbreviations: TPO-RA: thrombopoietin receptor agonist

Treatment pathway

ERG: clinical advisor to ERG broadly agreed with the treatment pathway presented



Is company's positioning of avatrombopag appropriate?

Source: company submission figure 1. **Abbreviations**: IVIg: intravenous immunoglobulin g; TPO-RA: thrombopoietin receptor agonist;

Key issue: Positioning of rituximab in the treatment pathway

ERG: positioning of avatrombopag relative to rituximab unclear

Background: Variation in use of rituximab in practice

- Rituximab increasingly used before TPO-RAs prior to COVID-19 pandemic; use reduced due to immunosuppression;
- TPO-RAs now used before rituximab; unclear if this will change again – uncertain if rituximab relevant comparator

Company

- Highly varied across treatment centres and lines of therapy - does not represent established clinical practice
- Not considered rituximab to be a relevant comparator for avatrombopag

ERG comments

- Company's positioning of eltrombopag and romiplostim most relevant comparators reasonable
- Recognises uncertainty about positioning of rituximab in treatment pathway

Other considerations

- TA293 (eltrombopag); rituximab positioned before eltrombopag or romiplostim
- TA221 (romiplostim); rituximab positioned after romiplostim but considered romiplostim to be used in those who are refractory to or intolerant of rituximab
- **Clinical experts:** treatment is individualised, rituximab typically used after steroids and TPO-RAs

Is rituximab a relevant comparator for avatrombopag?
Are eltrombopag and romiplostim the most appropriate comparators for avatrombopag?

Abbreviations: TPO-RA: thrombopoietin-receptor agonist.

Recent NICE appraisals for chronic immune thrombocytopenia (ITP)

NICE has previously approved 2 TPO-RAs for chronic ITP

Table 2 Recent NICE appraisals

Technology appraisal	Drug	Recommendation
NICE TA759* (January 2022)	Fostamatinib*	Not recommended, within its marketing authorisation, for treating refractory chronic immune thrombocytopenia in adults.
NICE TA293 (last updated October 2018)	Eltrombopag	Recommended as an option for treating chronic immune (idiopathic) thrombocytopenic purpura in adults, only if: • their condition is refractory to standard active treatments and rescue therapies or • they have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies.
NICE TA221 (last updated October 2018)	Romiplostim	Recommended as an option for treating chronic immune (idiopathic) thrombocytopenic purpura in adults, only if: • their condition is refractory to standard active treatments and rescue therapies or • they have severe disease and a high risk of bleeding that needs frequent courses of rescue therapies.

NICE **Abbreviations**: TPO-RA: thrombopoietin receptor agonist; * fostamatinib is not a TPO-RA and not recommended. `

Patient perspectives

Avatrombopag offers a new option for what is a chronic condition

Submissions from The ITP Support Association

- Platelet levels can fluctuate unexpectedly and without obvious cause
- Significant worry and anxiety
- Often accompanied by fatigue, affecting their quality of life
- Unmet need for what is a chronic, lifelong condition
- Current treatments often cause side effects, and carry risk of infection
- Treatment to increase platelet count should be with minimal toxicity
- TPO-RAs offer good response rate and do not suppress immune system
- Avatrombopag preferred as:
    - Preferred treatment route (oral)
    - No dietary restrictions
    - Non-immunosuppressive option
    - Good response rate

Abbreviations: ITP: immune thrombocytopenia; TPO-RA: thrombopoietin receptor agonist

Clinical perspectives

Avatrombopag is a welcome addition to current treatments

Submissions from UK ITP Forum

- Treatment should be individualised, prevent severe bleeding and maintain target platelet level of >20-30 X 10^9/L, and optimise health-related quality of life
- Current treatment starts with corticosteroids and/or intravenous immunoglobulins
- Not all patients respond to current standard of care for ITP, majority of patients relapse after treatment with first line steroids
- Use of surgical splenectomy is in decline
- TPO-RAs particularly important during COVID-19 pandemic, not immunosuppressive
- Patients that are intolerant or response to one TPO-RA can swap to other TPO-RAs
    - Have a reasonable chance of responding to alternative TPO-RA
- Avatrombopag:
    - does not cause liver issues (a side effect of other treatments for ITP)
    - is more convenient for patients as no dietary restrictions (improved compliance/HRQoL) and can be administered orally
    - reduces risks of fatal bleeding events and infection

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

Key issues (1)
Multiple issues; some resolved at technical engagement

Issue	Resolved?	ICER impact
Decision problem		
Positioning of rituximab in the treatment pathway	Partially resolved – for discussion	-
Clinical effectiveness		
Limited evidence base for avatrombopag due to recruitment and attrition issues	No – for discussion	Unknown impact
Exclusion of some TPO-RA trials from NMAs in company submission	Yes	-
Comparative effectiveness estimates from NMA for durable platelet response	No – for discussion	Large impact
Cost effectiveness		
Modelled time to treatment response	Partially resolved – for discussion	Small impact
Cost-effectiveness modelling only permits pairwise comparisons	Yes	-

Abbreviations: ICER: incremental cost effectiveness ratio; NMA: network meta analysis; TPO-RA: thrombopoietin receptor agonist

Key issues (2)

Multiple issues; some resolved at technical engagement

Issue	Resolved?	ICER impact
Cost effectiveness (cont.)		
Modelled treatment sequences	No – for discussion	Unknown impact
Drug dosages for non-TPO-RAs	Yes	-
Modelled treatment response rates for TPO-RAs and non-TPO-RAs	No – for discussion	Large impact
Long-term treatment duration	No – for discussion	Large impact
Costing for bleeds and rescue therapy events in model	No – for discussion	Large impact
Mortality risks associated with ITP	Yes	-
Health-related quality of life utility values	Yes	-
Administration costs for romiplostim	Yes	-
Romiplostim treatment acquisition costs	Yes	-

NICE **Abbreviations**: ICER: incremental cost effectiveness ratio; ITP: immune thrombocytopenia; TPO-RA: thrombopoietin receptor agonist

Decision problem (1)

ERG: population & intervention from company submission reflect scope

Table 2 Population, intervention, comparators and outcomes from the scope

	Final scope issued by NICE	Decision problem addressed in company submission	ERG comments
Population	Adults with chronic immune thrombocytopenia (ITP) refractory to other treatments.	Adults with chronic ITP refractory to other treatments. Anticipated that the population eligible for avatrombopag will be exactly the same as those who currently receive a TPO-RA.	Included trials broadly applicable to NHS setting
Intervention	Avatrombopag	Avatrombopag in addition to current clinical management	Intervention in company submission matches that of final scope

NICE **Source**: table 3, ERG report. **Abbreviations**: TPO-RA: thrombopoietin-receptor agonist

Decision problem (2)
Comparators in company submission differ from scope

	Final scope issued by NICE	Decision problem addressed in company submission	ERG comments

Comparators	Established clinical management without avatrombopag:
	
	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
		<u>Rationale:</u>
		• Inappropriate to include either splenectomy/rituximab given multiple TPO-RA alternatives available.
		  • Clinical opinion positions splenectomy as later-line treatment once all medical treatment options have been exhausted
		  • Rituximab use highly varied across treatment centres and lines of therapy - does not represent established clinical practice for the population under consideration
			Rituximab's positioning in treatment pathway unclear
			
			Agreed splenectomy is no longer used, or as a very last resort in UK.

NICE **Source**: table 3, ERG report. **Abbreviations**: TPO-RA: thrombopoietin-receptor agonist

Decision problem (3)
Outcomes considered by company reflect scope

	Final scope issued by NICE	Decision problem addressed in company submission	ERG comments
Outcomes	Outcome measures include: • Platelet count • Response rate and duration • Use of concurrent treatments and rescue treatments • Reduction in symptoms • Mortality • Adverse effects of treatment • HRQoL	Same as scope	Outcomes matched final scope issued by NICE. Company submission only reports durable response for platelet response, and did not report any shorter term response outcomes before 24 weeks. Per advice from clinical advisor, patients would be assessed at 8-12 weeks and discontinue treatment if not responsive.

NICE **Source**: table 3, ERG report. **Abbreviations**: HRQoL: health-related quality of life

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Key issues

Partially resolved
Unresolved
Unknown impact
Small impact
Large impact

Clinical effectiveness

- **Limited evidence base for avatrombopag due to recruitment and attrition issues**
  - What is the committee's view on the evidence from Study 302?
  - Is it appropriate to use data from Study 302 to determine key efficacy and safety outcomes?
- **Comparative effectiveness estimates from NMA for durable platelet response**
  - Is baseline platelet count a treatment effect modifier?
  - Which correction method used in the NMA is preferred?
  - Are the TPO-RAs considered to have similar effectiveness according to the NMAs?

NICE

Abbreviations: NMA: network meta-analysis; TPO-RA: thrombopoietin receptor agonist

Key clinical trials

Only study 302 data included in model

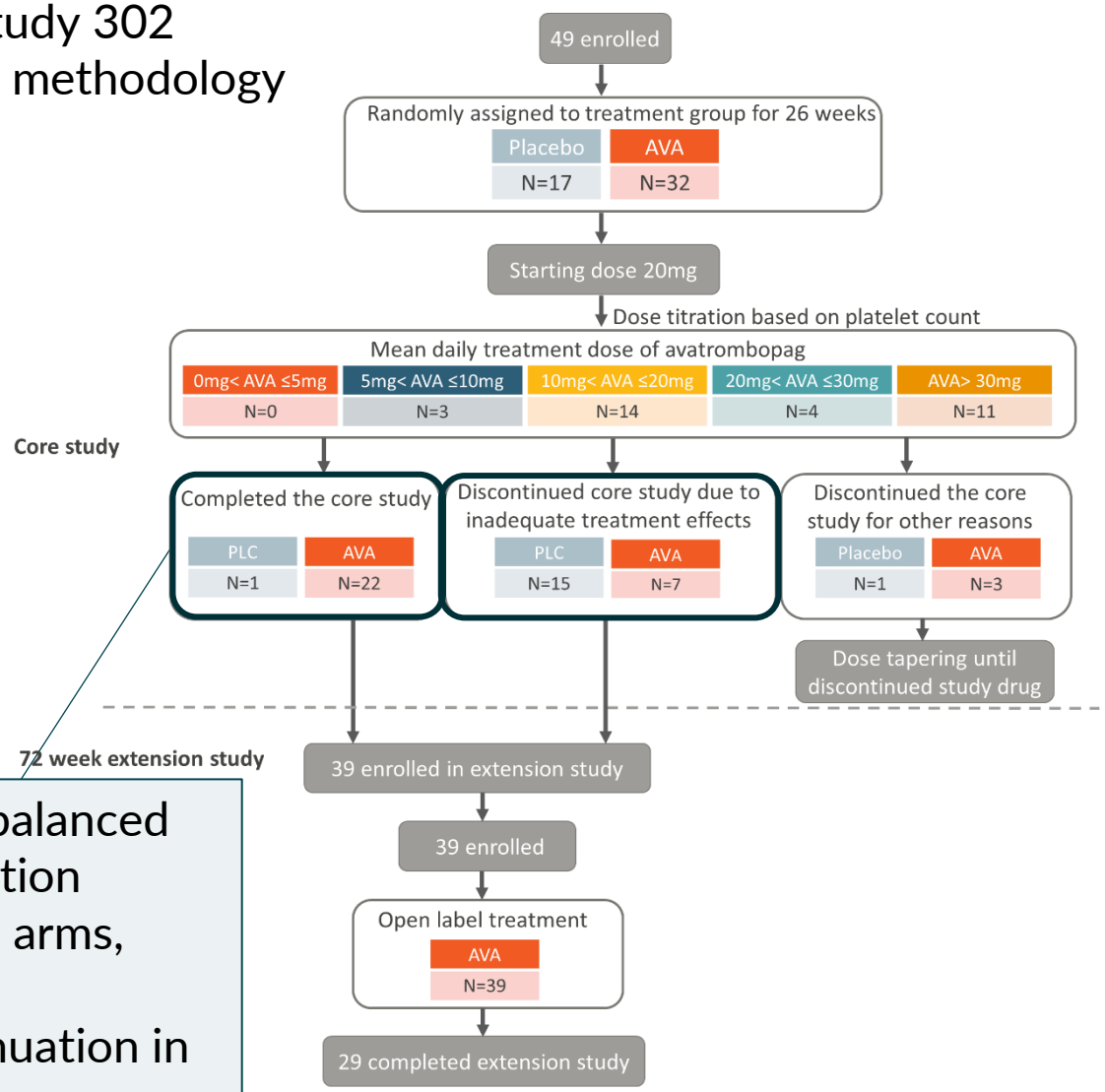
Table 3 Clinical trial design and outcomes of Study 302, included in model

	Study 302 (NCT01438840) – used in model
Design	Phase III, multicentre, randomised, double-blind, parallel-group study with open label extension phase
Population	Adults ≥18 years of age with ITP ≥12 months in duration, and an average of 2 platelet counts $<30\times10^9$/L as well as previous treatment with 1 or more therapies for ITP
Intervention	Avatrombopag 20mg with dose titrations (up to 40mg or down to 5mg)
Comparator	Placebo
Treatment duration	Main trial: 26 weeks; those entering extension phase: up to 72 weeks Mean treatment durations: Avatrombopag: 22.8 weeks; Placebo: 8.9 weeks
Primary outcome	Durable platelet response, time to response (cumulative number of weeks of platelet response $\geq50\times10^9$/L over 26 weeks)
Key secondary outcomes	Bleeding events (all grades), concomitant ITP medication, rescue therapy, HRQoL, reduction in symptoms, adverse effects of treatment, mortality
Locations	27 sites internationally (Australia, Belgium, Bulgaria, Czech Republic, Netherlands, New Zealand, Poland, Singapore, Slovakia, South Africa, Ukraine)
Follow-up time	6 months RCT phase

Abbreviations: HRQoL: health-related quality of life; ITP: immune thrombocytopenia; L: litres; RCT: randomised controlled trial

Study 302 Design and methodology

Figure 2 Study 302 design and methodology



ERG: imbalanced continuation between arms, higher discontinuation in placebo group

Table 4 Dose adjustment* based on platelet count during the core and extension phases of Study 302

Platelet count	Dose adjustment
$<50\times10^9$/L	Up titrate 1 dose level
$\geq50\times10^9$/L to $\leq150\times10^9$/L	Keep on the current dose
$>150\times10^9$/L to $\leq250\times10^9$/L	Down titrate 1 dose level
$>250\times10^9$/L	Stop dose, return for twice weekly platelet counts, then down titrate study drug 1 dose level when platelet count is $\leq150\times10^9$/L

*Doses adjusted according to individual responses to treatment

NICE **Source**: company submission, figure 3. **Abbreviations**: AVA: avatrombopag; PLC: placebo

Study 302 baseline characteristics

ERG: baseline characteristics aligned with patients seen in NHS

Is baseline platelet count a treatment effect modifier?

Table 4 Baseline characteristics of Study 302

Characteristic	Placebo (n=17) (%)	Avatrombopag (n=32) (%)	Total (n=49) (%)
Age (years)	41.2 (14.7)	46.4 (14.2)	44.6 (14.4)
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/m^2), mean (SD)	29.24 (6.64)	28.99 (7.32)	29.08 (7.02)
Baseline platelet count, N (%)			
≤15 x 10^9/L	10 (58.8)	18 (56.3)	28 (57.1)
15–30 x 10^9/L	7 (41.2)	13 (40.6)	20 (40.8)
≥30 x 10^9/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)
Concomitant ITP medication at baseline, N (%)	7 (41.2)	15 (46.9)	22 (44.9)

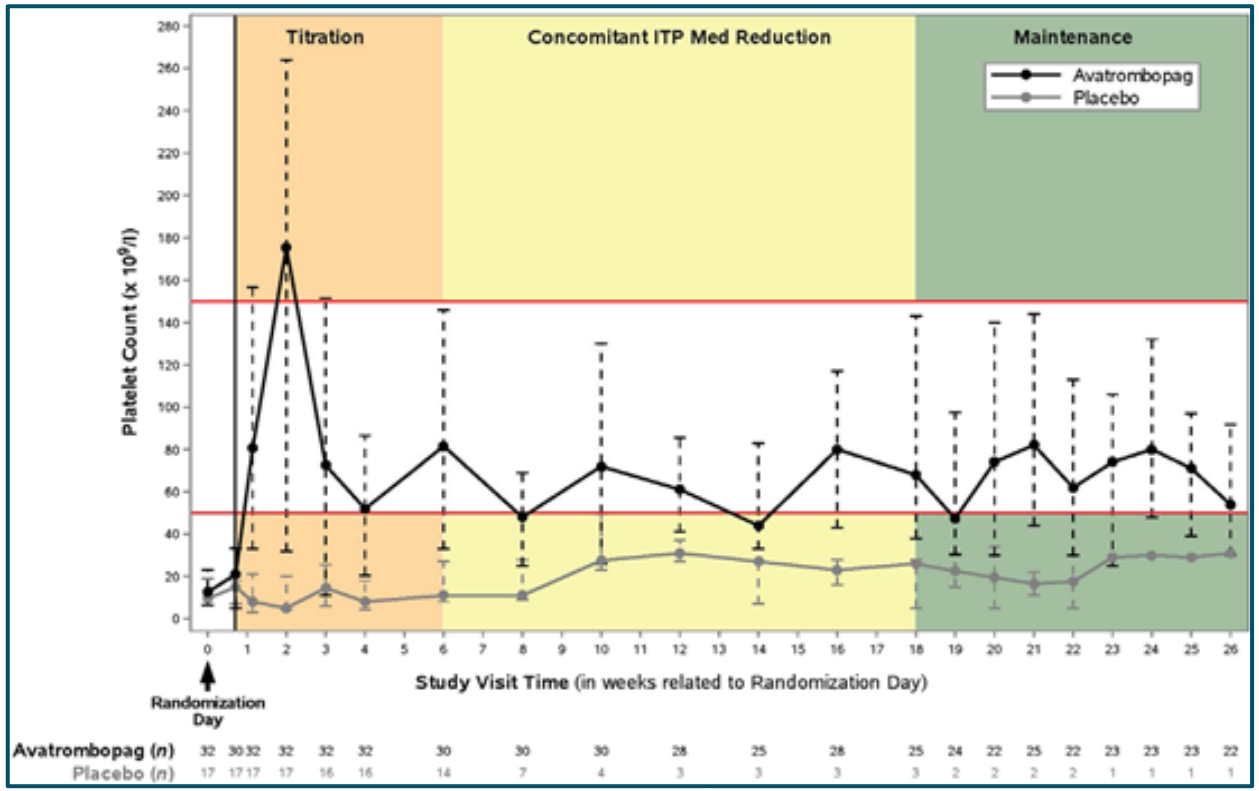
Source: table 8, company submission. **Abbreviations:** BMI: body mass index; ITP: immune thrombocytopenia; SD: standard deviation; TPO-RA: thrombopoietin receptor agonist

Study 302 results – platelet count

*p<0.0001

Median platelet count fluctuates but consistently higher for avatrombopag vs placebo

Figure 3 Study 302 results: median platelet count



Endpoint	Result	
	AVA	PLC
Median cumulative number of weeks of platelet response ≥50×10⁹/L over 26 weeks	12.4*	0

- Median platelet count in avatrombopag-treated patients consistently higher than placebo treatment group starting at Day 8 (80.5×10⁹/L vs. 8×10⁹/L, respectively) during core study
- Platelet count increased rapidly and remained within target platelet count range (50–150×10⁹/L) over 26 weeks
- Onset of platelet count increase observed within 3-5 days of avatrombopag treatment
  - Peak effect observed after 10-13 days
- During extension phase, platelet counts above 50×10⁹/L with avatrombopag maintained up to week 38
  - Beyond week 38, platelet response lower and more variable; small number of patients (n<15) limits further interpretation

NICE **Source**: figure 6, company submission. **Abbreviations**: AVA: avatrombopag; ITP: immune thrombocytopenia; L: litres; PLC: placebo

Study 302 results – secondary outcomes and exploratory endpoints

*p<0.0001
†p=0.009

Table 5 Secondary outcomes and exploratory endpoints for Study 302

Endpoint	Result	
	AVA (n=32)	PLC (n=17)
% of patients with platelet response (platelet count ≥50×10^9/L without rescue therapy) at Day 8	65.6*	0
% of subjects with reduction in concomitant ITP medication use	33.3	0
Durable platelet response rate (% of patients who had a platelet response for ≥6 of the last 8 weeks of treatment)	34.4†	0
% incidence of bleeding (any grade)	43.8	52.9
% Use of rescue therapy	21.9	11.8

ERG: when compared with placebo, avatrombopag:

- improves durable platelet response and platelet count at day 8 compared with placebo, differences statistically significant;
- appears to reduce concomitant ITP medications, incidence of bleeding, and use of rescue therapy, but results not statistically significant;
- Interpretation of results difficult given imbalance of missing data between 2 arms

NICE **Source**: table 15, company submission. **Abbreviations** AVA: avatrombopag; ITP: immune thrombocytopenia; L: litres; PLC: placebo

Study 302 - adverse events

ERG: Rate of TEAEs in avatrombopag arm comparable to comparators

Table 6 Adjusted (adjusted for treatment duration exposure) adverse event data from Study 302

	Core study exposure: adjusted incidence rate*		Core study + extension phase: adjusted incidence rate
	AVA (N=32) %	PLC (N=17) %	AVA (N=47) %
Any TEAEs	6.6	4.3	2.2
Any SAEs	0.7	1.2	0.7

Source: Table 30, CS

Table 9 Unadjusted adverse event data from Study 302

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

Source: Table 6, ERG report; *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; SAE: serious adverse event

Key issue: Limited evidence base for avatrombopag

Evidence for avatrombopag limited due to recruitment and attrition issues

Background

- Study 302: small (n=49), imbalance in outcome data (only 1 placebo patient completed the trial)
- Study 305: terminated early due to significant enrolment challenges; results not included in economic model

Company

- Acknowledges challenges in collecting evidence for avatrombopag
- Study 302 provides sufficient robust data to determine key efficacy and safety outcomes
- Performed an NMA to provide indirect comparison of effectiveness of avatrombopag and other TPO-RAs

ERG comments

- Concern with trial limitations: impact when estimating durable platelet response in placebo group
- Led to uncertainty surrounding company NMA estimates of comparative effectiveness between TPO-RAs
- Doesn't agree that Study 302 provides sufficient robust data to determine key efficacy and safety outcomes

Other considerations

- No alternative data; another trial comparing avatrombopag and eltrombopag would help resolve uncertainty
- Clinical experts: unaware of any real-world data available

What is the committee's view on the evidence from Study 302?
Is it appropriate to use data from Study 302 to determine key efficacy and safety outcomes?

Abbreviations NMA: network meta-analysis; TPO-RA: thrombopoietin receptor agonist

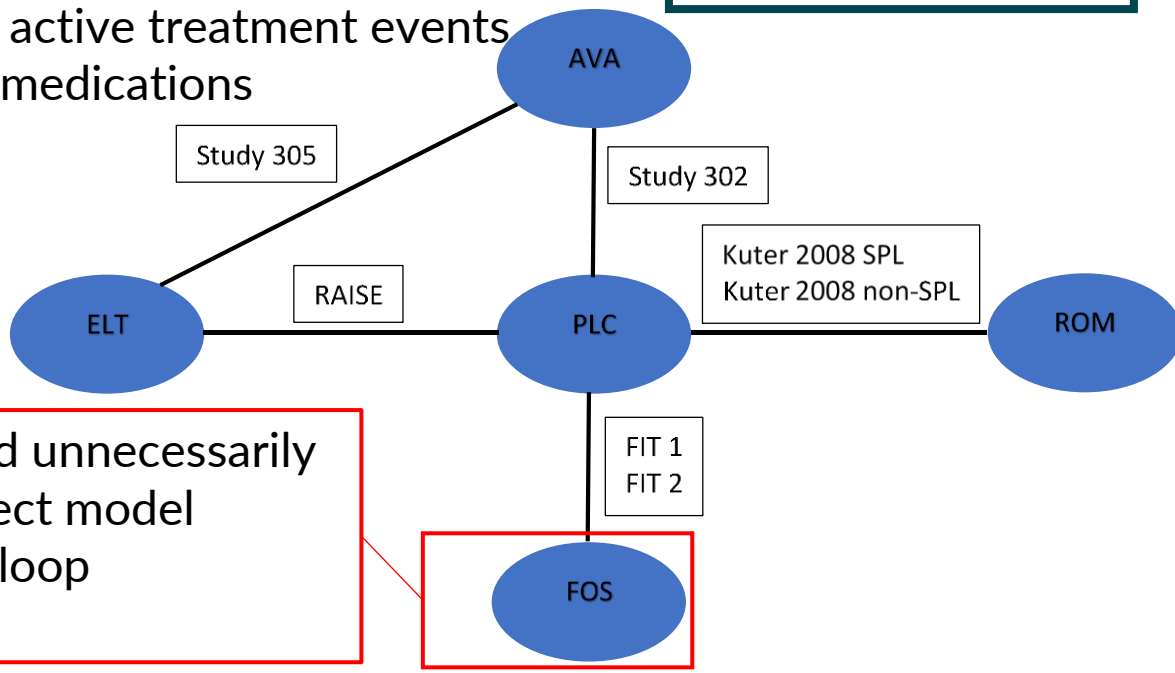
Network meta-analyses (NMAs)

- Absence of head-to-head comparison evidence between avatrombopag and other treatments; company conducted NMAs comparing avatrombopag's efficacy/safety with eltrombopag, fostamatinib, romiplostim and placebo

Company's NMAs

- Frequentist* approach; fixed effect models considered appropriate based on lower DIC value; assessed 6 outcomes:
  - **2 binary outcomes (reported as odds ratios):**
    - Proportion of patients with durable response
      - 3 RCTs (Study 302, Kuter 2008 SPL, FIT1) had zero cell in placebo arm
      - Company corrected zero cells and corresponding active treatment events
    - Proportion of patients with reduced concomitant ITP medications
  - **4 Incidence rate ratio outcomes:**
    - Any bleeding
    - Bleeding events WHO grade 2 to 4
    - Need for rescue therapy
    - Any adverse events

Overall network for all outcomes

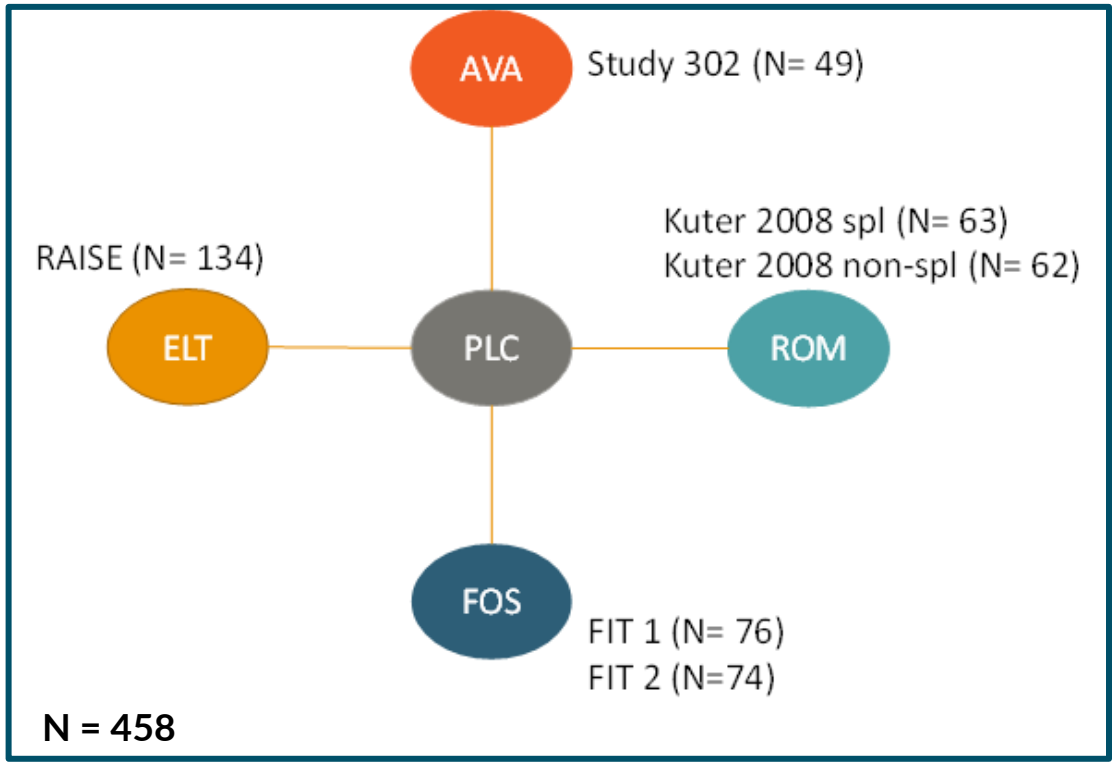


ERG: fostamatinib included unnecessarily
- No impact on fixed-effect model results as not in closed loop
- Not an important issue

Source: figure 3, ERG report. *Company adopted frequentist approach after TE; **Abbreviations**: AVA, avatrombopag; ELT, eltrombopag; DIC: deviance information criterion; FOS, fostamatinib; ITP: immune thrombocytopenia; NMA, network meta-analysis; PLC, placebo; RCT: randomised controlled trial; ROM, romiplostim; SPL: splenectomised

NMA results – durable platelet response

Company: results for durable platelet response appears to favour avatrombopag over comparators



ERG comments

- Multiple concerns about company's NMA for primary effectiveness outcome of durable platelet response; key efficacy outcome used to inform cost-effectiveness analysis

Odds ratios, avatrombopag vs. comparators (fixed effect model)*				Probability of being best
vs. placebo [95% CrI]	vs. eltrombopag [95% CrI]	vs. romiplostim [95% CrI]	vs. fostamatinib [95% CrI]	
102.80* [3.87, 2,796,448.5]	7.06 [0.21, 185,017.47]	2.16 [0.03, 69,340.75]	9.10 [0.12, 279,100.00]	58%

*Company NMA results before TE using Bayesian approach; **Source:** company submission appendices, figure 2, company submission, table 24.
Abbreviations: AVA: avatrombopag; ELT: eltrombopag; CrL: credible interval; FOS: fostamatinib; PLC: placebo; ROM: romiplostim;

Key issue: Comparative effectiveness estimates from NMA for durable platele response (1)

Company and ERG differed on continuity correction methods for zero events in NMAs
ERG: concerns with company's NMA for primary efficacy response

ERG comments

Company's NMA result for avatrombopag vs placebo lack face validity with respect to trial results from Study 302

- OR of 102.80 (95% CrI: 3.87 – 2,796,449), which company provided no explanation for adjustment values used, versus study specific OR of 18.72 (95% CI: 1.02 – 340) using conventional 0.5 continuity correction to both "events" and "non-events" arms

Company's continuity corrections used in NMAs for zero events in study arms not appropriate

- Company used different adjustment values across treatment arms within studies, and across studies
- Also adjusted number of response events, but did not perform adjustment to number of 'no events' or to total number of participants in each treatment arm;
- Could not verify company's unexplained adjustment methods for zero cells;

NMA cannot estimate between-study heterogeneity because of sparse nature of network

- Placebo effect and differences in placebo responses may contribute to high between-study heterogeneity; this cannot be estimated due to sparse nature of network

Abbreviations: CI: confidence interval; CrI: credible interval; ITT: intention to treat; NMA: network meta-analysis; OR: odds ratio

Key issue: Comparative effectiveness estimates from NMA for durable platelet response (2)

Company: revised continuity correction method so values added to adjusted zero cells proportional to sample size

Company response to TE:

- Does not consider ERG's 'study specific' OR of 18.72 as a credible estimate of avatrombopag efficacy
  - 11 and 0 events observed in avatrombopag and placebo arms, unable to divide by zero
  - OR of 18.72 is an estimate using 0.5 continuity correction; highly uncertain due to directional bias
  - Method of 0.5 correction may be inappropriate for studies with unequal groups (e.g. 1:2 ratio)
- 3 out of 6 studies reported zero events in control arms; proposed a continuity correction proportional to sample size, based on Sweeting et al. 2004
  - ❑ Any attempts of adjustment would require additional assumptions and continuity corrections leading to reduced credibility

Abbreviations: NMA: network meta-analysis; OR: odds ratio

Key issue: Comparative effectiveness estimates from NMA for durable platelet response (3)

ERG: preferred conventional 0.5 continuity correction for zero cells in treatment arms

ERG comments

- Acknowledged any zero-cell adjustments will introduce bias into NMA results, appropriate to use standard continuity correction of 0.5, typically reported in literature to correct zero events
  - Company values used for continuity correction are 'as arbitrary' as this value
- Maintained approach following technical engagement but provided sensitivity analyses to explore limitations with using 0.5 continuity correction highlighted by company
- Company's proportional approach not correctly implemented; ERG conducted sensitivity analysis which correctly implemented Sweeting 2004 adjustment method

Other considerations

- **Clinical experts:** experience is that TPO-RAs are very effective; trial data may be skewed due to strict criteria when defining a 'durable platelet response'
- Platelet level >30 x 10^9/L 'real world' measure of reduced risk of bleeding; risk based on how long below
- Anticipate avatrombopag to be 'as effective' as other TPO-RAs
- Would expect minority to respond to placebo, but some patients do experience spontaneous remission

Abbreviations: ITT: intention to treat; NMA: network meta-analysis; TPO-RA: thrombopoietin receptor agonist

Key issue: Comparative effectiveness estimates from NMA for durable platelet response, Study 302* as example (4)

ERG: sensitivity analysis exploring methods of applying continuity correction

	Events	No events	Total
1. No adjustment			
Avatrombopag	11	21	32
Placebo	0	17	17
Total	11	38	49
OR avatrombopag vs placebo = (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** (11.5+21.5)
Placebo	0.5	17.5	**18** (0.5+17.5)
Total	12	39	**51**
OR avatrombopag vs placebo = (11.5/21.5) / (0.5/17.5) = 18.72 (95% CI: 1.03, 340.54)			

ERG: adjustment of 0.5 added to all cells, including total number of participants in each arm; approach recommended by Cochrane handbook and Sweeting 2004 paper

* Study 302 as an example, Kuter 2008 SPL (ROM) required similar corrections; Source: ERG response to TE, table 3. **Abbreviations**: NMA: network meta-analysis; OR: odds ratio

Key issue: **Comparative effectiveness estimates from NMA for durable platelet response,** Study 302 as example **(5)**

ERG: sensitivity analysis exploring methods of applying continuity correction

	Events	No events	Total
3. Continuity correction in 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 avatrombopag vs placebo = (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** (11.65+21.65)
Placebo	0.35	17.35	**17.70** (0.35+17.35)
Total	12	39	**51**
OR avatrombopag vs placebo = (11.65/21.65) / (0.35/17.35) = 26.91 (95% CI: 0.87, 835.27)			

Company revised: adjustment values proportional to sample size added to "events" cells only but not to "no events" cells or "total" number of participants each arm

ERG sensitivity: adjustment values proportional to sample size added to "events" cells and "no event" cells, and total number of participants in each arm, as suggested by Sweeting 2004;

Key issue: Comparative effectiveness estimates from NMA for durable platelet response, Study 302 as example (6)

Com-parator vs. placebo	Company's submission NMA results (Bayesian fixed-effects model, CC values unexplained and applied to events only)	Company's revised NMA results (derived directly from studies, CC proportional to sample size 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)	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)
	Odds Ratio (95% CrI)	Odds Ratio (no CI provided)	Odds Ratio, (95% CI)	Odds Ratio, (95% CI)
AVA	102.80 (3.87, 2,796,448.5)	27.49	18.72 (1.03, 340.54)	26.91 (0.87, 835.27)
ELT	14.27 (5.14, 53.73)	10.60	10.60 (3.64, 30.87)	10.60 (3.64, 30.87)
ROM	46.49 (9.12, 670.61)	33.56	29.61 (5.42, 161.58)	33.39 (5.52, 201.98)
ROM vs AVA	0.46 (0.00, 30.02)	1.22	1.58 (0.05, 45.57)	1.24 (0.03, 59.99)

Which correction method used in the NMA is preferred?
Are the TPO-RAs considered to have similar effectiveness according to the NMAs?

Source: table 2, ERG response to TE. **Abbreviations**: CC: continuity correction; CI: confidence intervals; CrI: credible interval; ITT: intention to treat; NMA: network meta-analysis

Cost effectiveness

NICE National Institute for Health and Care Excellence

Key issues

Cost effectiveness

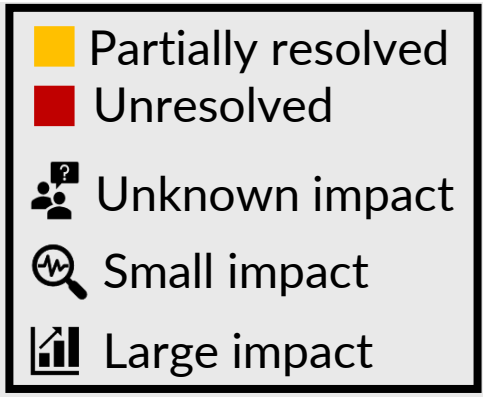
- **Modelled time to treatment response**
  - Is 24-week timeframe for assessing non-response in model appropriate?

- **Modelled treatment sequences**
  - What is committee's view on modelling treatment sequencing of TPO-RAs?
  - Is modelling treatment sequencing informative for decision making?

- **Modelled treatment response rates for TPO-RAs and non-TPO-RAs**
  - Is it appropriate to define response to treatment differently between TPO-RAs and non-TPO-RAs in model?

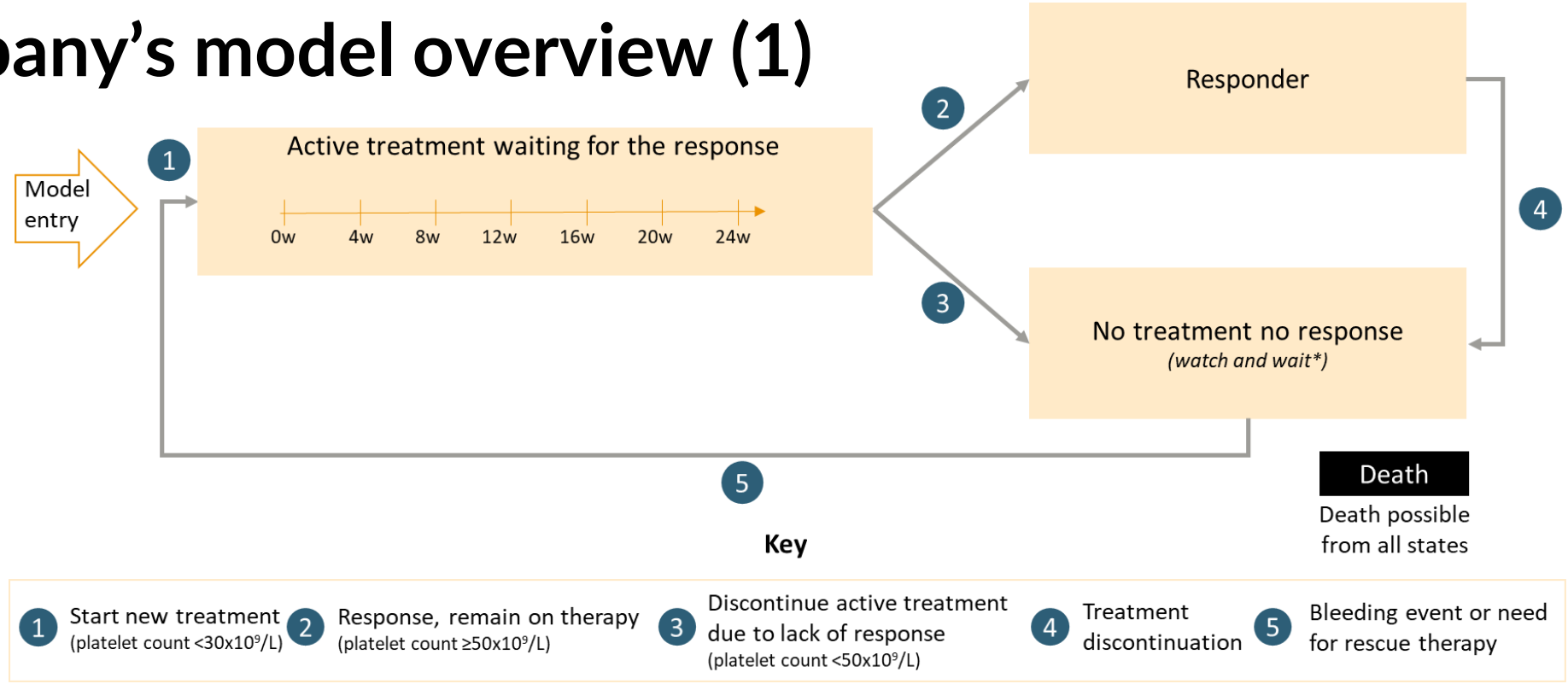
- **Long-term treatment duration**
  - Is the assumption that treatment duration is the same between TPO-RAs appropriate?
  - Is 109 cycles (4-week per cycle) a reasonable estimate for treatment duration?

- **Costs of bleeds and rescue therapy events used in model**
  - What is the committee's view on the company's approach to costing bleed events and rescue therapy? Is it appropriate?



Abbreviations: NMA: network meta-analysis; TPO-RA: thrombopoietin receptor agonist

Company's model overview (1)



Model structure	Markov cohort model consisting of 4 health states
Perspective	NHS and Personal Social Services (PSS)
Time horizon	56 years (assumed to represent a lifetime horizon)
Cycle length	4 weeks
Discounting	3.5% per annum, applied to model long-term costs and QALYs

ERG comments: model structure broadly appropriate for decision making

NICE **Source**: ERG report, figure 4. **Abbreviations**: L: litres; QALY; quality adjusted life year; w: weeks

How company incorporated evidence into the model (1)

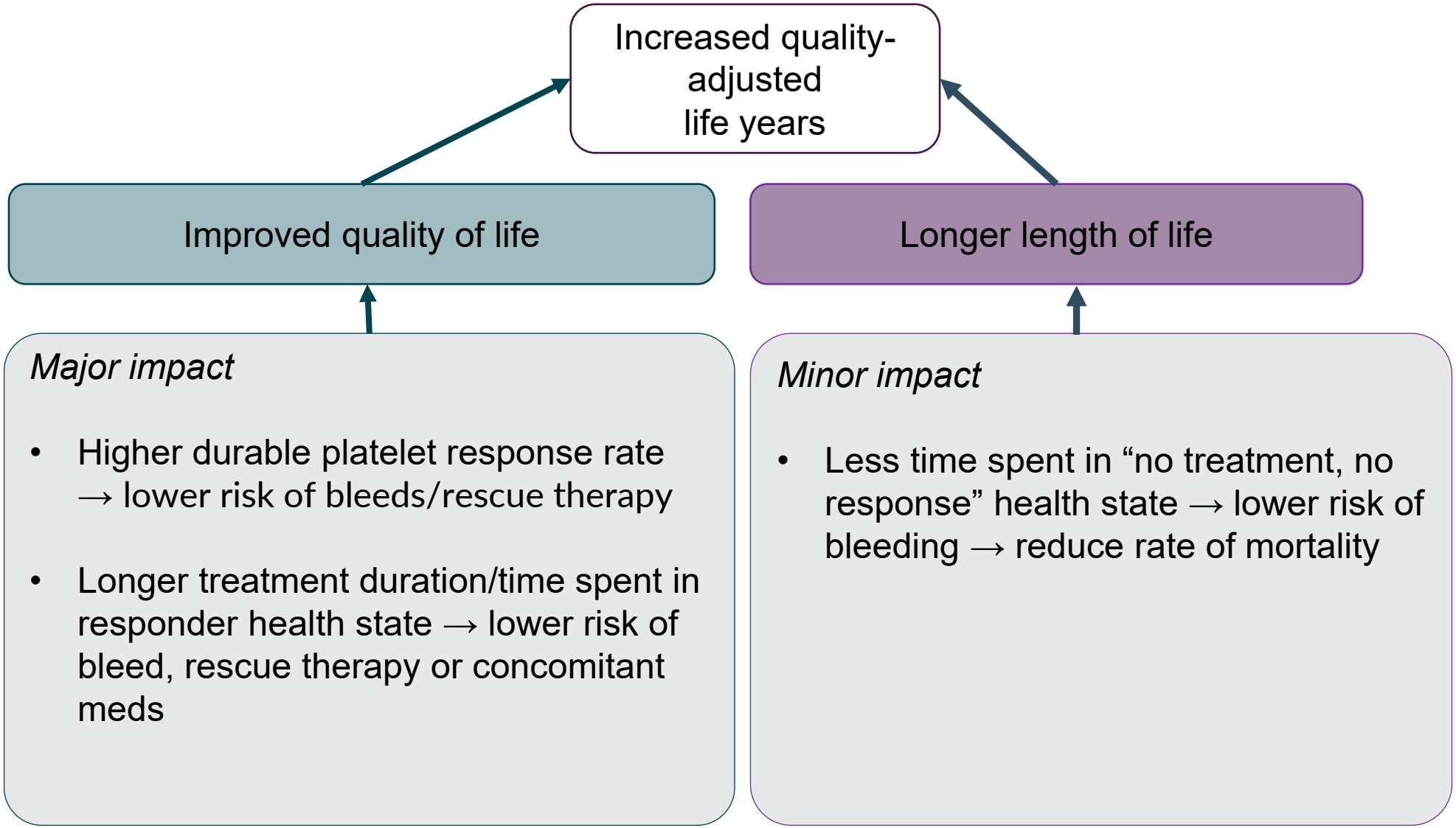
Input	Assumption and evidence source
Population	Study 302
Intervention	Avatrombopag in addition to current clinical management
Comparators	Eltrombopag, romiplostim
Treatment effect estimate	Platelet response rate: based on the NMA
Definition of treatment response	First-line treatment: durable platelet count >50 x 10^9/L Subsequent lines of treatment: mixed response definitions Definition of response at first line different from subsequent lines
Time to assessment response	24 weeks for first line; and 8 weeks for subsequent lines
Subsequent treatment	Up to 2 lines of subsequent treatments; 3rd line being watch and wait strategy (e.g., corticosteroids)
Bleeding	Risk of bleeding modelled according to platelet count only, independent of treatment

How company incorporated evidence into the model (2)

Input	Assumption and evidence source
Rescue therapy	Probability of usage according to platelet count, independent from treatment
Discontinuation/long term treatment duration	TPO-RAs: assumed identical length of treatment of 109 cycles, 0.9% discontinuation rate. Non-TPO-RAs: based on TA221 (romiplostim)
Utilities	EQ-5D data from Study 302 used to generate utility values stratified by responder status, bleeding events, splenectomy status and adverse events. Serious bleed utility values from TA293 (eltrombopag)
Mortality	All-cause and disease-related/ITP mortality (through severe bleeding events only); • Proportion of deaths with ITP-related hospitalisation for severe bleed, sourced from Danese et al. (also used in TA293 eltrombopag)
Costs for bleeding & rescue therapy	Informed by qualitative research commissioned by company, and units costs from UK sources. • Bleed related costs assumed to include proportion of rescue therapies caused by bleeding events (55.6%); rescue therapies caused by other factors (44.4%) costed separately
Adverse events	• Treatment specific adverse events: including serious adverse events and other adverse events; • TPO-RAs and non-TPO RAs assumed to have same risk of adverse events, modelled as one-off utility decrements; rates for TPO-RAs and non-TPO-RAs from TA221 romiplostim

Abbreviations: AE: adverse event; ITP: immune thrombocytopenia; L: litres; PSS: Personal Social Services; TPO-RA: thrombopoietin receptor

How quality-adjusted life years accrue in company's model



Key issue: Modelled time to treatment response

TPO-RA treatment duration likely below 24 weeks for non-responders in practice

Background: Model assumes patients wait full 24 weeks to assess non-response to all TPO-RA treatments

Company

- Durable platelet count used to measure response – defined as platelet count ≥50×109/L in at least 6 weekly platelet counts in final 8 weeks of a 24-26-week study
- Only platelet response measure which yielded comparative effectiveness data between TPO-RAs
- Took pragmatic approach and assumed 24-week timeframe to assess response to TPO-RA treatment

ERG comments

- Summary of Product Characteristics for TPO-RAs: stop treatment if response not achieved within timeframe of 4 weeks after maximum dose; considered 8-week timeframe appropriate to assess non-response, consistent with timeframe for subsequent lines of therapy
- Extending treatment for non-responders by a further 16 weeks ***increases*** costs but does not appear to increase response to treatment; cannot be assessed using durable platelet count as the measure of response
- Modelled response to treatment further complicated by concomitant ITP medication patients had in Study 302, leading to further dose adjustment for stable platelet response
- Company accepts issues raised by ERG during TE but no new analysis provided, uncertainties remain
- Scenario analysis for 24 week time to response shows small impact on cost effectiveness results

Other considerations

- Clinical experts would not expect non-responders to remain on treatment for 24 weeks, closer to 8 weeks

What is the committee's view on the 24 week timeframe for assessing non-response in the model? Is it appropriate?

Abbreviations: ITP: immune thrombocytopenia; L: litres; TE: technical engagement; TPO-RA: thrombopoietin receptor agonist

Key issue: Modelled treatment sequences

Optimum positioning of avatrombopag among TPO-RAs undetermined

Background

- Company uses a mixed treatment approach (% of individual therapies that follow first-line TPO-RA) when modelling subsequent lines of therapy; subsequent lines of therapy include both TPO-RAs and non-TPO-RAs, different from previous topics;
- Response rates for subsequent lines may be higher than first-line therapy in company's model

Company: treatment sequencing not likely to be considered plausible from clinical perspective because:

- Similar efficacy, safety and long term treatment duration between avatrombopag/other TPO-RAs
- Avatrombopag considered for use in patients who are suitable candidates for other TPO-RAs

ERG comments: comprehensive assessment of fixed treatment sequences, weighted by % of patients in UK clinical practice that follow each treatment pathway more appropriate; reflects variability of treatment

- Avatrombopag and other TPO-RAs not shown to have similar comparative efficacy/safety/long term treatment duration; this evidence required to assess most efficient use and positioning among TPO-RAs
- Also depends on time spent between treatments as non-responders, as well as treatment costs (e.g. starting with cheaper therapies first before progressing to more expensive options);
- Scenario analysis had small impact on ICER but this was based on identical treatment durations assumption

Clinical experts: currently no fixed sequence; most choose oral options. Can switch between TPO-RAs.

What is the committee's view on modelling treatment sequencing of TPO-RAs? Is assessing cost-effectiveness of treatment sequencing in model informative for decision making?

Abbreviations: ICER: incremental cost effectiveness ratio; TPO-RA: thrombopoietin receptor agonist

Key issue: Different definitions of response for TPO-RAs and non-TPO-RAs (1)

Company: lack of data precludes same definition of response for TPO-RAs and non-TPO-RAs

Background

- Definition of response for TPO-RAs is durable platelet count whereas for non-TPO-RAs it is unclear – based on TA221 (romiplostim)
- Subsequent lines of therapy (mix of TPO-RAs and non-TPO-RAs) have mixed treatment response definitions

Company

- Subsequent lines of therapy include treatments unlicensed for immune thrombocytopenia; lack of evidence for comparison on treatment response
- Fostamatinib and all 3 TPO-RA immune thrombocytopenia licensing studies had similar definition of durable platelet response (platelet response above 50×10^9/L for ≥6 of last 8 weeks of treatment).
  - Unable to match this definition for other therapeutic options as lack of data

ERG comments

- Alternative definitions of response results in very high response rates for non-TPO-RAs in subsequent lines of treatment compared to response rates from first-time TPO-RAs
- No new evidence, data or analyses presented by the company during technical engagement

Key issue: Different definitions of response for TPO-RAs and non-TPO-RAs (2)

Previous appraisals modelled subsequent lines of therapy as non-TPO-RAs only

Definition of response	Romiplostim appraisal (TA221)	Eltrombopag appraisal (TA293)
TPO-RAs	durable platelet response (platelet count of at least 50×10^9/L in at least 6 weekly assessments in last 8 weeks of treatment)	platelet count of 50 - 400×10^9/L at any time during 6 month study period
Subsequent lines of therapy (Non-TPO-RAs)	literature review - combined data on efficacy by taking a weighted average	literature review - pooled data regardless of definition of response, weighted averages

Other considerations

- In clinical practice, definition of response varies; based on symptoms, how the person is feeling, and whether platelet count is appropriate for their age and lifestyle. Also differs depending on treatment.

Is it appropriate to define response to treatment differently between TPO-RAs and non-TPO-RAs in model?

Abbreviations: L: litres; TPO-RA: thrombopoietin receptor agonist

Key issue: Long-term treatment duration of TPO-RAs (1)

Company believes same treatment duration between TPO-RAs, ERG does not agree

Background

- Long-term treatment duration assumed 109 model cycles for all TPO-RAs (436 weeks/8.4 years) over lifetime.
- Based on lowest mean time on treatment of 109 cycles for eltrombopag and 393 cycles for romiplostim. Difference in mean time estimates suggest possible difference in discontinuation rates between TPO-RAs.

Company

- Conducted clinician survey in UK which supports similar long-term treatment duration between TPO-RAs.
  - [redacted]
  - [redacted]
  - [redacted]

ERG comments

- Choice of estimate (109 vs 393 cycles) will impact cost-effectiveness i.e. longer treatment duration will increase time to 'no treatment, no response' which incurs higher risk of bleeding/need for rescue therapy
- For more effective treatments, lower discontinuation rates improve cost-effectiveness as delays in entering the 'no treatment, no response' health state discounts the eventual consequences of those future bleed/rescue therapy events
- Provided scenario analyses for exploration:
  - Longer treatment duration of 393 cycles for all TPO-RAs
  - Different treatment durations: 109 cycles for avatrombopag and eltrombopag, 393 cycles for romiplostim

NICE **Abbreviations**: TPO-RA: thrombopoietin receptor agonist

Key issue: Long-term treatment duration of TPO-RAs (2)

Other considerations

- **UK ITP Forum**:
  - Avatrombopag efficacy and tolerance appear similar to other TPO-RAs
  - No dietary restrictions with avatrombopag may improve compliance with medication
- **Clinical expert**: discontinuation rates similar between TPO-RAs. Experience of treatment for up to 10 years. Do try to wean off treatment if platelet counts stable.
- **Romiplostim appraisal (TA221):** Modelled time on treatment using patient data on time to failure from phase III 24 week trials and open-label extension study.
- **Eltrombopag appraisal (TA293):** Modelled time on treatment using patient data on treatment discontinuation from RAISE and EXTEND, and carried out parametric analysis. Assumed time on treatment was same for eltrombopag and romiplostim.
- **Fostamatinib appraisal (TA759):** Not a TPO-RA but modelled time on treatment using patient data on loss of response from open-label extension study.

Is the assumption that treatment duration is the same between TPO-RAs appropriate?
Is 109 cycles (4-week per cycle) a reasonable estimate for treatment duration?

Key issue: Approach to costing bleeding and rescue therapy events (1)

ERG and company differed on their approaches for costing

Background:

Company before TE:

- Rescue therapy events stratified by bleeding association, with bleed-related rescue therapies nested within bleed events. Bleed costs (inclusive of rescue therapy) sourced from independently commissioned market research

ERG before TE:

To aid consistency and interpretability, rescue therapy and bleed events costed independently, such that:

- Applied company's non-bleed related rescue therapy event costs to all rescue therapy events in model
- All bleed events costed according to NHS reference costs
- Rescue therapy rates observed in Study 302 + extension (as ERG could not verify the company's base case rates)

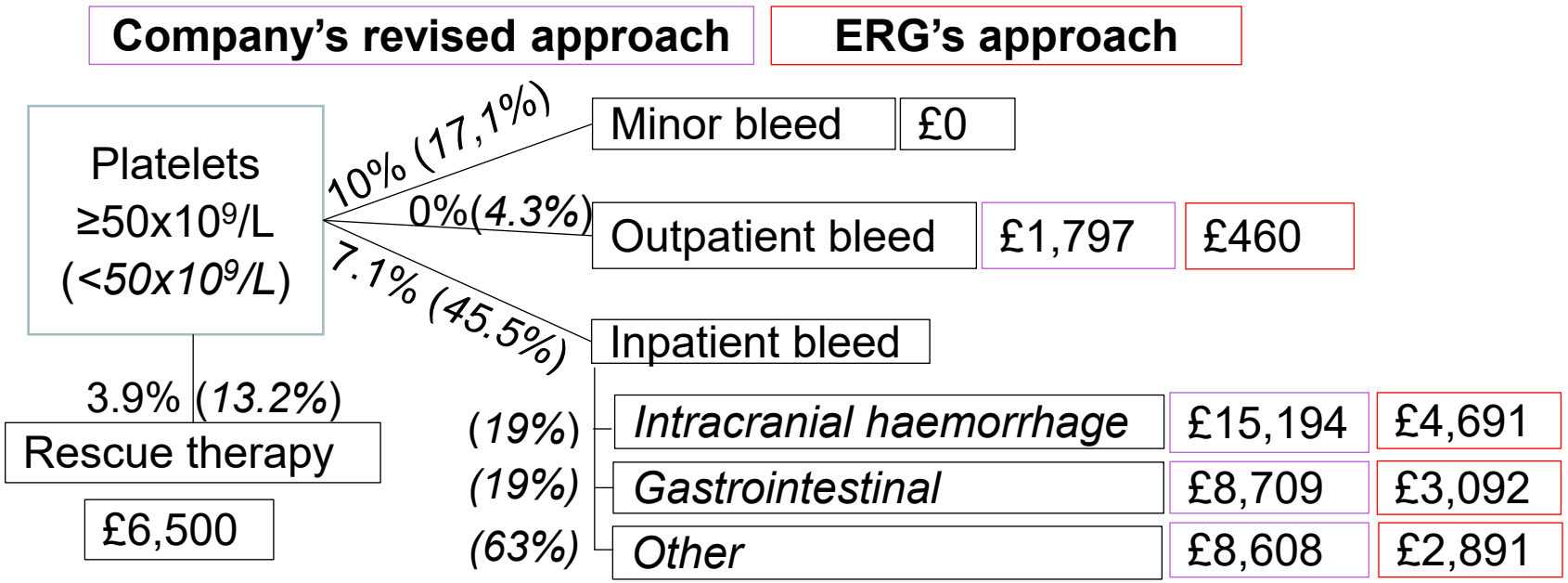
After TE:

Company:

- Aligned its configuration of bleed and rescue therapy rates and costs to ERG's, except for bleed-specific unit costs which applied the midpoint between ERG bleed costs (from NHS tariffs) and company's market research data

Abbreviations: TE: technical engagement

Key issue: Approach to costing bleeding and rescue therapy events (1): Company and ERG differ on sources of bleed-specific unit costs



ERG's key outstanding issue

The independent bleed costs applied in the company's revised model remain markedly higher than NHS reference costs and those applied in previous appraisals [TA293 and TA221].

ERG comments

- Using midpoint between NHS tariffs and the company's market research, which includes rescue therapies, to provide bleed-specific costs suggests may not be independent from costs of rescue therapy
- No justification for using market research; no indication of which bleed-specific costs are excluded from NHS tariff and how using this midpoint captures these alleged omissions
- Methodology used in market research to determine event-related resource use not provided and therefore cannot be validated.

Key issue: Approach to costing bleeding and rescue therapy events (3)

What is the committee's view on the company's approach to costing bleed events and rescue therapy? Is it appropriate?

ERG preferred assumptions

Assumption	ERG base case	Company accepted?
Approach to modelling subsequent treatments	Fully incremental comparison of avatrombopag, eltrombopag and romiplostim, removing TPO-RAs from subsequent lines of therapy so all treatment sequences have common set of subsequent non TPO-RA therapies	Yes ✓
Drug dosages for non-TPO-RAs	Active treatment drug dosing schedules aligned to latest guidance from Provan (2019)	Yes ✓
Estimates of comparative effectiveness for durable platelet response	Frequentist fixed-effect ITC for avatrombopag, eltrombopag, romiplostim and placebo	No ×
Utility values	Age adjusted, reflecting decreasing utility of patients through model over time	Yes ✓
Romiplostim administration costs	Based on one initial clinic visit followed by 12.5% of patients administering at haematological outpatient visit thereafter	Yes ✓
Romiplostim drug acquisition costs	Median doses from pivotal romiplostim trial used to inform in first 24-weeks of active treatment	Yes ✓
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	No ×

Source: ERG report, page 123. **Abbreviations**: ITC: indirect treatment comparison; TPO-RA: thrombopoietin receptor agonist

Comparison of company and ERG base case assumptions

Some differences remain between company and ERG base case

- Company accepted ERG's preferred assumptions for all issues except the approach to the durable platelet response NMA and approach to costing bleeding and rescue therapy events in the model

Table x Differences in base case assumptions between company and ERG base case following TE

Assumption	Company revised base case	ERG base case
Estimates of comparative effectiveness for durable platelet response	Frequentist fixed-effect NMA model, continuity correction proportional to sample size, applied to events only	Frequentist fixed-effect ITC for avatrombopag, eltrombopag, romiplostim and placebo, continuity correction of 0.5 applied to events and non-events
Approach to costing bleeding and rescue therapy events in the model	Rescue therapy and bleed events costed independently from Study 302 rescue treatments and NHS reference costs, respectively • For revised bleed-related unit costs, applied the midpoint between ERG bleed costs (from NHS tariffs) and company's market research data	Aligned to Study 302 and extension with rescue therapy and bleed events costed independently from Study 302 rescue treatments and NHS reference costs, respectively

Source: company response to technical engagement, ERG response to technical engagement.
Abbreviations: ITC: indirect treatment comparison; NMA: network meta-analysis; TE: technical engagement

Other considerations

No equality issues identified; offers more tolerated treatment option

Equality considerations

- Not anticipated that appraisal will:
    - Exclude from consideration any people protected by equality legislation
    - Lead to a recommendation that has a different impact on people protected by equality legislation than on the wider population
    - Lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Innovation

- Unlike other TPO-RAs, avatrombopag available orally without dietary restrictions, need for fasting or hepatoxicity monitoring
    - Reduce healthcare resource burden and increase likelihood of adherence/compliance
- Provides additional treatment option for those experiences adverse events or loss of response on other TPO-RAs
- Flexible dosage regimen; more accurate dose titration for maintaining platelet counts within target range than current TPO-RAs

Abbreviations: TPO-RA: thrombopoietin receptor agonist

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Thank you.

Back up slides

Key clinical trials not included in model (1)

ERG: [redacted] Study CL-003 limited by small placebo group and short follow-up

Table 5 Clinical trial designs and outcomes of studies not included in model

	Study 305 (NCT01433978)	CL-003 (NCT00441090)	CL-004 (NCT00625443)
Design	[redacted]	[redacted]	[redacted]
Population	[redacted]	[redacted]	
Intervention	[redacted]	Different doses of [redacted]	[redacted]
Comparator	[redacted]	[redacted]	[redacted]
Treatment duration	[redacted]	[redacted]	[redacted]

Source: company submission, table 4, figure 5. **Abbreviations**: ITC: immune thrombocytopenia

Key clinical trials not included in model (2)

Table 5 continued Clinical trial designs and outcomes of studies not included in model

	Study 305 (NCT01433978)	CL-003 (NCT00441090)	CL-004 (NCT00625443)
Primary outcome	[redacted]	[redacted]	
Key secondary outcomes	[redacted]	[redacted]	
Locations	[redacted]	[redacted]	
Used in model?	[redacted]	[redacted]	

NICE **Source**: company submission, table 4, figure 5. **Abbreviations**: n/a: not available

Study 305 and Study CL-003/CL-004 results

ERG: evidence appears to suggest avatrombopag improves response compared with eltrombopag or placebo, but limited by small sample sizes and short follow up time

Study 305

- Efficacy results for Study 305 available only in the Clinical Study Report, not company submission
  - [redacted]
  - [redacted]
    - [redacted]
    - [redacted]
- TEAEs similar between avatrombopag and eltrombopag treated groups during Study 305
  - [redacted]

Study CL-003

- Results from Study CL-003 limited by very small placebo group (n=5) and short follow up duration (28 days)
  - Response rate: 49.2% among all those who received avatrombopag versus 0% for placebo
  - Platelet count increased by Day 7, peaked at Day 14 for 10mg and 20mg avatrombopag groups
  - Platelet count >50 x 10^9/L at day 28: 20mg avatrombopag group: 80.0%; placebo: 0% (p=0.0036)
- TEAEs similar between avatrombopag and placebo treated groups during Study CL-003/004
  - [redacted]

NICE **Abbreviations**: L: litres; TEAE: treatment-emergent adverse event; PLC: placebo; SAE: serious adverse event

Studies included in company's NMAs (backup)

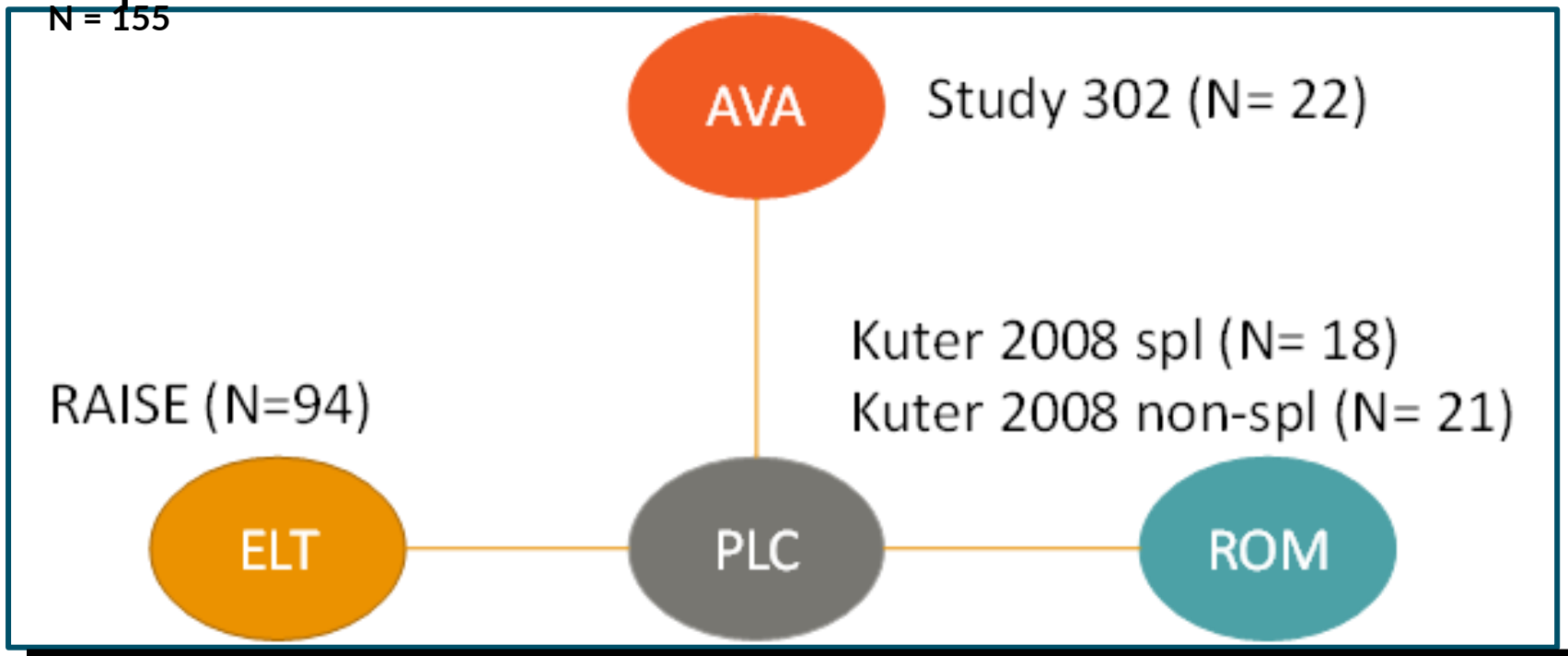
Comparator	Studies per outcome					
	Binary		Rate data			
	Durable response	Reduction in the use of concomitant ITP medication	Need for rescue therapy	Any bleeding events	Bleeding events WHO grade 2-4	Any adverse events
vs Placebo						
Avatrombopag	Study 302	Study 302	Study 302	Study 302	Study 302	Study 302
Eltrombopag	RAISE	RAISE	RAISE Yang* Huang*	RAISE Bussel 2007* Bussel 2009* Huang* Yang*	RAISE Yang*	RAISE Yang* Bussel 2007* Bussel 2009* Tomiyama*
Romiplostim	Kuter SPL Kuter non-SPL	Kuter SPL Kuter non-SPL	Kuter SPL Kuter non-SPL Shirasugi*	Kuter SPL Kuter non-SPL Shirasugi*	Kuter SPL Kuter non-SPL	Kuter SPL Kuter non-SPL Shirasugi*
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
vs SoC						
Romiplostim	----------	----------	----------	Kuter 2010*	Kuter 2010*	----------

*included at technical engagement, excluded from original NMA in company submission

Source: adapted from table 11, ERG report. **Abbreviations**: SoC: standard of care; SPL: splenectomised

NMA results – use of concomitant medications (1)

Results for concomitant medications appears to favour avatrombopag over comparators



ERG comments

- Includes a study (Kuter 2008 spl) with zero cell in the placebo arm; adjusted by company
- Convergence issues due to shared evidence base between both outcomes (durable platelet response and use of concomitant medications)

Source: company submission appendices, figure 4. **Abbreviations**: AVA: avatrombopag; ELT: eltrombopag; PLC: placebo; ROM: romiplostim; SPL: splenectomised

NMA results – use of concomitant medications (2)

Results for concomitant medications favour avatrombopag over comparators

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)

Source: ERG report, table 22. **Abbreviations**: CC: continuity correction; CI: confidence interval; MCMC: Markov Chain Monte Carlo; spl: splenectomised

NMA results – other outcomes

Company updated NMAs[+] for other outcomes during TE, ERG did not critique further

Outcome	Incidence rate ratios, avatrombopag vs. comparators (Bayesian approach, fixed effect model)					Probability of being best
	vs. placebo	vs. eltrombopag	vs. romiplostim	vs. fostamatinib	vs. SOC	
Any bleeding events	0.32* (0.16, 0.61)	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%
Bleeding: WHO grade 2-4	0.49 (0.12, 1.94)	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%
Need for rescue therapy	0.73 (0.15, 3.52)	2.03 (0.39, 10.44)	2.02 (0.37, 10.88)	1.97 (0.37, 10.55)	-	13%
Adverse events	0.65 (0.38, 1.13)	0.61 (0.35, 1.07)	0.65 (0.34, 1.24)	0.94 (0.48, 1.86)	-	56%

[+] **included 7 additional studies into NMAs during TE; Source:** company technical engagement response. *highlights significant results.
Abbreviations: AVA: avatrombopag; ELT: eltrombopag; FOS: fostamatinib; PLC: placebo; ROM: romiplostim; SoC: standard of care; TE: technical engagement

Comparison of assumptions with Previous appraisals

NICE previously recommended 2 TPO-RAs (romiplostim, eltrombogpag) for chronic ITP

Evidence/ Assumption	Romiplostim [TA221; last updated October 2018]	Eltrombopag [TA293; last updated October 2018]	Fostamatinib [[TA759; January 2022]	Avatrombopag [Current topic]
Positioning of rituximab	Before TPO-RAs	Before TPO-RAs	Either before or after TPO-RAs	Either before or after TPO-RAs
Treatment sequencing of TPO-RAs	NA	Eltrombopag and romiplostim broadly interchangeable; no single clinical treatment pathway as routine in practice.	NA	Mixed treatment approach
Treatment response	Platelet count of at least 50×10^9/L in at least 6 weekly assessments in last 8 weeks of treatment	Platelet count of 50 - 400×10^9/L at any time during 6 month study period	Platelet count of 50 $\times10^9$/L or more in at least 4 out of 6 assessments between week 14 and week 24	Platelet count of at least 50×109/L in at least 6 weekly assessments in last 8 weeks of treatment
Non-TPO-RA response	literature review - pooled data regardless of definition of response, weighted averages	literature review - combined data on efficacy by taking a weighted average	NA (subsequent treatment 'watch and rescue')	Mixed treatment response definitions

Comparison of assumptions with previous appraisals

Evidence/ Assumption	Romiplostim [TA221; last updated October 2018]	Eltrombopag [TA293; last updated October 2018]	Fostamatinib [TA759; January 2022]	Avatrombopag [Current topic]
Time for response/ non-response assessment	assumed to be 28 days (standard error 7 days), based on the Kuter et al. (2008) trials	15 days (standard error 3.75 days), as observed in RAISE trial	12 weeks	Company: 24 weeks
Stopping rule	In CHMP opinion: 4 weeks after maximum dosing	In CHMP opinion: 4 weeks after maximum dosing	In CHMP opinion: 12 weeks	In CHMP opinion: 4 weeks after maximum dosing
Treatment duration & long-term treatment duration	In pivotal trial: 24 weeks In model: Modelled using patient data from trials, no. weeks NR	In pivotal trial: 6 months In model: Modelled using patient data from trials. Assumed same for eltrombopag and romiplostim. No. weeks NR	In pivotal trial: 24 weeks In model: Modelled using patient data from trials. No. weeks NR	In pivotal trial: 26 weeks In model: 109 cycles, ~434 weeks
Rates of rescue therapies	Responder: 0% Non-responder: 33% (non-splenectomised); 68% (splenectomised)	Responder: 0% Non-responder: 33% (non-splenectomised); 68% (splenectomised)	UK ITP registry data to inform frequency and type of rescue treatments. Numbers not reported in FAD	Responder: 3% Non-responder: 22%
Costs of bleed events	rescue medication costs from trial data, addition of NHS reference costs when rescue therapy related to bleed event	rescue medication costs from trial data, addition of NHS reference costs when rescue therapy related to bleed event	Not specified in FAD	Company commissioned independent research