NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Avatrombopag and lusutrombopag for treating thrombocytopenia in people with chronic liver disease needing an elective procedure [ID1520]

Committee papers

NICE National Institute for Health and Care Excellence

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MULTIPLE TECHNOLOGY APPRAISAL

Avatrombopag and lusutrombopag for treating thrombocytopenia in people with chronic liver disease needing an elective procedure [ID1520]

Contents:

NICE National Institute for Health and Care Excellence

MTA: avatrombopag and lusutrombopag for treating thrombocytopenia in people with chronic liver disease needing an elective procedure

Pre-meeting briefing

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

– the key evidence and views submitted by the companies, the consultees and their nominated clinical experts and patient experts and
– the Assessment Group report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document is a summary of the information available before comments on the assessment report have been received.

The lead team may use, or amend, some of these slides for their presentation at the committee meeting.

[redacted]

Key issues (1)

N.B. Avatrombopag does not currently have an agreed list price. Therefore the clinical effectiveness of avatrombopag can be considered, but the cost effectiveness will be considered at a later meeting. For now, the AG have assumed the list price is the same as lusutrombopag

- What treatments do patients currently receive in clinical practice?
  - When are platelets indicated?
  - Are any other prophylactic treatments given?
  - What types of rescue therapy are given?
- How soon before surgery would a patient be eligible for treatment with avatrombopag/lusutrombopag?
- What affects risk of a bleed with invasive procedure in people with thrombocytopenia?
- Are the trial protocols generalisable to UK treatment pathway?
- How do differences between trials affect
  - Robustness of results from network meta analysis?

[redacted]

Key issues (2)

- Platelet transfusions are a large cost in the model. What volume (or “adult therapeutic dose”) would be given in clinical practice?
- What is the expected mortality due to platelet transfusion in people with chronic liver disease?
- Indirect analyses show almost no statistically significant differences between the 2 therapies for key outcomes. Should the model assume there are differences?
- In clinical practice, operations may be cancelled if the patient is not fit enough. Should this carry a sunk cost in the model?
- What proportion of patients currently receive platelet transfusions prior to surgery in clinical practice?
- Is there evidence that some people become refractory to platelet transfusion?
- These are the first oral treatments for this disease area. Can the treatments be considered innovative?
  - Are there benefits not captured in the model
    - e.g. avoidance of blood products, which are more difficult for the NHS logistically compared with an oral treatment, and carry more risk of infection?
- The AG base case suggests that the treatment is highly cost-ineffective. However, this is driven by very small utilities, making the ICER unstable

[redacted]

Disease background: thrombocytopenia

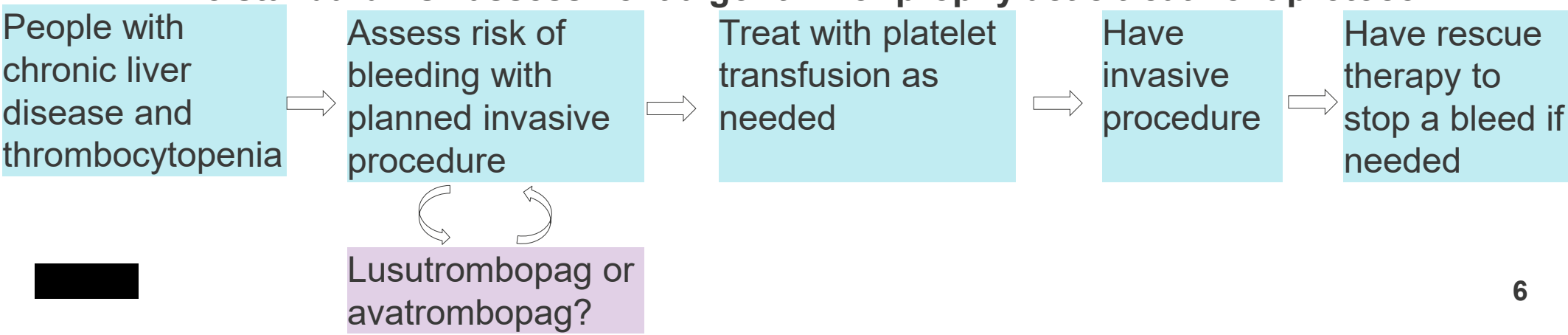
- Reduced number of circulating platelets in blood
  - Normally classified as platelet count <150,000/μL of blood
  - This increases risk of excessive bleeding
- Common complication of chronic liver disease because of:
  - The disease itself
  - A consequence of interferon-based antiviral therapy following liver infection
- Severe thrombocytopenia increases risk of excessive bleeding during liver transplantation or procedures such as liver biopsy
- Prevalence among people with chronic liver disease estimated 15 to 70%, depending on stage of disease and differences in thrombocytopenia definition

[redacted]

Current treatments

- No other licensed treatments
- Therapies include stimulation of megakaryocyte maturation and platelet production
- Options for severe thrombocytopenia include platelet transfusion, splenic artery emoblisation and splenectomy
- NICE clinical guideline (CG24) recommends considering platelet transfusion before an invasive procedure or surgery to raise platelet count above:
  - 50,000/μL for any type of patient
  - 50,000-75,000/μL for patients with high risk of bleeding, depending on procedure, aetiology, whether platelet count is stable, any other cause of abnormal haemostasis
  - 100,000/μL in critical sites, e.g. central nervous system (including posterior segment of the eyes)

No standard risk assessment algorithm or prophylactic treatment protocol



Professional organisation submissions (1)

British Society of Gastroenterology:

- Variable disease management across the NHS because:
  - lack of clear evidence base
  - poor understanding of platelet function in liver disease
- Thrombocytopenia in advanced liver disease usually seen with cirrhosis with portal hypertension; can be permanent and progressive
- Avatrombopag and lusutrombopag would act as a substitute to prophylactic platelet transfusion, advantages of this are:
  - gradual and predictable increase in platelet count (in outpatient care)
  - sustained elevation in platelet count
  - avoids use of a blood product (limited national resource, potential for cross contamination and potential serious adverse effects)
  - hypothetical advantage of stopping delayed bleeding after procedures

Professional organisation submissions (2)

British Association of the Study of the Liver (endorsed by Royal College of Physicians):

- No alternative drug therapies; current treatment is platelet transfusion at time of procedure
- No consensus about whether platelet transfusion reduces risk for medium or small procedures
- Avatrombopag and lusutrombopag could be used for all cirrhotic patients with thrombocytopaenia who require an intervention
- As these are new technologies experience in use and monitoring of dose/ duration required

Interventions

	Lusutrombopag (Mulpleta)	Avatrombopag (Doptelet)
Company	Shionogi Inc	Dova Pharmaceuticals
Mechanism of action	Small molecule thrombopoietin receptor agonist, stimulates platelet production	
Marketing authorisation	"treatment of severe thrombocytopenia in adult patients with chronic liver disease… *"…undergoing invasive procedures"* (lusutrombopag) "…*who are scheduled to undergo an invasive procedure*" (avatrombopag)	
Administration and dose	Oral administration: • 3mg* for 7 days • Baseline count <50,000/μL	Oral administration: • 60mg if baseline platelet count <40,000/μL • 40 mg if baseline platelet count is 40,000 to <50,000/μL For 5 days
Timing of procedure	9 days after start of treatment	10 to 13 days after start of treatment
Price	£x for seven days of 3 mg	TBC: AG assumes same as lusutrom

*Assessment Group reports lusutrombopag results by subgroups based on avatrombopag dosing regimen

[redacted]

Decision problem

	Final NICE scope	Assessment group
Population	Adults with thrombocytopenia associated with chronic liver disease needing an elective procedure	Population split into 2 subgroups to allow comparison of lusutrobopag with the 2 doses of avatrombopag, platelet count: • <40,000/µL • 40,000 to <50,000/µL
Interventions	• Avatrombopag • Lusutrombopag	Stated that avatrombopag and lusutrombopag are used alongside established clinical management
Comparators	Established clinical management (including, but not limited to platelet transfusion)	Established clinical management (including, but not limited to platelet transfusion) without thrombopoietin receptor agonists
Outcomes	• Platelet count • Response rate • Number of platelet transfusions • Number of blood transfusions • Return to operating theatre • Need for rescue treatments • Bleeding score • Mortality • Adverse effects of treatment • Health-related quality of life	• Same as scope

Clinical evidence: lusutrombopag

	L-PLUS 1	L-PLUS 2	JAPIC CTI-121944
Study design	Multicentre, double-blind, randomised controlled trials		
Countries	Japan	International (inc. UK)	Japan
n	96	215	31
Population	Chronic liver disease, platelet count <50,000/μL		Hepatocellular carcinoma, platelet count <50,000/μL
Intervention	Lusutrombopag		
Comparator	Placebo		
Primary outcome	Proportion who did not need platelet transfusion before the procedure	Proportion not needing platelet transfusion or rescue procedure from randomisation to 7 days after procedure	Proportion who did not need platelet transfusion before the procedure
Follow up	5 weeks	3 weeks	5 weeks

Clinical evidence: avatrombopag

	ADAPT-1	ADAPT-2	Study 202*
Study design	Multicentre, double-blind, randomised controlled trials		
Countries	International (inc. UK)		USA
n	231	204	32
Population	Chronic liver disease, platelet count <50,000/μL		
Intervention	Avatrombopag 40mg/60mg		Avatrombopag 40mg
Comparator	Placebo		
Primary outcome	Proportion not needing platelet transfusion or a rescue procedure from randomisation to 7 days after procedure		% with increase in platelet count ≥ 20,000/μL and ≥1 platelet count >50,000/μL from days 4-8
Follow up	5 weeks		
***Study not considered by AG (see next slide)**			

Outcomes

- Trials reported different primary outcomes – AG considered the following:
  - proportion having neither platelet transfusion prior to elective procedure nor rescue therapy
  - proportion who did not require platelet transfusion prior to primary elective procedure
  - proportion who did not require rescue therapy, given no receipt of platelets

- Rescue therapy → treatments for bleeding events

- Because study 202 did not report comparable outcomes, it is not considered in AG's assessment of clinical or cost effectiveness

[redacted]

No platelet transfusions or rescue therapy

		n	% with neither	RR vs PBO (95% CI)	n	% with neither	RR vs PBO (95% CI)
		Baseline platelet count <40,000/µL			Baseline platelet count 40,000/µl to <50,000/µl		
JapicCTI-121944	LUS 3mg	xxx	xxx	xxx	xxx	xxx	xxx
	Placebo	xxx	xxx		xxx	xxx	
L-PLUS 1	LUS 3mg	xxx	xxx	xxx	xxx	xxx	xxx
	Placebo	xxx	xxx		xxx	xxx	
L-PLUS 2	LUS 3mg	xxx	xxx	xxx	xxx	xxx	xxx
	Placebo	xx	xxx		xxx	xxx	
ADAPT-1	AVA 60/40mg	90	66%	2.86 (1.67, 4.91)	59	88%	2.31 (1.49, 3.57)
	Placebo	48	23%		34	38%	
ADAPT-2	AVA 60/40mg	70	69%	1.97 (1.27, 3.05)	58	88%	2.64 (1.61, 4.31)
	Placebo	43	35%		33	33%	

Abbreviations: CI, confidence interval; PBO, placebo; LUS, lusutrombopag; AVA, avatrombopag; RR, risk ratio

[redacted]

No platelet transfusion before procedure

		n	% no transfusion	RR vs PBO (95% CI)	n	% no transfusion	RR vs PBO (95% CI)
		Baseline platelet count <40,000/µL			Baseline platelet count 40,000/µl to <50,000/µl		
JapicCTI -121944	LUS 3mg	xxx	xxx	xxx	xx	xxx	xxx
	Placebo	xxx	xxx		xx	xxx	
L-PLUS 1	LUS 3 mg	xxx	xxx	xxx	xx	xxx	xxx
	Placebo	xxx	xxx		xx	xxx	
L-PLUS 2	LUS 3 mg	xxx	xxx	xxx	xx	xxx	xxx
	Placebo	xxx	xxx		xx	xxx	
ADAPT-1	AVA 60/40mg	90	79%	1.46 (1.10, 1.93)	59	93%	1.86 (1.32, 2.63)
	Placebo	48	54%		34	50%	
ADAPT-2	AVA 60/40mg	70	83%	1.62 (1.19, 2.21)	58	95%	1.74 (1.27, 2.39)
	Placebo	43	51%		33	55%	

Abbreviations: CI, confidence interval; PBO, placebo; LUS lusutrombopag; AVA, avatrombopag; RR, risk ratio

[redacted]

No rescue therapy, given no platelets

		n	% no rescue	RR vs PBO (95% CI)	n	% no rescue	RR vs PBO (95% CI)
		Baseline platelet count <40,000/µL			Baseline platelet count 40,000/µl to <50,000/µl		
JapicCTI-121944	LUS 3mg	xxx	xxx	xxx	xxx	xxx	xxx
	Placebo	xxx	xxx		xxx	xxx	
L-PLUS 1	LUS 3 mg	xxx	xxx	xxx	xxx	xxx	xxx
	Placebo	xxx	xxx		xxx	xxx	
L-PLUS 2	LUS 3 mg	xxx	xxx	xxx	xxx	xxx	xxx
	Placebo	xxx	xxx		xxx	xxx	
ADAPT-1	AVA 60/40mg	71	83%	1.96 (1.24, 3.11)	55	95%	1.24 (0.94, 1.62)
	Placebo	26	42%		17	77%	
ADAPT-2	AVA 60/40mg	58	82%	1.21 (0.89, 1.65)	55	93%	1.52 (1.04, 2.21)
	Placebo	22	68%		18	61%	

Abbreviations: CI, confidence interval; PBO, placebo; LUS, lusutrombopag; AVA, avatrombopag; RR, risk ratio

[redacted]

Results – AG comment

- Results show lusutrombopag trials are different to the avatrombopag trials in the frequency of rescue therapy, regardless of treatment arm
- Only x patients received any rescue therapy in the lusutrombopag trials → defined as platelets or red blood cells only
- In the avatrombopag trials, as few as 42% did not receive rescue therapy → much broader definition of rescue therapy:
  - platelet transfusion, fresh frozen plasma, adrenalin injected at bleeding site, tranexamic acid, acidum aminomethyl benzoicum, aminocaproic acid, carbazochrome sodium, sulfonate hydrate, dicynone, glypressin

[redacted]

Indirect treatment comparison

- No head to head trials of avatrombopag vs. lusutrombopag, so AG used an indirect treatment comparison
- Only one statistically significant difference between avatrombopag and lusutrombopag (see red box)

	Type of effect	RR: no platelet transfusions or rescue therapy	RR: no platelet transfusions	RR: no rescue therapy
Baseline platelet count <40,000/µl				
LUS 3mg vs. AVA 60mg	Fixed effect	xxx	xxx	xxx
	Random effect	xxx	xxx	xxx
Baseline platelet count 40,000/µl to <50,000/µl				
LUS 3mg vs. AVA 40mg	Fixed effect	xxx	xxx	xxx
	Random effect	xxx	xxx	xxx

Abbreviations: LUS, lusutrombopag; AVA, avatrombopag; RR, risk ratio

[redacted]

Heterogeneity

- Type of invasive procedure that patients were undergoing across trials is a source of heterogeneity:
  - L-PLUS 1 and L-PLUS 2 trials did not restrict inclusion to the elective procedure
  - JapicCTI-121944, only included patients undergoing radiofrequency ablation → excluding that study in a sensitivity analysis increased the heterogeneity in all cases
- Each subgroup regardless of outcome had moderate statistical heterogeneity
- For no rescue therapy outcome, AG suggests caution in comparing avatrombopag to lusutrombopag:
  - lusutrombopag trials appear to be different to avatrombopag trials with much lower frequency of rescue therapy, regardless of treatment arm

[redacted]

Adverse events

		Any death	Any serious AE	Drug withdrawal due to AE	Any AE
JapicCTI-121944	Lusutrombopag	0	1 (6%)	0	16 (100%)
	Placebo	0	1 (7%)	0	15 (100%)
L-PLUS 1	Lusutrombopag	0	1 (2%)	NR	45 (94%)
	Placebo	0	4 (8%)	NR	48 (100%)
L-PLUS 2	Lusutrombopag	3 (3%)	7 (7%)	0	51 (48%)
	Placebo	0	7(7%)	1 (1%)	52 (49%)
ADAPT-1	AVA 60mg	0	10 (11%)	2 (2%)	53 (60%)
	Placebo 60mg	0	11 (23%)	0	31 (65%)
	AVA 40mg	2 (4%)	8 (14%)	0	31 (53%)
	Placebo 40mg	0	1 (3%)	0	18 (56%)
ADAPT-2	AVA 60mg	0	1 (1%)	0	36 (51%)
	Placebo 60mg	0	1 (1%)	0	22 (51%)
	AVA 40mg	0	1 (2%)	0	28 (49%)
	Placebo 40mg	1 (3%)	1 (3%)	0	15 (46%)

Abbreviations: AE, adverse event; AVA, avatrombopag; NR, not reported

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Cost-effectiveness

Company cost-effectiveness submission: avatrombopag

- Dova did not include any cost-effectiveness analyses in their submission
- Identified some costs (also identified by the AG in their systematic review)
- Highlighted that costs of platelet transfusions are high, and there is a lot of wastage because platelets have:
  - specific storage requirements
  - short shelf life
  - unpredictability of demand
- Highlighted that people may become refractory to platelets after multiple transfusions

[redacted]

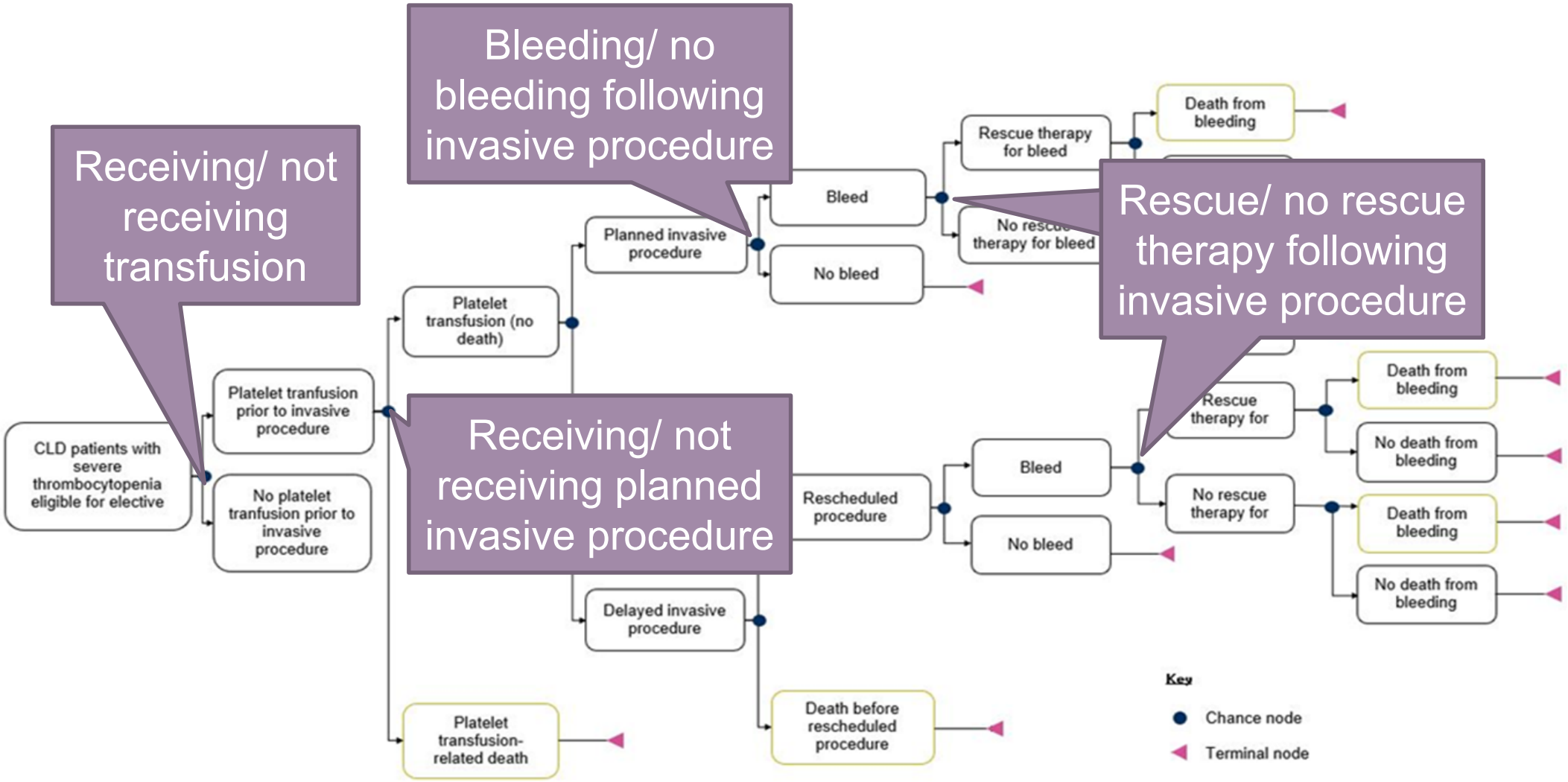
Company cost-effectiveness submission: lusutrombopag

- Shionogi submission compared lusutrombopag with platelet transfusion in people with chronic liver disease and a platelet count <50,000/µL scheduled to undergo a planned invasive procedure
- Economic model consisted of:
  - a short-term decision tree model, representing 35-day clinical trial period, based on RCT data
  - a longer-term Markov model over a lifetime time horizon of 50 years, based on literature values for mortality and quality of life

[redacted]

Short-term decision tree - Shionogi model

- Includes chance nodes based on pooled data from the trials
- Literature values for all other chance nodes



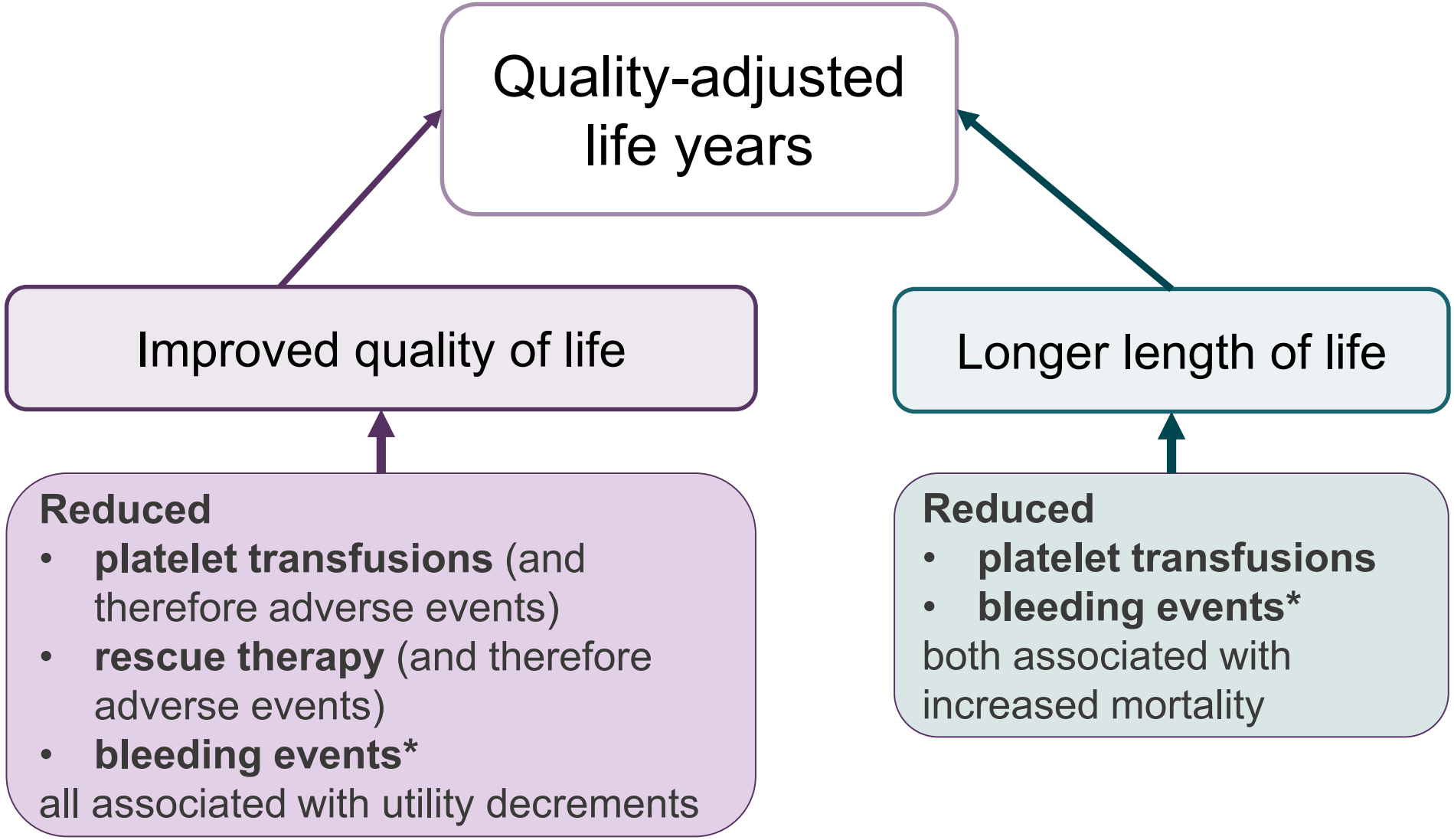
Markov model structure – Shionogi model

In the long-term Markov model:

- Data from the literature on chronic liver disease related mortality and utility values used to estimate the number of QALYs that would accrue over the expected remaining life of the patient
- Cycle length of 1 year
- QALYs discounted at a rate of 3.5%
- No cost discounting; costs are only included in the short-term model

[redacted]

Overview:
how quality-adjusted life years accrue



[redacted]

* Not modelled separately by assessment group

Key model assumptions (1)

Assumption	Source/justification
All patients on placebo have platelet transfusion prior to planned procedure	Clinical expert opinion (however AG note trial data showed rate of xx%)
Mortality can occur due to platelet transfusion or bleeding events	• Eerd et al (2010) transfusion mortality rate: 0.3315% • Takaki et al (2012) major or minor bleeding after radiofrequency ablation: 0.83%
Baseline utility value of 0.544	Sullivan et al (2011) estimated EQ-5D index score for chronic liver disease
Chronic liver disease mortality in longer-term Markov model	D'Amico et al (2016) survival estimated 1-year survival: 84%
0.1 disutility for serious platelet transfusion or rescue therapy adverse events (4 weeks)	NICE TA293 for thrombocytopenia purpura
All bleeding events major (1 week)	Disutility of 0.397 (Jugrin et al, 2015)
No administration costs for lusutrombopag	Oral administration
Sunk costs of £566 assumed for each cancelled/delayed procedures	Not enough time to reallocate a clinician or hospital bed to another procedure

Key assumptions (2): cost of platelet transfusion

- Cost of platelet transfusion based on TA293 in which:
  - cost of blood transfusion (£57.72) + cost of **2** units of platelets (2x £230.39) = £518.50 in 2011/12 prices
- Company assumed **3** units per transfusion based on expert opinion: total cost = £812.61 (inflated to 2017/2018)
- Scenario with cost of a single transfusion using NHS reference costs = £517.28
- Scenario using Varney et al (2003) estimate of £1493.21 (inflated to 2017/2018)

AG comment

- Substantial uncertainty over what constitutes a unit – UK clinical experts refer to "pools" of platelets
- AG calculates an estimate of **xxx** units per transfusion based on:
  - mean volume of platelets transfused per transfusion in lusutrombopag trials
  - divided by mean number of platelets contained within a unit of apheresis platelets (280,000/µL) from the Handbook of Transfusion Methods
- AG calculates cost of transfusion from Stokes et al (2018)
- Total cost **xxx**

[redacted]

Shionogi base case results

	Total costs	Total QALYs	Life years	Δ costs	Δ QALYs	ICER £/QALY
Usual Care	£3,744	4.021	10.066	-	-	-
Lusutrombopag	xxxx	4.035	10.031	xxxx	0.015	Dominant

Dominant means intervention is less expensive and more effective

Probabilistic sensitivity analyses showed that:

- at a willingness-to-pay threshold of £20,000/QALY, the mean net monetary benefit (NMB) was xxx
- at a threshold of £30,000/QALY, the mean NMB was xxx

[redacted]

Assessment Group model

- Assessment Group used Shionogi model as the basis of their analysis
- Identified several limitations of Shionogi model and adapted accordingly (next slide)
- Included data for avatrombopag and subgroups to match avatrombopag dosing
- Used pooled baseline characteristics and surgical mortality from trials of both avatrombopag and lusutrombopag
- Standard of care → patients have platelet transfusion if platelet count does not reach ≥ 50,000/μL on the day of the scheduled procedure
- Used long-term Markov model without change
- Included severe thrombus-related events and portal vein thrombosis in model because of likely relationship with the drugs
- Used AG calculated cost for platelet transfusion (previous slide)

[redacted]

AG amendments to Shionogi model

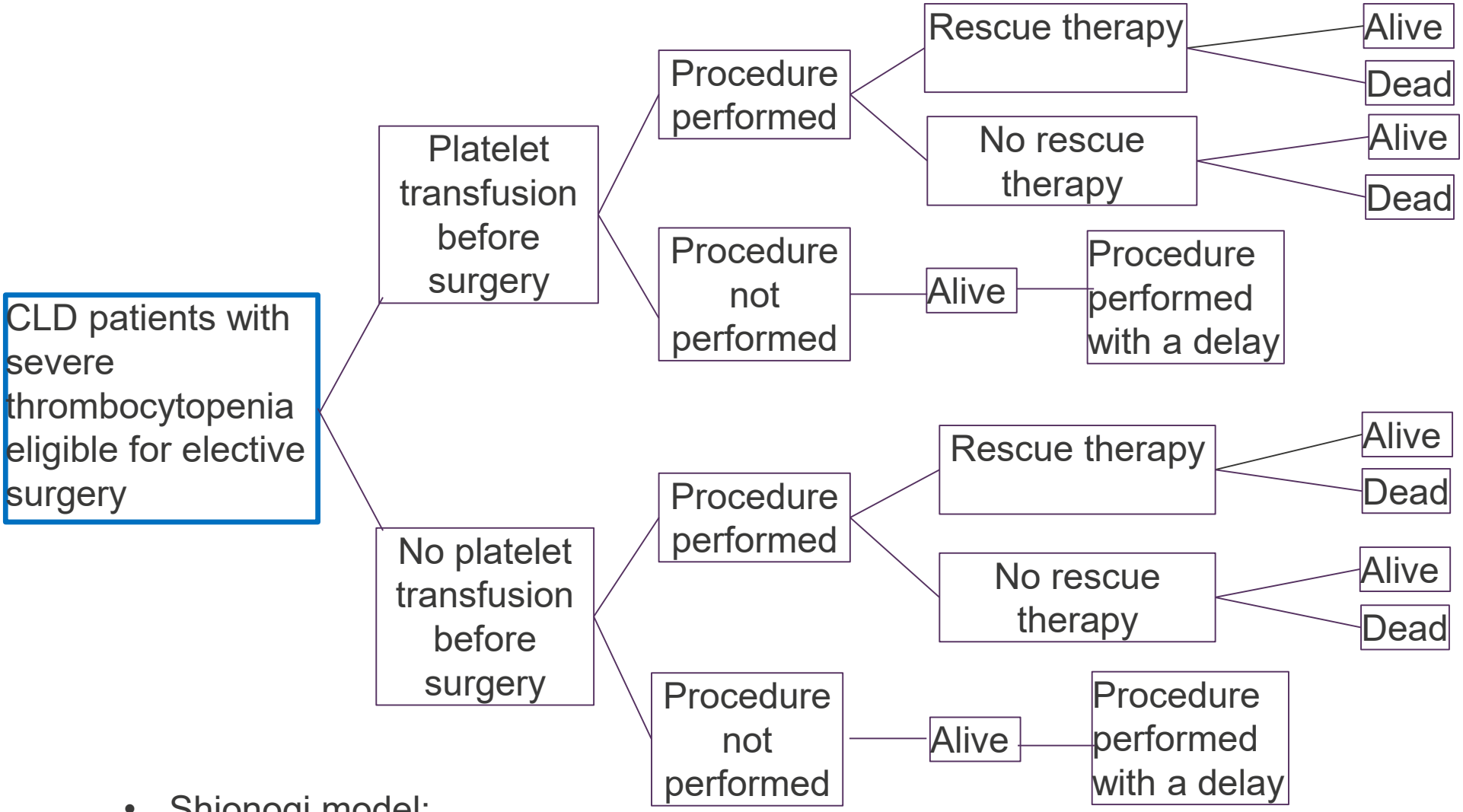
Limitation	Amendment
Assuming 100% on placebo have platelet transfusion before procedure contradicts trial evidence (xx%)	Used data from trial
Mortality from platelet transfusion can occur after surgery	Moved chance node after surgery/rescue
May not be appropriate to incorporate bleeding as separate event because of extremely low numbers	Modelled bleeding as a complication of surgery
Utility loss from bleeding may be overestimated as company assumes all were major bleeds	Assumed 30% grade 3+ based on trials, excluded <3
Transfusion mortality rate too high (0.3315%)	Serious Hazards of Transfusion data 0.000458%
Including sunk costs inappropriate: surgical slots usually filled; no longer in NHS reference costs	Did not include sunk costs in model

AG also felt that a delay to planned procedure would have an impact on quality of life:

- average decrement for a 1-level increase in anxiety and depression on EQ-5D-5L is 0.072
- AG applied this value for 4 weeks in base case for a delayed procedure

[redacted]

Assessment group model structure



- Shionogi model:
  - Models chance of bleeds separately. Assessment group model utility decrements and death from bleeds included in surgery complications
  - Death due to platelet transfusion only before surgery in Shionogi model

[redacted]

Assessment Group base case
deterministic results

ICERs may be uninformative because of very small QALY differences

	Total costs	Total LYGs	Total QALYs	Δ costs	Δ QALYs	ICER (£/QALY)
Platelet count < 40,000 / µL Subgroup						
Usual care	xxxx	xxxx	xxxx	-	-	
Lusutrombopag	xxxx	xxxx	xxxx	xxxx	xxxx	£3,424,742
Avatrombopag 60 mg	xxxx	xxxx	xxxx	xxxx	xxxx	Dominated
Platelet count 40,000- 50,000 / µL Subgroup						
Usual care	xxxx	xxxx	xxxx	-	-	
Avatrombopag 40 mg	xxxx	xxxx	xxxx	xxxx	xxxx	£1,198,519
Lusutrombopag	xxxx	xxxx	xxxx	xxxx	xxxx	Dominated

Dominated means an alternative intervention is less expensive and more effective

Abbreviations: LYG, life years gained; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio

Net monetary benefit vs. usual care

Net monetary benefit calculations show that QALY difference is so small, **net monetary benefit approximates to incremental cost compared with usual care** → disaggregated costs next slide

	Δ costs	Δ QALYs	ICER (£/QALY)	NMB at 20k	NMB at 30k
Platelet count < 40,000 / µL Subgroup					
Lusutrombopag	xxxx	xxxx	£3,424,742	xxxx	xxxx
Avatrombopag 60 mg	xxxx	xxxx	Dominated	xxxx	xxxx
Platelet count 40,000- 50,000 / µL Subgroup					
Avatrombopag 40 mg	xxxx	xxxx	£1,198,519	xxxx	xxxx
Lusutrombopag	xxxx	xxxx	Dominated	xxxx	xxxx

Abbreviations: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit

Assessment Group base case

disaggregated costs

Incremental cost driven by higher intervention cost partially offset by lower platelet transfusion and rescue therapy costs

	Intervention	Platelet transfusion	Adverse events	Elective procedure	Rescue therapy	Total
Platelet count < 40,000 / µL Subgroup						
Usual care	£0	XXXX	XXXX	XXXX	XXXX	XXXX
Lusutrombopag	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Avatrombopag 60 mg	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Platelet count 40,000- 50,000 / µL Subgroup						
Usual care	£0	XXXX	XXXX	XXXX	XXXX	XXXX
Lusutrombopag	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX
Avatrombopag 40 mg	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX

[redacted]

Assessment group key scenarios analyses

Effect on incremental costs vs. usual care

		<40,000/µL		40 to <50,000/µL	
		LUS	AVA	LUS	AVA
Base case		xxxx	xxxx	xxxx	xxxx
Increase number of units per platelet transfusion from xxx to	xxx	xxxx	xxxx	xxxx	xxxx
	3*	xxxx	xxxx	xxxx	xxxx
Increase cost of platelet transfusion from £xxx	to £517	xxxx	xxxx	xxxx	xxxx
	to £813*	xxxx	xxxx	xxxx	xxxx
***Shionogi base case values**					

Other AG scenario analyses included:

- Inclusion of grade 2 bleeding adverse events (disutility 0.122)
- Varying bleeding disutility by +/-25%
- Increasing disutility from 0.1 to 0.17 for platelet transfusion adverse events

None had a substantial effect on incremental QALYs

[redacted] Abbreviations: LUS, lusutrombopag; AVA, avatrombopag

Innovation - lusutrombopag

Submission highlighted:

- First non-surgical alternative to platelet transfusion
- Use of platelet transfusions can be avoided not only for the initial planned procedure but for any additional procedures that might be needed
  - over 20% of patients in lusutrombopag studies had 2nd or subsequent procedures during study period
- Potential benefits not captured in QALY:
  - reassurance for patients that they will be less likely to require repeated, invasive platelet transfusion with the associated risks
  - may plausibly reduce the long-term risk of jeopardising liver transplant outcomes should patients become platelet refractory
- Administered orally so hospital attendance might be required by fewer patients the day before an invasive procedure to receive a platelet transfusion, and patients may be discharged from the hospital setting sooner post-operatively, freeing beds

[redacted]

Innovation - avatrombopag

Submission highlighted:

- Costs of platelet transfusions are high, and there is a lot of wastage because platelets have:
  - specific storage requirements
  - short shelf life
  - unpredictability of demand
- People may become refractory to platelets after multiple transfusions
  - Juskewitch et al, 2017 suggests refractory patients use 8-fold more platelet products, stay in hospital more than twice as long, and have hospitalisation costs nearly 3 times higher than nonrefractory counterparts

[redacted]

Comments on Assessment Report (1)

Only received from Shionogi (lusutrombopag)

- Inappropriate to exclude relevant individual patient level data for lusutrombopag because equivalent data not available for avatrombopag
- <40,000 µL and 40,000-50,000/µL platelet count subgroups analysis inappropriate. Driven by avatrombopag dosing and do not reflect lusutrombobag marketing authorisation, NICE Final Scope, trial randomisation or clinical guidelines
- Correct consideration of bleeding events “absolutely crucial”
  - mortality risk of bleeding should be in the model (rather than arbitrarily assuming same chance of surgery related death in all treatment arms).
  - Bleeding events associated with longer length of stay in hospital
  - Data were available for whole licensed population for lusutrombopag. Meta-analysis showed reduction in bleeding events for lusutrombopag vs. placebo xxx. Assessment group only requested data for platelet count subgroups- less robust
- SHOT report is for the general population so incidence of “pneumological” adverse events not generalisable to chronic liver disease patients. Shionogi consider their estimate of 1.10% conservative and was validated by clinical experts

[redacted]

Comments on Assessment Report (2)

Comments on platelet costs

- Agree there is notable uncertainty around the content and cost of platelet transfusions.
  - Not recognised by assessment group that people with chronic liver disease and thrombocytopenia are a distinct population with higher bleeding risks
  - Shionogi had been advised by UK clinical experts that patients with severe TCP and CLD would typically receive multiple bags of platelets; Shionogi were therefore surprised by the AG base case assumption, based on the general recommendations from the Handbook and NG24, that only one ATD would be used in typical practice.
  - "**The [guideline development group]** considered dosing of platelets in platelet function disorders, **such as thrombocytopenia**, and **agreed that higher doses e.g. a dose of 2 adult units** may be **considered** in the presence of **bleeding** or as prophylaxis in advance of major surgery'" (NG24 – Full Guideline – Page 234, 18 May 2015; emphasis added)
  - Shionogi reconsulted with clinical experts after assessment report issued. Clarified that platelets may be used before, during and after procedure

[redacted]

Comments on Assessment Report (3)

- Sunk costs remain in latest NHS reference costs (code names were changed) and remain appropriate for inclusion in the economic model
- WH50A “procedure not carried out for medical or patient reasons”;£406.29 from National Schedule of Reference Costs Year: 2017-18 All NHS trusts and NHS foundation trusts HRG Data.
  - £566 costs used in Shionogi original base case based on 2009/10 data.

[redacted]

Equality

- At scoping, noted that the treatment may improve access to further treatments and reduce inequalities for certain social and religious groups by providing an alternative treatment option to platelet transfusions
- Not considered an equalities issues because a potential recommendation would not make it harder for these groups to access treatments

[redacted]

Authors

Victoria Gillis-Elliott, Adam Brooke
Technical Leads

Ross Dent, Carl Prescott
Technical Advisers

with input from the Lead Team (Veline Lesperance, John Cairns, Tony Wooton) Chair Amanda Adler

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Avatrombopag and lusutrombopag for treating thrombocytopenia in people with chronic liver disease needing an elective procedure

Produced by	Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University
Authors	Nigel Armstrong, Health Economist, KSR Ltd Nasuh Büyükkaramikli, Health Economics Researcher, EUR Hannah Penton, Health Economics Researcher, EUR Rob Riemsma, Reviews Manager, KSR Ltd Pim Wetzelaer, Health Economics Researcher, EUR Vanesa Huertas Carrera, Systematic Reviewer, KSR Ltd Stephanie Swift, Systematic Reviewer, KSR Ltd Thea Drachen, Systematic Reviewer, KSR Ltd Heike Raatz, Systematic Reviewer, KSR Ltd Steve Ryder, Health Economist, KSR Ltd Dhwani Shah, Health Economist, KSR Ltd Titas Buksnys, Health Economist, KSR Ltd Gill Worthy, Statistician, KSR Ltd Steven Duffy, Information Specialist, KSR Ltd Maiwenn Al, Health Economics Researcher, EUR Jos Kleijnen, Director, KSR Ltd, Professor of Systematic Reviews in Health Care, Maastricht University

Correspondence to	Nigel Armstrong, Kleijnen Systematic Reviews Unit 6, Escrick Business Park Riccall Road, Escrick York, UK YO19 6FD
Date completed	20 September 2019

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Declared competing interests of the authors

None.

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Nigel Armstrong acted as project lead, devised the clinical effectiveness methods and evidence and economic model and contributed to the writing of the report. Nasuh Büyükkaramikli acted as health economic project lead, devised the economic model, critiqued the economics literature and contributed to the writing of the report. Hannah Penton and Pim Wetzelaer devised the economic model, critiqued the company submissions and contributed to the writing of the report. Steve Ryder, Dhwani Shah and Titas Buksnys acted as health economist and systematic reviewer, devised the clinical effectiveness methods and evidence and economic model and contributed to writing of the report. Rob Riemsma, Stephanie Swift, Vanessa Huertas Carrera, Thea Drachen and Heike Raatz acted as systematic reviewers, devised the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician and contributed to the writing of the report. Steven Duffy acted as information specialist, devised the searches and contributed to the writing of the report. Maiwenn Al devised the economic model, contributed to the writing of the report and provided general health economic guidance. Jos Kleijnen contributed to the writing of the report and supervised the project.

Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

ABSTRACT

Thrombocytopenia is a common complication in chronic liver disease (CLD). It means a reduction in the number of platelets within the blood, which increases the risk of bleeding during procedures including liver biopsy or liver transplantation. It can delay or prevent such procedures and lead to morbidity and mortality. Established clinical management largely involves platelet transfusion prior to the procedure or as rescue therapy for bleeding due to the procedure. There are currently no licensed treatments in the UK for treating thrombocytopenia in people with CLD requiring surgery. The purpose of this report is to systematically review the effectiveness and estimate the cost effectiveness of two recently licensed treatments, thrombopoietin receptor agonists (TPO-RAs), avatrombopag and lusutrombopag, administered in addition to established clinical management versus established clinical management (no TPO-RA) within the licensed populations.

The licensed dose of lusutrombopag is 3 mg for platelet count of <50,000/μL. That for avatrombopag is dependent on baseline platelet count: i.e. 60 mg if baseline platelet count <40,000/μL and 40 mg if 40,000 to <50,000/μL. Therefore, both clinical effectiveness and cost effectiveness analyses were conducted in each of these two subgroups. From a comprehensive search, which retrieved 11,305 records, 35 references pertaining to six studies were included. Analysis by subgroup showed that avatrombopag and lusutrombopag were superior to no TPO-RA in avoiding both platelet transfusion or rescue therapy and mostly with a statistically significant difference i.e. 95% confidence intervals did not overlap the point of no difference. However, only avatrombopag seemed to be superior to no TPO-RA in reducing the risk of rescue therapy, although far fewer patients in the lustrombopag than in the avatrombopag trials received rescue therapy.

When assessing the cost effectiveness of lusutrombopag and avatrombopag it was found that although both were successful in avoiding platelet transfusions prior to surgery, this did not translate into additional long-term health benefits over placebo in terms of quality adjusted life years. Therefore, cost minimisation becomes the focus. For both platelet count subgroups, no TPO-RA was clearly cheaper than both lusutrombopag and avatrombopag, as cost savings due to avoiding platelet transfusions were more than offset by the cost of the drugs. Lusutrombopag is about 25% more costly in the < 40,000/μL subgroup compared to no TPO-RA, and avatrombopag 28% more costly. For the 40,000 – 50,000/μL subgroup, avatrombopag and lusutrombopag are 28% and 27% more expensive than no TPO-RA, respectively. The probabilistic sensitivity analysis showed that for all thresholds below £100,000, no TPO-RA had a 100% probability of being cost effective. Uncertainty surrounding the price of avatrombopag, the content and costs of platelet transfusions and the potential under reporting in the data used to estimate platelet transfusion specific mortality had most impact on results. However even when extreme values were tested incremental cost effectiveness ratios (ICERs) comparing lusutrombopag and avatrombopag to no TPO-RA remained substantially higher than National Institute for Health and Care Excellence (NICE) thresholds.

1. SCIENTIFIC SUMMARY

Background

Thrombocytopenia is characterised as a reduction in the number of circulating platelets within the blood. Platelets come from megakaryocytes in the bone marrow. They play a critical role in haemostasis, a process which causes bleeding to stop. Thrombocytopenia can generally be classified on the basis of the platelet count in the blood. It is usually defined as a platelet count of less than 150,000/µL per litre of blood.

Thrombocytopenia is a common complication in people with CLD either as a direct result of the liver pathology or as a consequence of interferon-based antiviral therapy following liver infection. While mild to moderate thrombocytopenia rarely causes bleeding during procedures such as liver biopsy or liver transplantation, severe thrombocytopenia increases the risk of excessive bleeding during and after surgery and can have a significant impact on the clinical management of CLD. It can delay or prevent the start of appropriate therapy leading to increased morbidity and mortality and a reduced quality of care.

Between 2016 and 2017, Hospital Episode Statistics showed 27,927 admissions with liver disease in England. The prevalence of thrombocytopenia in people with CLD varies from 15% to 70% depending on the stage of liver disease and differences in platelet count cut-off used to define thrombocytopenia.

There are currently no licensed treatment options in the UK for treating thrombocytopenia in people with CLD requiring surgery. Therapies include stimulation of megakaryocyte maturation and platelet production. Treatment for severe thrombocytopenia can include platelet transfusion, splenic artery embolisation and surgical splenectomy.

The interventions studied are small molecule thrombopoietin receptor agonists (TPO-RAs), avatrombopag (Doptelet®, Dova Pharmaceuticals) and lusutrombopag (Mulpleo®, Shionogi BV). They target the c-MpI thrombopoietin cell surface receptor on megakaryocytes to stimulate platelet production. The licensed dose of avatrombopag will be dependent on baseline platelet count: i.e. 60 mg if baseline platelet count <40,000/µL and 40 mg if 40,000 to <50,000/µL. The recommended dose of lusutrombopag is 3 mg once daily for seven days and the elective procedure should be performed from day nine after treatment initiation.

Objectives

- To determine the clinical and cost effectiveness of avatrombopag and lusutrombopag within their marketing authorisations in comparison to no TPO-RA (established clinical management without either TPO-RA, including, but not limited to platelet transfusion) for treating thrombocytopenia in people with chronic liver disease needing an elective procedure.

Because the licensed dose for avatrombopag is dependent on baseline platelet count: i.e. 60 mg if baseline platelet count <40,000/µL and 40 mg if 40,000 to <50,000/µL, both clinical effectiveness and cost effectiveness analyses were conducted in each of these two subgroups.

Methods

Throughout the review, the methods recommended by the Cochrane Collaboration Handbook and the Centre for Reviews and Dissemination (CRD), York were applied in order to reduce the risk of bias and error. Literature searches were conducted to identify relevant information on the clinical

effectiveness, safety and cost effectiveness of avatrombopag and lusutrombopag. The searches also identified studies on the clinical effectiveness, safety and cost effectiveness of established clinical management of thrombocytopenia in people with CLD**.** The following inclusion criteria were applied for screening: adults with thrombocytopenia associated with CLD needing an elective procedure; avatrombopag or lusutrombopag as intervention and any one of a range of clinical effectiveness outcomes. Titles and abstracts identified through electronic database and other searches were independently screened by two reviewers. During this initial phase of the screening process any references which could be determined from the title or abstract did not meet the inclusion criteria were excluded. Full paper copies were obtained for all of the remaining references. These were then independently examined in detail by two reviewers in order to determine whether they met the criteria for inclusion in the review. Data extraction and quality assessment using the Cochrane Collaboration Quality Assessment Tool for RCTs was carried out by two reviewers. Meta-analysis was conducted using both fixed effect and random effects models and forest plots of effect sizes were presented for each of the main outcomes, which were proportion of patients receiving no platelets prior to the elective procedure or rescue therapy for bleeding; and proportion of patients receiving no platelets prior to the elective procedure. These outcomes were determined on the basis that they were the primary outcomes in all but one of the trials. Another outcome of interest was the proportion of patients receiving no rescue therapy for bleeding (referred to as 'rescue therapy'). Neither quality of life nor survival were outcomes in any study, although mortality was reported. Subgroup analysis according to degree of thrombocytopaenia (<40,000/μL or 40,000 to <50,000/μL) was performed in order to match the expected licensed doses of avatrombopag. Sensitivity analysis according to clinical and statistical heterogeneity (I^2) was conducted.

Study results

From a comprehensive search, which retrieved 11,305 records, after screening, 35 references pertaining to six studies have been included. The quality of all six studies was at least moderate in both sets of the trials for each of the thrombopoietin receptor agonists (TPO-RAs) i.e. ADAPT-1, ADAPT-2 and study 202 for avatrombopag and L-PLUS, L-PLUS 2 and JapicCTI-121944 study for lusutrombopag.

The main finding was that both avatrombopag (for both platelet subgroups) and lusutrombopag, were clearly effective in comparison to no TPO-RA in terms of primary outcome, including that for three of the main trials, ADAPT-1, ADAPT-2 and L-PLUS 2, i.e. avoidance of platelet transfusion or rescue procedure for bleeding. Neither avatrombopag nor lusutrombopag were unequivocally better than no TPO-RA in terms of adverse events (AEs) and there was some small amount of evidence to show a higher percentage of deaths with both TPO-RAs.

The main outcomes of avoidance of the composite outcome no platelets before the elective procedure or rescue therapy or avoidance of platelets only, were analysed according to the subgroups that matched the expected licensed doses of avatrombopag (<40,000/μL for 60 mg or 40,000 to <50,000/μL for 40 mg) (See Tables 1.1 and 1.2). Both avatrombopag and lusutrombopag were superior to placebo and mostly with a statistically significant difference i.e. 95% confidence intervals did not overlap the point of no difference. However, when the outcome of avoidance of rescue therapy was considered alone, albeit only in those who did not receive platelets before the elective procedure, the lusutrombopag trials were revealed to have a much lower frequency than the avatrombopag trials regardless of treatment arm, the explanation for which is not obvious. They also show that there was no statistically significant difference between lusutrombopag and placebo. However, there was a statistically significant difference for avatrombopag in the <40,000/μL subgroup of ADAPT-1 and the

40,000 to <50,000/µL subgroup in ADAPT-2. This did imply an advantage to avatrombopag versus lusutrombopag in the risk of avoiding rescue therapy from the indirect comparison, but which was only statistically significant in the fixed effect analysis on the relative risk scale of the <40,000/µl subgroup (See Table 1.3).

Table 1.1: Relative risks (95% CI) for lusutrombopag vs. placebo for three main outcomes

Study	No platelet transfusion prior to the elective procedure nor rescue therapy	No platelet transfusion	No rescue therapy
Subgroup with baseline platelet count <40,000/µl			
JapicCTI-121944	[redacted]	[redacted]	[redacted]
L-PLUS 1	[redacted]	[redacted]	[redacted]
L-PLUS 2	[redacted]	[redacted]	[redacted]
Subgroup with baseline platelet count 40,000/µl to <50,000/µl			
JapicCTI-121944	[redacted]	[redacted]	[redacted]
L-PLUS 1	[redacted]	[redacted]	[redacted]
L-PLUS 2	[redacted]	[redacted]	[redacted]

Table 1.2: Relative risks (95% CI) for avatrombopag vs. placebo for three main outcomes

Study	No platelet transfusion prior to the elective procedure nor rescue therapy	No platelet transfusion	No rescue therapy
Subgroup with baseline platelet count <40,000/µl			
ADAPT-1	2.86 (1.67, 4.91)	1.46 (1.10, 1.93)	1.96 [1.24, 3.11]
ADAPT-2	1.97 (1.27, 3.05)	1.62 (1.19, 2.21)	1.21 [0.89, 1.65]
Subgroup with baseline platelet count 40,000/µl to <50,000/µl			
ADAPT-1	2.31 (1.49, 3.57)	1.86 (1.32, 2.63)	1.24 [0.94, 1.62]
ADAPT-2	2.64 (1.61, 4.31)	1.74 (1.27, 2.39)	1.52 [1.04, 2.21]

Table 1.3: Relative risks (95% CI) for lusutrombopag vs. avatrombopag for three main outcomes from indirect comparison

Type of effect	No platelet transfusion prior to the elective procedure nor rescue therapy	No platelet transfusion	No rescue therapy
Subgroup with baseline platelet count <40,000/µl			
Fixed effect	1.29 (0.72, 2.31)	1.93 (1.15, 3.22)	0.71 (0.54, 0.93)
Random effects	1.63 (0.61, 4.37)	2.43 (0.95, 6.27)	0.67 (0.41, 1.08)
Subgroup with baseline platelet count 40,000/µl to <50,000/µl			

Fixed effect	1.02 (0.62, 1.66)	1.31 (0.86, 2.01)	0.81 (0.62, 1.05)
Random effects	1.13 (0.61, 2.11)	1.62 (0.63, 4.18)	0.81 (0.62, 1.05)

Most of the data needed to make the comparison between lusutrombopag and avatrombopag in the <40,000/µL and 40,000 to <50,000/µL subgroups was also obtained. However, the total number of rescue procedures in these subgroups was either not available or not reliable. There was also clinical heterogeneity between the lusutrombopag trials as well as between the lusutrombopag and avatrombopag sets of trials. However, statistical heterogeneity was no more than moderate and robustness of outcomes in term of the extent of difference between TPO-RA and no TPO-RA and between both TPO-RAs was demonstrated by sensitivity analyses. Survival was not an efficacy outcome and mortality data were only provided for very short-term follow-up, although there appeared to be little difference between treatments. No quality of life data were provided, although it is plausible that TPO-RAs have little clinical impact other than to reduce the need for platelets.

When the cost effectiveness was assessed of both TPO-RAs versus no TPO-RA, it was clear that in terms of quality adjusted life-years (QALYs) there is only a marginal benefit of TPO-RAs over care as usual (See Table 1.4). When uncertainty is taken into account, both lusutrombopag and avatrombopag have about 50% chance of being more effective than no TPO-RA. This essentially reduces the cost effectiveness analysis to a cost minimisation analysis. For both subgroups, no TPO-RA clearly has the lowest costs, even when taking uncertainties into account. Lusutrombopag is about 25% more costly in the <40,000/µL subgroup compared to no TPO-RA, and avatrombopag 28% more costly. For the 40,000 – 50,000/µL subgroup, avatrombopag and lusutrombopag are 28% and 27% more expensive than no TPO-RA, respectively.

Table 1.4: Deterministic base-case discounted AG model results

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER (£/QALY)
Platelet count < 40,000 / µL Subgroup							
No TPO-RA	£2,320	7.3961	3.3626				
Lusutrombopag	£2,911	7.3961	3.3627	£592	0.00002	0.00017	£3,422,801
Avatrombopag 60 mg	£2,961	7.3961	3.3627	£49	-0.000006	-0.000079	Dominated
Platelet count 40,000- 50,000 / µL Subgroup							
No TPO-RA	£2,283	7.3961	3.3625				
Lusutrombopag	£2,907	7.3961	3.3625	£624	0.00002	0.00000	£84,890,361,589
Avatrombopag 40 mg	£2,916	7.3961	3.3629	£9	0.00000	0.00041	£21,947
ICER = incremental cost effectiveness ratio, Incr. = incremental, LYGs = life years gained, QALYs = quality-adjusted life years.							

In the probabilistic sensitivity analysis, it was shown that for all thresholds below £100,000, no TPO-RA had a 100% probability of being cost effective.

Various scenario analyses showed that the results are most sensitive to the (currently unknown) price of avatrombopag. If its price were to be 80% below the price of lusutrombopag, avatrombopag would become cost saving in the 40,000 – 50,000/μL subgroup.

A similar pattern is seen for three of the 15 other scenarios, "number of ATDs per platelet transfusion", "cost of platelet transfusion" and "under reporting factor for SHOT data platelet transfusion specific mortality". In each of these cases, the avatrombopag costs would decrease in the 40,000 – 50,000/μL subgroup to values around 10% more than no TPO-RA, in the most extreme scenarios. However, even then the ICERs would remain very high and clearly out of the range of acceptable ICERs.

Conclusions

If the aim of service provision is to reduce platelet transfusion prior to elective procedures in those with CLD then both lusutrombopag 3 mg and avatrombopag, 60 mg or 40 mg for the <40,000/μL or 40,000 to <50,000/μL subgroups respectively would seem to be able to do that safely. The evidence suggests that avatrombopag might also be able to reduce the need for rescue therapy for bleeding. However, given the large difference between the rates of rescue therapy between the lusutrombopag and avatrombopag trials, it is uncertain what the circumstances are under which this might be observed in clinical practice. When assessing the cost effectiveness of lusutrombopag and avatrombopag it confirmed that, although both were successful in avoiding platelet transfusions prior to surgery, this did not translate into additional long-term health benefits over placebo in terms of QALYs. Therefore, cost minimisation becomes the focus. For both platelet count subgroups, no TPO-RA was clearly cheaper than both lusutrombopag and avatrombopag, as cost savings due to avoiding platelet transfusions were more than offset by the cost of the drugs. Lusutrombopag is about 25% more costly in the <40,000/μL subgroup compared to no TPO-RA, and avatrombopag 28% more costly. For the 40,000 – 50,000/μL subgroup, avatrombopag and lusutrombopag are 28% and 27% more expensive than no TPO-RA, respectively. The probabilistic sensitivity analysis showed that for all thresholds below £100,000, no TPO-RA had a 100% probability of being cost effective. Uncertainty surrounding the price of avatrombopag, the content and costs of platelet transfusions and the potential under reporting in the data used to estimate platelet transfusion specific mortality had most impact on results. However even when extreme values were tested incremental cost effectiveness ratios (ICERs) comparing lusutrombopag and avatrombopag to no TPO-RA remained substantially higher than National Institute for Health and Care Excellence (NICE) thresholds.

Given the need to compare the two TPO-RAs and the potential lack of comparability of the extant trials, a head-to-head trial is warranted. This should ideally measure all relevant outcomes, including risk of platelet transfusion separate to rescue therapy and with a longer follow-up at least of mortality and quality of life. The trial should be of a size that permits subgroup analysis according to baseline platelet count as well as in terms of CLD type and elective procedure. Any future trials in this area should focus on consistent collection of data on the content of platelet transfusions in terms of the volume of platelets transfused or consistent and clear definitions such as of units or doses so that accurate costs can be calculated. This is particularly important given that the avoidance of platelet transfusion does not seem to translate into differences in QALYs. Therefore, accurate costing is of crucial importance for decision making.

2. PLAIN ENGLISH SUMMARY

Thrombocytopenia is a common complication in chronic liver disease (CLD). It means a reduction in the number of platelets within the blood, which increases the risk of bleeding during procedures including liver biopsy or liver transplantation. It can delay or prevent such procedures and lead to morbidity and mortality. Established clinical management largely involves platelet transfusion prior to the procedure or as rescue therapy for bleeding due to the procedure. There are currently no licensed treatments in the UK for treating thrombocytopenia in people with CLD requiring surgery. The purpose of this report is to systematically review the effectiveness and estimate the cost effectiveness of two recently licensed treatments, thrombopoietin receptor agonists (TPO-RAs), avatrombopag and lusutrombopag, administered in addition to established clinical management versus established clinical management along (no TPO-RA) within the licensed populations.

The licensed dose of lusutrombopag is 3 mg for platelet count of <50,000/μL. That for avatrombopag is dependent on baseline platelet count: i.e. 60 mg if baseline platelet count <40,000/μL and 40 mg if 40,000 to <50,000/μL. Therefore, both clinical effectiveness and cost effectiveness analyses were conducted in each of these two subgroups. From a comprehensive search, which retrieved 11,305 records, 35 references pertaining to six studies were included. Analysis by subgroup showed that avatrombopag and lusutrombopag were superior to no TPO-RA in avoiding both platelet transfusion or rescue therapy and mostly with a statistically significant difference i.e. 95% confidence intervals did not overlap the point of no difference. However, only avatrombopag seemed to be superior to no TPO-RA in reducing the risk of rescue therapy, although far fewer patients in the lustrombopag than in the avatrombopag trials received rescue therapy.

When assessing the cost effectiveness of lusutrombopag and avatrombopag it was found that although both were successful in avoiding platelet transfusions prior to surgery, this did not translate into additional long-term health benefits over TPO-RA in terms of quality adjusted life years. Therefore, the cost of each option became most important. For both platelet count subgroups, TPO-RA was clearly cheaper than both lusutrombopag and avatrombopag, as cost savings due to avoiding platelet transfusions were more than offset by the cost of the drugs. Lusutrombopag is about 25% more costly in the <40,000/μL subgroup compared to TPO-RA, and avatrombopag 28% more costly. For the 40,000 – 50,000/μL subgroup, avatrombopag and lusutrombopag are 28% and 27% more expensive than TPO-RA, respectively. The probabilistic sensitivity analysis showed that for all thresholds below £100,000, TPO-RA had a 100% probability of being cost effective. Uncertainty surrounding the price of avatrombopag, the content and costs of platelet transfusions and the potential under reporting in the data used to estimate platelet transfusion specific mortality had most impact on results.

If the price of avatrombopag were to be 80% below the price of lusutrombopag, avatrombopag would become cost saving in the 40,000 – 50,000/μL subgroup. A similar pattern is seen for the number of adult therapeutic doses per platelet transfusion, the cost of platelet transfusion, the cost of rescue therapy and the under reporting factor for the data used to estimate platelet transfusion specific mortality. In each of these cases the avatrombopag costs would decrease in the 40,000 – 50,000/μL subgroup to values around 10% more than TPO-RA, in the most extreme scenarios. However, even then the ICERs would remain very high and clearly out of the range of acceptable ICERs, meaning that lusutrombopag and avatrombopag would still not be considered cost effective.

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DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader.

AE	Adverse events
AG	Assessment Group
BI	Budget impact
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company's submission
CSR	Clinical study report
DALY	Disability-adjusted life year
Den	Denominator
df	Degrees of freedom
EMA	European Medicines Agency
EPAR	European public assessment report
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-3L	European Quality of Life-5 Dimensions, three-level scale
ESMO	European Society for Medical Oncology
EUR	Erasmus University Rotterdam
FDA	Food and Drug Administration
FFP	Fresh Frozen Plasma
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
IC	Indirect comparison
ICD	International Classification of Diseases
ICER	Incremental cost effectiveness ratio
IFN	Interferon
ITT	Intention to treat
IV	Intravenous
JAPIC	Japic Clinical Trials Information
KM	Kaplan–Meier
KSR	Kleijnen Systematic Reviews
LYS	Life year saved
MAH	Marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
MeSH	Medical subject headings
MHRA	Medicines and Healthcare Products Regulatory Agency
mg	Milligram
MRU	Medical resource utilisation
MTC	Mixed treatment comparison
NA	Not applicable
NHS	National Health Services
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NR	Not reported
Num	Numerator
od	Once daily

OR	Odds ratio
OS	Overall survival
PCT	Primary Care Trust
PEIP	Planned elective inpatient procedure
PK	Pharmacokinetic
PRESS	Peer Review of Electronic Search Strategies
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analyses
PSS	Personal Social Services
QALY(s)	Quality-adjusted life year(s)
QoL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk; risk ratio
SAE	Serious adverse events
ScHARR	School of Health and Related Research
SD	Standard deviation
SF-36	Short form 36
SHOT	Serious hazards of transfusion
SHTAC	Southampton Health Technology Assessments Centre
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SPC	Summary of product characteristics
STA	Single technology appraisal
TEAEs	Treatment-emergent adverse events
TESAEs	Treatment-emergent serious adverse events
TPO-RA	Thrombopoietin receptor agonist
TRALI	Transfusion-related acute lung injury
UK	United Kingdom
UMC	University Medical Centre
WHO	World Health Organisation

3. BACKGROUND

3.1 Description of the health problem

Thrombocytopenia is characterised as a reduction in the number of circulating platelets within the blood. Platelets come from megakaryocytes in the bone marrow. They play a critical role in haemostasis, a process which causes bleeding to stop. Thrombocytopenia can generally be classified on the basis of the platelet count in the blood. It is usually defined as a platelet count of less than 150,000/μL of blood.[1]

Thrombocytopenia is a common complication in people with CLD either as a direct result of the liver pathology or a consequence of interferon-based antiviral therapy following liver infection. While mild to moderate thrombocytopenia rarely causes bleeding during procedures such as liver biopsy or liver transplantation, severe thrombocytopenia increases the risk of excessive bleeding during and after surgery and can have a significant impact on the clinical management of CLD. It can delay or prevent the start of appropriate therapy leading to increased morbidity and mortality and a reduced quality of care.[1]

Adults with thrombocytopenia associated with CLD can undergo various types of elective procedure. Such procedures might be classified by the associated bleeding risk based on the published literature into three categories:[2]

- Low risk (paracentesis, thoracentesis, gastrointestinal endoscopy),
- Moderate risk (liver biopsy, bronchoscopy, ethanol ablation therapy, chemoembolisation), and
- High risk (vascular catheterisation, transjugular intrahepatic portosystemic shunt, dental procedures, renal biopsy, biliary interventions, nephrostomy tube placement, radiofrequency ablation, laparoscopic interventions).

Between 2016 and 2017, Hospital Episode Statistics showed 27,927 admissions with liver disease in England.[3] The prevalence of thrombocytopenia in people with CLD varies from 15% to 70% depending on the stage of liver disease and differences in platelet count cut-off used to define thrombocytopenia.

3.2 Current service provision

There are currently no licensed treatment options that have been recommended by NICE for treating thrombocytopenia in people with CLD requiring surgery. Typical therapies include stimulation of megakaryocyte maturation and platelet production. Treatment for severe thrombocytopenia can include platelet transfusion, splenic artery embolisation and surgical splenectomy.

NICE clinical guideline CG24 recommends, for anyone having an invasive procedure or surgery, to consider platelet transfusion in order to raise the platelet count to above:[4]

- 50,000/μL for any type of patient
- 50,000 – 75,000/μL for patients with a high risk of bleeding, depending on procedure, aetiology, whether platelet count is stable, any other cause of abnormal haemostasis
- 100,000/μL "…in critical sites, such as the central nervous system (including the posterior segment of the eyes)." (p.12)

3.3 Description of technology under assessment

Avatrombopag (Doptelet®, Dova Pharmaceuticals) is a small molecule thrombopoietin receptor agonist (TPO-RA) that targets the c-MpI thrombopoietin cell surface receptor on megakaryocytes to stimulate platelet production. Avatrombopag is administered orally. It has been studied in clinical trials compared with placebo in people with thrombocytopenia associated with CLD requiring an elective procedure. It has, as of 25 June 2019, a marketing authorisation in the UK.[5] The full indication is: "Doptelet is indicated for the treatment of severe thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo an invasive procedure." According to the European Medicines Agency (EMA), it is recommended that avatrombopag is administered for five days at a dose of:[6]

- 60 mg if baseline platelet count <40,000/μL
- 40 mg if baseline platelet count is 40,000 to <50,000/μL

The elective procedure should be performed from day 10 to 13 after treatment initiation.

Lusutrombopag (Mulpleo®, Shionogi BV) is a small molecule TPO-RA which targets the c-MpI thrombopoietin cell surface receptor on megakaryocytes to stimulate platelet production. Lusutrombopag is administered orally. It has been studied in clinical trials compared with placebo in adults with thrombocytopenia with a platelet count of $<50 \times 10^9$ per blood litre associated with CLD requiring elective invasive surgery. It received its marketing authorisation on 14 March 2019.[7] The following indication was agreed: "Treatment of severe thrombocytopenia in adult patients with chronic liver disease undergoing invasive procedures." According to the EMA, the recommended dose is 3 mg once daily for seven days and the elective procedure should be performed from day nine after treatment initiation.[8]

4. DEFINITION OF THE DECISION PROBLEM

The purpose of this section is to specify the decision problem and to translate it into research objectives. Where the background section provides the overall summary of the topic, the decision problem states the key factors to be addressed and the scope of the assessment of the key factors as defined through the NICE scoping process.

4.1 Decision problem

- Interventions:
  - Avatrombopag, dose as reported in trials, although the focus will be on the licensed dose:
    - 60 mg if baseline platelet count <40,000/μL
    - 40 mg if baseline platelet count is 40,000 to <50,000/μL
  - Lusutrombopag, dose as reported in trials, although the focus will be on the licensed dose i.e. 3 mg.
- Population:
  - Adults with thrombocytopenia associated with CLD needing an elective procedure, although the focus will be on platelet count <50,000/μL and, in order to match to the licences dose of avatrombopag, within the subgroups, platelet count <40,000/μL and 40,000 to 50,000/μL.
- Relevant comparators:
  - Established clinical management without avatrombopag and lusutrombopag (including, but not limited to platelet transfusion)
- Outcomes
  - Platelet count
  - response rate (by some definition related to change in platelet count)
  - number of platelet transfusions
  - number of blood transfusions
  - return to operating theatre
  - need for rescue treatments
  - use of concurrent treatments
  - bleeding score
  - mortality
  - adverse effects of treatment
  - health-related quality of life.

4.2 Overall aims and objectives of assessment

The review aims to:

- evaluate the clinical effectiveness of each intervention
- evaluate the adverse effect profile of each intervention
- evaluate the incremental cost-effectiveness of each intervention compared to:
  - each other and
  - established clinical management without avatrombopag or lusutrombopag

5. ASSESSMENT OF CLINICAL EFFECTIVENESS

5.1 Methods for reviewing effectiveness

Throughout this review, the methods recommended by the Cochrane Collaboration Handbook[9] and the Centre for Reviews and Dissemination (CRD), York[10] were applied in order to reduce the risk of bias and error.

5.1.1 Identification of studies

Literature searches were conducted to identify relevant information on the clinical effectiveness, safety and cost effectiveness of avatrombopag and lusutrombopag. The searches also identified studies on the clinical effectiveness, safety and cost effectiveness of established clinical management of thrombocytopenia in people with CLD, including: platelet transfusion; stimulation of megakaryocyte maturation and platelet production; splenic artery embolisation; and surgical splenectomy. All literature searches were undertaken to the highest standard to meet best practice requirements recommended by the Centre for Reviews and Dissemination, and Cochrane.[9, 10]

The search strategies combined relevant search terms comprising indexed keywords (e.g. Medical Subject Headings, MeSH and EMTREE) and free text terms appearing in the title and/or abstract of database records. Search terms were identified through discussion with the review team, by scanning background literature and 'key articles' already known to the review team, and by browsing database thesauri. Search strategies were developed specifically for each database and the keywords adapted according to the configuration of each database. Only studies conducted in humans were sought. Searches were not limited by language, publication status (unpublished or published) or date of publication. Methodological study design search filters were not included in the search strategies to ensure sensitivity and the optimal identification of clinical effectiveness, safety and cost-effectiveness studies.

Full details of the search strategies are presented in Appendix 1.

The following databases and resources were searched:

- MEDLINE (Ovid): 1946-2019/January Week 3
- MEDLINE In-Process Citations, Daily Update and Epub Ahead of Print (Ovid): January 22, 2019
- PubMed (NLM): up to 24 January 2019
- Embase (Ovid): 1974 to 2019 Week 3
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): Issue 1 of 12, January 2019
- Cochrane Database of Systematic Reviews (CDSR) (Wiley): Issue 1 of 12, January 2019
- KSR Evidence (https://ksrevidence.com/): Database last updated 24 January 2019
- Epistemonikos (https://www.epistemonikos.org/): up to 24 January 2019
- Database of Abstracts of Reviews of Effects (DARE) (CRD): up to 31 March 2015*
- Health Technology Assessment (HTA) database (CRD): up to 31 March 2018*
- NHS Economic Evaluation Database (NHS EED) (CRD): up to 31 March 2015*
- PROSPERO (CRD): up to 24 January 2019
- Science Citation Index (SCI) (Web of Science): 1988-2019-01-23
- CINAHL (EBSCO): 1982-20190123
- LILACS (BIREME): 1982 to 24 January 2019

- Northern Light Life Sciences Conference Abstracts (Ovid): 2010-2019/week 02
- Transfusion Evidence Library (www.transfusionevidencelibrary.com): up to 23 January 2019
- RePEc: Research Papers in Economics (repec.org/): up to 23 January 2019

*DARE and NHS EED have ceased; records were published until 31st March 2015. HTA database records were added until 31st March 2018; updating and addition of new records will resume on the International Network of Agencies for Health Technology Assessment (INAHTA) platform, when it is ready.

Supplementary searches were conducted to identify completed and ongoing trials by searching the following clinical trials registers:

- ClinicalTrials.gov (http://www.clinicaltrials.gov/): up to 23 January 2019
- WHO International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/): up to 23 January 2019

Grey literature was identified from searches of the following resources:

- US Food & Drug Administration (FDA) (https://www.fda.gov/): up to 23 January 2019
- European Medicines Agency (EMA) (http://www.ema.europa.eu/ema/): up to 23 January 2019
- OAIster (http://oaister.worldcat.org/): up to 23 January 2019
- OpenGrey (www.opengrey.eu/): up to 23 January 2019
- COPAC (https://copac.jisc.ac.uk/): up to 23 January 2019

Relevant organisation websites were also searched, including: British Society for Haematology, European Hematology Association, International Society on Thrombosis & Haemostasis, and American Society of Hematology.

Reference checking

The bibliographies of identified research and review articles were checked for relevant studies.

Handling of citations

Identified references were downloaded into EndNote bibliographic management software for further assessment and handling. Individual records within the EndNote library were tagged with searching information, such as searcher, date searched, database host, database searched, strategy name and iteration, theme or search question. This enabled the Information Specialist to track the origin of each individual database record, and its progress through the screening and review process.

Quality assurance within the search process

For all searches undertaken by the Kleijnen Systematic Reviews Information Team, the main Embase strategy was independently peer reviewed by a second KSR Information Specialist. Search strategy peer review was informed by items based on the CADTH checklist.[11, 12]

5.1.2 Inclusion criteria

The following is a list of inclusion criteria for the systematic review:

- Population:
    - Adults with thrombocytopenia associated with CLD needing an elective procedure.

- Intervention:
    - Avatrombopag
    - Lusutrombopag
- Comparator:
    - Any comparator or none
- Outcomes:
    - Platelet count
    - Response rate
    - number of platelet transfusions
    - number of blood transfusions
    - return to operating theatre
    - need for rescue treatments for bleeding (referred to as 'rescue therapy')
    - use of concurrent treatments
    - bleeding score
    - mortality
    - adverse effects of treatment
    - health-related quality of life.
- Study design:
    - RCTs
    - Observational studies (cohort or case series) of at least 20 participants

5.1.3 Data abstraction strategy

Study selection

Titles and abstracts identified through electronic database and other searches were independently screened by two reviewers. During this initial phase of the screening process any references which obviously did not meet the inclusion criteria listed previously were excluded. Full paper copies were obtained for all of the remaining references. These were then independently examined in detail by two reviewers in order to determine whether they meet the criteria for inclusion in the review. All papers excluded at this second stage of the screening process have been documented in a table along with the reasons for exclusion (see Appendix 3). These reasons were categorised as follows:

- Not relevant population (i.e. not thrombocytopenia associated with CLD needing an elective procedure)
- Not relevant intervention
- Not relevant outcome data (i.e. does not assess at least one of the specified outcomes or does not report relevant data or information so as to allow the calculation of relevant data)
- Not relevant study (i.e. not an RCT, cohort or case series)
- Insufficient study size (< 20 participants)

With respect to both screening stages, any discrepancies between reviewers were resolved through discussion or the intervention of a third reviewer.

A flow diagram of the numbers of studies included and excluded at each stage has been provided following guidance in the PRISMA statement (www.prisma-statement.org).

Data extraction

Data extraction sheets were individually designed and piloted using Microsoft Excel. The extraction process was performed by two reviewers with one checking the extraction of the other. Any discrepancies were resolved through discussion or through the intervention of a third reviewer. Studies are identified by the trial name. To avoid the duplication of data where studies (or study populations) have multiple publications the most complete report is used as the main reference, but additional details have been extracted from the other publications as necessary. Details of the general information and data to be extracted for each study, regardless of review topic are reported below:

- Endnote ID
- Study ID or name (if reported or otherwise surname of first author)
- Year of publication
- Other related publications
- Study group (if reported)
- Study country(ies)
- Recruitment dates (if relevant)
- Location/setting
- Study funding (public/pharma/not reported)
- Study aim
- Sample size
- Study design
- Study methods
- Patient characteristics
- Treatment characteristics
- Results (all outcomes reported in section 4.1)
- Study conclusions

5.1.4 Critical appraisal strategy

The quality of each individual study was assessed using the following quality assessment tool:

- RCTs – Cochrane Collaboration Quality Assessment Tool for RCTs[13]

Further details of the individual assessment tools are provided in Appendix 2.

The findings of the quality assessment were used to ensure that the conclusions and findings of these reviews are based on the best available evidence and that any potential sources of bias in the data are identified.

5.1.5 Methods of data synthesis

Data is summarised in the context of variation in population in terms of aetiology of liver disease, degree of thrombocytopaenia, bleeding risk and type of elective procedure. Sub-group analysis by degree of thrombocytopaenia is also presented.

Quantitative analysis and meta-analysis methods (Direct 'head-to-head' methods)

Forest plots of effect sizes are presented for each of the main efficacy outcomes. Dichotomous outcomes (e.g. proportion of patients experiencing each type of outcome) are reported as relative risks (RR) with 95% confidence intervals (CIs).

Pooled effect sizes and 95% CIs using random effects models are presented where there are two or more trials which are considered to be clinically and statistically homogeneous.

The judgment of clinical homogeneity is based on the baseline characteristics of the trial populations, (i.e. age, gender, aetiology of liver disease, degree of thrombocytopaenia, bleeding risk and type of elective procedure). Statistical homogeneity will be assessed using the I^2 statistic.[14] This measures the degree of inconsistency between the study results which is due to genuine heterogeneity rather than chance. The value of I^2 lies between 0% and 100%. For the purposes of this review, a simplified categorisation of heterogeneity will be used: low (0 to 25%), moderate (26 to 75%), and high (>75%). Studies will only be considered to be sufficiently similar for the purposes of pooling if $I^2 < 75\%$.[14]

Publication bias could not be assessed given that there are too few trials to use funnel plots of the point estimate plotted against the standard error (SE).[15]

Indirect comparisons

Where the intervention and comparator are not compared in the same RCT (i.e. 'head-to-head' trials A versus B), but instead are separately compared to a common comparator e.g. placebo, an indirect comparison between them was performed. Point estimates (with 95% CIs) were estimated using 'indirect' methods e.g. from A versus C and B versus C, where C is a common control group (e.g. placebo). All methods are applied with consideration for the basic assumptions of homogeneity, similarity, and consistency as reported in Song 2009.[3] All indirect comparisons are consistent with NICE methodological guidance for the conduct of direct and indirect meta-analysis, which include indirect comparisons using the method of Bucher 1997.[16]

Indirect meta-analysis was performed using Microsoft Excel using the Bucher method.[17] RR with 95% CIs were calculated for each outcome and available treatment comparison.

Heterogeneity was investigated using the I^2 statistic for each of the pairwise comparisons.[14] Where there are concerns about heterogeneity, or any trials appear to have results which differ substantially from the others, then one or more trials were removed in a sensitivity analysis.

Network meta-analysis

Because of the possibility of risks exceeding 1 in the cost-effctiveness analysis (CEA), network meta-analysis (NMA) using WinBUGs version 1.4.3 (http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/contents.shtml) was applied using a Bayesian approach consistent with international recommendations. This method generates a set of simulated values in the form of a posterior distribution for each of the odds ratios (ORs) between each TPO-RA and no TPO-RA. Specification of a baseline average risk with its standard error then permits the simulation of an absolute risk for each of the three treatments, lusutrombopag, avatrombopag and no TPO-RA as described in NICE Technical Support Document (TSD) 2. Each of the simulated risks are then input in the CEA model and the expected values of cost and QALYs are calculated by the use of Monte Carlo Simulation (MCS) with a function that prevents any risks from exceeding 1.

Posterior distribution parameter estimates were obtained from 100,000 simulations after a burn-in period of 30,000 Markov Chain Monte Carlo (MCMC) simulations, using two chains. Non-informative normal priors (mean 0, variance 10,000) were used for treatment effects and a non-informative uniform prior (0, 1) was used for the between study standard deviation. Convergence and auto-correlation were assessed by monitoring the trace and autocorrelation plots in WinBUGS. The ORs estimated by this method were almost identical to those estimated by use of the Bucher method.

5.2 Results

5.2.1 Quantity and quality of research available

As a result of all searching, after de-duplication, 11,305 records were screened at the title and abstract stage. From these, 91 were selected to be re-screened at the full paper stage. On completing full paper screening of the 91 records, 35 references were included that fulfilled the inclusion criteria. No additional references were found by reference checking. Therefore, in total 35 references pertaining to six studies were included. The results of screening are shown in Figure 5.1. The list of included studies is shown in Table 5.1: is n, ADAPT-1[18], ADAPT-2[18], L-PLUS 1[19], L-PLUS 2[20] and the study registered by Japic Clinical Trials Information (JAPIC) as CTI-121944.[21] Note that the studies referred to as ADAPT-1, ADAPT-2, L-PLUS 1 and L-PLUS-2 are mentioned more than once to indicate that some references report on only one of the studies whilst others report on two of them.

All studies were generally at low risk of bias as shown in Table 5.2. Also, both sets of main trials for each of the TPO-RAs (ADAPT-1, ADAPT-2, L-PLUS 1 and L-PLUS 2) were of high quality, being found to be at low risk of bias for all criteria.

Figure 5.1: Summary of study flow

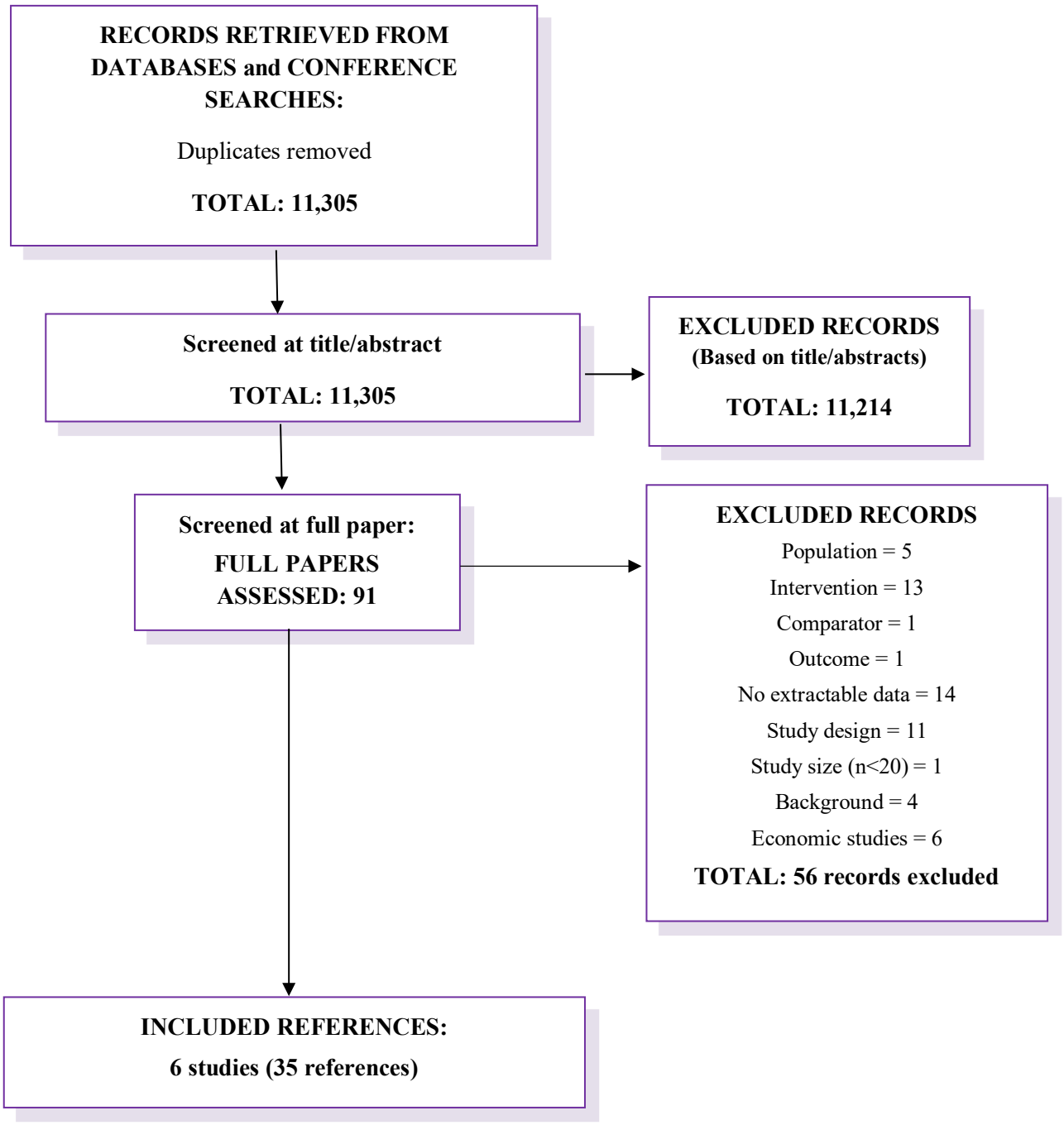


Table 5.1: List of included studies

Trial Name	NCT (or other register) number	Reference
ADAPT-1	NCT01972529	Eisai Inc 2017[22]
ADAPT-2	NCT01976104	Eisai Co., L. 2014 [accessed 23.1.19][23]
		Eisai Inc 2017[24]
ADAPT-1, ADAPT-2	NCT01972529, NCT01976104	Caldwell, S. 2018[25]
		Center for Drug Evaluation and Research 2017 [accessed 23.1.19][26]
		Center for Drug Evaluation and Research 2017 [accessed 23.1.19][27]
		Center for Drug Evaluation and Research 2018 [accessed 23.1.19][28]
		Frelinger, A.L. 2017[29]
		Poordad, F. 2018[30]
		Poordad, F. 2018[31]
		Poordad, F. 2018[32]
		Reau, N.S. 2018[33]
		Saab, S. 2018[34]
		Saab, S. 2018[35]
		Sammy, S. 2018[36]
		Sammy, S. 2018[37]
		Terrault, N. 2017[38]
		Terrault, N. 2017[39]
		Terrault, N. 2018[18]
		Vredenburg, M. 2018[40]
L-PLUS 1	JapicCTI-132323	Hidaka, H. 2018[19]
		Izumi, N. 2015[41]
L-PLUS-2	NCT02389621	Afdhal, N. 2017[42]

Trial Name	NCT (or other register) number	Reference
		Afdhal, N.H. 2017[43]
		Peck-Radosavljevic, M. 2017[44]
		Shionogi 2017[45]
L-PLUS-1, L-PLUS 2	JapicCTI-132323, NCT02389621	Alkhouri, N. 2018[46]
		Brown, R.S. 2018[47]
		Brown, R.S. 2018[48]
		Center for Drug Evaluation and Research 2017 [accessed 23.1.19][49]
Study 202	NCT00914927	Eisai, I. 2011[50]
		Terrault, N. 2012[51]
		Terrault, N.A. 2014[52]
Not reported	JapicCTI-121944	Izumi, N. 2014[53]
		Tateishi, R. 2018[21]
NCT = National Clinical Trials		

Table 5.2: Cochrane Risk of Bias Tool

Study ID	Trial	Randomisation	Allocation concealment	Participant blinding	Personnel blinding	Blinding of outcome assessors	Incomplete outcome data	Selective reporting	Other biases	Criteria "low"	Criteria "unclear"	Criteria "high"
Terrault 2018[18]	ADAPT - 1	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	8	0	0
Terrault 2018[18]	ADAPT - 2	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	8	0	0
Hidaka 2018[19]	L-PLUS 1	Unclear risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	4	4	0
Peck-Radosavljevic 2019[20]	L-PLUS 2	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	8	0	0
Tateishi R. 2019[21]	JapicCTI-121944	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	7	1	0
Terrault 2014[52]	Study 202	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	6	2	0

5.2.2 Study characteristics

As shown in Table 5.3, they were all multi-centre, placebo-controlled, double-blind, parallel randomised controlled trials. Participation was restricted to adults. Three of these trials studied avatrombopag compared to placebo (Study 202[52], ADAPT-1[18], ADAPT-2[18]) whilst the other three trials studied lusutrombopag compared to placebo (L-PLUS 1[19], L-PLUS 2[20] and JAPIC CTI-121944[21]). Patients were recruited worldwide with the exception of three studies: one of avatrombopag i.e. Study 202 (solely based in USA[52]); and two of lusutrombopag i.e. L-PLUS 1 and JAPIC CTI-121944 (exclusively based in Japan[19, 21]). Follow up time was limited to between three and five weeks. With the exception of Study 202, which was carried out in 2014, all studies were carried out in 2018 or later[18-21]. As shown in Table 5.4, the sample size of individual arms in the included studies ranged from 15 to 108 participants. The trials studying avatrombopag reported on a total of 467 participants whilst the trials comparing lusutrombopag reported on a total of 342 participants.

5.2.2.1 Degree of thrombocytopaenia

As described in Table 5.4, all six studies restricted patients to a platelet count of <50,000/μL. ADAPT 1 and ADAPT 2 differed from the other studies in that results were published only according to the subgroups <40,000 and 40,000 to <50,000/μL, given variation in dose of avatrombopag according to these subgroups.[18] Given the need to compare lusutrombopag with avatrombopag, data in these subgroups was requested of Shionogi and is presented in Section 5.2.5.

5.2.2.2 Disease type

As shown in Table 5.4, in terms of the type of CLD reported by each study, one study reported including a single type of disease (hepatocellular carcinoma (HCC); JapicCTI-121944), while five studies reported on a mixed CLD population (ADAPT-1, ADAPT-2, L-PLUS 1, L-PLUS 2, Study 202). Three studies (ADAPT-1, ADAPT-2, Study 202) reported on a CLD definition based on a model for end-stage liver disease (MELD) score ≤ 24. Two studies (L-PLUS 1, L-PLUS 2) reported on a CLD definition based on Child-Pugh class A or B; of note, the exclusion criteria reported by the L-PLUS 1 study implied that inclusion was based on Child-Pugh class A or B, but this was not explicitly stated. In contrast, the percentage in Child-Pugh class C was not zero in the ADAPT trials. It was generally low in ADAPT-1 i.e. no higher than 8.6% in the avatrombopag arm of the 40,000 to <50,000/μL subgroup, although it was as high as 15.2% in the placebo arm of the same subgroup in ADAPT-2.[18]

5.2.2.3 Elective procedure type

In terms of the elective procedures reported by each study, these were quite varied (Table 5.5). Only one study reported a single type of procedure (liver radiofrequency ablation; JapicCTI-121944). The other five studies reported including mixed types of elective procedures. Only ADAPT-1 and ADAPT-2 explicitly stated something regarding risk of bleeding, stating that they included both 'low risk' procedures, e.g. liver biopsy and 'high risk' procedures, e.g. radiofrequency ablation. Both L-PLUS 1 and L-PLUS 2 also, according to this definition included mixed risk procedures, including, for example, liver biopsy and radiofrequency ablation.

5.2.2.4 Decision rule for determining treatment dose

There appeared to be some variation regarding the decision rule for administration of platelets prior to the elective procedure. The L-PLUS studies mandated this on the basis of a drop in platelet count

below the 50,000/μL threshold whereas this rule was not explicitly reported for the ADAPT trials.[18-20] However, since the eligible population for the ADAPT studies was "…risk of bleeding that would require a platelet transfusion, unless there was a clinically significant increase in platelet counts from baseline." It seems likely that in practice the same rule would be applied.[18] There was also a difference in the decision rule for administration of the intervention. In the ADAPT trials, all patients received avatrombopag for five days, whereas in the L-PLUS trials, lusutrombopag was administered for between five and seven days depending on platelet count i.e. if the platelet count was at least 50 $x10^9$ per litre with an increase of at least 20 x 10^9 per litre then no additional dose was given. The implication of this difference is that lusutrombopag was administered on average over a longer period than avatrombopag.

Table 5.3: Study characteristics

Trial name	Reference	Countries	No. of centres	Age range (low; high)	Study start date	Study end date	Follow-up weeks	Intervention	Comparator	NCT/ other trial number
Study 202	Terrault 2014[52]	USA	27	18;NR	May-09	Nov-11	5	Avatrombopag	Placebo	NCT00914927 ; E5501-G000-202
ADAPT-2	Terrault 2018[18]	Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, Czech Republic, France, Germany, Hungary, Israel, Italy, Japan, Mexico, Republic of Korea, Romania, Russia, Poland, Portugal, Spain, Taiwan, Thailand, United Kingdom, United States	74	18;NR	Dec-13	Jan-17	5	Avatrombopag	Placebo	NCT01976104
ADAPT-1			75	18;NR	Feb-14	Jan-17	5			NCT01972529
L-PLUS 1	Hidaka 2018[19]	Japan	81	20;NR	Oct-13	May-14	5	Lusutrombopag	Placebo	JapicCTI-132323
L-PLUS 2	Peck-Radosavljevic 2019[20]	Argentina, Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Hungary, Israel, Italy, Poland, Republic of Korea, Romania, Russian	138	18;NR	Jun-15	Apr-17	3	Lusutrombopag	Placebo	NCT02389621

Trial name	Reference	Countries	No. of centres	Age range (low; high)	Study start date	Study end date	Follow-up weeks	Intervention	Comparator	NCT/ other trial number
		Federation, Spain, Taiwan, Thailand, Turkey, Ukraine, United Kingdom, United States								
NR	Tateish R. 2019[21]	Japan	63	20; NR	Aug-12	Apr-13	5	Lusutrombopag	Placebo	JapicCTI-121944

Table 5.4: Study aims, conclusions and inclusion criteria

Trial name	Reference	Population - liver disease	Study aim	Study conclusions	Inclusion criteria
Study 202	Terrault 2014[52]	Mixed	To investigate the efficacy and safety of avatrombopag (E5501), an investigational second-generation thrombopoietin receptor agonist, administered one week prior to elective procedures in patients with thrombocytopenia secondary to chronic liver disease	Avatrombopag was generally well-tolerated and increased platelet counts in patients with chronic liver disease undergoing elective invasive procedures.	Age≥ 18 years of age; thrombocytopenia (defined as a platelet count ≥ 10,000 - ≤ 50,000 (+15%)/mm^3); Model for End-Stage Liver Disease (MELD) scores ≤ 24; Chronic liver diseases due to chronic Viral Hepatitis, NASH or alcoholic liver disease; scheduled to undergo an elective invasive procedure between 1 to 4 days post last dose of study drug; adequate renal function as evidenced by a calculated creatinine clearance ≥50 mL/minute per the Cockcroft and Gault formula; life expectancy ≥3 months
ADAPT-1 ADAPT-2	Terrault 2018[18]	Mixed	To evaluate the safety and efficacy of avatrombopag in increasing platelet counts in patients with thrombocytopenia and chronic liver disease undergoing scheduled procedures	In 2 phase 3 randomized trials, avatrombopag was superior to placebo in reducing the need for platelet transfusions or rescue procedures for bleeding in patients with thrombocytopenia and CLD undergoing a scheduled procedure.	CLD (Model for End-Stage Liver Disease [MELD] score 24); thrombocytopenia with a mean baseline platelet count of < 50,000 /μL; scheduled to undergo a procedure with an associated risk of bleeding that would require a platelet transfusion, unless there was a clinically significant increase in platelet counts from baseline

Trial name	Reference	Population - liver disease	Study aim	Study conclusions	Inclusion criteria
L-PLUS 1	Hidaka 2018[19]	Mixed	To evaluate the superiority of Lusutrombopag over placebo in efficacy in thrombocytopenic patients with chronic liver disease receiving 3mg of Lusutrombopag as a pre-treatment of invasive procedures based in the proportion of patients who required no platelet transfusion prior to invasive procedures.	In a placebo-controlled trial, lusutrombopag was effective in achieving and maintaining the target platelet count in patients with chronic liver disease and thrombocytopenia undergoing invasive procedures. No significant safety concerns were raised.	Male or female patients aged ≥20 years; thrombocytopenia associated with chronic liver disease; platelet count of <50,000/μL; undergoing invasive procedures (excluding laparotomy, thoracotomy, craniotomy, open-heart surgery, organ resection, or partial organ resection) between 9 and 14 days after initiation of study treatment; Eastern Cooperative Oncology Group performance status grade 0 or 1; and agreement to use an appropriate method of contraception during the study
L-PLUS 2	Peck-Radosavljevic 2019[20]	Mixed	To compare the efficacy of lusutrombopag with placebo for the treatment of thrombocytopenia in patients with chronic liver disease who are undergoing elective invasive procedures.	None posted on clinical trials.gov (L-Plus 2)	Able to understand the study and comply with all study procedures; Willing to provide written informed consent prior to Screening; Male or female; 18 years of age or older at the time of signing informed consent; Platelet count < 50,000/μL at baseline on Day 1 prior to randomization; Undergoing an elective invasive procedure; In the opinion of the investigator, able to meet study requirements; Male patients who are sterile or who agree to use an appropriate method of contraception (including use of a condom with spermicide) from Screening to completion of the Post-treatment Period; Female patients who are not postmenopausal or surgically sterile need to agree to use a highly effective contraception (including contraceptive implant, injectable contraceptive, combination hormonal contraceptive [including vaginal rings], intrauterine contraceptive device or

Trial name	Reference	Population - liver disease	Study aim	Study conclusions	Inclusion criteria
					vasectomised partner) from Screening to completion of the Post-treatment Period. Barrier method with or without spermicide, double barrier contraception and oral contraceptive pill are insufficient methods on their own.
JapicCTI-121944	Tateishi R. 2019[21]	HCC	To estimate the appropriate dose and evaluate the efficacy and safety of lusutrombopag for the treatment of thrombocytopenia before percutaneous liver radiofrequency ablation (RFA) for primary hepatic cancer in patients with CLD.	Lusutrombopag 3 mg once daily for 7 days was effective without raising concerns about excessive increases in platelet count.	Men or women aged 20 years or older; thrombocytopenia due to CLD, platelet count of <50,000/μL; undergoing RFA for primary hepatic carcinoma; Eastern Cooperative Oncology Group performance status grade 0 or 1; able to remain hospitalized between 5 and 14 days after the initiation of the study treatment

Table 5.5: Study elective procedures

	ADAPT-1[18]	ADAPT-2[18]	L-PLUS 1[19]	L-PLUS 2[20]	JapicCTI-121944[21]	Study 202[52]	No. RCTs reported
Argon plasma coagulation	No	No	Yes	No	No	No	1
Biliary interventions	Yes	Yes	No	No	No	No	2
Biopsy (renal)	Yes	Yes	No	No	No	No	2
Biopsy (bone marrow)	No	No	No	Yes	No	No	1
Biopsy (liver)	Yes	Yes	Yes	Yes	No	Yes	5
Bronchoscopy	Yes	Yes	No	No	No	Yes	3
Catheterisation (heart)	No	No	No	No	No	Yes	1
Catheterisation (vascular)	Yes	Yes	No	No	No	Yes	3
Cervical polyp removal	No	No	No	Yes	No	No	1
Chemoembolisation	Yes	Yes	No	No	No	Yes	3
Colonoscopy	No	No	No	No	No	Yes	1
Colonoscopy plus endoscopy	No	No	No	No	No	Yes	1
Colonoscopy plus polypectomy	No	No	No	No	No	Yes	1
Cystoscopy and biopsy of urinary bladder	No	No	No	Yes	No	No	1
Dental extraction	No	No	No	Yes	No	No	1
Dental implant	No	No	No	Yes	No	No	1
Dental procedures	Yes	Yes	No	No	No	Yes	3
Periodontal scaling/root planning	No	No	No	No	No	Yes	1
EGD (oesophagogastroduodenoscopy)	No	No	No	No	No	Yes	1
EGD with banding	No	No	No	No	No	Yes	1
Endonasal maxillectomy	No	No	No	Yes	No	No	1
Endoscopic injection sclerosis/sclerotherapy	No	No	Yes	Yes	No	No	2

	ADAPT-1[18]	ADAPT-2[18]	L-PLUS 1[19]	L-PLUS 2[20]	JapicCTI-121944[21]	Study 202[52]	No. RCTs reported
Endoscopic variceal ligation	No	No	Yes	Yes	No	No	2
Endoscopy	No	No	No	No	No	Yes	1
Endoscopy (gastrointestinal) - Operative or Diagnostic	No	No	No	Yes	No	No	1
Endoscopy (upper GI) and chemoembolisation	No	No	No	No	No	Yes	1
Endoscopy with banding	No	No	No	No	No	Yes	1
Endoscopy with possible oesophageal banding	No	No	No	No	No	Yes	1
Ethanol ablation therapy	Yes	Yes	No	No	No	No	2
Hernia (inguinal)	No	No	No	Yes	No	No	1
Hernia repair (prosthetic inguinal)	No	No	No	Yes	No	No	1
Hernia repair (umbilical)	No	No	No	No	No	Yes	1
Laparocentesis (diagnostic)	No	No	No	Yes	No	No	1
Laparoscopy (any)	Yes	Yes	No	No	No	No	2
Liver-related procedures	No	No	No	Yes	No	No	1
Mastoidectomy/Tympanoplasty	No	No	No	Yes	No	No	1
Nephrostomy tube placement	Yes	Yes	No	No	No	No	2
Paracentesis	No	No	No	No	No	Yes	1
Paracentesis (diagnostic)	No	No	No	Yes	No	No	1
Percutaneous ethanol injection therapy	No	No	Yes	No	No	No	1
Percutaneous RFA/microwave coagulation therapy	No	No	No	Yes	No	No	1
Pleurocentesis/pleural biopsy	No	No	No	No	No	Yes	1
Radiofrequency ablation (RFA)	Yes	Yes	Yes	No	Yes	Yes	5

	ADAPT-1[18]	ADAPT-2[18]	L-PLUS 1[19]	L-PLUS 2[20]	JapicCTI-121944[21]	Study 202[52]	No. RCTs reported
Septoplasty	No	No	No	Yes	No	No	1
Splenic artery aneurysm embolisation	No	No	No	Yes	No	No	1
Thoracentesis (diagnostic)	No	No	No	Yes	No	No	1
Transcatheter arterial chemoembolisation	No	No	Yes	Yes	No	Yes	3
Transjugular Intragepatic Portosystemic Shunt (TIPS)	Yes	Yes	No	No	No	Yes	3

Table 5.6: Patient characteristics

Trial name	Reference	NCT/other trial number	Arm name	Population - liver disease	Lower / Upper platelets	No. of patients randomised to study arm	Mean age (yrs)	SD (yrs)	Age range lower	Age range upper	Male (%)
Study 202	Terrault 2014[52]	NCT00914927; E5501-G000-202	Avatrombopag 40mg	Mixed	10,000-50,000	16	52.8	7.78	NR	NR	81.3
			Placebo			16	54.2	6.87	NR	NR	68.8
ADAPT-1	Terrault 2018[18]	NCT01972529	Avatrombopag 40mg		40,000 - 50,000	59	57.5	10.1	19	77	62.7
			Placebo 40mg			34	57.8	11.1	30	76	70.6
			Avatrombopag 60mg		<40,000	90	55.6	9.1	29	78	72.2
			Placebo 60mg			48	55.1	11	25	76	66.7
ADAPT-2		NCT01976104	Avatrombopag 40mg		40,000 - 50,000	58	57.9	11.1	29	77	56.9
			Placebo 40mg			33	59.2	10.3	39	81	51.5
			Avatrombopag 60mg		<40,000	70	58.6	14.2	20	86	71.4
			Placebo 60mg			43	57.3	12	27	77	62.8
L-PLUS 1	Hidaka 2018[19]	JapicCTI-132323	Lusutrombopag 3mg		<50,000	48	68.9	6.6	51	40	43.8
			Placebo			48	66.8	10.2	81	88	62.5
L-PLUS 2	Peck-Radosavljevic 2019[20]	NCT02389621	Lusutrombopag 3mg		<50,000	108	55.2	11.6	NR	NR	60.2
			Placebo			107	56.1	11	NR	NR	64.5
NR	Tateishi R. 2019[21]	JapicCTI-121944	Lusutrombopag 3mg	HCC	<50,000	16	66.8	8.1	NR	NR	56.3
			Placebo			15	70.9	8.6	NR	NR	53.3

HCC = hepatocellular carcinoma; NR = NR

5.2.3 Assessment of effectiveness

Not all studies employed precisely the same primary outcome (Table 5.7). Two studies (JapicCTI-121944, L-PLUS 1) reported that the proportion of patients who did not require platelet transfusion before the elective procedure as the primary outcome. Three studies (ADAPT-1, ADAPT-2 and L-PLUS 2) reported a composite outcome of the proportion of patients who did not require platelet transfusion or a rescue procedure for bleeding from randomisation up to seven days following the elective procedure as the primary outcome. One study (Study 202) reported the percentage of participants with an increase in platelet count ≥ 20,000/μL above baseline; and at least one platelet count >50,000/μL from days 4-8 as the primary outcome.

Despite the differences in primary outcome, both avatrombopag (for both platelet subgroups) and lusutrombopag, were clearly effective in comparison to no TPO-RA in terms of the primary outcome (Table 5.8).[18, 20] The difference between intervention and comparator for proportion of patients receiving neither platelet transfusion nor rescue therapy following procedure was generally greater for avatrombopag at any dose than lusutrombopag, the only exception being in ADAPT-2 in the <40,000/μL subgroup where the difference was lowest. However, it should be noted that the extent to which the outcomes in the two sets of trials are comparable is unclear. There appears to be a difference in terms of the timing of measurements of platelet transfusion avoided, with the JapicCTI-121944 and L-PLUS 1 studies specifying that this was prior to the elective procedure and the ADAPT-1 and L-PLUS 2 studies specifying that it was up to seven days following randomisation. Since the primary outcome is also a composite between number of platelet transfusions and number of rescue procedures for the ADAPT-1 and L-PLUS 2 studies, it is also unclear what the independent contributions of these two variables are. As shown in Table 5.9, lusutrombopag was effective in both the international study, L-PLUS 2 and the Japanese study, L-PLUS 1 in avoiding platelet transfusion.[19, 20] However, no such data were reported in the ADAPT trials and no data were reported for rescue procedure separately for either TPO-RA. However, as described in Section 5.2.5, these data were obtained by request for clarification.[54, 55]

Both avatrombopag and lusutrombopag were reported to increase the proportion of patients with increased platelet counts as shown in Table 5.10 in terms of the primary outcome for Study 202[52]. For lusutrombopag this was observed in both of the L-PLUS trials.[19, 56] It was also observed in the Japanese study in patients with HCC.[21] The ADAPT trials did not use this outcome, but avatrombopag was shown to be effective in achieving the target platelet level of 50 x 10^9 /μL.

Table 5.7: Primary outcomes by study

Trial name	Reference	Intervention	Primary outcome
L-PLUS 1	Hidaka 2018[19]	Lusutrombopag	Proportion of patients who did not require platelet transfusion prior to the primary invasive procedure
L-PLUS 2	Peck-Radosavljevic 2019[20]		Percentage of patients who did not require platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomization through 7 days after the primary elective procedure
JapicCTI-121944	Tateish R. 2019[21]		Proportion of patients who did not require platelet transfusion prior to the primary invasive procedure
Study 202	Terrault 2014[52]	Avatrombopag	Proportion of Participants with an increase in platelet count ≥ 20 x 10^9 per litre above baseline; and at least one platelet count >50 x 10^9 per litre from days 4-8
ADAPT-1, ADAPT-2	Terrault 2018[18]		Proportion of patients who did not require platelet transfusion or rescue procedure for bleeding after randomisation and up to 7 days after a scheduled procedure

Table 5.8: Proportion of patients receiving neither platelet transfusion prior to the elective procedure nor rescue therapy following procedure

Outcome	Study ID	Lower / Upper platelets (per µL)	Arm name	N	% with event	Type of effect size	Size of effect	LCI	UCI	p-value	Arm favoured
Percentage of patients who did not require a platelet transfusion or rescue procedure for bleeding after randomisation and up to 7 days after a scheduled procedure	Terrault 2018[18] - ADAPT-1	<40,000	Avatrombopag 60mg	90	65.6	% difference	42.6	27.2	58.1	<0.0001	Avatrombopag 60mg
			Placebo 60mg	48	22.9		NA				
		40,000-50,000	Avatrombopag 40mg	59	88.1		49.9	31.6	68.2	<0.0001	Avatrombopag 40mg
			Placebo 40mg	34	38.2		NA				
	Terrault 2018[18] - ADAPT-2	<40,000	Avatrombopag 60mg	70	68.6		33.7	15.8	51.6	0.0006	Avatrombopag 60mg
			Placebo 60mg	43	34.9		NA				
		40,000-50,000	Avatrombopag 40mg	58	87.9		54.6	36.5	72.7	<0.0001	Avatrombopag 40mg
			Placebo 40mg	33	33.3		NA				
Percentage of participants who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomisation through 7 days after the primary elective procedure	Peck-Radosavljevic 2019[20] - L-PLUS 2	<50,000	Lusutrombopag	108	64.8	% difference	36.7	24.9	48.5	<0.0001	Lusutrombopag
			Placebo	107	29.0		NA				

Table 5.9: Proportion of patients not receiving platelet transfusion at any time on study

Outcome	Study ID	Arm name	Time (wks)	(N)	% with event	Type of effect size	Size of effect	LCI	UCI	p-value	Arm favoured
The proportion of patients who received no platelet transfusion during the study	Hidaka 2018[19] - L-PLUS 1*	Lusutrombopag	NR	48	79.2	RR[$]	6.16	2.92	13.00	<0.0001	Lusutrombopag
		Placebo		48	12.5	NA					
Percentage of Participants Who Required no Platelet Transfusion During the Study	Peck-Radosavljevic 2019[20] - L-PLUS 2	Lusutrombopag	5	108	63	Difference	34.8	22.8	46.8	<0.0001	Lusutrombopag
		Placebo	5	107	29	NA					
The proportion of patients who received no platelet transfusion prior to RFA	Tateishi R. 2019[21] – JapicCTI-121944	Lusutrombopag 3mg	NR	16	81.2	NR					
		Placebo		15	20						
[$] Table 8, company submission, Shionogi[57]											

Table 5.10: Participants who achieved platelet count of ≥ 50,000/µL with an increase of ≥ 20,000/µL from baseline

Study ID	Arm name	Time (wks)	N	% with event	Type of effect size	Size of effect	LCI	UCI	p-value	Arm favoured

Study ID	Arm name	Time (wks)	N	% with event	Type of effect size	Size of effect	LCI	UCI	p-value	Arm favoured
Tateishi R. 2019[21]	Lusutrombopag	5	16	68.8	NR					Lusutrombopag
	Placebo	5	15	6.7	NA					
Terrault 2014[52] - Study 202	Avatrombopag 40mg	1	16	31.3	NR				0.1719	Avatrombopag 40mg
	Placebo	1	16	6.3	NA					
Hidaka 2018[19] - L-PLUS 1	Lusutrombopag	NR	48	77.1	RR	11.9	4	35.4	<0.0001	Lusutrombopag
	Placebo		48	6.3	NA					
Peck-Radosavljevic 2019[20] - L-PLUS 2	Lusutrombopag	5	108	64.8	Difference	52.5	42	62.9	<0.0001	Lusutrombopag
	Placebo	5	107	13.1	NA					

5.2.4 Safety

As shown in Table 5.11, neither avatrombopag nor lusutrombopag were unequivocally better than no TPO-RA in terms of adverse events (AEs). In particular, L-PLUS 2 showed a higher percentage of deaths with lusutrombopag (3 out of 107; 2.8%) compared to placebo (0 out of 107; 0%).[20] However, it was judged by the investigator that none of these deaths was related to treatment with lusutrombopag. Indeed, one patient who died was a protocol violation with Child-Pugh class C liver disease, which does imply a much higher mortality rate. The second patient died due to progression of hepatic cirrhosis, the third due to procedurally related vessel perforation. ADAPT -1 also showed more deaths with avatrombopag 40 mg in the 40,000 to <50,000/μL subgroup, although again the investigator deemed these deaths to be not associated with the study drug, one having suffered hepatic coma, which is due to the underlying cirrhosis. The other was stated to have died due to multi-organ system failure.[18] However, the clinical study report (CSR) revealed the individual had suffered a bleeding event: "Bleeding oesophageal varices/Oesophageal varices".(p.870)[58] On the other hand, there was only one death in this subgroup in ADAPT-2 and this was in the placebo arm.[18] There were no deaths in the <40,000/μL subgroup.

The outcome with regards to serious adverse events (SAEs) was a little more favourable towards lusutrombopag. with more SAEs reported in the placebo arm in L-PLUS 1 and equal percentages in L-PLUS 2.[19, 20] The outcome for avatrombopag was mixed; there were higher percentages of SAEs in the placebo arm, except in the 40,000 to <50,000/μL subgroup in ADAPT-1, where this was reversed.[18] Discontinuations due to AE were only reported in the <40,000/μL subgroup in ADAPT-1 for avatrombopag (2 out of 89; 2.2%) compared to placebo (0 out of 48; 0%).[18] There was no clear difference in the percentage of AEs (of any severity) between TPO-RAs vs. no TPO-RA.[18-21, 52] Specific SAEs were too rare to make any inference as to the effect of the intervention (See Appendix 4).

Table 5.11: Percentage of adverse events by main category

Main category	Study ID	Trial name	NCT/other trial number	Lower / Upper platelets (per μL)	Follow-up time point (weeks)	Arm name	No. patients with event (n)	No. patients analysed (N) or "NR"	% with event or "NR"
Any Death	Hidaka 2018[19]	L-PLUS 1	JapicCTI-132323	<50,000	NR/Unclear	Lusutrombopag	0	48	0.0
						Placebo	0	48	0.0
	Peck-Radosavljevic 2019[20]	L-PLUS 2	NCT02389621	<50,000	NR/Unclear	Lusutrombopag	3	107	2.8
						Placebo	0	107	0.0
	Tateishi R. 2019[21]	NR	JapicCTI-121944	<50,000	NR/Unclear	Lusutrombopag	0	16	0.0
						Placebo	0	15	0.0
	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	NR/Unclear	Avatrombopag 60mg	0	89	0.0
						Placebo 60mg	0	48	0.0
				40,000 - 50,000	NR/Unclear	Avatrombopag 40mg	2	58	3.5
						Placebo 40mg	0	32	0.0
		ADAPT-2	NCT01976104	<40,000	NR/Unclear	Avatrombopag 60mg	0	70	0.0
						Placebo 60mg	0	43	0.0
				40,000 - 50,000	NR/Unclear	Avatrombopag 40mg	0	57	0.0
						Placebo	1	33	3.0
	Terrault 2014[52]	Study 202	NCT00914927; E5501-G000-202	<50,000	NR/Unclear	Avatrombopag 40mg	0	16	0.0
						Placebo	0	16	0.0
Any Serious	Hidaka 2018[19]	L-PLUS 1	JapicCTI-	<50,000	NR/Unclear	Lusutrombopag	1	48	2.1

Main category	Study ID	Trial name	NCT/other trial number	Lower / Upper platelets (per µL)	Follow-up time point (weeks)	Arm name	No. patients with event (n)	No. patients analysed (N) or "NR"	% with event or "NR"
Adverse Event			132323			Placebo	4	48	8.3
	Peck-Radosavljevic 2019[20]	L-PLUS 2	NCT02389621	<50,000	NR/Unclear	Lusutrombopag	7	107	6.5
						Placebo	7	107	6.5
	Tateishi, R. 2019[21]	NR	JapicCTI-121944	<50,000	5	Lusutrombopag	1	16	6.3
						Placebo	1	15	6.7
	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	NR/Unclear	Avatrombopag 60mg	10	89	11.2
						Placebo 60mg	11	48	22.9
				40,000 - 50,000	NR/Unclear	Avatrombopag 40mg	8	58	13.8
						Placebo 40mg	1	32	3.1
		ADAPT-2	NCT01976104	<40,000	NR/Unclear	Avatrombopag 60mg	1	70	1.4
						Placebo 60mg	1	43	2.3
				40,000 - 50,000	NR/Unclear	Avatrombopag 40mg	1	57	1.8
						Placebo 40mg	1	33	3.0
Drug withdrawal / discontinuation due to AE	Peck-Radosavljevic 2019[20]	L-PLUS 2	NCT02389621	<50,000	NR/Unclear	Lusutrombopag	0	107	0.0
						Placebo	1	107	0.9
	Tateishi, R. 2019[21]	NR	JapicCTI-121944	<50,000	5	Lusutrombopag	0	16	0.0
						Placebo	0	15	0.0
	Terrault 2014[52]	Study 202	NCT00914927;	10,000-	6	Avatrombopag	0	16	0.0

Main category	Study ID	Trial name	NCT/other trial number	Lower / Upper platelets (per µL)	Follow-up time point (weeks)	Arm name	No. patients with event (n)	No. patients analysed (N) or "NR"	% with event or "NR"
			E5501-G000-202	50,000		40mg			
						Placebo	0	16	0.0
	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	NR/Unclear	Avatrombopag 60mg	2	89	2.2
						Placebo 60mg	0	48	0.0
				40,000 - 50,000	NR/Unclear	Avatrombopag 40mg	0	58	0.0
						Placebo 40mg	0	32	0.0
		ADAPT-2	NCT01976104	<40,000	NR/Unclear	Avatrombopag 60mg	0	70	0.0
						Placebo 60mg	0	43	0.0
				40,000 - 50,000	NR/Unclear	Avatrombopag 40mg	0	57	0.0
						Placebo 40mg	0	33	0.0
Any Adverse Event	Hidaka 2018[19]	L-PLUS 1	JapicCTI-132323	<50,000	NR/Unclear	Lusutrombopag	45	48	93.8
						Placebo	48	48	100.0
	Peck-Radosavljevic 2019[20]	L-PLUS 2	NCT02389621	<50,000	NR/Unclear	Lusutrombopag	51	107	47.7
						Placebo	52	107	48.6
	Tateishi, R. 2019[21]	NR	JapicCTI-121944	<50,000	5	Lusutrombopag	16	16	100.0
						Placebo	15	15	100.0
	Terrault 2014[52]	Study 202	NCT00914927; E5501-G000-202	10,000-50,000	6	Avatrombopag 40mg	11	13	81.3
						Placebo	9	12	75.0

Main category	Study ID	Trial name	NCT/other trial number	Lower / Upper platelets (per µL)	Follow-up time point (weeks)	Arm name	No. patients with event (n)	No. patients analysed (N) or "NR"	% with event or "NR"
	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	NR/Unclear	Avatrombopag 60mg	53	89	59.6
						Placebo 60mg	31	48	64.6
				40,000 - 50,000	NR/Unclear	Avatrombopag 40mg	31	58	53.4
						Placebo 40mg	18	32	56.3
		ADAPT-2	NCT01976104	<40,000	NR/Unclear	Avatrombopag 60mg	36	70	51.4
						Placebo 60mg	22	43	51.2
				40,000 - 50,000	NR/Unclear	Avatrombopag 40mg	28	57	49.1
						Placebo 40mg	15	33	45.5
NR = not reported									

5.2.5 Subgroup analyses

Because the dose of avatrombopag varies by platelet count, in order to make a comparison between avatrombopag and lusutrombopag the outcomes needed to be estimated by subgroup analysis. Therefore, the Assessment Group (AG) requested these data from Shionogi and they were provided in their response. They were first used to estimate the relative risks vs. placebo, which are summarised in Tables 5.12 to 5.15. What can be observed is that for both subgroups both avatrombopag and lusutrombopag are superior to placebo and mostly with a statistically significant difference i.e. 95% confidence intervals do not overlap the point of no difference, the only exception being for the very small Japic CTI-121944 study. This interpretation does not vary with the use of the OR scale (see Appendix 5). Study 202 wad excluded from these analyses and thus those reported in Section 5.2.6 because of the lack of collection of the necessary data, as revealed in the CSR.[59]

In addition to these outcomes, the proportions of those who required no rescue procedure given no receipt of platelets were also estimated and are shown in Tables 5.16 and 5.17. These numbers were calculated by dividing the number who had neither platelets nor recue therapy by the number who had no platelets prior to the elective procedure. They show that the lusutrombopag trials are different to ADAPT trials in the frequency of rescue therapy, regardless of treatment arm, the explanation for which is not obvious. Very few patients received rescue therapy in the lusutrombopag trials: only two patients and only in the 40,000/µl to <50,000/µl subgroup. Also, the only type of rescue other than platelets was red blood cells.[54] This contrasts with the ADAPT trials, where as few as 42.3% did not receive rescue and any of the following rescue therapy was administered:

- Platelet transfusion
- Fresh Frozen Plasma (FFP)
- Adrenalin injected at bleeding site
- Tranexamic acid
- Acidum aminomethyl benzoicum
- Aminocaproic acid
- Carbazochrome sodium
- Sulfonate hydrate
- Dicynone
- Glypressin

Regardless of the difference in the absolute risk, Table 5.16 shows that there is no statistically significant difference between lusutrombopag and placebo. However, there is a difference for avatrombopag in the <40,000/µL subgroup of ADAPT-1 and the 40,000 to <50,000/µL subgroup in ADAPT-2. This interpretation is similar with the use of the OR scale, although the OR for lusutrombopag in the <40,000/µL is not estimable and there is also a statistically significant difference for avatrombopag in both ADAPT trials in the 40,000 to <50,000/µL subgroup (see Appendix 5).

The proportion of those who received no rescue given receipt of platelets was not available to the AG.

Table 5.12: Proportion of patients receiving neither platelet transfusion prior to the elective procedure nor rescue therapy

Study	Arm	n/N[a]	% with event	RR LUSU 3mg vs. PBO (95% CI)
Subgroup with baseline platelet count <40,000/µl				
JapicCTI-121944	LUSU 3 mg	[redacted]	[redacted]	[redacted]
	PBO	[redacted]	[redacted]	
L-PLUS 1	LUSU 3 mg	[redacted]	[redacted]	[redacted]
	PBO	[redacted]	[redacted]	
L-PLUS 2	LUSU 3 mg	[redacted]	[redacted]	[redacted]
	PBO	[redacted]	[redacted]	
Subgroup with baseline platelet count 40,000/µl to <50,000/µl				
JapicCTI-121944	LUSU 3 mg	[redacted]	[redacted]	[redacted]
	PBO	[redacted]	[redacted]	
L-PLUS 1	LUSU 3 mg	[redacted]	[redacted]	[redacted]
	PBO	[redacted]	[redacted]	
L-PLUS 2	LUSU 3 mg	[redacted]	[redacted]	[redacted]
	PBO	[redacted]	[redacted]	

Source: Table 1 and Table2, Response to request for clarification from the AG, Shionogi BV[54]
Abbreviations: CI, confidence interval; LUSU, lusutrombopag; RR, relative risk; PBO, placebo.
[a]Number of patients measured at follow-up.

Table 5.13: Proportion of subjects who required no platelet transfusion prior to the primary elective procedure

Study	Arm	n/N[a]	% with event	RR LUSU 3mg vs. PBO (95% CI)
Subgroup with baseline platelet count <40,000/µl				
JapicCTI-121944	LUSU 3 mg	[redacted]	[redacted]	[redacted]
	PBO	[redacted]	[redacted]	
L-PLUS 1	LUSU 3 mg	[redacted]	[redacted]	[redacted]
	PBO	[redacted]	[redacted]	

L-PLUS 2	LUSU 3 mg	[redacted]	[redacted]	[redacted]
	PBO	[redacted]	[redacted]	
Subgroup with baseline platelet count 40,000/µl to <50,000/µl				
JapicCTI-121944	LUSU 3 mg	[redacted]	[redacted]	[redacted]
	PBO	[redacted]	[redacted]	
L-PLUS 1	LUSU 3 mg	[redacted]	[redacted]	[redacted]
	PBO	[redacted]	[redacted]	
L-PLUS 2	LUSU 3 mg	[redacted]	[redacted]	[redacted]
	PBO	[redacted]	[redacted]	

Source: Table 3 and Table 4, Response to request for clarification from the AG, Shionogi BV[54]
Abbreviations: CI, confidence interval; LUSU, lusutrombopag; RR, relative risk; PBO, placebo.
[a]Number of patients measured at follow-up.

Table 5.14 Proportion of patients receiving neither platelet transfusion prior to the elective procedure nor rescue therapy

Study	Arm	n/N	% with event	RR AVA vs. PBO (95% CI)
Subgroup with baseline platelet count <40,000/µl				
ADAPT-1	AVA 60mg	59/90	65.6%	2.86 (1.67, 4.91)
	PBO	11/48	22.9%	
ADAPT-2	AVA 60 mg	48/70	68.6	1.97 (1.27, 3.05)
	PBO	15/43	34.9%	
Subgroup with baseline platelet count 40,000/µl to <50,000/µl				
ADAPT-1	AVA 40mg	52/59	88.1%	2.31 (1.49, 3.57)
	PBO	13/34	38.2%	
ADAPT-2	AVA 40 mg	51/58	87.9%	2.64 (1.61, 4.31)
	PBO	11/33	33.3%	

Source: Terrault 2018[18]
Abbreviations: CI, confidence interval; AVA, avatrombopag; RR, relative risk; PBO, placebo.

Table 5.15:Proportion of subjects who received no platelet transfusion prior to elective procedure

Study	Arm	n/N	% with event	RR AVA vs. PBO (95% CI)
Subgroup with baseline platelet count <40,000/µl				
ADAPT-1	AVA 60mg	71/90	78.9%	1.46 (1.10, 1.93)
	PBO	26/48	54.2%	
ADAPT-2	AVA 60 mg	58/70	82.9%	1.62 (1.19, 2.21)
	PBO	22/43	51.2%	
Subgroup with baseline platelet count 40,000/µl to <50,000/µl				
ADAPT-1	AVA 40mg	55/59	93.2%	1.86 (1.32, 2.63)
	PBO	17/34	50.0%	
ADAPT-2	AVA 40 mg	55/58	94.8%	1.74 (1.27, 2.39)
	PBO	18/33	54.5%	
Source: Response to clarification[55] Abbreviations: CI, confidence interval; AVA, avatrombopag; RR, relative risk; PBO, placebo				

Table 5.16: Proportion of subjects who required no rescue therapy given no receipt of platelets

Study	Arm	n/N[a]	% with event	RR LUSU 3mg vs. PBO (95% CI)
Subgroup with baseline platelet count <40,000/µl				
JapicCTI-121944	LUSU 3 mg	[redacted]	[redacted]	[redacted]
	PBO	[redacted]	[redacted]	
L-PLUS 1	LUSU 3 mg	[redacted]	[redacted]	[redacted]
	PBO	[redacted]	[redacted]	
L-PLUS 2	LUSU 3 mg	[redacted]	[redacted]	[redacted]
	PBO	[redacted]	[redacted]	
Subgroup with baseline platelet count 40,000/µl to <50,000/µl				
JapicCTI-121944	LUSU 3 mg	[redacted]	[redacted]	[redacted]
	PBO	[redacted]	[redacted]	
L-PLUS 1	LUSU 3 mg	[redacted]	[redacted]	[redacted]
	PBO	[redacted]	[redacted]	

L-PLUS 2	LUSU 3 mg	[redacted]	[redacted]	[redacted]
	PBO	[redacted]	[redacted]	

Source: Numbers calculated by dividing number required no platelets or rescue therapy by number who required no platelets prior to the elective procedure. **Abbreviations**: CI, confidence interval; LUSU, lusutrombopag; RR, relative risk; PBO, placebo.

Table 5.17 Proportion of patients receiving no rescue therapy given no receipt of platelets

Study	Arm	n/N	% with event	RR AVA vs. PBO (95% CI)
Subgroup with baseline platelet count <40,000/µl				
ADAPT-1	AVA 60mg	59/71	83.1%	1.96 [1.24, 3.11]
	PBO	11/26	42.3%	
ADAPT-2	AVA 60 mg	48/58	82.8%	1.21 [0.89, 1.65]
	PBO	15/22	68.2%	
Subgroup with baseline platelet count 40,000/µl to <50,000/µl				
ADAPT-1	AVA 40mg	52/55	94.5%	1.24 [0.94, 1.62]
	PBO	13/17	76.5%	
ADAPT-2	AVA 40 mg	51/55	92.7%	1.52 [1.04, 2.21]
	PBO	11/18	61.1%	

Source: Numbers calculated by subtracting number required no platelets or rescue therapy from number who required no platelets prior to the elective procedure. Abbreviations: CI, confidence interval; LUSU, lusutrombopag; RR, relative risk; PBO, placebo.
Abbreviations: CI, confidence interval; AVA, avatrombopag; RR, relative risk; PBO, placebo.

5.2.6 Meta-analysis

In the absence of head-to-head clinical trials of avatrombopag and lusutrombopag, the indirect comparison approach was used to assess the relative effect of these treatment interventions. On the basis of the published trials, placebo was used as the common comparator. Since the dose of avatrombopag varies by platelet count, subgroup analyses were performed. Forest plots of each of the interventions versus placebo are presented in Appendix 5.

As shown in Tables 5.18 and 5.19, the outcome on the RR scale was a little more favourable towards lusutrombopag in both outcomes that counted platelet transfusions prior to the elective procedure. In all cases regardless of therapies required prior to the procedure and regardless of the subgroups. There was only one statistically significant difference between avatrombopag and lusutrombopag identified. This was only in a fixed effect analysis of the ratio of patients who required no platelet transfusion prior to elective procedure in the subgroup where patients' baseline platelet count was lower than 40,000/µL. It

was in favour of lusutrombopag (RR 1.93, 95% CI 1.15, 3.22). On the OR scale, there was no statistically significant difference in any subgroup, although there was a reversal in the point estimate to an advantage for avatrombopag in the 40,000/µl to <50,000/µl in terms of both outcomes.

The following results are based on pooling the study data reported in Tables 5.12 and 5.14:

Table 5.18: Indirect comparison results: number of subjects who required neither platelet transfusion nor rescue therapy

Comparison	Type of effect	RR LUSU 3mg vs. AVA 60mg/40mg (95% CI)	OR LUSU 3mg vs. AVA 60mg/40mg (95% CI)
Platelet count <40,000/µl			
LUSU 3 mg vs. AVA 60 mg	FE	1.29 (0.722, 2.31)	1.22 (0.49, 3.06)
	RE	1.63 (0.61, 4.37)	2.03 (0.37, 11.20)
Platelet count 40,000/µl to <50,000/µl			
LUSU 3 mg vs. AVA 40 mg	FE	1.02 (0.62, 1.66)	0.59 (0.21, 1.68)
	RE	1.13 (0.61, 2.11)	0.68 (0.20, 2.39)
CI, confidence interval; AVA, avatrombopag; LUSU, lusutrombopag; RR, relative risk; FE, fixed effect; RE, random effect			

The following results are based on pooling the study data reported in Tables 5.13 and 5.15:

Table 5.19: Indirect comparison results: number of subjects who required no platelet transfusion

Comparison	Type of effect	RR LUSU 3mg vs. AVA 60mg/40mg (95% CI)	OR LUSU 3mg vs. AVA 60mg/40mg (95% CI)
Platelet count <40,000/µl			
LUSU 3 mg vs. AVA 60 mg	FE	1.93 (1.15, 3.22)	1.68 (0.67, 4.20)
	RE	2.43 (0.95, 6.27)	2.77 (0.50, 15.36)
Platelet count 40,000/µl to <50,000/µl			
LUSU 3 mg vs. AVA 40 mg	FE	1.31 (0.86, 2.01)	0.53 (0.17, 1.68)
	RE	1.62 (0.63, 4.18)	0.68 (0.15, 3.12)
CI, confidence interval; AVA, avatrombopag; LUSU, lusutrombopag; RR, relative risk; FE, fixed effect; RE, random effect			

In contrast, Table 5.20 shows an advantage to avatrombopag in terms of avoidance of rescue therapy, but again this is not statistically significant, except for the fixed effect analysis in the <40,000/µl subgroup. On the OR scale, the value for the <40,000/µL subgroup was not estimable and, as for the RR scale and the other outcomes, there was an advantage for avatrombopag in the 40,000/µl to <50,000/µl.

The following results are based on pooling the study data reported in Tables 5.16 and 5.17:

Table 5.20: Indirect comparison results: number of subjects who required no rescue therapy

Comparison	Type of effect	RR LUSU 3mg vs. AVA 60mg/40mg (95% CI)	OR LUSU 3mg vs. AVA 60mg/40mg (95% CI)
Platelet count <40,000/µl			
LUSU 3 mg vs. AVA 60 mg	FE	0.71 (0.54, 0.93)	Not estimable[1]
	RE	0.67 (0.41, 1.08)	Not estimable[1]
Platelet count 40,000/µl to <50,000/µl			
LUSU 3 mg vs. AVA 40 mg	FE	0.81 (0.62, 1.05)	0.53 (0.04, 6.87)
	RE	0.81 (0.62, 1.05)	0.53 (0.04, 6.87)

CI, confidence interval; AVA, avatrombopag; LUSU, lusutrombopag; RR, relative risk; FE, fixed effect; RE, random effect
[1]See Appendix 5

5.2.6.1 Heterogeneity

There was clinical heterogeneity in terms of invasive procedure that patients were undergoing. In both of the L-PLUS trials[19, 56] patients were not restricted to the elective procedure, while in the study by Tateishi, 2019[21], only patients who were undergoing radiofrequency ablation were included. However, sensitivity analysis by exclusion of this study increased the heterogeneity in all cases. Also, there was moderate statistical heterogeneity within each subgroup regardless of the outcome e.g. for no platelet transfusion prior to the elective procedure I^2 = 53% and 34% in <40,000/µl and 40,000/µl to <50,000/µl subgroups respectively (See Appendix 5). Sensitivity analysis revealed that the removal of one of the L-PLUS studies would remove this heterogeneity and reduce the I^2 to 0%. However, the study that was required to be removed to reduce the heterogeneity depended on the subgroup. More specifically, it was the L-PLUS 1 study in the <40,000/µl subgroup, and the L-PLUS 2 study in the 40,000/µl to <50,000/µl subgroup. Most importantly, this did not make any substantial change to the results.

For no rescue therapy, there was no statistical heterogeneity in the L-PLUS trials, but there was moderate heterogeneity in the <40,000/µl subgroup. Nevertheless, given no obvious clinical difference between the ADAPT-1 and ADAPT-2 studies, the AG did not consider exclusion of either was warranted. As already discussed in Section 5.2.5, the lusutrombopag trials also appear to be quite different to the ADAPT trials in the much lower frequency of rescue therapy, regardless of treatment arm. This highlights the caution needs to be exercised in comparing avatrombopag to lusutrombopag.

6. ASSESSMENT OF COST EFFECTIVENESS

This section explores the cost effectiveness of avatrombopag and lusutrombopag for treating thrombocytopenia in people with CLD needing an elective procedure.

For this purpose, in Section 6.1, the systematic review of the existing cost effectiveness, cost/resource use and health-related quality of life (HRQoL) evidence is summarised. In Section 6.2, the summary and critique of the industry submissions to NICE on the cost effectiveness of avatrombopag and lusutrombopag are provided. Finally, in section 6.3, the AG provides its own independent economic assessment on the cost effectiveness of avatrombopag and lusutrombopag.

6.1 Systematic review of existing cost effectiveness evidence

6.1.1 Search methods

The literature searches described in Section 5.1.1 were used to identify cost effectiveness studies. Identified cost effectiveness studies were critically assessed using a published critical appraisal checklist for economic evaluations, i.e. Drummond, et al.[60]

Additional searches were conducted to identify health-related quality of life and resource use data related to thrombocytopenia. Methodological search filters designed to identify HRQoL and resource use data were combined with search terms for thrombocytopenia. The search strategies were developed using the same methods described in Section 5.1.1. Searches were not limited by language, publication status (unpublished or published) or date of publication.

Full details of the search strategies are presented in Appendix 1.

The following databases and resources were searched:

- MEDLINE (Ovid): 1946-2019/January Week 3
- MEDLINE In-Process Citations, Daily Update and Epub Ahead of Print (Ovid): January 22, 2019
- PubMed (NLM): up to 24 January 2019
- Embase (Ovid): 1974 to 2019 Week 3
- NHS Economic Evaluation Database (NHS EED) (CRD): up to 31 March 2015
- Health Technology Assessment (HTA) database (CRD): up to 31 March 2018
- Science Citation Index (SCI) (Web of Science): 1988-2019-01-23
- CINAHL (EBSCO): 1982-20190123
- LILACS (BIREME): 1982-2019/01/24
- Northern Light Life Sciences Conference Abstracts (Ovid): 2010-2019/week 02
- CEA Registry (www.cearegistry.org): up to 24 January 2019
- ScHARRHUD (https://www.scharrhud.org/): up to 24 January 2019

Grey literature was identified from searches of the following resources:

- OAIster (http://oaister.worldcat.org/): up to 23 January 2019
- OpenGrey (www.opengrey.eu/): up to 23 January 2019
- COPAC (https://copac.jisc.ac.uk/): up to 23 January 2019
- ISPOR (https://www.ispor.org/): up to 23 January 2019

- HTAi (https://htai.org/)

Supplementary searches were conducted to identify data to help populate the economic model:

- PubMed search for National Institute for Health Research (NIHR) Health Technology Assessment reports with similar economic models
- Literature searches to identify rates of procedures with bleeding risk in patients with chronic liver disease
- Literature searches to identify UK mortality data associated with platelet transfusion
- Literature searches to identify platelet transfusion refractoriness studies
- Literature searches to identify chronic liver disease/thrombocytopenia cost of illness studies

Handling of citations

Identified references were downloaded into EndNote bibliographic management software for further assessment and handling. Individual records within the EndNote library were tagged with searching information, such as searcher, date searched, database host, database searched, strategy name and iteration, theme or search question. This enabled the Information Specialist to track the origin of each individual database record, and its progress through the screening and review process.

Quality assurance within the search process

For all searches undertaken by the Kleijnen Systematic Reviews Information Team, the main Embase strategy is independently peer reviewed by a second KSR Information Specialist. Search strategy peer review was informed by items based on the CADTH checklist.[11, 12]

6.1.2 Inclusion criteria

Table 6.1 below presents an overview of inclusion criteria used for the review.

Table 6.1: Inclusion criteria for the study selection

Criteria	Inclusion
Patients	Studies including chronic liver disease adult (≥18 years) patients with thrombocytopenia, eligible for elective surgery
Interventions	No restrictions
Comparators	No restrictions
Outcomes	• Cost of illness analyses • Cost utility analyses • Cost effectiveness analyses • Cost benefit analyses • Cost minimisation analyses • Budget impact analyses and • Cost consequence analyses • For resource use/costs: any study report on the resource utilisation/costs related to thrombocytopenia in the population of interest • For HRQoL: any study reporting on the HRQoL of the population of interest
Geography	No restrictions
Language	English only
Source: Systematic literature review performed by the AG.	

6.1.3 Results

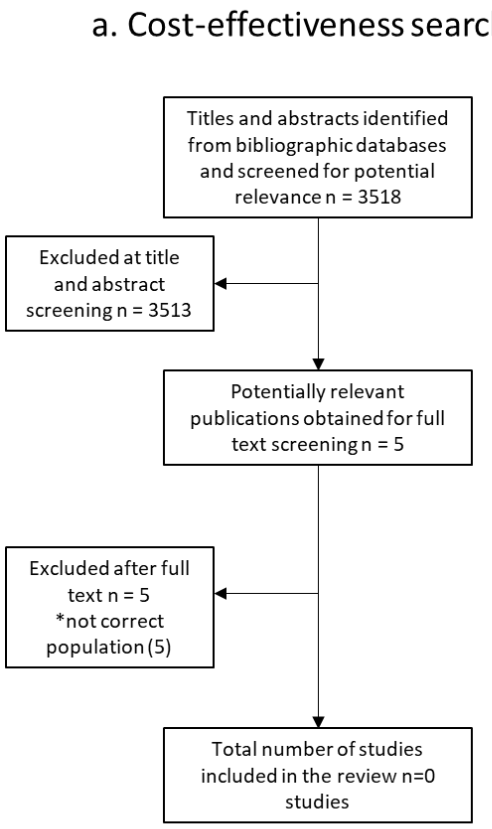
The cost effectiveness search identified 3,518 records. However, none of the identified records fulfilled the inclusion criteria. The potentially relevant studies (n=5) were economic evaluation studies in other populations (e.g. interferon-based treatment-induced thrombocytopenia of patients with hepatitis C) and they were excluded after full-text screening.

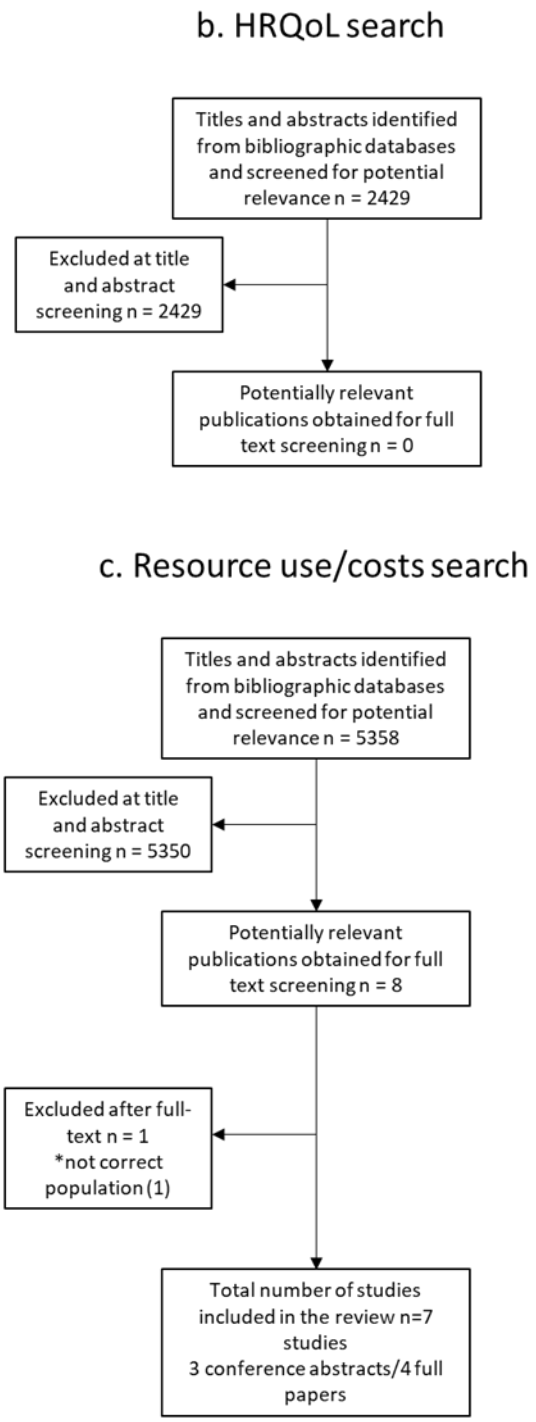
The HRQoL search identified 2,429 records. However, none of the identified records fulfilled the inclusion criteria, all these records were excluded during title/abstract screening.

The resource use/costs search identified 5,358 records, of which seven studies fulfilled the inclusion criteria. Three of these studies were only available as conference abstracts,[32, 61, 62] whereas the other four were available as full texts, which are summarised in Section 6.1.3.1.

The PRISMA diagrams below in Figure 6.1 depict the flow of the selection of the studies through the cost effectiveness, HRQoL and resource use/costs search processes.

Figure 6.1: PRISMA flowchart for cost effectiveness (a), HRQoL (b) and resource use/costs (c) searches





Source: Systematic literature review performed by the AG.

6.1.3.1 Identified resource use/costs studies

The systematic review of resource use/costs identified four full text articles[63-66] and three conference presentation abstracts,[32, 61, 62] discussing five separate studies. Two of the conference abstracts have since been published as full text publications (the Poordad 2007 abstract[61] corresponds to the Poordad 2012[63] article and Poordad 2008 abstract[62] is covered by Poordad 2011 article[64]) and therefore for these studies,

only their full text publications were discussed. For the remaining conference abstract, no full text publication was available and therefore only the content in the abstract is discussed.[67]

Barnett et al. (2018) conducted a study to estimate the cost of platelet transfusion for CLD patients with thrombocytopenia undergoing elective procedures in the US.[65] The authors developed a conceptual framework aiming to identify all direct, indirect and intangible costs of platelet transfusion. Then they estimated the costs using the developed framework and cost data from the literature. The framework included the cost of generating the supply of platelets, the transfusion itself, adverse events associated with platelet transfusion and refractoriness. The total direct cost, obtained from considering all framework categories, of platelet transfusion in CLD patients with thrombocytopenia scheduled to undergo an elective procedure was estimated to be in the range of $5,258 and $13,117 (2017 USD). The majority of costs were attributable to the transfusion itself ($3,723 - $4,436), followed by the cost of refractoriness (which included the opportunity cost of a delayed procedure and subsequent transfusions with human leukocyte antigen-matched platelets) ($874-$7,578). A potential limitation of this study is that it is literature based, drawing cost elements from different sources with different study designs. These sources were not based on CLD patients with thrombocytopenia, as the authors could not identify published sources for this population. Therefore, the estimate may not well reflect the target population if differences exist in the costs of transfusion and the rates of related adverse events and refractoriness in a CLD thrombocytopenia population in the UK. It is also noted that this study was funded by Dova Pharmaceuticals, the owner of avatrombopag.

Brown et al. (2007) published a review article discussing the pharmacoeconomic analysis of thrombocytopenia in CLD.[66] The review discussed the negative impact that thrombocytopenia and its treatment can have on costs and treatment outcomes in CLD. The impact of thrombocytopenia on patient outcomes was discussed in terms of the increased likelihood of complications during routine medical procedures as well as the cancellation, delay or prolonging of procedures which can increase morbidity and mortality. The negative patient outcomes which can arise from platelet transfusions, such as refractoriness, infection, allergic reaction, iron overload and other transfusion reactions were also outlined. The review also discussed the economic burden of costs associated with platelet transfusion and resulting adverse events which can require further treatment and increased utilisation of healthcare resources.

In a conference abstract, Poordad et al. (2018) conducted a case-control study examining the economic burden of platelet transfusion in CLD patients with thrombocytopenia.[32] A retrospective analysis was conducted in a large national US administrative claims database to examine the impact of platelet transfusion on health resource utilisation and expenditure, including hospitalisations, A&E visits and outpatient visits among CLD patients with thrombocytopenia. Data from 2012-2015 was used to match adult CLD patients with thrombocytopenia who received a platelet transfusion 1:2 based on age and gender to CLD patients with thrombocytopenia who did not receive a platelet transfusion. Of the 1,173 CLD patients with thrombocytopenia included in the analysis, CLD patients with thrombocytopenia who received a platelet transfusion had a statistically significantly higher probability of having an additional outpatient office visit (1.04; p=0.021), a non-significantly higher probability of hospitalisation (1.08; p=0.174) and a significantly lower probability of an A&E visit (0.86; p=0.001) than those who did not receive a platelet transfusion. Platelet transfusions were associated with significantly increased hospitalisation costs ($25,802; CI $11,220 - $40,660), outpatient office costs ($3,367; CI $1,082 - $5,652)

and total costs ($29,717; CI $$15,096 - $44,339) and non-significantly decreased A&E costs (-$371; CI -$1,019 - $277) compared to the costs of patients without transfusion.

In Poordad et al. 2011, the aim was to examine medical resource utilisation and healthcare costs in Hepatitis C Virus (HCV) patients with and without thrombocytopenia from a longitudinal administrative claims database using ICD-9-CM diagnosis codes.[64] The prevalence of thrombocytopenia in HCV patients identified was found to be 3.6%, while the prevalence of thrombocytopenia in the subset of patients for whom platelet count laboratory results were available was 10.8%. HCV patients diagnosed with thrombocytopenia had a greater incidence of bleeding events (27.3% vs 9.9%) and platelet transfusions (8.5% vs <1%). HCV patients diagnosed with thrombocytopenia also had a higher incidence of liver disease-related ambulatory visits (10.4% vs 4.4%; OR 2.3 p<0.001), ER visits (OR=8.6 p<0.01) and inpatient hospital stays (OR=17.7 p<0.01) during the year before and after HCV diagnosis compared to HCV patients without a thrombocytopenia diagnosis. HCV patients diagnosed with thrombocytopenia had significantly higher overall healthcare costs ($37,924 vs $12,174 p<0.001) and liver disease-related costs ($14,569 vs $4,107 p<0.001) than those without thrombocytopenia. Overall healthcare and liver disease-related costs in the subset of HCV patients with complete lab results also found significantly higher costs in HCV patients diagnosed with thrombocytopenia than those without thrombocytopenia (overall healthcare costs $25,482 vs $16,412 p<0.001; liver disease-related costs $23,608 vs $7,354 p<0.001). Where results are presented according to the two different strategies for identifying thrombocytopenia (coding identification and laboratory results) these results differ quite substantially.

Poordad et al., 2012 estimated the prevalence of thrombocytopenia and evaluated medical resource use and costs associated with thrombocytopaenia in chronic liver disease (CLD) patients.[63] A retrospective study was performed on a longitudinal administrative claims database that included 56,445 patients with an ICD-9-CM diagnosis code for CLD in the period Jan. 2001 – Dec. 2003. For patients with available laboratory results data including platelet counts (35.7%), the numbers of bleeding events or platelet transfusions were also determined. Annual prevalence of thrombocytopaenia among patients with CLD ranged from 3.3% – 4.1%. In comparison to patients without a thrombocytopaenia diagnosis, patients with a thrombocytopaenia diagnosis consist of a larger proportion of males (62.6% vs 49.4%), had more platelet count assessments (3.68 vs 2.47), more anaemia (54.2% vs 18.5%), more neutropenia (20.8% vs 1.7%), more liver cancer (5.7% vs 1.5%), more liver transplants (2.1% vs <1%), received more interferon (IFN) therapy (5.9% vs 2.0%), had more bleeding events (27.8% vs 10.0%), and received more platelet transfusions (8.1% vs <1%). Patients with a thrombocytopaenia diagnosis had 2.5 times more liver disease-related ambulatory visits, 3.9 times more liver disease-related ER visits, and 12.9 times more liver disease-related inpatient hospital stays than patients without a thrombocytopaenia diagnosis. Overall medical care costs were 3.5-fold greater in patients with a thrombocytopaenia diagnosis, with liver disease-related costs being seven-fold greater in patients with a thrombocytopaenia diagnosis than in patients without a thrombocytopaenia diagnosis. Similar results were obtained for patients with a platelet count indicating thrombocytopaenia.

In summary, the findings from the literature review that were presented above indicate that the health care costs due to thrombocytopaenia in patients with CLD are substantial. Most notably, the costs of, and associated with, platelet transfusions make a relatively large contribution to those costs. This emphasises the importance of evaluating how an alternative strategy through the (additional) use of thrombopoietin

receptor agonists (TPO-RAs) compares to platelet transfusions as the current standard treatment for thrombocytopaenia in patients with CLD.

6.2 Independent economic assessment

6.2.1 Review of the avatrombopag submission

In the company submission by Dova, no cost effectiveness analysis was presented, and no cost effectiveness model was provided by the company.[68]

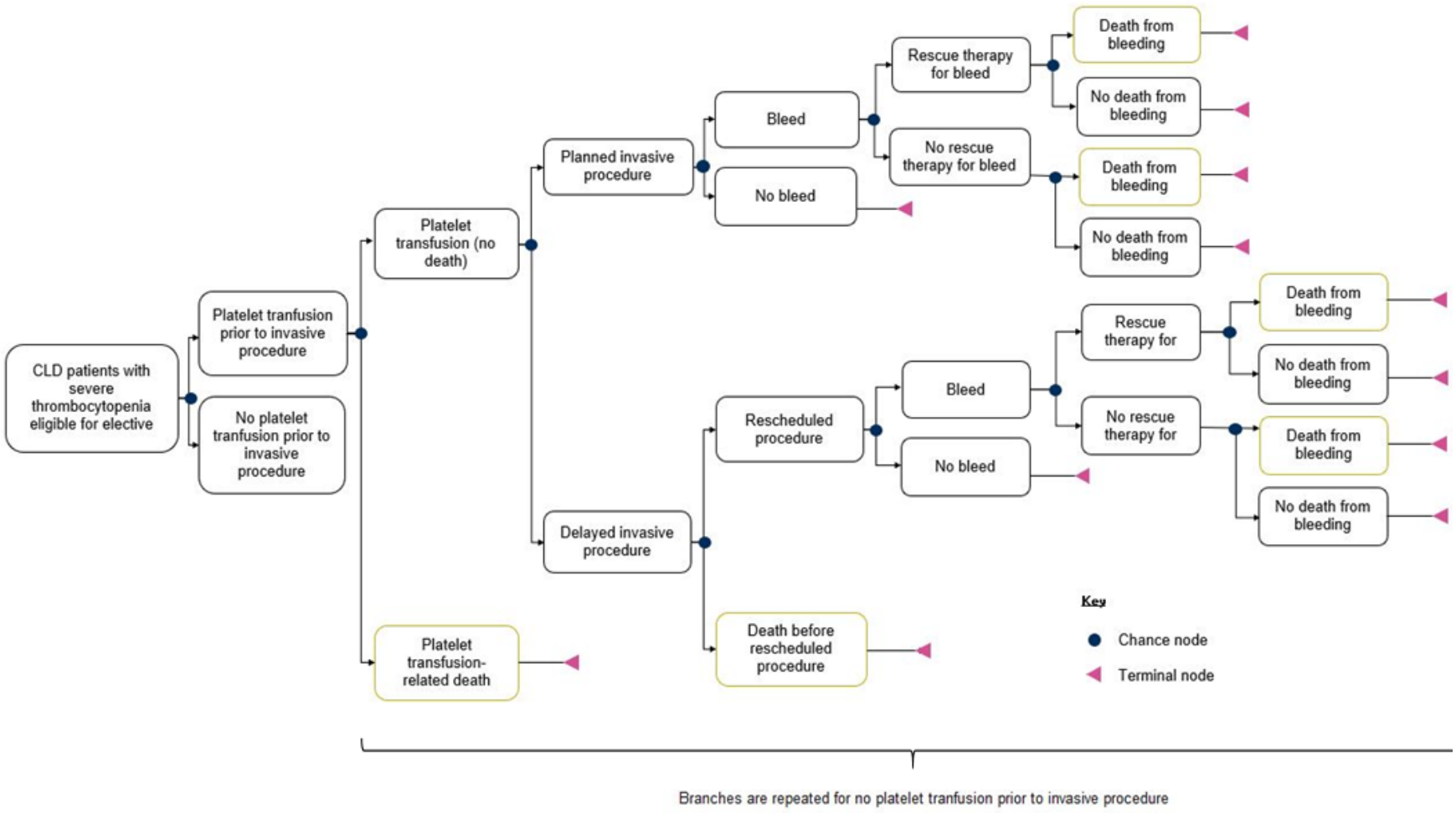
Relevant details were provided for the costs of thrombocytopaenia with references to studies that were also identified by the AG (see subsection 6.1.3.1 of this report). These include the study by Brown (2007) on increased direct and indirect costs due to thrombocytopaenia and its associated complications; the studies by Poordad et al. (2011 and 2012) on costs of HCV patients with thrombocytopaenia compared to those without, and costs of CLD patients with thrombocytopaenia compared to those without (respectively).[63, 64, 66] Subsequently, details were provided on the costs of platelet transfusions. It was argued that the costs of platelet transfusions are high due to a combination of specific storage requirements, a short shelf life, and the unpredictability of the demand for platelets that causes a high degree of wastage due to expiration issues.[69, 70] It was also noted that platelet transfusion refractoriness (i.e. the repeated failure to achieve the desired level of blood platelets in a patient following a platelet transfusion) generally occurs after multiple transfusions.[71, 72] Finally, an estimate of the costs of a platelet transfusion was provided with reference to Barnett et al., 2018, which was also identified by the AG in its literature review as outlined in subsection 6.1.3.1 of this report.[65]

6.2.2 Review of the lusutrombopag submission

The lusutrombopag submission included a model-based cost effectiveness analysis, which compared lusutrombopag (once daily at a dose of 3 mg for seven days) with no TPO-RA for CLD patients with severe thrombocytopenia (platelet count <50,000/μL), who are scheduled to undergo a planned invasive procedure. The efficacy data incorporated into the decision tree model was based on the results from the three controlled trials of lusutrombopag (L-PLUS 1, L-PLUS 2 and Phase 2b).[57] In the base-case, the company pooled the results of the three trials. In a scenario analysis the model efficacy data was based solely on the L-PLUS 2 international trial, excluding the other two studies which were both undertaken in Japan.

The model combined a short-term decision tree (see structure in Figure 6.2) considering costs and QALYs over a 35-day period (matching the trial time horizons) and a long-term Markov model, which assessed QALYs and mortality over a lifetime time horizon of 50 years. The short-term decision tree model had the following binary (i.e. yes/no) chance nodes: receiving platelet transfusion (trial data), death following platelet transfusion (literature), receiving planned invasive procedure within study period (trial data), death before rescheduled procedure (literature), bleeding following invasive procedure (trial data), rescue therapy following bleeding (trial data), death from bleeding for those not receiving rescue therapy (literature), death from bleeding for those receiving rescue therapy (literature).

Figure 6.2: Structure of the short-term decision tree from the lusutrombopag submission



Source: Shionogi CS for lusutrombopag[57]

In the short-term model, costs were attributed to any platelet transfusions, procedures and rescue therapies given, drug acquisition and administration, and AE monitoring. One-off QALY decrements were included for platelet transfusions, bleeding events, rescue therapies and AEs.

In the long-term Markov model, data from the literature regarding CLD related mortality and utility values were used to estimate the number of QALYs that would be accrued over the expected remaining life of the patient with a cycle length of one year. QALYs in the long-term model are discounted at a rate of 3.5%. No cost discounting was incorporated as costs are only included in the short-term model where discounting is inappropriate.

6.2.2.1 Efficacy summary

Efficacy inputs in the model included the following for each treatment arm:

1. Proportion of patients receiving a platelet transfusion prior to the planned invasive procedure
2. Proportion of patients experiencing bleeding events following a planned elective invasive procedure
3. Proportion of patients not receiving their planned invasive procedure during the trial period (conditional based on receipt of prior platelet transfusion)
4. Proportion of patients receiving rescue therapy following bleeding (conditional based on receipt of prior platelet transfusion and receipt of planned invasive procedure)

For efficacy inputs 1 and 2, the proportion of patients achieving each outcome in the placebo/platelet transfusion arm was taken directly from the placebo arm of the pooled lusutrombopag clinical trials (or L-PLUS 2 only in scenario analysis). For the lusutrombopag arm, ORs for lusutrombopag versus placebo were estimated from the pooled trials (or L-PLUS 2 alone as a scenario) and were applied to the placebo/platelet transfusion arm data. Inputs 3 and 4 were calculated as conditional probabilities in the base case, using individual patient level data from the pooled lusutrombopag trials. In a scenario analysis, these conditional probabilities could be turned off and replaced with unconditional inputs, calculated using ORs as seen for inputs 1 and 2.

In the base case the company assumed, contrary to evidence from the lusutrombopag trials, that 100% of patients in the placebo/platelet transfusion arm would receive a platelet transfusion prior to a planned invasive procedure due to less intensive monitoring of platelet count prior to procedures in clinical practice. This assumption was based on clinical expert opinion. In the trials, [redacted]% of placebo arm patients in the pooled trials and [redacted]% in the L-PLUS 2 trial received a platelet transfusion prior to surgery.

Mortality in the short-term model could occur due to platelet transfusion or bleeding events. The company identified two different data sources for the probability of platelet transfusion related mortality. In the base case, the company adopted values from a study by van Eerd et al. (2010), in which the base case mortality risk associated with transfusion was estimated to be 0.3315%.[73] The company also identified an alternative source of mortality data, from a study by Vamvakas et al. (2009), that estimated an incidence of transfusion related death of 0.0004% from UK Serious Hazards of Transfusion (SHOT) data.[74]

In the base case, bleeding related mortality was taken from a study by Takaki et al. (2012), which estimated the incidence of death due to either major or minor bleeding following radiofrequency ablation

(RFA) to be 0.83%.[75] Two alternative sources of estimates for bleeding related mortality were included in the model. Lo et al (2009) estimated a mortality rate of 6% due to upper gastrointestinal haemorrhage and oesophageal variceal bleeds (assumed to be a major bleed) and Triantos (2014)[76] estimated a 20% mortality rate due to acute variceal bleeding (assumed major bleed).[77]

CLD related mortality was incorporated into the long-term model in order to estimate lifetime QALYs for those patients surviving the short-term model. In the base case model, data were used from a systematic review by D'Amico et al. (2006), with one-year survival estimated at 84%.[78]

The model included AEs relating to the treatment and to platelet transfusion. Severe adverse events which were possibly or probably related to the drug were included in the model. Thrombus-related AEs are particularly relevant to TPO-RAs, therefore any severe thrombus-related events, in any of the three lusutrombopag trials (3 mg dose) were included in the model. In the CS, the company state that comprehensive data for all platelet transfusion-specific AEs were not available. Therefore data for platelet transfusion AEs was taken from the van Eerd et al. (2010) study, which reports the incidence of AEs per unit of fresh frozen plasma transfused.[73]

6.2.2.2 HRQoL summary

HRQoL data were not collected in the trials. The base-case adopts a baseline utility value of 0.544 in both treatment groups, estimated for patients with CLD/cirrhosis. This utility value is from a study by Sullivan et al. (2011)[79], that provides EQ-5D index scores for a wide variety of chronic conditions based on UK community preferences (using US-based panel survey data). One-off disutilities were included in the model for platelet transfusions, bleeding events, rescue therapy and AEs. In the base case, a disutility of 0.1 for patients experiencing serious platelet transfusion related AEs was applied for 1 model cycle (four weeks). This value was taken from TA293, a previous NICE appraisal of eltrombopag for thrombocytopenia purpura.[80] In the base-case, the company assumed the same disutility for rescue therapy as for platelet transfusion, stating that clinical experts advised that platelet transfusion would be most common in clinical practice.

6.2.2.3 Utilities summary

Disutilities for bleeds were also identified from the literature. The literature provides separate disutilities for bleeds classified as major and minor. The company assumed that all bleeds were major, stating that no studies were identified reporting the proportion of bleeds classified as major or minor following a planned invasive procedure in this population and that minor bleeds would be expected to have a minor impact on costs and QALYs. Therefore a disutility associated with a major bleeding event of 0.397 for a duration of 1 week was adopted from Jugrin et al. (2015).[81] For thrombus-related AEs the company incorporate a disutility of 0.029, applied over one week, estimated by Jugrin et al (2015) for related thrombotic events (index deep vein thrombosis and index pulmonary embolism).

The baseline utility value for CLD/cirrhosis patients adopted in the short-term model was also used to calculate QALYs throughout the long-term model. Utility values were adjusted to incorporate the natural decline in utility observed with ageing using the Ara and Brazier (2010) equation to generate utility multipliers by age and sex.[82]

6.2.2.4 Costs summary

The drug acquisition cost of £800 for seven days of 3 mg lusutrombopag was included in the model. As it is an oral medication no administration costs were required. The base-case cost of platelet transfusion was based on the TA293 appraisal of eltrombopag.[80] In the eltrombopag appraisal this was assumed to comprise of a cost of blood transfusion (weighted average cost of £57.72 in 2011/2012, code 821 blood transfusion) and the cost of two units of platelets (2 x £230.393 in 2011/2012), which resulted in a cost per transfusion of £517.28 in 2011/2012. The company used expert opinion to inform the average number of units of platelets that would be received per transfusion. The expert stated that most often platelet transfusions would contain either two or four units and therefore, it was assumed that an average of three units of platelets would be received per transfusion. This resulted in a base-case cost of £812.61 (inflated to 2017/2018), which included both administration and platelet acquisition. Two alternative costs of platelet transfusion were included in the model. One alternative was based on the NHS Reference Cost for Single Plasma Exchange or Other Intravenous Blood Transfusion.[83] Here it was assumed that a single transfusion was sufficient to transfuse the required number of units of platelets, which resulted in a cost per transfusion of £517.28. The final option was based on a poster by Varney et al. (2003), which estimated the cost per unit of adult platelet concentrate to be £347 in 2002/2003, resulting in a cost per transfusion of £1,493.21 (inflated to 2017/2018).[84]

Costs associated with treating transfusion related complications were based on costs of fresh frozen plasma transfusion complications, reported in van Eerd et al. (2010).[73] The cost of managing portal vein thrombosis in lusutrombopag patients was assumed to be £958.95, based on the NHS reference cost for Percutaneous Transluminal, Embolectomy or Thrombolysis, of Blood Vessel, with CC Score 0-4 in a day case setting.[83] The same cost as one platelet transfusion was assumed for all rescue therapies.

All patients in both treatment arms are assumed to receive a planned invasive procedure and incur the relevant costs. While the short-term model allowed for the possibility of delaying the procedure outside the 35 cycle, all patients were assumed to receive their procedure at some point. Base-case procedural costs were estimated using the pooled proportion of patients receiving each procedure in the three trials and the relevant NHS reference costs (2017-18) in the elective inpatient setting.[83] In the base-case, the company included a sunk cost for cancelled/delayed procedures, assuming that there may not be enough time to reallocate a pre-assigned clinician or hospital bed to another patient procedure, wasting clinician time. A sunk cost of £566.05 was included from the NHS reference costs 2009-10.[83] This cost was subsequently removed from the NHS reference costs, suggesting it was no longer considered appropriate practice to cost this.

Critique

The AG generally agreed with the model structure and input values included. However, the AG considered that the model had the following limitations:

- The model does not consider subgroups in terms of thrombocytopaenia (either a baseline platelet count <40,000/μL, or 40,000 to <50,000/μL), which is relevant given that avatrombopag uses different dosages for these two subgroups.
- The model does not incorporate other available drugs i.e. avatrombopag.

- The AG could not trace back the numbers from the CSRs, to understand where the probabilities for bleeding, conditional probability of surgery rescheduling and conditional probabilities of receiving rescue therapy are derived from.
- Considering the lack of a clear definition of the bleeding events used in the Shionogi economic model, as well as the extremely low numbers, and lack of difference between WHO grade 2 bleeding rates between two groups from L-PLUS data (Appendix C.5.3 of the Shionogi submission), the AG is doubtful about using these conditional probabilities and also doubtful about incorporating bleeding and rescue events as separate chance nodes to the decision tree.
- The company assumed 100% of the placebo arm would receive a platelet transfusion prior to the planned invasive procedure in the base case. This is contrary to the evidence from the trials that indicates that in L-PLUS 1, L-PLUS 2 and the JapicCTI-121944 trial, respectively [redacted] and [redacted] of placebo patients did not require platelet transfusion prior to the planned invasive procedure (see Table 5.9).
- The model considers that the only mortality due to a surgery is the bleeding associated mortality, whereas there are other causes of death (such as infection etc.).
- Platelet transfusion related mortality can also occur after the surgery.
- Two potential values were identified from the literature for platelet transfusion related mortality. Neither study was specific to CLD patients or patients with thrombocytopenia. Also, neither study actually estimated the mortality associated to platelet transfusion, with one investigating fresh frozen plasma transfusion and the other whole blood transfusion. These studies resulted in substantially different estimates of transfusion related mortality of 0.33% and 0.0004%. The choice to go with the higher value was justified as recommended by expert opinion.
- It is unclear why data regarding AEs experienced due to platelet transfusion from within the trials were not available to the company. AEs would have had to have been noted and monitored and therefore data should have been available. Again, by using the van Eerd et al. (2010) study as a source for input values, the model uses values not specific to the population or to platelet transfusion.[73]
- By assuming that all bleeds were major, the company may be overestimating the utility loss resulting from bleeding events. The AG does not consider stating that minor bleeds would be expected to have a minor impact on costs and QALYs a sufficient justification for assuming all bleeds to be major.
- The company assumed an average of three units of platelets per transfusion. Data were not provided by the company on the average number of units used per transfusion in the lusutrombopag trials. The company clarified in their clarification response that there is a lack of standardisation across countries (and potentially even centres) regarding the size of a "unit" in terms of "what volume of platelets this equates to or how this relates to definitions of units in UK clinical practice".[54] Therefore, while information on the number of units of platelets transfused was collected, the variation in reporting led the company to question the reliability of the data and its relevance to UK definitions and practice. They therefore used expert opinion and the median number of units per transfusion from the eltrombopag ELEVATE trial, both of which resulted in expectations of an average of 3 units of platelets per platelet transfusion.[54] The AG understand this issue of variation in the definition of "units" of platelets, which was further supported through contact with their own clinical expert. In response to clarification questions, both companies provided additional information on the number of units of platelets transfused per

platelet transfusion.[54, 55] However, only the data provided by Shionogi came with accompanying information on the content of a unit by providing the mean number of platelets per platelet transfusion. For the data provided by Dova, it was not clear to which number of platelets a unit would correspond. Therefore, only the data from Shionogi on the mean number of platelets per platelet transfusion could be translated into a mean number of ATDs, and were used for the calculation of the costs of a platelet transfusion.

- The company included a sunk cost for delayed planned elective inpatient procedures (PEIPs). It is considered unlikely that in the case of a procedure delay, a clinician could not find another useful way to fill this time. The fact that this cost was removed from the NHS reference costs almost 10 years ago suggests that this is no longer considered an appropriate cost.

6.3 Independent economic assessment

The AG decided to adapt the model submitted by Shionogi, due to the limitations discussed in 6.2.

6.3.1 Methods

6.3.1.1 Patient population

The patient population considered is CLD patients with severe thrombocytopenia (platelet count <50,000/µL) who are scheduled to undergo a planned invasive procedure.

The patient population is divided into two subgroups:

- Patients with platelet count < 40,000/µL
- Patients with platelet count 40,000/µL to < 50,000/µL

This immediate division of the population into platelet count subgroups is necessitated by the fact that different avatrombopag doses are given to these subgroups, as described below. Therefore, it is not possible to conduct a direct comparison between lusutrombopag and avatrombopag without this subgroup separation.

6.3.1.2 Interventions

Lusutrombopag is administered orally, once daily at a dose of 3 mg for up to seven days, starting the first administration a minimum of nine days prior to the scheduled procedure.[8]

Avatrombopag for patients with a platelet count < 40,000/µL is administered orally, once daily at a dose of 60 mg (three tablets of 20 mg), with the first dose administered 10 to 13 days prior to the scheduled procedure, and continuing for five days (i.e. procedure is scheduled five to eight days after the last dose). For patients with a platelet count of 40,000/µL to < 50,000/µL the administration and timing thereof is the same, but the dose is reduced to 40 mg (two tablets of 20 mg).

Standard of care entails that patients are given a platelet transfusion if platelet counts fail to reach ≥ 50,000/µL on the day of the scheduled procedure.

6.3.1.3 Model structure

The AG model is based on the structure submitted by Shionogi for lusutrombopag. Similar to that model, the AG model combines a short-term decision tree considering costs and QALYs over a 35-day period (matching the time horizon of all trials, as shown in Table 5.3), during which severely thrombocytopenic

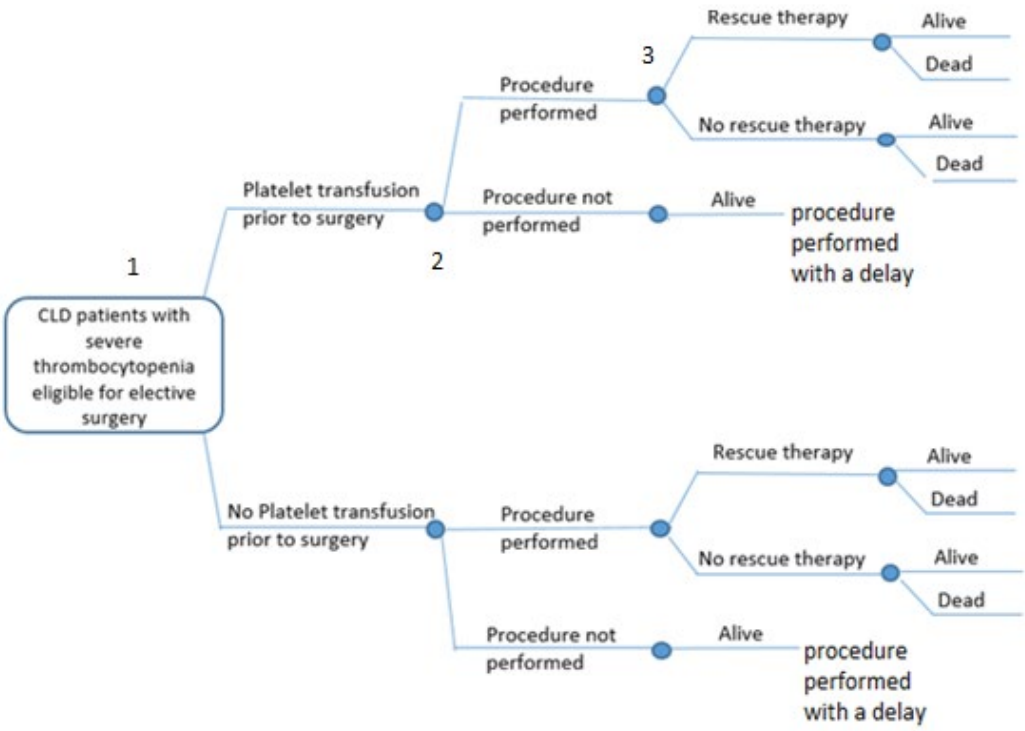
CLD patients are scheduled to undergo a planned elective invasive procedure (PEIP). Those patients alive at the end of the short-term model enter the long-term Markov model, which assesses QALYs and mortality over a lifetime time horizon of 50 years. The AG short-term decision tree model has the following chance nodes:

- Receiving/not receiving platelet transfusion (taken from avatrombopag and lusutrombopag trials)
- Receiving/not receiving the planned invasive procedure within the 35-day study period
- Rescue therapy/no rescue therapy (taken from avatrombopag and lusutrombopag trials)
- Death/no death due to platelet transfusion, surgery or rescue therapy (taken from the literature)

The structure of the AG short term decision tree model, shown in Figure 6.3, differs in several ways from the original Shionogi model discussed in Section 6.2.2 of this report. In the Shionogi model, a chance node for death due to platelet transfusion was placed directly after the receipt of transfusion, prior to the chance node for undergoing PEIP. In the AG model, mortality due to platelet transfusion prior to PEIP and mortality due to surgical complications were both considered after the chance nodes for undergoing surgery and requiring rescue therapy.

The Shionogi model also allowed for the probability of delays to scheduled procedures, and modelled the potential impact of delays on quality of life, mortality and the additional costs that may be incurred as a result of such delays. Additional costs due to surgery delays included the potential to carry out an additional platelet transfusion, as well as sunk costs resulting from last minute delays leading to wasted surgeon and surgical theatre time. The AG did not feel that the inclusion of a sunk cost was necessary, as surgical slots would usually be filled by other procedures and surgeons could effectively fill their time with other tasks. Also, the fact that Shionogi identified a sunk cost unit cost from the NHS reference costs from 2009/10, but note that it was subsequently removed from the reference costs, suggests that this is no longer considered an appropriate cost to include in a model. The Shionogi model also contained a chance node for death due to surgery delay. However, this was assumed to carry a probability of 0 in the base-case and was removed by the AG.

Figure 6.3: Structure of the short-term decision tree model



Source: Assessment Group model

The Shionogi model structure contained a separate chance node for bleeding events and a subsequent chance node for the requirement of rescue therapy. However, the AG had concerns regarding this structure and the data it was based on. The AG was unable to trace back the numbers used to calculate bleeding event efficacy to the lusutrombopag trials' CSRs.[85-87] On clarification request, the company provided data for the number of bleeding events in each trial and treatment group.[54, 55] However, these numbers did not suggest that lusutrombopag substantially reduced the odds of bleeding, as it was implemented in the original Shionogi submission model. In addition, these conditional probabilities were not available for avatrombopag. The small number of WHO grade 2 bleeding events and the rescue events seen in the trials led to concerns surrounding the confidence that can be placed in conditional probabilities based on such data. As such, the AG felt that bleeding events were better modelled as a surgical complication rather than a separate event. Therefore, bleeding events, and their impact on the mortality and quality of life of patients were modelled as a surgical related AE and source of mortality. The chance node for requiring rescue therapy was retained.

The long-term Markov model presented by Shionogi was utilised without changes in the AG model. In the long-term model, data from the literature regarding CLD related mortality and utility values were used to estimate the number of QALYs that would accrue over the expected remaining life of the patient with a cycle length of one year. QALYs, in the long-term model, are discounted at a rate of 3.5%. No cost

discounting was incorporated as costs are only included in the short-term model where discounting is inappropriate.

6.3.1.4 AG Input parameters

Baseline characteristics

Pooled baseline characteristics were calculated by the AG from the three included lusutrombopag trials (L-PLUS 1, L-PLUS 2, and the Phase 2b trial) and two avatrombopag trials (ADAPT-1 and ADAPT-2). The overall average of each baseline characteristic was obtained from reported trial-specific means, weighted proportional to the trial population size. These baseline characteristics, including age, gender and Child-Pugh category are outlined below in Table 6.2.

Table 6.2: Pooled baseline characteristics

	Age		**Gender**	**Child-Pugh category**		
	Mean	SD	Male	A	B	C
Pooled	58.6	10.8	62.7%	57.5%	38.9%	3.6%
Source: Calculations performed by the AG based on patients from all trials pooled. Abbreviation: SD = standard deviation.						

Based on the characteristics of patients in all trials pooled, patients were of mean age 85.6 years (SD: 10.8 years), 62.7% of the patients were male, and patients were categorised as Child-Pugh A, B, or C in proportions of 57.5%, 38.9%, and 3.6%, respectively.

Efficacy

As lusutrombopag and avatrombopag were not directly compared in a head-to-head trial, indirect comparisons had to be made. This was possible since both were compared to placebo. Methods utilised for the data synthesis of the efficacy outcomes of interest for the short-term model are described in Section 5.1.5 of this report and the results provided in Section 5.2.6.

From evidence submitted in the response to the clarification letters of each company, the AG had data on the number of patients in each treatment arm and platelet count subgroup who:

- Did not require platelet transfusion prior to invasive procedure
- Did not require rescue therapy given there was no platelet transfusion prior to invasive procedure

From these data, for each outcome, an indirect treatment comparison was performed using Bayesian meta-analysis methods to obtain estimates for the proportions/probabilities of each of the above outcomes. First, the proportions for the placebo group (all trials pooled) were obtained for each platelet count subgroup in a separate Bayesian meta-analysis. These values were used to inform the baseline probabilities for the natural history, i.e. for no TPO-RA. They were also combined in a Bayesian evidence synthesis model with odds ratios estimated using a logit function in order to calculate the corresponding probabilities for avatrombopag and lusutrombopag. Such a Bayesian model, due to the Monte-Carlo-Markov-Chain framework of the statistical software, ensures that the generated probabilities for each of the TPO-RAs remain between 0 and 1 without additional programming, which cannot be guaranteed, if an odds ratio was estimated using the frequentist statistical method reported in Section 5.2.6 and applied to

the baseline probability. Also, as shown in Table 5.20, odds ratios are not estimable for proportion who required no rescue therapy for the <40,000/µl subgroup. Both fixed effect and random effects models were run in all cases. Random effects models were used in the base case, due to the better statistical fit.[1] The suggestions for numerical stability in the presence of the zero cells, as outlined in NICE Technical Support Document 2 (Section 6.3), were followed.[88] The WinBUGS code used in the Bayesian fixed-effect and random-effects analyses are provided in Appendix 6. It should be noted that the base case Bayesian model odds ratios were very similar to those in Table 5.19 and 5.20, apart from the one that was not estimable.

The first chance node in the model requires the probability or proportion of patients in each group who require platelet transfusion prior to PEIP. In the base-case, the proportion of patients in each treatment arm (for each subgroup) not requiring platelet transfusion prior to PEIP was estimated from the posterior distribution parameter estimates of the Bayesian meta-analysis, derived from the baseline placebo proportions and the ORs obtained from the random effects model, using the number of patients that received platelet transfusion before PEIP as provided in Tables 5.13 and 5.15. These proportions were then subtracted from 1 to find the proportion of patients in each treatment arm who *do not* require platelet transfusion prior to PEIP.

For the second chance node, data on the proportion of PEIPs not performed within the trial period was provided in Table 11-3 of the L-PLUS 2 CSR, which stated that [redacted] and [redacted] of lusutrombopag and placebo patients respectively did not receive their planned procedure within the trial period.[87] This was the only trial that provided these data. Therefore, the lusutrombopag value of [redacted] was also assumed for avatrombopag, and the same values were assumed for both platelet count subgroups. Patients were assumed to go on to receive their procedure at some point in the near future. Therefore, these patients were assumed to be at risk of receiving an additional platelet transfusion just before their postponed procedure, and also, they were assumed to be at risk of requiring rescue therapy and death during the postponed procedure. These risks for the additional platelet transfusion before the postponed procedure were assumed to be identical to the risks of placebo patients whose procedures were not postponed. Although these postponed procedures do not necessarily occur in the first cycle, the costs and impacts on mortality and quality of life were assigned in the first cycle for simplicity.

Table 6.3: Overview of input parameters for clinical efficacy

	Mean (95% CI)	**Mean (95% CI)**	**Mean (95% CI)**	**Mean (95% CI)**	**Mean (95% CI)**	**Mean (95% CI)**	**Source**
Treatment	No TPO-RA		Avatrombopag		Lusutrombopag		
Platelet count subgroup	<40 x10^9/L	40 to < 50 x10^9/L	<40 x10^9/L	40 to < 50 x10^9/L	<40 x10^9/L	40 to < 50 x10^9/L	

[1] While assessing the statistical fit of a model, the global deviance information criteria statistics and the posterior mean residual deviance statistics are consulted. It is assumed that the model with lower values for these statistics provided a better fit.

Proportion requiring platelet transfusion prior to surgery (RE)**	0.699 (0.302, 0.945)	0.615 (0.347, 0.837)	0.439 (0.023, 0.957)	0.114 (0.022, 0.320)	0.242 (0.007, 0.801)	0.164 (0.039, 0.400)	ITC
Proportion requiring platelet transfusion prior to surgery (FE)**	0.700 (0.301, 0.945)	0.615 (0.348, 0.837)	0.431 (0.095, 0.831)	0.115 (0.023, 0.309)	0.297 (0.048, 0.717)	0.171 (0.044, 0.406)	ITC
Proportion requiring platelet transfusion prior to surgery (International trials only)* **	0.700 (0.299, 0.944)	0.615 (0.348, 0.837)	0.438 (0.019,0.964)	0.114 (0.022, 0.317)	0.406 (0.004, 0.987)	0.300 (0.069, 0.631)	ITC
Proportion procedure not performed	[redacted]		[redacted]				L-PLUS 2
Proportion requiring rescue procedure (RE) **	0.181 (0.002, 0.817)	0.184 (0.010, 0.664)	0.077 (0.0004,0.531)	0.044 (0.001, 0.252)	0.097 (0.0002, 0.711)	0.103 (0.0006, 0.629)	ITC
Proportion requiring rescue procedure (FE) **	0.180 (0.812, 0.002)	0.183 (0.655, 0.010)	0.075 (0.522, 0.0004)	0.044 (0.250, 0.001)	0.104 (0.738, 0.0002)	0.104 (0.633, 0.0008)	ITC

* Due to the low number of events, the proportion of patients requiring rescue procedure (given no platelet transfusion) cannot be estimated using only the international trials.

** Discrepancies between the values seen in this table and in the model are due to differences in the number of iterations used to calculate the values. The values presented in the table were obtained from the WINBUGS output summary from 100,000 iterations (after a burn-in of 30,000 iterations). In the excel model we use 2,000 iterations from the WINBUGS to provide values for the PSA of the model

Source: Indirect treatment comparisons performed by the AG (where applicable, data as provided otherwise) using data provided by the company in the original CS, as well as in response to clarification questions. Abbreviations: CI = credible interval; FE = Fixed effects; RE = Random Effects; ITC = Indirect treatment comparison.

Platelet transfusion

There is substantial uncertainty surrounding the mean number of units of platelets transfused in each platelet transfusion received by patients in the trials. This uncertainty is in large part caused by a lack of standardisation in terminology and definitions used across countries and centres, regarding the size of a "unit" in terms of what number of platelets this equates to. When data on the number of units of platelets transfused per platelet transfusion was requested from Shionogi, they clarified that while this data was collected, it became clear when it came to analysis that different definitions and terms were being used in different trial centres and there was no way to standardise this or to understand how these varying definitions related to UK clinical practice and UK unit costs.[54] Therefore, the company felt they had no better solution than to use expert clinical opinion. The experts approached by Shionogi stated that patients would receive either two or four units and therefore an average of three units per transfusion was assumed.[57] This assumption was used in the estimation of the safety and cost of platelet transfusion, with platelet transfusion AE incidences and unit costs multiplied by three in both cases. Given the importance of the cost of platelet transfusion in the model, the AG sought to validate this assumption of three units further.

First, the AG consulted their own clinical expert.[89] When asked how many units of platelets he would expect to be used per platelet transfusion, the clinician stated that he was unfamiliar with the definition/term "unit" in the context of platelets, as in his experience they were referred to as "pools" of platelets. He was not aware of the volume of platelets contained in a pool, but stated that one pool was usually sufficient to increase platelet levels by the required amount. This increased the concern within the AG surrounding the lack of a consistent definition for the volume of platelets usually transfused in a platelet transfusion.

The AG then turned to the literature to investigate UK platelet transfusion practice. The Handbook of Transfusion Medicine, produced in conjunction with the Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC) and NHS Blood and transplant, provided some useful information relating to UK practice.[90] This publication referred to an adult therapeutic dose (ATD) of platelets, stating this could either include a pool of four units of platelets derived from whole blood or a single-donor apheresis unit. The handbook also noted that the UK Blood Services aim to provide more than 80% of platelet doses by apheresis, to reduce the exposure of patients to multiple donors (a vCJD risk-reduction measure). Therefore, the AG assumed platelets would be obtained through apheresis in UK practice.

An ATD was described as containing >240,000/μL platelets per transfusion, while the mean number of platelets contained within a unit of apheresis platelets was 280,000/μL (range 165–510).[90] While Shionogi had been unable to supply data on the mean number of units of platelets transfused per platelet transfusion, they were able to supply estimates of the mean number of platelets (i.e. platelet content per transfusion) transfused across the lusutrombopag trials for each treatment group and platelet subgroup both prior to surgery and as a rescue therapy. These estimates of mean number of platelets per transfusion ranged from [redacted]/μL.[54] This suggests an estimate of [redacted] ATDs per transfusion. The NICE Blood Transfusion guideline states that clinicians should not routinely transfuse more than a single dose of platelets per transfusion, suggesting one ATD may be sufficient per transfusion.[91]

Dova did provide data on the mean number of units transfused per platelet transfusion for each platelet subgroup and treatment group prior to PEIP in the ADAPT trials. However, these means, ranging from 3.9 to 7.5 did not correspond well to the abovementioned expectations of UK clinical practice definitions and no information was provided on the assumed platelet content within a unit. Therefore, these data were not used in the calculation of the costs of a platelet transfusion.

Therefore, in the calculation of the mean number of ATDs included in each platelet transfusion prior to surgery the AG utilised the data provided by Shionogi, detailing the mean volume of platelets transfused per transfusion, divided by the mean number of platelets contained within a unit of apheresis platelets was 280,000/μL obtained from the Handbook of Transfusion Methods.[54, 90] This provided an estimate of the number of ATDs per transfusion (as the handbook also stated that an ATD was equivalent to a single-donor apheresis unit). This calculation resulted in mean numbers of ATDs for lusutrombopag and no TPO-RA patients in each platelet count subgroup, both prior to surgery and as a rescue therapy as shown in Table 6.4. No clear pattern was seen in these data to suggest to the AG that the content of platelet transfusions varied substantially according to treatment group, subgroup or reason for transfusion. Therefore, the AG assumed a pooled estimate of [redacted] ATDs per transfusion across all transfusions given in the model. This figure corresponds well with recommendations from clinical expert opinion and the NICE blood transfusion guideline, that a single ATD should be sufficient per platelet transfusion.[91] This assumed number of ATDs per transfusion will be tested in scenario analysis.

Table 6.4: Estimated number of ATDs per platelet transfusion

Number of ATDs per transfusion	**Platelet count subgroup**		
	<40,000	40-50,000	Both subgroups
Prior to PEIP	[redacted]	[redacted]	[redacted]
Rescue Therapy	[redacted]	[redacted]	[redacted]
Overall	[redacted]	[redacted]	[redacted]

Source: Calculations performed by the AG, based on data provided by Shionogi in response to clarification questions.
Abbreviations: ATD = Adult therapeutic dose; PEIP = planned invasive elective procedure

Mortality

The short-term AG model includes sources of mortality due to:

- Platelet transfusion prior to the surgery
- Surgery
- Rescue therapy

In the paragraphs below, more detail is provided for each of these sources of mortality, respectively.

In the Shionogi submission, the probability of death due to platelet transfusion was based on the Vamvakas et al (2009) study.[74] This study estimated the number of deaths due to allogenic blood transfusions using the 'Serious Hazards of Transfusion' (SHOT) data from 1996-2004. There were 167 transfusion-related deaths during this period, resulting in an incidence of 0.00035%.[74] The alternative value for platelet transfusion related mortality provided in the Shionogi submission of 0.3315%, was obtained from a study by van Eerd et al. (2010),[73] which in turn cites the incidence of complications due to fresh frozen plasma transfusion and associated mortality in critically ill patients on an ICU.[92] This

value was considered inappropriate by the AG as it is approximately 1,000 times higher than the value obtained by the SHOT data. The AG feel this high estimate was likely due to the critical health status of participants in the Gajic study (all admitted to an ICU), which does not match this trial population and would likely overestimate the mortality in our population.

The AG decided to use neither of these mortality rates, the latter being unrealistically high for the current population, and the first being outdated. The Vamvakas et al (2009) study used SHOT data from 1996 to 2004, so the AG decided to also use SHOT data but from 2012-2017 instead (see Table 6.5 below).[93-97] As a first step the probability of an early transfusion reaction was determined (the transfusion transmitted infections, which manifest later, do not lead to mortality). FAHR (Febrile, Allergic, Hypotensive Reactions) and pulmonary complications (TRALI, TACO, TAD) were selected as relevant. Probabilities were obtained in the following steps:

1. Number of reactions per year from 2012 to 2017 were taken and added up. They were split up in FAHR and Pulmonary (TRALI, TACO and TAD). FAHR were reported for platelets specifically, unspecified reactions were not included. Pulmonary reactions were reported over all components issued.

2. Overall numbers were divided by total number of platelet units issued (FAHR) or total number of blood components issued (pulmonary) to get the probability of the reaction per component issued.

3. These probabilities were divided by the average survey participation to correct for it.

The resulting probability of FAHR was 0.0288% and for pulmonary reactions 0.00395% per transfusion. The probability of death from a transfusion reaction was estimated using the number of deaths reported in the early transfusion reactions by SHOT UK. FAHR has had no mortality over 2012-2017 so mortality was based on deaths from pulmonary complications. The probability of dying from an early transfusion reaction was estimated using the following steps:

1. Take the number of deaths from pulmonary reactions over 2012-2017 and divide it by the total number of pulmonary reactions to get mortality rate from pulmonary reactions.

2. Calculate the proportion of pulmonary reactions in early transfusion reactions and multiply with the mortality rate from pulmonary reactions to get the probability for death from an early transfusion reaction.

This yielded a mortality probability, given a transfusion reaction, of 1.4%. By combining this with the probability of a transfusion reaction, we find an overall mortality due to platelet transfusion of 0.0004592% (see Table 6.5).

There have been arguments in the literature that hemovigilance systems under report transfusion related morbidity and mortality.[98] Therefore in scenario analyses underreporting factors were included for transfusion related mortality to adjust the base-case estimate of 0.0004592%

Since rescue therapies given in the trials often took the form of additional platelet transfusions, the estimate of platelet transfusion related mortality was also applied to those receiving rescue therapy. The mortality associated with platelet transfusion is repeated each time patients receive a transfusion in the model.

The probability of surgical related mortality in this population was estimated from the trial mortality data. As suggested in NICE technical support document 5, a binomial likelihood model was used to estimate the baseline mortality risk using a random effects model with the predictive distribution (see Appendix 6 for the statistical code used).[99] The mortality figures from the five studies are used, which are reporting mixed types of elective procedures and the mortality risk from the predictive distribution, which resulted in pooled risk (95% CI) of 0.0195 (0.0004, 0.13), was used in the base-case (see Table 6.5). As a scenario analysis, the mortality risk from the posterior distribution, which resulted in pooled risk (95% CI) of 0.006955 (0.0004, 0.019), was used (see Table 6.5). This risk was incorporated into the model for patients in both platelet count subgroup who received their planned surgery.

CLD related mortality was incorporated into the long-term model in order to estimate lifetime QALYs for those patients surviving the short-term model in the same way as in the Shionogi submission.[57] In the base case, data were used from a systematic review by D'Amico et al. (2006),[78] which used survival at 1 and 2 years for each Child-Pugh grade to estimate an extrapolated survival curve, weighted based on the proportions of patients with each Child-Pugh grade. An alternative data source was also investigated by Shionogi, using data from the UK Medicines Information (UKMi), for which linear interpolation was used to estimate survival per year, based on reported survival at 1, 5 and 10 years for each Child-Pugh category, with survival again weighted according to the proportions of patients with each Child-Pugh score.[100] The D'Amico estimate was chosen for the base case as Shionogi's clinical experts considered the UKMi estimates too low, with one-year survival estimated at 84%. The AG concurred with this assessment.

Table 6.5: Overview of input parameters for mortality

	Value	Source	Analysis
Mortality due to platelet transfusion	0.0004592%	SHOT 2012-2017	Base case
Mortality due to surgery	1.95%	Predictive distribution of the baseline random effects model	Base case
Mortality due to surgery (alternative)	0.7%	Posterior distribution of the baseline random effects model	Scenario
CLD mortality	Multiple values*	D'Amico et al. (2006)	Base case
CLD mortality (alternative)	Multiple values*	UK Medicines Information	Scenario

* not possible to report as a single value, as these values are obtained from a curve or multiple data points.
Abbreviations: SHOT = Serious Hazards of Transfusion, CLD = Chronic liver disease.

Safety

Adverse events due to treatment, platelet transfusion and surgery were included in the model (see Table 6.6 for an overview). In the CS, Shionogi state that comprehensive data for all platelet transfusion-

specific AEs were not available.[57], in the AG model, estimates for the probability of experiencing transfusion related AEs were taken from the SHOT report 2012-2017. [93-97] Earlier the probabilities for FAHR and pulmonary reactions were already presented, at 0.0288% and 0.00395% per transfusion, respectively. However, not all FAHR events are major, SHOT data shows that only 25.6% of all FAHR responses is major, thus inducing an effect on costs and QoL Furthermore, also the transfusion transmitted infections were extracted from the SHOT reports, yielding some very small probabilities of bacterial infections, hepatitis A, B and E virus infection and parvovirus infection. The incidences of the remaining transfusion-related AEs were multiplied by the assumed number of ATDs per transfusion ([redacted] units, calculated by the AG, the details are explained under the *platelet transfusion* section). Patients were assumed to be at equal risk of experiencing a transfusion related AE each time they underwent a platelet transfusion, with the risk repeated in the model.
A table including all SAEs which were experienced by at least 1% of the patients in any treatment arm of any of the randomized lusutrombopag and avatrombopag trials can be found in Appendix 4 of this report. A large number of AEs is expected when considering the severity of the underlying condition. The only AE in this table which was experienced by >5% of any treatment arm was transfusion reaction, which was assumed to be accounted for in the transfusion related AE data outlined above. Thrombus-related AEs have been judged to be particularly relevant to TPO-RAs.[57] Therefore, any severe thrombus-related events, possible/probably related to treatment were included in the model. Cases of portal vein thrombosis, which were judged to be severe, possibly or probably related, thrombus-related treatment-emergent AE, were seen across the trials. Given the severity and probable relationship with the drugs, portal vein thrombosis (PVT) AEs were included in the model. Incidence of PVT in each treatment arm (for each subgroup) was estimated from the posterior distribution parameter estimates of the WinBUGS code, derived from the baseline placebo proportions and the ORs obtained from the random effects model.

Grade 2 and above bleeding events were incorporated into the model as surgical adverse events. Bleeding data was provided by both companies in their clarification response, clarifying the number of bleeds, according to severity, in each treatment arm of each trial for each platelet subgroup. The AG interpreted the moderate/severe bleeding categorisations provided by the company to be in line with the World Health Organisation bleeding severity scale. Again, the incidence of bleeding in each treatment arm (for each subgroup) was estimated from the posterior distribution parameter estimates of the WinBUGS code, derived from the baseline placebo proportions and the ORs obtained from the random effects model. It is assumed that around 30% of the grade 2 and above bleeding events were grade 3 and above, since 6 out of 20 grade 2 and above bleeding events were grade 3.

Table 6.6: Overview of input parameters for the incidence of AEs

AE	**AE incidence**						**Source**
Treatment	Placebo		Avatrombopag		Lusutrombopag		
Platelet count subgroup	<40 x10^9/L	40 to < 50 x10^9/L	<40 x10^9/L	40 to < 50 x10^9/L	<40 x10^9/L	40 to < 50 x10^9/L	
Treatment-emergent AEs							

Portal vein trombosis Median (95% CI)*	0.0009 (0.0000, 0.1326)	0.0011 (0.0000, 0.1575)	0.0005 (0.000, 0.2030)	0.0039 (0.0000, 0.8962)	0.0005 (0.0000, 0.1244)	0.0019 (0.0000, 0.3685)	ITC
Surgery-related AEs							
Bleeding Events (Grade 2 and 3) Median (95% CI)*	0.0286 (0.0029, 0.2279)	0.0287 (0.0029, 0.0760)	0.0256 (0.0013, 0.3715)	0.0104 (0.0013, 0.0817)	0.0085 (0.0004, 0.1374)	0.0802 (0.0004, 0.5768)	ITC
Proportion of grade 3 bleeding events	30% (6/20)						Pooled from all trials
Platelet transfusion-related AEs							
Pneumological	0.0039500%						SHOT reports 2012-2017
FAHR (major)	0.0073831%						
Bacteria	0.0000063%						
HAV	0.0000063%						
HBV	0.0000063%						
HEV	0.0000634%						
Parvovirus	0.0000063%						

* Discrepancies between the values seen in this table and in the model are due to differences in the number of iterations used to calculate the values. The values presented in the table were obtained from the WINBUGS output summary from 100,000 iterations (after a burn-in of 30,000 iterations). In the excel model we use 2,000 iterations from the WINBUGS to provide values for the PSA of the model

Source: Indirect treatment comparisons performed by the AG using data provided by the company in the original CS, as well as in response to clarification questions, and otherwise as indicated.

Abbreviations: AE= adverse event; ; ITC = indirect treatment comparison; CI = credibility interval; FAHR = febrile, allergic and hypotensive reactions; HAV = hepatitis A virus; HBV = hepatitis B virus; HEV = hepatitis E virus.

Utilities

HRQoL data were not collected in any of the lusutrombopag or avatrombopag trials. As in the Shionogi submission, the base-case adopts a baseline EQ-5D-3L utility value in both treatment groups, estimated for patients with CLD/cirrhosis in a study by Sullivan et al. (2011).[79] An alternative EQ-5D-3L utility value was incorporated into the Shionogi model, based on a study by Scalone et al. (2013), which compared the performance of the EQ-5D-3L and EQ-5D-5L in patients with chronic hepatic diseases. This was considered in scenario analysis.[101]

One-off disutilities were included in the model for platelet transfusions, not receiving a planned procedure, bleeding events, rescue therapy and AEs (see Table 6.7 for an overview). In the base case, a disutility of 0.1 for patients experiencing serious platelet transfusion related AEs was applied for one model cycle (four weeks). This value, included in the Shionogi model, was taken from TA293, a previous NICE appraisal of eltrombopag for thrombocytopenia purpura.[80] An alternative disutility for platelet

transfusion of 0.17 was available from van Eerd et al. (2010).[73] However the company selected the disutility of 0.1 for the base-case, as it had been previously accepted by the committee in NICE TA293 and TA221 and was more conservative than the alternative value available. The AG concurred with this decision. An incidence of serious transfusion-related reactions of 0.0114% was assumed based on the sum of all reactions listed in Table 6.5. The disutility of 0.1 for a duration of four weeks was multiplied with the incidence of 0.0114%, which equated to a total QALY decrement of 0.000000876. This QALY decrement was multiplied by the number of times in the model that a patient received a platelet transfusion.

The AG felt that the delay of a PEIP outside of the first cycle would have an impact on patients HRQoL. No established value could be found from the literature for the disutility associated with surgery delay or cancellation. Therefore, the AG assumed that, while the impact on the HRQoL of patients could be seen in a number of domains of the EQ-5D, it was most likely that lengthy delays would cause patients increased worry about their surgery and condition and therefore would increase patients' anxiety/depression. Therefore, the AG investigated the decrements associated with anxiety and depression in the UK EQ-5D-5L value set.[102] The average decrement for a one level increase in anxiety and depression was 0.072 (note that the average decrement for losing one level of any item is 0.064). The AG felt this value was reasonable as an expected magnitude of the impact of surgery delay on patients' HRQoL. In the base-case this value was applied for four weeks. This duration was assumed as it approximated the cycle length and therefore accounted for the fact that patients would not receive the surgery in this cycle, but would receive it one cycle later. These values will be adjusted in scenario analysis.

In their response to clarification, the company clarified that, in L-PLUS 2, rescue therapies included platelet transfusion, other blood product transfusion and volume expanders, while in the remaining two trials (L-PLUS 1 and the Phase 2b trial), platelet transfusion was the only permitted rescue therapy (despite this, one patient in the lusutrombopag group of L-PLUS 2 received thrombin, and one patient in the placebo group received thrombin and red blood cells, in addition to platelet transfusion as rescue therapies).[54] In the ADAPT trials, rescue therapies included platelet transfusion, fresh frozen plasma transfusion, adrenalin injections, tranexamic acid and more. In the model submitted by Shionogi, the disutility set for rescue therapy was equal to that of platelet transfusion, following on from their argument that rescue therapy would most likely take the form of platelet transfusion. While the AG does not agree with this assumption, especially given the range of rescue therapies seen in the trial, the disutility of 0.1 was felt to be reasonable to cover the disutility of rescue therapy in general and this value was applied.

Disutilities for bleeding events and thrombotic events were also identified from the literature by Shionogi. Disutilities of 0.397 for major bleeding events and 0.122 for clinically relevant non-major bleeding events were identified from Jugrin et al. (2015).[81] The AG base-case model only included bleeding AEs of grade 3 or higher, which were assumed to be equivalent to major bleeding events. Therefore, the disutility of 0.397 for major bleeds was incorporated into the model base-case, with a duration of one week. When Grade 2 bleeding events were included in the model in scenario analysis, the disutility of 0.122 for clinically relevant non-major bleeding events was applied to these events for a duration of one week. For thrombus-related AEs the company incorporate a disutility of 0.029, applied over one week, estimated by Jugrin et al. (2015) for related thrombotic events (index deep vein thrombosis and index pulmonary embolism). [81]

The baseline utility value for CLD/cirrhosis patients adopted in the short-term model was also used to calculate QALYs throughout the long-term model. Utility values were adjusted to incorporate the natural decline in utility observed with ageing using the Ara and Brazier (2010) equation to generate utility multipliers by age and gender.[82]

Table 6.7: Overview of input parameters for utilities and disutilities

	Value	Source
Baseline utilities		
CLD utility (base case)	0.544	Sullivan et al. (2011)[79]
CLD utility (alternative)	0.801	Scalone et al. (2013)[101]
Treatment-emergent AE disutility and duration		
Portal vein thrombosis disutility	0.029	Jugrin et al. (2015)[1]
Portal vein thrombosis duration	1 week	Clinical expert validation consulted by Shionogi[57]
Platelet transfusion-related AE disutilities		
Serious reaction (base case)	0.1	NICE TA293 (2012)[80]
TRALI (alternative)	0.4	van Eerd et al. (2010)[73]
Severe allergic reactions (alternative)	0.4	van Eerd et al. (2010)[73]
Platelet transfusion-related AE durations		
Serious reaction (overall, alternative)	4 weeks	NICE TA293 (2012)
TRALI (alternative)	4 weeks	Clinical expert validation consulted by Shionogi[57]
Severe allergic reactions (alternative)	4 weeks	Clinical expert validation consulted by Shionogi[57]
Surgery-related AE disutility and duration		
Bleeding Events (Grade 3) disutility	0.397	Jugrin et al. (2015)[81]
Bleeding Events (Grade 3) duration	1 week	Assumption
Bleeding Events (Grade 2) disutility (only in scenario analysis)	0.122	Jugrin et al. (2015)[81]
Bleeding Events (Grade 2) duration (only in scenario analysis)	1 week	Assumption
Delay of procedure-related disutility and duration		
Delay of procedure-related disutility	0.072	Assumption[102]
Delay of procedure-related disutility duration	4 weeks	Assumption
Age-related utility adjustments		
Sex	0.0212126	Ara and Brazier (2010)[82]
Age	-0.0002587	
age2	-0.0000332	
_cons	0.9508566	

[1] Based on a disutility for related thrombotic events: index deep vein thrombosis and index pulmonary embolism.
CLD = chronic liver disease; TRALI = transfusion-related acute lung injury

Costs

Costs were attributed to any platelet transfusions, procedures and rescue therapies given, drug acquisition and administration and AE monitoring (see Table 6.8 for an overview).

- Drug acquisition costs

The cost for a seven-day course of lusutrombopag is £800. While not all patients in the trials received the full seven-day treatment course (L-PLUS 1 [redacted] L-PLUS 2 [redacted] the EMA recommends that lusutrombopag should be administered for seven days.[8] Additionally, in real world practice it is likely that the full seven-day course would be dispensed and therefore remaining tablets would be wasted. Therefore, the full cost of seven days was included in the model.

Avatrombopag is administered orally, once daily. For patients with a platelet count < 40,000/µL the daily dose is 60 mg (three tablets of 20 mg) with the first dose administered 10 to 13 days prior to the scheduled procedure, and continuing for five days (i.e. procedure is scheduled five to eight days after the last dose). For patients with a platelet count ≥ 40,000/µL and < 50,000/µL the administration and timing thereof are the same, but the dose is reduced to 40 mg (two tablets of 20 mg). No price has yet been provided for avatrombopag. Wastage will again be taken into account, with full pack costs charged. As both treatments are oral tablets no administration costs are required.

- Platelet transfusion costs

The estimated costs of a platelet transfusion consist of 1) the costs of the platelets, and 2) the costs of the administration of the platelets. This estimate is multiplied with the number of platelet transfusions a patient receives prior to the PEIP, which were calculated from the data provided in response to the clarification letter, for each treatment arm for each subgroup.

For the costs of platelets, the cost price for one adult therapeutic dose (ATD) of apheresis-derived platelets was sourced from the NHS Blood and Transplant (NHSBT) Pricing Proposals 2017/2018.[103] This was multiplied by the estimate of [redacted] ATDs per transfusion (details provided in *platelet transfusion* section of 6.3.1.4), which led to a cost of [redacted] per transfusion.

The costs of the administration of the platelets were sourced from Stokes et al., 2018, which provides separate cost estimates for the first unit that is administered, as well as for subsequent units that are administered.[104] The costs of administration were inflated from 2014 /2015 to 2017/2018 using the Hospital & Community Health Services (HCHS) indices provided in PSSRU (2017).[105] This led to a transfusion cost estimate of £68.96.

In the Shionogi submission, the base-case cost of platelet transfusion was based on the TA293 appraisal of eltrombopag.[80] In the eltrombopag appraisal this was assumed to comprise of a cost of blood transfusion (weighted average cost of £57.72 in 2011/2012, code 821 blood transfusion) and the cost of two units of platelets (2 x £230.393 in 2011/2012). The company used expert opinion to inform the average number of units of platelets that would be received per transfusion. The expert stated that most often platelet transfusions would contain either two or four units and therefore, it was assumed that an

average of three units of platelets would be received per transfusion. This resulted in a base case cost of £812.61 (inflated to 2017/2018), which included both administration and platelet acquisition. This assumption will be tested in scenario analysis.

- Cost of the planned elective invasive procedures

The AG estimated a weighted cost of procedures conducted across all the trials, calculated using the NHS reference costs (2017-18) in the elective inpatient setting.[83] The procedure specific cost estimates and their frequency are provided in Table 6.8, below. This cost was incorporated into the AG model for all treatment arms, for all patients, as they were all assumed to receive their planned procedure at some point in time.

- Rescue procedure costs

In the Shionogi model, it was assumed that in clinical practice, rescue therapy would be an additional platelet transfusion. The AG noted that this assumption was not matched by the data presented by the companies, where other methods of rescue were also used by clinicians. However, in the face of uncertainty surrounding what would actually be given in UK practice, the AG cost of platelet transfusion of [redacted] was used in the base-case.

The AG clinical expert stated that he would consider giving a combination of platelet transfusion, clotting factors, and tranexamic acid. An alternative value for scenario analysis was calculated by the AG based on this assumed combination. For platelet transfusions given as rescue procedures, a dosage of one ATD of platelets was costed using the NHSBT Pricing Proposals 2017/2018, including administration costs sourced from Stokes et al., 2018. For clotting factors, recombinant thrombin was costed using a price ($ 104 in 2009) from Plesca (2009), which was converted using purchasing power parities, and inflated from 2009/10 to 2017/18 using the HCHS indices from the PSSRU.[105] [106, 107] A dosage of 5000 units was assumed (i.e. 5 ml of 1000 units per ml). For tranexamic acid, a dosage of 2 g was assumed based on CRASH-2 (CRASH -2 trial collaborators, 2010), and costed using the July 2019 NHS reference price sourced from the eMIT database. The sum of these costs yielded an alternative unit rescue procedure cost estimate of [redacted]. This unit cost is multiplied with the number of platelet transfusions required per rescue therapy for each treatment arm, in each subgroup, calculated from the pooled estimates from the trials. The remaining alternative value was based on the Shionogi base-case cost of platelet transfusion of £812.61.

- Transfusion related AE costs

Costs associated with treating transfusion-related AEs were taken from the report by Whiting et al (2015), [108] with costs inflated from 2013 to 2019, see Table 6.8. These costs were multiplied by the incidences of transfusion related reactions estimated from the SHOT data. [93-97] [109] This resulted in an estimated cost of treating transfusion related reactions of £0.22 per transfusion. This was added to the cost of platelet transfusion, creating a base-case total cost of platelet transfusion of [redacted].

In the AG model the proportion of each treatment group experiencing portal vein thrombosis was found for each subgroup. This was multiplied by the unit price of £958.95 based on the NHS reference code YR23B: Percutaneous Transluminal, Embolectomy or Thrombolysis, of Blood Vessel, with CC Score 0-4

in the day case setting.[83] This provided a treatment group specific expected cost of treating portal vein thrombosis.

Table 6.8: Overview of input parameters for costs

	Value	Source
Treatment costs		
Lusutrombopag (3 mg, pack of 7 tablets)	£ 800	Shionogi[57]
Avatrombopag (20 mg tablet)	-	Dova
Treatment dosage		
Lusutrombopag (3 mg): all patients	1 tablet per day for 7 days	EPAR[8]
Avatrombopag (20 mg): patients with platelet count <40 x10^9/L	3 tablets per day for 5 days	EPAR[6]
Avatrombopag (20 mg): patients with platelet count of 40 to <50 x10^9/L	2 tablets per day for 5 days	EPAR[6]
Platelet transfusion		
Costs for administering first unit of platelets	£ 64.18	Stokes et al. (2018)[104]
Costs for administering subsequent units of platelets	£ 42.16	Stokes et al. (2018)[104]
Apheresis-derived platelets per ATD	£ 219.30	NHSBT Pricing Proposals 2017 / 2018[109]
Number of ATDs transfused per platelet transfusion	[redacted]	L-PLUS 1, L-PLUS 2, Phase 2b trial
Cost of platelet transfusion (base case)	[redacted]	Calculation by AG
Cost of platelet transfusion (scenario)	£ 812.61	Based on Shionogi submission model
Average number of platelet transfusions for patients on lusutrombopag, who were transfused prior to procedure, and with a platelet count <40 x10^9/L	[redacted]	Calculated from data provided in response to clarification questions
Average number of platelet transfusions for patients on lusutrombopag, who were transfused prior to procedure, and with a platelet count of 40 to <50 x10^9/L	[redacted]	Calculated from data provided in response to clarification questions
Average number of platelet transfusions for patients on avatrombopag, who were transfused prior to procedure, and	1.0000	Calculated from data provided in response to clarification questions

with a platelet count <40 x10^9/L		
Average number of platelet transfusions for patients on avatrombopag, who were transfused prior to procedure, and with a platelet count of 40 to <50 x10^9/L	1.0000	Calculated from data provided in response to clarification questions
Average number of platelet transfusions for patients on no TPO-RA, who were transfused prior to procedure, and with a platelet count <40 x10^9/L	[redacted]	Calculated from data provided in response to clarification questions
Average number of platelet transfusions for patients on no TPO-RA, who were transfused prior to procedure, and with a platelet count of 40 to <50 x10^9/L	[redacted]	Calculated from data provided in response to clarification questions
Treatment-emergent AE costs		
Management of portal vein thrombosis	£ 958.95	NHS reference code YR23B: Percutaneous Transluminal, Embolectomy or Thrombolysis, of Blood Vessel, with CC Score 0-4; day case setting
Platelet transfusion-related AE costs		
Pneumological	£2640	Whiting, 2015[108]
FAHR (major)	£1134	
Bacteria	£2024	
HAV	£6488	
HBV	£8971	
HEV	£6488	assumed same as HAV
Parvovirus	£1095	Whiting, 2015
Surgical procedures: costs		
Percutaneous radiofrequency ablation (RFA)	£2,309.03	NHS reference costs (2017–2018, elective inpatient setting): Percutaneous Ablation of Lesion of, Liver or Pancreas, with CC Score 0-1
Endoscopic variceal ligation	£4,202.11	NHS reference costs (2017–2018, elective inpatient setting): Major, Oesophageal, Stomach or Duodenum Procedures, 19 years and over, with CC Score 0-1
Endoscopic injection sclerotherapy	£2,410.75	NHS reference costs (2017–2018, elective inpatient setting): Endoscopic, Sclerotherapy or Rubber Band Ligation, of Lesion of Upper Gastrointestinal Tract, with

		CC Score 0-2
Transcatheter arterial chemoembolization	£2,921.50	NHS reference costs (2017–2018, elective inpatient setting): Minor, Hepatobiliary or Pancreatic Procedures, with CC Score 0
Liver biopsy	£1,546.72	NHS reference costs (2017–2018, elective inpatient setting): Percutaneous Transvascular Biopsy of Lesion of Liver
Dental extraction	£680.04	NHS reference costs (2017–2018, elective inpatient setting): Minor Extraction of Tooth, 19 years and over
Vascular catheterisation	£1,125.62	NHS reference costs (2017–2018, elective inpatient setting): Peripheral Insertion of Central Venous Catheter, 19 years and over
Argon plasma coagulation	£4,202.11	NHS reference costs (2017–2018, elective inpatient setting): Major, Oesophageal, Stomach or Duodenum Procedures, 19 years and over, with CC Score 0-1
Percutaneous ethanol injection therapy	£2,921.50	NHS reference costs (2017–2018, elective inpatient setting): Minor, Hepatobiliary or Pancreatic Procedures, with CC Score 0
Endoscopy w/wo polypectomy/biopsy	£1,213.27	NHS reference costs (2017–2018, elective inpatient setting): Therapeutic Endoscopic Upper Gastrointestinal Tract Procedures, 19 years and over
Percutaneous RFA/microwave coagulation therapy	£2,309.03	NHS reference costs (2017–2018, elective inpatient setting): Percutaneous Ablation of Lesion of, Liver or Pancreas, with CC Score 0-1
Paracentesis	£1,090.43	NHS reference costs (2017–2018, elective inpatient setting): Percutaneous Drainage of Hepatobiliary System
Other liver procedures	£2,921.50	NHS reference costs (2017–2018, elective inpatient setting): Minor, Hepatobiliary or Pancreatic Procedures, with CC Score 0
Other gastrointestinal procedures	£4,202.11	NHS reference costs (2017–2018, elective inpatient setting): Major, Oesophageal, Stomach or

		Duodenum Procedures, 19 years and over, with CC Score 0-1
Others	£2,309.03	NHS reference costs (2017–2018, elective inpatient setting): Percutaneous Ablation of Lesion of, Liver or Pancreas, with CC Score 0-1
Surgical procedures: incidence		
Percutaneous radiofrequency ablation (RFA)	8.6%	All lusutrombopag and avatrombopag trials
Endoscopic variceal ligation	10.2%	
Endoscopic injection sclerotherapy	0.4%	
Transcatheter arterial chemoembolisation	13.1%	
Liver biopsy	3.4%	
Dental extraction	8.6%	
Vascular catheterisation	2.0%	
Argon plasma coagulation	0%	
Percutaneous ethanol injection therapy	0%	
Endoscopy w/wo polypectomy/biopsy	36.8%	
Percutaneous RFA/microwave coagulation therapy	6.3%	
Paracentesis	0.7%	
Other liver procedures	0.8%	
Other gastrointestinal procedures	0%	
Others	8.7%	
Rescue procedures for bleeding		
Rescue procedure cost estimate from the AG (base case)	[redacted]	Calculated by AG based on clinical expert opinion
Rescue procedure cost estimate from Shionogi (scenario)	£ 812.61	Shionogi[57]

Source: As indicated in column 'Source'.
Abbreviations: ATD = adult therapeutic dose, AE = adverse event, EPAR = European Public Assessment Report, FAHR = febrile, allergic and hypotensive reactions; HAV = hepatitis A virus; HBV = hepatitis B virus; HEV = hepatitis E virus , RFA = radiofrequency ablation

6.3.1.5 Probabilistic sensitivity analysis and scenario analyses

Given the parametric uncertainty surrounding the input parameters utilised in the model, probabilistic sensitivity analysis, consisting of 2,000 iterations was run to test parameter uncertainty within the model. All parameters except drug prices, drug doses and discount rates were included in the PSA (See Appendix

7). As is standard practice, appropriate distributions were fitted to included parameters. Beta distributions were used for probabilities, proportions, risks and utilities, gamma distributions for costs, beta tree for Child-Pugh categories and normal distributions for age and the number of ATDs per transfusion. Where standard errors were unknown, they were estimated as 20% of the mean value. For efficacy parameters obtained from WINBUGs, probabilistic values were drawn from CODA output. Cost-effectiveness planes and cost-effectiveness acceptability curves will be provided to examine the uncertainty related to the decision.

Given the structural uncertainty surrounding the input parameters utilised in the model, the AG conducted a series of scenario analyses for various efficacy, mortality, safety, cost and utility parameters. These scenario analyses are listed below and explained in more detail in the following text.

1. Drug prices
2. Number of ATDs per platelet transfusion
3. Cost of platelet transfusion
4. Cost of rescue therapy
5. Inclusion of Grade 2 bleeding AEs
6. Probability of requiring platelet transfusion estimated from international trials only
7. Efficacy model input parameters are derived from fixed-effect meta-analysis models
8. Literature source for long-term Child-Pugh grade-specific mortality
9. Underreporting factor for SHOT data platelet transfusion specific mortality
10. Alternative literature source for surgery-related mortality
11. Alternative literature source for baseline CLD utility
12. Alternative literature source for bleeding disutility
13. Alternative literature source for PVT disutility
14. Alternative literature source for transfusion-related AE disutilities
15. Alternative values for PEIP delay disutility and duration

Scenarios explained

1. Drug prices
   Given that the AG do not have a price for avatrombopag (with the base-case assuming the same price as lusutrombopag for both doses of avatrombopag), some scenarios around drug pricing were thought to be of value. In this scenario analysis, the prices of avatrombopag was lowered.

2. Number of ATDs per platelet transfusion
   Given the substantial uncertainty surrounding the number of units/ATDs transfused in each platelet transfusion, which has already been explained throughout the cost-effectiveness section of this report, the AG felt it was important to examine the impact of different assumptions of number of units/ATDs on the results.

   The calculation of the AG base-case assumption of each platelet transfusion containing [redacted] ATDs was explained in the *platelet transfusion* Section of 6.3.1.4. This value was used to calculate the cost of each platelet transfusion, as well as the cost of expected platelet transfusion AEs, by multiplying the unit cost of platelets and the incidence of AEs per unit of platelets by the number of ATDs. In the Shionogi model, clinical expert opinion led to the assumption of an

average of three units of platelets transfused per platelet transfusion. The AG included this as an upper bound scenario, although given that the base case unit cost of platelets identified from the NHSBT pricing proposals is per ATD, the AG note that a three unit assumption is likely to overestimate the costs of platelet transfusion. Scenarios of 1 and 2 ATDs per transfusion will also be included to provide a range of estimates, and the impact on the results.

3. Cost of platelet transfusion
   In the AG base-case the cost of platelet transfusion is calculated from Stokes et al. 2018, while the unit cost of an ATD of platelets (obtained from apheresis) is taken from the NHSBT pricing proposals.[110] The cost of treating transfusion related reactions was estimated at £0.22 per transfusion, using costs from Whiting et al. (2015) and incidences from the SHOT data. [93-97] [108] This resulted in a cost per platelet transfusion of [redacted]. Two alternative sources of costs were taken from the Shionogi model.

   The first scenario will use Shionogi base-case cost of platelet transfusion. This estimate was obtained from the TA293 appraisal, which estimated a cost of blood transfusion from code 821, blood transfusion of £57.72 in 2011/2012 and a cost per unit of platelets of £230.393 in 2011/2012. The company used expert opinion to inform the average number of units of platelets that would be received per transfusion. The expert stated that most often platelet transfusions would contain either 2 or 4 units and therefore, it was assumed that an average of three units of platelets would be received per transfusion. This resulted in a cost of £812.61 (inflated to 2017/2018), which will be tested in this scenario.

   The second scenario provided by Shionogi used the HRG codes for Single Plasma Exchange or Other Intravenous Blood Transfusion for day case and elective inpatient transfusions. These were weighted by the proportions of transfusions which have been conducted as day case and elective inpatient cases, resulting in a weighted cost of £517.28.

4. Cost of rescue therapy
   In the Shionogi model, it was assumed that in clinical practice, rescue therapy would be an additional platelet transfusion. The AG noted that this assumption was not matched by the data presented by the companies, where other methods of rescue were also used by clinicians. However, in the face of uncertainty surrounding what would actually be given in UK practice, the AG cost of platelet transfusion of [redacted] was used in the base-case. The AG clinical expert stated that he would consider giving a combination of platelet transfusion, clotting factors, and tranexamic acid. The cost of this combination was used as an alternative, with a value of [redacted] The remaining alternative value was based on the Shionogi base-case cost of platelet transfusion of £812.61.

5. Inclusion of Grade 2 bleeding AEs
   The AG base-case only includes bleeding events of Grade 3 (severe) or higher. In scenario analysis, Grade 2 (moderate) bleeding events are also included, with a disutility for clinically relevant, non-major bleeding events attached.

6. Probability of requiring platelet transfusion prior to surgery estimated from international trials only

In the AG base-case the probability of requiring platelet transfusion was calculated from all pooled trials. In order to investigate whether there is a difference in efficacy between the two trials conducted in Japan only versus the international trials, the probability of requiring platelet transfusion will be estimated from only international trials in this scenario. This scenario would have also been relevant for the probabilities of Grade 3 bleeding events and requiring rescue therapy. However, the numbers of events in these cases were too small to generate reliable results from only the international trials. Therefore, only the probability of requiring platelet transfusion prior to surgery was adjusted.

7. Efficacy parameters obtained from fixed-effects meta-analysis model
   In the base-case, the efficacy input parameters (i.e. proportion of no platelet transfusion and proportion of patients did not require a request therapy) were obtained from random-effects meta-analysis models. In this scenario analysis, the impact of using efficacy parameters from fixed effects models will be elaborated.

8. Literature source for long-term Child-Pugh grade-specific mortality
   In the base-case long-term CLD mortality was estimated using data from a systematic review by D'Amico et al. (2006),[78] which used survival at 1one and two years for each Child-Pugh grade to estimate an extrapolated survival curve. This was weighted based on the proportions of patients with each Child-Pugh grade, pooled from all trials.

   For the scenario analysis, the alternative data source identified by Shionogi, using data from the UK Medicines Information (UKMi), to estimate survival,[100] again using the Child-Pugh categories pooled from the trials was utilised.

9. Under reporting factor for SHOT data platelet transfusion specific mortality
   In the AG base case, platelet transfusion related mortality was estimated by the AG from 'Serious Hazards of Transfusion' (SHOT) data from 2012-17. There have been concerns in the literature that the SHOT data underreports the incidence of deaths due to TRALI.[98] Therefore, the AG included an underreporting factor relating to this parameter in the model. In the base-case, the estimate from the SHOT data was unadjusted. However, in scenario analysis, this value was multiplied by 2, 5 and 10, to investigate the impact on model results.

10. Alternative literature source for surgery-related mortality
    The probability of surgical related mortality was estimated from the trial mortality data. In the base-case, a binomial likelihood model was used to estimate the baseline mortality risk using a random effects model with the predictive distribution, which resulted in pooled risk (95% CI) of 0.0195 (0.0004, 0.13). As a scenario analysis, the mortality risk from the posterior distribution, which resulted in pooled risk (95% CI) of 0.006955 (0.0004, 0.019), was used.

11. Alternative literature source for baseline CLD utility
    In the base case, a baseline EQ-5D-3L utility value, estimated for patients with CLD/cirrhosis was adopted from a study by Sullivan et al. (2011).[79] In their original model, Shionogi provided an alternative baseline utility value from a study by Scalone et al. (date), which was used as the scenario analysis value.[101]

12. Alternative literature source for bleeding disutility

The AG could not find any alternative literature sources for the disutility of a major bleed. Therefore, the base-case value was increased and decreased by 25%.

13. Alternative literature source for PVT disutility
    The AG could not find any alternative literature sources for the disutility of PVT. Therefore, the base-case value was increased and decreased by 25%.

14. Alternative literature source for transfusion-related AE disutilities
    In the base case, a disutility of 0.1 for patients experiencing serious platelet transfusion related AEs was applied for one model cycle (four weeks). This value was taken from TA293, a previous NICE appraisal of eltrombopag for thrombocytopenia purpura.[80] In their model, Shionogi provided an alternative disutility for platelet transfusion of 0.17, taken from van Eerd et al. (2010).[73] This value was used in the scenario analysis.

15. Alternative values for PEIP delay disutility and duration
    In the base-case the AG assumed a disutility for the delay of the planned procedure of 0.072 (calculated from the average decrement associated with a one level increase in anxiety and depression on the EQ-5D-5L UK value set).[102] This disutility was varied between 0 and 0.144 by halving and doubling the assumed decrement, as well as assuming no decrement. In the base-case, this decrement was assumed for four weeks, to account for PEIPs being delayed outside of the 35-day initial cycle. This duration was varied between two and six weeks to investigate the impact on model results.

6.3.2 Results

6.3.2.1 AG Base-case deterministic results

Base-case deterministic model results from the AG model are shown in Table 6.9 below. The price of avatrombopag for both subgroups is assumed to be £800, equal to the price of lusutrombopag.

Table 6.9: Deterministic base-case discounted AG model results

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER (£/QALY)
Platelet count < 40,000 / µL Subgroup							
No TPO-RA	£2,320	7.3961	3.3626				
Lusutrombopag	£2,911	7.3961	3.3627	£592	0.00002	0.00017	£3,422,801
Avatrombopag 60 mg	£2,961	7.3961	3.3627	£49	-0.000006	-0.000079	Dominated
Platelet count 40,000- 50,000 / µL Subgroup							
No TPO-RA	£2,283	7.3961	3.3625				
Lusutrombopag	£2,907	7.3961	3.3625	£624	0.00002	0.00000	£84,890,361,589

Avatrombopag 40 mg	£2,916	7.3961	3.3629	£9	0.00000	0.00041	£21,947
ICER = incremental cost effectiveness ratio, Incr. = incremental, LYGs = life years gained, QALYs = quality-adjusted life years.							

In both subgroups no TPO-RA incurred the lowest costs and QALYs. In the <40,000/µL subgroup, lusutrombopag is the next cheapest option, with an incremental cost compared to no TPO-RA of £592 and incremental QALYs of 0.00017 (which is equivalent to a gain of 1.5 quality-adjusted life hour), resulting in a deterministic ICER around £3,400,000. Avatrombopag 60 mg is the most expensive option in this subgroup but incurs a lower QALY gain than lusutrombopag, with an incremental QALY of -0.000079. Avatrombopag 60 mg is therefore dominated by lusutrombopag in the <40,000/µL subgroup. In the 40,000- 50,000/µL subgroup, lusutrombopag is the next cheapest option after no TPO-RA, with an incremental cost of £624 and an incremental QALY of 0.000000007, resulting in an ICER over £84,000,000,000 compared to no TPO-RA. Avatrombopag 40 mg is the most expensive option in this subgroup but provides a higher QALY gain, with an incremental QALY gain of 0.00041 over lusutrombopag. This results in an ICER of £21,947 for avatrombopag 40mg versus lusutrombopag. However, note that the incremental QALYs are extremely small and in both subgroups, all treatments resulted in almost identical QALYs.

Table 6.10: Disaggregated costs

Disaggregated costs	Drug costs	Platelet transfusion costs	AE costs	PEIP costs	Rescue therapy costs	Total costs
Platelet count < 40,000 / µL Subgroup						
no TPO-RA	£0	£265	£15	£1,977	£63	£2,320
Lusutrombopag	£800	£91	£12	£1,977	£31	£2,911
Avatrombopag 60 mg	£800	£148	£11	£1,977	£24	£2,961
Platelet count 40,000- 50,000 / µL Subgroup						
no TPO-RA	£0	£231	£14	£1,977	£62	£2,283
Lusutrombopag	£800	£64	£31	£1,977	£35	£2,907
Avatrombopag 40 mg	£800	£44	£83	£1,977	£12	£2,916
ICER = incremental cost effectiveness ratio, Incr. = incremental, LYGs = life years gained, QALYs = quality-adjusted life years.						

Table 6.11: Disaggregated QALYs

Disaggregated QALYs	QALY Decrement				Total long-term disc. QALYs
	Platelet transfusion	Bleeding	Rescue Therapy	AEs	
Platelet count < 40,000 / µL Subgroup					
No TPO-RA	0.0000007	0.0000315	0.0000002	0.0000085	3.310993
Lusutrombopag	0.0000002	0.0000241	0.0000001	0.0000071	3.311002
Avatrombopag 60 mg	0.0000004	0.0001003	0.0000001	0.0000066	3.310999
Platelet count 40,000- 50,000 / µL Subgroup					
No TPO-RA	0.0000006	0.0000744	0.0000002	0.0000079	3.310994
Lusutrombopag	0.0000002	0.0002274	0.0000001	0.0000182	3.311002
Avatrombopag 40 mg	0.0000001	0.0000481	0.0000000	0.0000482	3.311004

Disaggregated cost results, displayed in Table 6.10, show that, while the costs of platelet transfusion, AE management and rescue therapy are higher for no TPO-RA than for lusutrombopag and avatrombopag (except for AE costs in the 40,000- 50,000/µL subgroup), the combined difference is still substantially lower than the drug costs for lusutrombopag and avatrombopag. This results in incremental costs of over £500 for both treatments versus no TPO-RA. In the face of such small incremental QALYs, this incremental cost has a large impact on the ICER. In both subgroups, the dominance of one treatment over the other is mostly due to the differences in the QALY decrements due to bleeding, which cause small but important differences in total QALYs (Table 6.11).

6.3.2.2 Probabilistic Sensitivity analysis results

Table 6.12: PSA results

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Platelet count < 40,000 / µL Subgroup					
no TPO-RA	£2,222	3.5681			
Lusutrombopag	£2,822	3.5683	£600	0.0001	£4,006,891
Avatrombopag 60 mg	£2,860	3.5682	£38	-0.0000	Dominated
Platelet count 40,000- 50,000 / µL Subgroup					
no TPO-RA	£2,189	3.5551			
Lusutrombopag	£2,815	3.5555	£626	0.0004	£1,555,549
Avatrombopag 40 mg	£2,825	3.5550	£10	-0.0005	Dominated

ICER = incremental cost effectiveness ratio, Incr. = incremental, LYGs = life years gained, QALYs = quality-adjusted life years.

The probabilistic results, displayed in Table 6.12, for the <40,000/µL subgroup follow the same pattern as the deterministic results. Lusutrombopag is more expensive than no TPO-RA by £600 (i.e. 25% more expensive) and more effective by 0.0001 QALYs, resulting in an ICER of approximately £4,000,000. Avatrombopag 60 mg is slightly more expensive than lusutrombopag and slightly less effective and is therefore dominated. In the 40,000- 50,000/µL subgroup, no TPO-RA is again the cheapest option. Lusutrombopag is the next cheapest and most effective, with an incremental cost of £626 and incremental QALYs of 0.0004. Avatrombopag 40 mg is £10 more expensive than lusutrombopag and -0.0005 QALYs less effective and is therefore dominated by lusutrombopag.

The cost effectiveness planes (Figures 6.4 and 6.5) for both subgroups show that, for the majority of iterations, both treatments are more costly and more effective than no TPO-RA. However, in each diagram it can also be seen that a substantial proportion of iterations fall in the NW quadrant, where the treatments are more expensive but less effective than no TPO-RA. This can be most prominently seen for avatrombopag in the 40,000-50,000/µL subgroup, where it appears that approximately half of the iterations suggest the avatrombopag is less effective than no TPO-RA (orange points). This indicates that given the uncertainties in the model, the treatments should be regarded as having equivalent effectiveness in terms of QALYs.

The CEACs in turn (Figures 6.6 and 6.7) show that for all threshold ICERs up to £100,000, no TPO-RA has a 100% probability of being most cost-effective.

Figure 6.4: Cost effectiveness plane for subgroup: Platelet count <40,000/µL

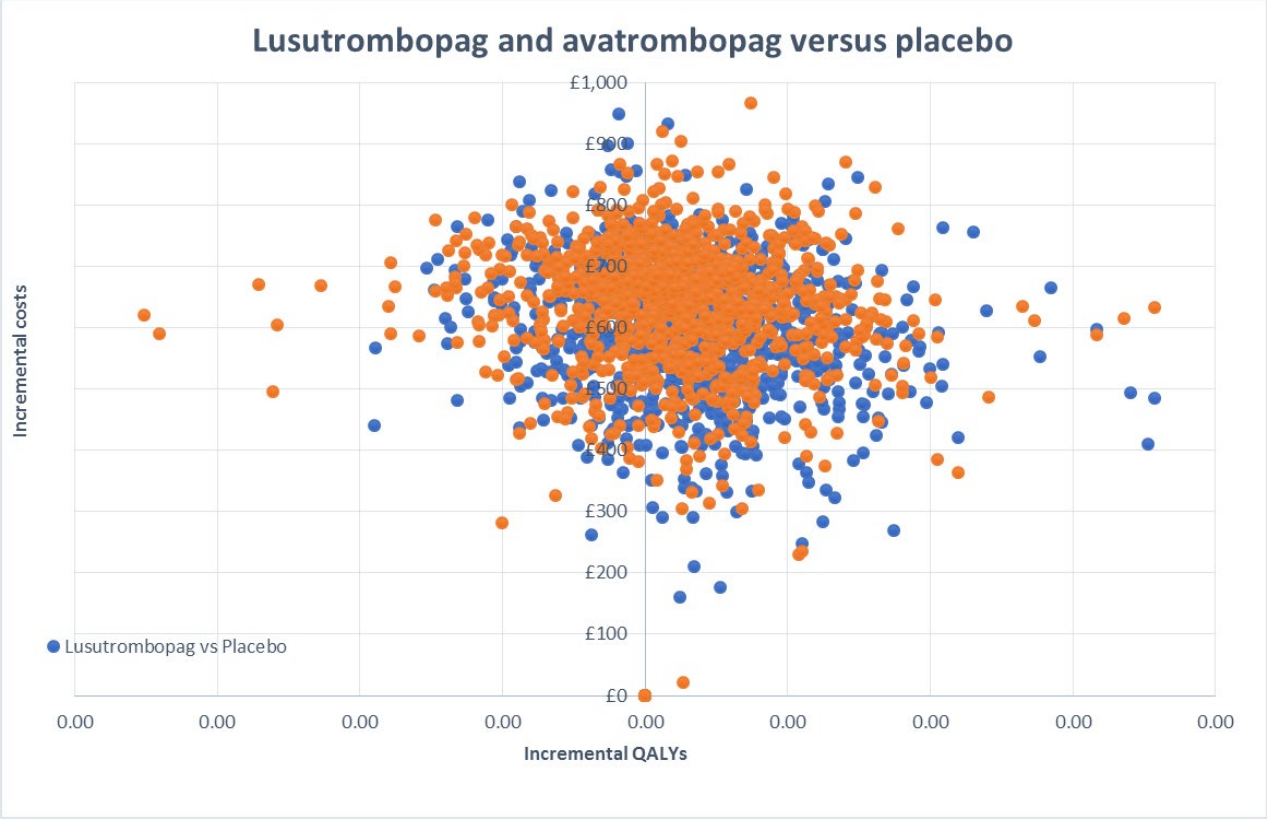


Figure 6.5: Cost effectiveness plane for subgroup: Platelet count 40,000-<50,000/µL

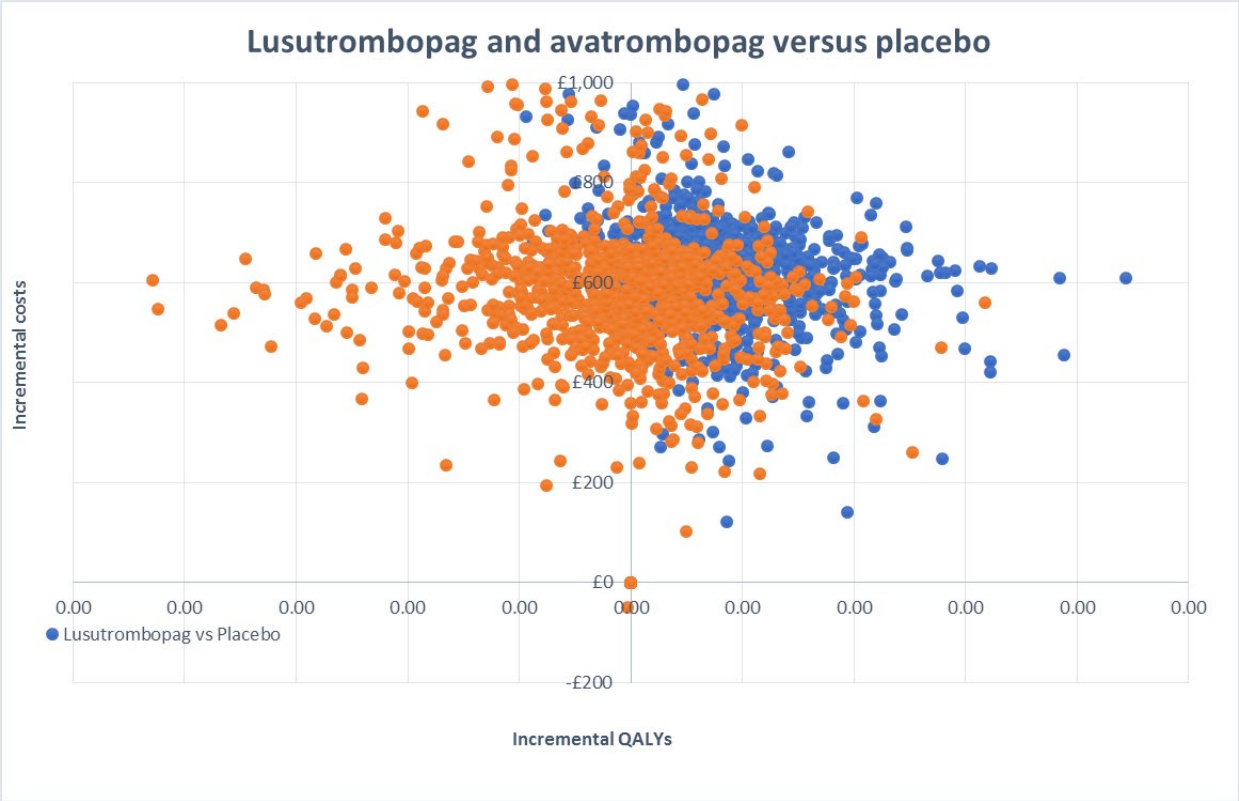


Figure 6.6: Cost effectiveness acceptability curve for platelet count <40,000/µL

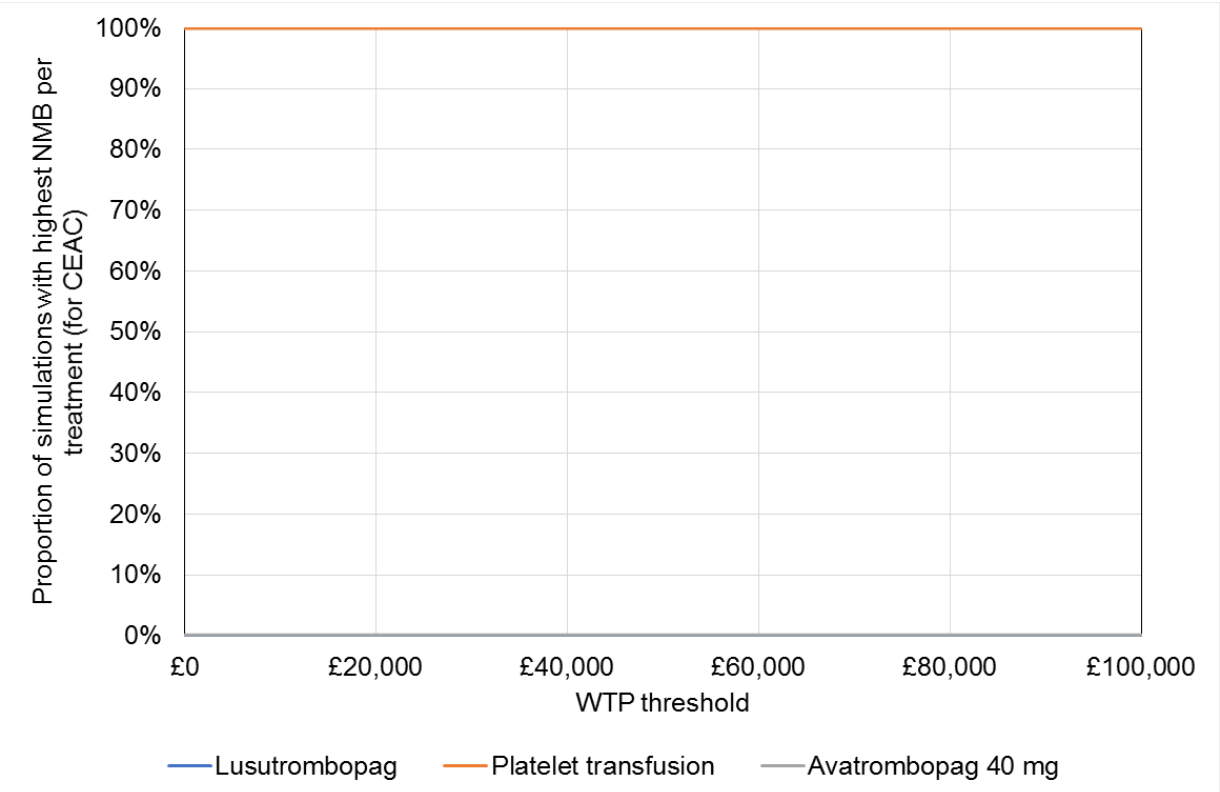
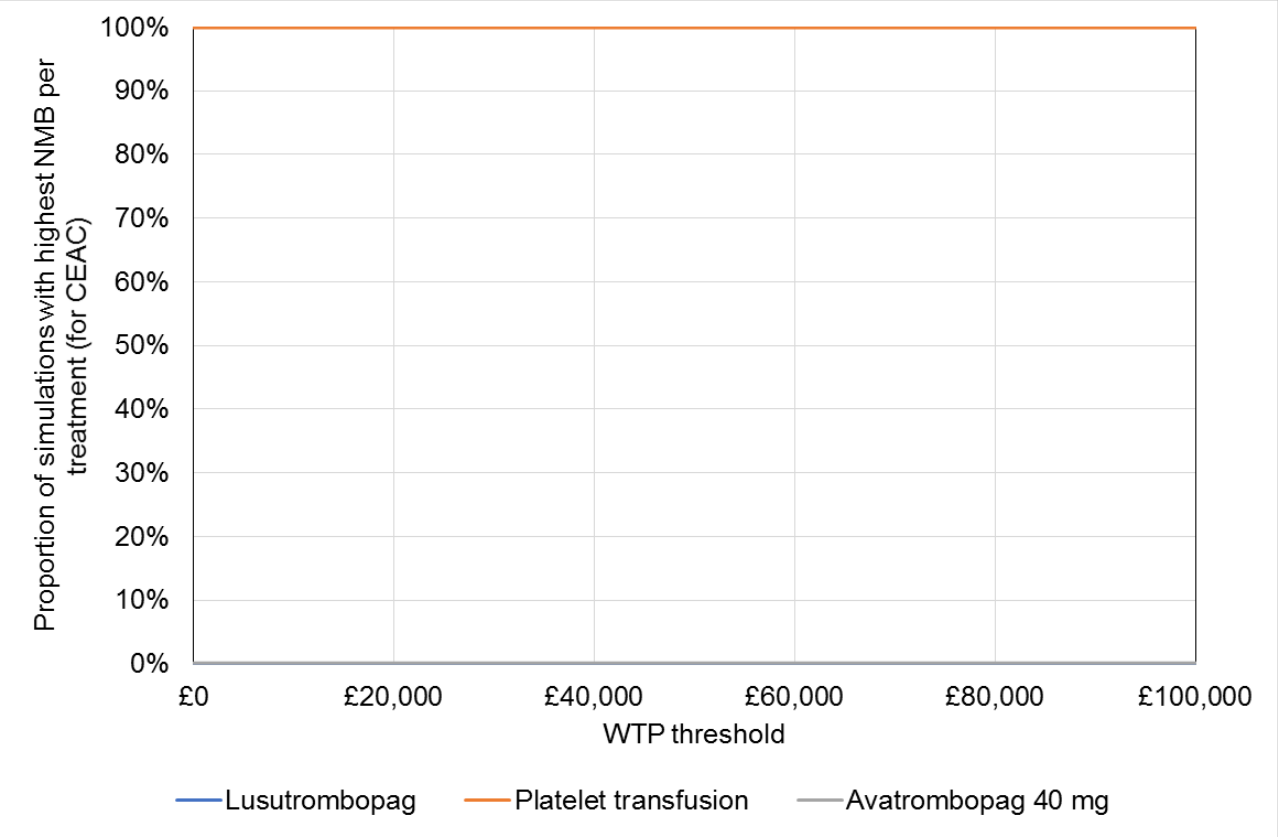


Figure 6.7: Cost effectiveness acceptability curve for platelet count 40,000-50,000/µL



6.3.2.3 Scenario analysis results

Given the uncertainty surrounding the input parameters utilised in the model, the AG conducted a series of scenario analyses for various efficacy, mortality, safety, cost and utility parameters. These scenario analyses are listed below and results for each are provided in the following section.

1. Drug prices
2. Number of ATDs per platelet transfusion
3. Cost of platelet transfusion
4. Cost of rescue therapy
5. Inclusion of Grade 2 bleeding AEs
6. Probability of requiring platelet transfusion estimated from international trials only
7. Cost of PEIP taken from international trials only
8. Literature source for long-term Child-Pugh grade-specific CLD mortality
9. Underreporting factor for SHOT data platelet transfusion specific mortality
10. Alternative literature source for surgery-related mortality
11. Alternative literature source for baseline CLD utility
12. Alternative literature source for bleeding disutility

13. Alternative literature source for PVT disutility
14. Alternative literature source for transfusion-related AE disutilities
15. Alternative values for PEIP delay disutility and duration

1. Drug prices

Given that the AG do not have a price for avatrombopag and given that, when both treatments have such a small impact on total QALYs, costs become very important, some scenarios around the pricing of avatrombopag were thought to be of value. In this scenario analysis, the prices of avatrombopag were lowered, in increments of 10%, by 10-80% from the assumed price of £800. Results displayed in Table 6.13 below show that these drug price reductions slowly reduce the incremental costs and ICER comparing avatrombopag with no TPO-RA. At a 80% price reduction, avatrombopag 40mg dominates no TPO-RA in the 40,000-50,000/µL subgroup and the ICER is within the NICE threshold for avatrombopag 60mg in the <40,000/µL subgroup.

Table 6.13: Scenario analysis – Drug price

Platelet count <40,000/µL Subgroup												
Drug Price	**Lusutrombopag**		**Avatrombopag 60 mg**		no TPO-RA		**Lus vs.** no TPO-RA			**Ava 60 mg vs.** no TPO-RA		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**
£800 (BC)	£2,911	3.3627	£2,961	3.3627	£2,320	3.3626	£592	0.0002	£3,422,801	£641	0.0001	£6,803,898
£720	£2,911	3.3627	£2,881	3.3627	£2,320	3.3626	£592	0.0002	£3,422,801	£561	0.0001	£5,954,692
£640	£2,911	3.3627	£2,801	3.3627	£2,320	3.3626	£592	0.0002	£3,422,801	£481	0.0001	£5,105,486
£560	£2,911	3.3627	£2,721	3.3627	£2,320	3.3626	£592	0.0002	£3,422,801	£401	0.0001	£4,256,281
£480	£2,911	3.3627	£2,641	3.3627	£2,320	3.3626	£592	0.0002	£3,422,801	£321	0.0001	£3,407,075
£400	£2,911	3.3627	£2,561	3.3627	£2,320	3.3626	£592	0.0002	£3,422,801	£241	0.0001	£2,557,869
£320	£2,911	3.3627	£2,481	3.3627	£2,320	3.3626	£592	0.0002	£3,422,801	£161	0.0001	£1,708,664
£240	£2,911	3.3627	£2,401	3.3627	£2,320	3.3626	£592	0.0002	£3,422,801	£81	0.0001	£859,458
£160	£2,911	3.3627	£2,321	3.3627	£2,320	3.3626	£592	0.0002	£3,422,801	£1	0.0001	£10,252
Platelet count 40,000/µL to 50,000/µL Subgroup												
Drug Price	**Lusutrombopag**		**Avatrombopag 40 mg**		**Placebo**		**Lus vs. Placebo**			**Ava 40 mg vs. Placebo**		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**
£800 (BC)	£2,907	3.3625	£2,916	3.3629	£2,283	3.3625	£624	0.0000	£84,890,361, 589	£633	0.0004	£1,529,560
£720	£2,907	3.3625	£2,836	3.3629	£2,283	3.3625	£624	0.0000	£84,890,361, 589	£553	0.0004	£1,336,283
£640	£2,907	3.3625	£2,756	3.3629	£2,283	3.3625	£624	0.0000	£84,890,361, 589	£473	0.0004	£1,143,006
£560	£2,907	3.3625	£2,676	3.3629	£2,283	3.3625	£624	0.0000	£84,890,361,	£393	0.0004	£949,729

									589			
£480	£2,907	3.3625	£2,596	3.3629	£2,283	3.3625	£624	0.0000	£84,890,361, 589	£313	0.0004	£756,452
£400	£2,907	3.3625	£2,516	3.3629	£2,283	3.3625	£624	0.0000	£84,890,361, 589	£233	0.0004	£563,174
£320	£2,907	3.3625	£2,436	3.3629	£2,283	3.3625	£624	0.0000	£84,890,361, 589	£153	0.0004	£369,897
£240	£2,907	3.3625	£2,356	3.3629	£2,283	3.3625	£624	0.0000	£84,890,361, 589	£73	0.0004	£176,620
£160	£2,907	3.3625	£2,276	3.3629	£2,283	3.3625	£624	0.0000	£84,890,361, 589	-£7	0.0004	Dominates
BC = base-case, ICER = incremental cost effectiveness ratio, iDFS = invasive disease-free survival; Incr. = incremental, QALY = quality-adjusted life year												

2. Number of ATDs per platelet transfusion

Given the uncertainty surrounding the number of ATDs per platelet transfusion, scenarios surrounding this variable are important. As shown in Table 6.14 below, the assumption of one ATD per transfusion results in the highest ICER as this results in the lowest cost for platelet transfusion and therefore the biggest incremental cost difference between the treatments and no TPO-RA. The Shionogi base-case of three ATDs per transfusion (equivalent to treating ATDs as the assumed units in the Shionogi model) provides the lowest ICER versus no TPO-RA. However, none of the assumed number of ATDs result in a cost effective option, with an ICER of £631,735 for avatrombopag 40 mg versus no TPO-RA being the lowest ICER observed in these scenarios.

Table 6.14: Scenario analysis – Number of ATDs per platelet transfusion

Platelet count <40,000/µL Subgroup												
No. ATDs	**Lusutrombopag**		**Avatrombopag 60 mg**		no TPO-RA		**Lus vs.** no TPO-RA			**Ava 60 mg vs.** no TPO-RA		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**
[redacted]	£2,900	3.3627	£2,944	3.3627	£2,288	3.3626	£611	0.0002	£3,537,235	£656	0.0001	£6,962,585
[redacted] (AG BC)	£2,911	3.3627	£2,961	3.3627	£2,320	3.3626	£592	0.0002	£3,422,801	£641	0.0001	£6,803,898

[redacted]	£3,001	3.3627	£3,088	3.3627	£2,562	3.3626	£440	0.0002	£2,544,402	£526	0.0001	£5,585,808
3 (Sh BC)	£3,103	3.3627	£3,232	3.3627	£2,835	3.3626	£268	0.0002	£1,551,568	£397	0.0001	£4,209,031
Platelet count 40,000/µL to <50,000/µL Subgroup												
No. ATDs	**Lusutrombopag**		**Avatrombopag 40 mg**		no TPO-RA		**Lus vs.** no TPO-RA			**Ava 40 mg vs.** no TPO-RA		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**
[redacted]	£2,898	3.3625	£2,911	3.3629	£2,255	3.3625	£643	0.0000	£87,422,995,623	£656	0.0004	£1,584,466
[redacted] (AG BC)	£2,907	3.3625	£2,916	3.3629	£2,283	3.3625	£624	0.0000	£84,890,361,589	£633	0.0004	£1,529,560
[redacted]	£2,980	3.3625	£2,958	3.3629	£2,499	3.3625	£481	0.0000	£65,449,720,055	£459	0.0004	£1,108,100
3 (Sh BC)	£3,062	3.3625	£3,004	3.3629	£2,743	3.3625	£320	0.0000	£43,476,444,487	£261	0.0004	£631,735
AG = assessment group, ATD = adult therapeutic dose, BC = base-case, ICER = incremental cost effectiveness ratio, iDFS = invasive disease-free survival; Incr. = incremental, QALY = quality-adjusted life year, Sh = Shionogi												

3. Cost of platelet transfusion

The AG also adjusted the costs of platelet transfusion. The AG base-case cost of [redacted] was replaced by two values calculated by Shionogi in their model. The scenario prices of £517.28, based on the HRG codes for Single Plasma Exchange or Other Intravenous Blood Transfusion, and the Shionogi base-case value of £812.61, assuming three units per transfusion, both resulted in lower ICERs than the AG base-case (Table 6.15). However, none reduced the ICER sufficiently for it to be considered cost effective, with the lowest ICER being £620,415 for avatrombopag 40 mg versus lusutrombopag.

Table 6.15: Scenario analysis – Cost of platelet transfusion

Platelet count <40,000/µL Subgroup					
Cost PT	**Lusutrombopag**	**Avatrombopag 60 mg**	**No TPO-RA**	**Lus vs. No TPO-RA**	**Ava 60 mg vs. No TPO-RA**

	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Incr. Costs (£)	Incr. QALYs	ICER (£)	Incr. Costs (£)	Incr. QALYs	ICER (£)
[redacted]	£2,911	3.3627	£2,961	3.3627	£2,320	3.3626	£592	0.0002	£3,422,801	£641	0.0001	£6,803,898
£517.28	£2,991	3.3627	£3,073	3.3627	£2,533	3.3626	£458	0.0002	£2,649,449	£540	0.0001	£5,731,478
£812.61	£3,106	3.3627	£3,235	3.3627	£2,842	3.3626	£264	0.0002	£1,527,976	£393	0.0001	£4,176,316
Platelet count 40,000/µL to <50,000/µL Subgroup												
Cost PT	**Lusutrombopag**		**Avatrombopag 40 mg**		**No TPO-RA**		**Lus vs. No TPO-RA**			**Ava 40 mg vs. No TPO-RA**		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**
[redacted] (BC)	£2,907	3.3625	£2,916	3.3629	£2,283	3.3625	£633	0.0004	£1,529,560	£633	0.0004	£1,529,560
£517.28	£2,971	3.3625	£2,953	3.3629	£2,473	3.3625	£498	0.0000	£67,774,610,741	£480	0.0004	£1,158,502
£812.61	£3,064	3.3625	£3,005	3.3629	£2,749	3.3625	£316	0.0000	£42,954,304,853	£257	0.0004	£620,415

BC = base-case, ICER = incremental cost effectiveness ratio, iDFS = invasive disease-free survival; Incr. = incremental, PT = platelet transfusion, QALY = quality-adjusted life year

4. Cost of rescue therapy

In the Shionogi model, it was assumed that in clinical practice, rescue therapy would be an additional platelet transfusion. The AG noted that this assumption was not matched by the data presented by the companies, where other methods of rescue were also used by clinicians. However, in the face of uncertainty surrounding what would actually be given in UK practice, the AG cost of platelet transfusion of [redacted] was used in the base-case. The AG clinical expert stated that he would consider giving a combination of platelet transfusion, clotting factors, and tranexamic acid. The cost of this combination was used as an alternative, with a value of [redacted]. The remaining alternative value was based on the Shionogi base-case cost of platelet transfusion of £812.61. As shown in Table 6.16, increasing the cost of rescue therapy decreased the ICER, but not sufficiently to make any of the comparisons with no TPO-RA cost effective.

Table 6.16: Scenario analysis – Cost of rescue therapy

Platelet count <40,000/µL Subgroup												
Cost Rescue	**Lusutrombopag**		**Avatrombopag 60 mg**		**No TPO-RA**		**Lus vs. No TPO-RA**			**Ava 60 mg vs. No TPO-RA**		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**
[redacted] (BC)	£2,911	3.3627	£2,961	3.3627	£2,320	3.3626	£592	0.0002	£3,422,801	£641	0.0001	£6,803,898
[redacted]	£2,917	3.3627	£2,965	3.3627	£2,331	3.3626	£586	0.0002	£3,388,557	£634	0.0001	£6,728,367
£812.61	£2,960	3.3627	£2,999	3.3627	£2,421	3.3626	£540	0.0002	£3,122,610	£579	0.0001	£6,141,783
Platelet count 40,000/µL to <50,000/µL Subgroup												
Cost Rescue	**Lusutrombopag**		**Avatrombopag 40 mg**		**No TPO-RA**		**Lus vs. No TPO-RA**			**Ava 40 mg vs. No TPO-RA**		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**
[redacted] (BC)	£2,907	3.3625	£2,916	3.3629	£2,283	3.3625	£624	0.0000	£84,890,361,589	£633	0.0004	£1,529,560
[redacted]	£2,914	3.3625	£2,919	3.3629	£2,295	3.3625	£619	0.0000	£84,223,078,121	£624	0.0004	£1,507,873
£812.61	£2,963	3.3625	£2,936	3.3629	£2,382	3.3625	£581	0.0000	£79,040,824,307	£554	0.0004	£1,339,450
BC = base-case, ICER = incremental cost effectiveness ratio, iDFS = invasive disease-free survival; Incr. = incremental, QALY = quality-adjusted life year												

5. Inclusion of Grade 2 bleeding AEs

The direction and magnitude of the impact on the ICER due to the inclusion of Grade 2 bleeding events varied depending on which treatment had the highest probability of bleeding, as can be seen in Table 6.17. In the < 40,000 subgroup, avatrombopag patients had the highest probability of bleeding. Including Grade 2 events increased the ICER dramatically. A large impact on the ICER was also seen for lusutrombopag, which had the highest bleeding probability in

the 40-50,000 subgroup, with the inclusion of Grade 2 events decreasing the ICER substantially. However, in the remaining two comparisons, the inclusion of Grade 2 bleeding events had little impact on the ICER.

Table 6.17: Scenario analysis – Inclusion of Grade 2 bleeding AEs

Platelet count < 40,000/µL Subgroup												
Bleed events	**Lusutrombopag**		**Avatrombopag 60 mg**		**No TPO-RA**		**Lus vs. No TPO-RA**			**Ava 60 mg vs. No TPO-RA**		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**
Grade 3+ (BC)	£2,911	3.3627	£2,961	3.3627	£2,320	3.3626	£592	0.0002	£3,422,801	£641	0.0001	£6,803,898
Grade 2+	£2,911	3.3627	£2,961	3.3626	£2,320	3.3625	£592	0.0002	£3,321,286	£641	0.0000	£14,285,918
Platelet count 40,000/µL to < 50,000/µL Subgroup												
Bleed events	**Lusutrombopag**		**Avatrombopag 40 mg**		**No TPO-RA**		**Lus vs. No TPO-RA**			**Ava 40 mg vs. No TPO-RA**		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**
Grade 3+ (BC)	£2,907	3.3625	£2,916	3.3629	£2,283	3.3625	£624	0.0000	£84,890,361,589	£633	0.0004	£1,529,560
Grade 2+	£2,907	3.3624	£2,916	3.3629	£2,283	3.3625	£624	-0.0001	Dominated	£633	0.0004	£1,463,076
BC = base-case, ICER = incremental cost effectiveness ratio, iDFS = invasive disease-free survival; Incr. = incremental, QALY = quality-adjusted life year												

6. Probability of requiring platelet transfusion estimated from international trials only

Using the probability of platelet transfusion estimated only from international trials does not have a substantial impact on the ICER, as shown in Table 6.18. The direction of the impact varies, with the ICER decreasing slightly for the comparison between avatrombopag 60 mg and no TPO-RA, but increasing for all other comparisons with no TPO-RA.

Table 6.18: Scenario analysis – Probability of requiring platelet transfusion estimated from international trials only

Platelet count < 40,000/µL Subgroup												
Prob PT	**Lusutrombopag**		**Avatrombopag 60 mg**		**No TPO-RA**		**Lus vs. No TPO-RA**			**Ava 60 mg vs. No TPO-RA**		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**
All trials (BC)	£2,911	3.3627	£2,961	3.3627	£2,320	3.3626	£592	0.0002	£3,422,801	£641	0.0001	£6,803,898
Inter-national trials	£2,969	3.3627	£2,959	3.3627	£2,319	3.3626	£650	0.0002	£3,821,767	£640	0.0001	£6,796,147
Platelet count 40,000/µL to < 50,000/µL Subgroup												
Prob PT	**Lusutrombopag**		**Avatrombopag 40 mg**		**No TPO-RA**		**Lus vs. No TPO-RA**			**Ava 40 mg vs. No TPO-RA**		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**
All trials (BC)	£2,907	3.3625	£2,916	3.3629	£2,283	3.3625	£624	0.0000	£84,890,361,589	£633	0.0004	£1,529,560
Inter-national trials	£2,946	3.3625	£2,922	3.3629	£2,284	3.3625	£661	-0.0000	Dominated	£638	0.0004	£1,561,315

BC = base-case, ICER = incremental cost effectiveness ratio, iDFS = invasive disease-free survival; Incr. = incremental, PT = platelet transfusion, QALY = quality-adjusted life year

7. Efficacy input from fixed-effects model

As can be seen in Table 6.19, ICERs are very similar between the fixed effect and random effects model for all comparisons.

Table 6.19: Scenario analysis – Efficacy input from fixed-effect model

Platelet count < 40,000/µL Subgroup												
Cost PEIP	**Lusutrombopag**		**Avatrombopag 60 mg**		**No TPO-RA**		**Lus vs. No TPO-RA**			**Ava 60 mg vs. No TPO-RA**		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**
Random effects (BC)	£2,911	3.3627	£2,961	3.3627	£2,320	3.3626	£592	0.0002	£3,422,801	£641	0.0001	£6,803,898
Fixed-effects	£2,939	3.3627	£2,964	3.3627	£2,324	3.3626	£615	0.0002	£3,580,458	£640	0.0001	£6,791,874
Platelet count 40,000/µL to < 50,000/µL Subgroup												
Cost PEIP	**Lusutrombopag**		**Avatrombopag 40 mg**		**No TPO-RA**		**Lus vs. No TPO-RA**			**Ava 40 mg vs. No TPO-RA**		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**
All trials (BC)	£2,907	3.3625	£2,916	3.3629	£2,283	3.3625	£624	0.0000	£84,890,361,589	£633	0.0004	£1,529,560
Fixed-effects	£2,908	3.3625	£2,921	3.3629	£2,285	3.3625	£624	0.0000	£78,479,066,324	£636	0.0004	£1,553,910

BC = base-case, ICER = incremental cost effectiveness ratio, iDFS = invasive disease-free survival; Incr. = incremental, PEIP = planned elective invasive procedure, QALY = quality-adjusted life year

8. Literature source for long-term Child-Pugh grade-specific mortality

While using the UKMi data as the source of long-term mortality estimation substantially reduces the QALYs gained in all treatment groups, the incremental QALYs remain very similar, as shown in Table 6.20. Therefore, the choice of long-term mortality data source has little impact on the ICER.

Table 6.20: Scenario analysis – Long-term Child-Pugh grade-specific CLD mortality

Platelet count <40,000/µL Subgroup												
CLD mortality	**Lusutrombopag**		**Avatrombopag 60 mg**		**No TPO-RA**		**Lus vs. No TPO-RA**			**Ava 60 mg vs. No TPO-RA**		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**
D'amico (BC)	£2,911	3.3627	£2,961	3.3627	£2,320	3.3626	£592	0.0002	£3,422,801	£641	0.0001	£6,803,898
UKMi	£2,911	2.2304	£2,961	2.2303	£2,320	2.2302	£592	0.0002	£3,484,979	£641	0.0001	£6,960,183
Platelet count 40,000/µL to <50,000/µL Subgroup												
CLD mortality	**Lusutrombopag**		**Avatrombopag 40 mg**		**No TPO-RA**		**Lus vs. No TPO-RA**			**Ava 40 mg vs. No TPO-RA**		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**
D'amico (BC)	£2,907	3.3625	£2,916	3.3629	£2,283	3.3625	£624	0.0000	£84,890,361,589	£633	0.0004	£1,529,560
UKMi	£2,907	2.2302	£2,916	2.2306	£2,283	2.2302	£624	-0.0000	Dominated	£633	0.0004	£1,543,029

BC = base-case, ICER = incremental cost effectiveness ratio, iDFS = invasive disease-free survival; Incr. = incremental, QALY = quality-adjusted life year, UKMi = UK Medicines information

9. Under reporting factor for SHOT data platelet transfusion specific mortality

To test the potential impact of under reporting of deaths due to platelet transfusion on the model results, under reporting factors of 10 and 50 (corresponding to incidences of platelet transfusion related deaths of 0.00046% and 0.023%) were tested in scenario analyses. As can be seen in Table 6.21, these increases in platelet transfusion related mortality did substantially decrease the ICER. However, particularly the under reporting factor of 50 was chosen as an extreme value and it is unlikely that incidences would in fact be this high.

Table 6.21: Scenario analysis – Under reporting factor for SHOT data platelet transfusion specific mortality

Platelet count < 40,000/µL Subgroup					
Adjust	**Lusutrombopag**	**Avatrombopag 60**	**No TPO-RA**	**Lus vs. No TPO-RA**	**Ava 60 mg vs. No TPO-RA**

ment			mg									
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Incr. Costs (£)	Incr. QALYs	ICER (£)	Incr. Costs (£)	Incr. QALYs	ICER (£)
Unadjusted (BC)	£2,911	3.3627	£2,961	3.3627	£2,320	3.3626	£592	0.0002	£3,422,801	£641	0.0001	£6,803,898
10	£2,911	3.3627	£2,961	3.3626	£2,320	3.3624	£592	0.0003	£2,329,181	£641	0.0001	£4,276,706
50	£2,911	3.3625	£2,961	3.3622	£2,320	3.3618	£592	0.0006	£962,453	£641	0.0004	£1,613,356
Platelet count 40,000/µL to < 50,000/µL Subgroup												
Adjustment	**Lusutrombopag**		**Avatrombopag 40 mg**		**No TPO-RA**		**Lus vs. No TPO-RA**			**Ava 40 mg vs. No TPO-RA**		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**
Unadjusted (BC)	£2,907	3.3625	£2,916	3.3629	£2,283	3.3625	£624	0.0000	£84,890,361,589	£633	0.0004	£1,529,560
10	£2,907	3.3625	£2,916	3.3629	£2,283	3.3624	£624	0.00007561	£8,253,003	£633	0.0005	£1,243,840
50	£2,907	3.3623	£2,916	3.3628	£2,283	3.3619	£624	0.0004	£1,515,978	£633	0.0009	£679,613
BC = base-case, ICER = incremental cost effectiveness ratio, iDFS = invasive disease-free survival; Incr. = incremental, QALY = quality-adjusted life year												

10. Alternative method for surgery-related mortality

As can be seen in Table 6.22, using the alternative posterior distribution method for calculating pooled surgery-related mortality from the trial data increased QALYs gained by all groups by approximately 0.042 QALYs but did not change the incremental QALYs and therefore the ICER remained unchanged.

Table 6.22: Scenario analysis – Surgery related mortality

Platelet count < 40,000/µL Subgroup					
Surgery mortality	**Lusutrombopag**	**Avatrombopag 60 mg**	**No TPO-RA**	**Lus vs. No TPO-RA**	**Ava 60 mg vs. No TPO-RA**

	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Incr. Costs (£)	Incr. QALYs	ICER (£)	Incr. Costs (£)	Incr. QALYs	ICER (£)
Binomial likelihood with predictive dist (BC)	£2,911	3.3627	£2,961	3.3627	£2,320	3.3626	£592	0.0002	£3,422,801	£641	0.0001	£6,803,898
Posterior dist	£2,911	3.4050	£2,961	3.4049	£2,320	3.4048	£592	0.0002	£3,422,801	£641	0.0001	£6,803,898
Platelet count 40,000/µL to < 50,000/µL Subgroup												
Surgery mortality	**Lusutrombopag**		**Avatrombopag 40 mg**		**No TPO-RA**		**Lus vs. No TPO-RA**			**Ava 40 mg vs. No TPO-RA**		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**
Binomial likelihood with predictive dist (BC)	£2,907	3.3625	£2,916	3.3629	£2,283	3.3625	£624	0.0000	£84,890,361,589	£633	0.0004	£1,529,560
Posterior dist	£2,907	3.4048	£2,916	3.4052	£2,283	3.4048	£624	0.0000	£84,890,371,846	£633	0.0004	£1,529,560

BC = base-case, ICER = incremental cost effectiveness ratio, iDFS = invasive disease-free survival; Incr. = incremental, QALY = quality-adjusted life year

11. Alternative literature source for baseline CLD utility

As shown in Table 6.23, using the Scalone et al. (2013) baseline utility value of 0.801, compared to the base case value of 0.544, increased the QALYs gained by all groups by approximately 1.5 QALYs and resulted in slightly lower ICERs in all comparisons with no TPO-RA.[101] The biggest impact was seen for lusutrombopag versus no TPO-RA in the 40-50,000 subgroup with the ICER approximately halving, however this could be expected as this is the comparison with by far the smallest incremental QALYs, and therefore an increase (even a small one) makes a large impact on the very large ICER.

Table 6.23: Scenario analysis –Baseline CLD utility

Platelet count < 40,000/µL Subgroup												
Utility	**Lusutrombopag**		**Avatrombopag 60 mg**		**No TPO-RA**		**Lus vs. No TPO-RA**			**Ava 60 mg vs. No TPO-RA**		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**
Sullivan (BC)	£2,911	3.3627	£2,961	3.3627	£2,320	3.3626	£592	0.0002	£3,422,801	£641	0.0001	£6,803,898
Scalone	£2,911	4.9559	£2,961	4.9558	£2,320	4.9557	£592	0.0002	£3,340,250	£641	0.0001	£6,598,656
Platelet count 40,000/µL to < 50,000/µL Subgroup												
Utility	**Lusutrombopag**		**Avatrombopag 40 mg**		**No TPO-RA**		**Lus vs. No TPO-RA**			**Ava 40 mg vs. No TPO-RA**		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**
Sullivan (BC)	£2,907	3.3625	£2,916	3.3629	£2,283	3.3625	£624	0.0000	£84,890,361,589	£633	0.0004	£1,529,560
Scalone	£2,907	4.9557	£2,916	4.9561	£2,283	4.9557	£624	0.0000	£156,520,686	£633	0.0004	£1,511,287

BC = base-case, ICER = incremental cost effectiveness ratio, iDFS = invasive disease-free survival; Incr. = incremental, QALY = quality-adjusted life year

12. Alternative literature source for bleeding disutility

The AG could not find any alternative literature sources for the disutility of major bleeds. Therefore, the base-case value was increased and decreased by 25%. The direction of the impact of changes to the bleeding disutility value on the ICER varied depending on which treatment had the highest probability of bleeding, as can be seen in Table 6.24. In the <40,000/µL subgroup, avatrombopag patients had the highest probability of bleeding. Therefore, decreasing the disutility for a major bleed decreased the ICER. The same was seen for lusutrombopag, which had the highest bleeding probability in the 40-50,000/µL subgroup. However, in the remaining two comparisons, increasing the disutility decreased the ICER. However, changes in the ICER were never large enough to change the cost effectiveness decision.

Table 6.24: Scenario analysis - Alternative literature source for bleeding disutility

Platelet count <40,000/µL Subgroup												
Disutility bleed	**Lusutrombopag**		**Avatrombopag 60 mg**		**No TPO-RA**		**Lus vs. No TPO-RA**			**Ava 60 mg vs. No TPO-RA**		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**
0.397	£2,911	3.3627	£2,961	3.3627	£2,320	3.3626	£592	0.0002	£3,422,801	£641	0.0001	£6,803,898
0.298	£2,911	3.3627	£2,961	3.3627	£2,320	3.3626	£592	0.0002	£3,459,576	£641	0.0001	£5,755,569
0.496	£2,911	3.3627	£2,961	3.3626	£2,320	3.3626	£592	0.0002	£3,386,800	£641	0.0001	£8,319,164
Platelet count 40,000/µL to <50,000/µL Subgroup												
Disutility bleed	**Lusutrombopag**		**Avatrombopag 40 mg**		**No TPO-RA**		**Lus vs. No TPO-RA**			**Ava 40 mg vs. No TPO-RA**		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**
0.397	£2,907	3.3625	£2,916	3.3629	£2,283	3.3625	£624	0.0000	£84,890,361,589	£633	0.0004	£1,529,560
0.298	£2,907	3.3626	£2,916	3.3630	£2,283	3.3625	£624	0.0000	£16,349,327	£633	0.0004	£1,554,120
0.496	£2,907	3.3625	£2,916	3.3629	£2,283	3.3625	£624	0.0000	Dominated	£633	0.0004	£1,505,764
BC = base-case, ICER = incremental cost effectiveness ratio, iDFS = invasive disease-free survival; Incr. = incremental, QALY = quality-adjusted life year												

13. Alternative literature source for PVT disutility

The AG could not find any alternative literature sources for the disutility of PVT. Therefore, the base-case value was increased and decreased by 25%. In all cases, decreasing the disutility increased the ICER and vice-versa. However, the impact was small for all comparisons as shown in Table 6.25.

Table 6.25: Scenario analysis - Alternative literature source for PVT disutility

Platelet count < 40,000/µL Subgroup					
Disutility	**Lusutrombopag**	**Avatrombopag 60 mg**	**No TPO-RA**	**Lus vs. No TPO-RA**	**Ava 60 mg vs. No TPO-RA**

PVT	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs	Incr. Costs (£)	Incr. QALYs	ICER (£)	Incr. Costs (£)	Incr. QALYs	ICER (£)
0.029 (BC)	£2,911	3.3627	£2,961	3.3627	£2,320	3.3626	£592	0.0002	£3,422,801	£641	0.0001	£6,803,898
0.022	£2,911	3.3627	£2,961	3.3627	£2,320	3.3626	£592	0.0002	£3,429,543	£641	0.0001	£6,837,935
0.036	£2,911	3.3627	£2,961	3.3627	£2,320	3.3626	£592	0.0002	£3,416,086	£641	0.0001	£6,770,198
Platelet count 40,000/µL to < 50,000/µL Subgroup												
Disutility PVT	**Lusutrombopag**		**Avatrombopag 40 mg**		**No TPO-RA**		**Lus vs. No TPO-RA**			**Ava 40 mg vs. No TPO-RA**		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**
0.029 (BC)	£2,907	3.3625	£2,916	3.3629	£2,283	3.3625	£624	0.0000	£84,890,361,589	£633	0.0004	£1,529,560
0.022	£2,907	3.3625	£2,916	3.3630	£2,283	3.3625	£624	0.0000	£248,437,463	£633	0.0004	£1,494,367
0.036	£2,907	3.3625	£2,916	3.3629	£2,283	3.3625	£624	0.0000	Dominated	£633	0.0004	£1,566,450
BC = base-case, ICER = incremental cost effectiveness ratio, iDFS = invasive disease-free survival; Incr. = incremental, QALY = quality-adjusted life year												

14. Alternative literature source for transfusion-related AE disutilities

Increasing the disutility from 0.1 to 0.17 decreased the ICER marginally in all cases, as can be seen in Table 6.26. However, the impact of the change was small in all cases.

Table 6.26: Scenario analysis –Platelet transfusion AE disutilities

Platelet count < 40,000/µL Subgroup												
Disutility PT AEs	**Lusutrombopag**		**Avatrombopag 60 mg**		**No TPO-RA**		**Lus vs. No TPO-RA**			**Ava 60 mg vs. No TPO-RA**		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**
0.1	£2,911	3.3627	£2,961	3.3627	£2,320	3.3626	£592	0.0002	£3,422,801	£641	0.0001	£6,803,898

(BC)												
0.17 (van Eerd)	£2,911	3.3627	£2,961	3.3627	£2,320	3.3626	£592	0.0002	£3,415,869	£641	0.0001	£6,786,757
Platelet count 40,000/µL to < 50,000/µL Subgroup												
Disutility PT AEs	**Lusutrombopag**		**Avatrombopag 40 mg**		**No TPO-RA**		**Lus vs. No TPO-RA**			**Ava 40 mg vs. No TPO-RA**		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**
0.1 (BC)	£2,907	3.3625	£2,916	3.3629	£2,283	3.3625	£624	0.0000	£84,890,361,589	£633	0.0004	£1,529,560
0.17 (van Eerd)	£2,907	3.3625	£2,916	3.3629	£2,283	3.3625	£624	0.0000	£1,877,500,949	£633	0.0004	£1,528,052
BC = base-case, ICER = incremental cost effectiveness ratio, iDFS = invasive disease-free survival; Incr. = incremental, QALY = quality-adjusted life year												

15. Alternative values for PEIP delay disutility and duration

The ICER is very sensitive to the choice of PEIP delay disutility and duration, as shown in Table 6.27. A 0 disutility results in dominated ICERs for avatrombopag 60 mg versus no TPO-RA in the <40,000/µL subgroup, dominated ICERs for both treatments versus no TPO-RA in the 40-50,000µL subgroup and an ICER over £30,000,000 for the remaining comparison versus no TPO-RA in the <40,000/µL subgroup. Doubling the disutility to 0.144 provides substantially lower ICERs, but they are still not low enough to consider the treatments cost effective.

Table 6.27: Scenario analysis – PEIP delay disutility and duration

Platelet count < 40,000/µL Subgroup												
PEIP delay Disutility	**Lusutrombopag**		**Avatrombopag 60 mg**		**No TPO-RA**		**Lus vs. No TPO-RA**			**Ava 60 mg vs. No TPO-RA**		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**
0	£2,911	3.3631	£2,961	3.3630	£2,320	3.3630	£592	0.0000	£32,339,613	£641	-0.0001	Dominated

0.036, 4weeks	£2,911	3.3629	£2,961	3.3628	£2,320	3.3628	£592	0.0001	£6,190,414	£641	0.0000	£37,853,996
0.072, 4weeks (BC)	£2,911	3.3627	£2,961	3.3627	£2,320	3.3626	£592	0.0002	£3,422,801	£641	0.0001	£6,803,898
0.144, 4weeks	£2,911	3.3624	£2,961	3.3624	£2,320	3.3621	£592	0.0003	£1,807,028	£641	0.0002	£2,576,727
0.072, 2weeks	£2,911	3.3629	£2,961	3.3628	£2,320	3.3628	£592	0.0001	£6,190,414	£641	0.0000	£37,853,996
0.072, 6weeks	£2,911	3.3626	£2,961	3.3625	£2,320	3.3623	£592	0.0003	£2,365,315	£641	0.0002	£3,737,872
Platelet count 40,000/µL to < 50,000/µL Subgroup												
PEIP delay Disutility	**Lusutrombopag**		**Avatrombopag 40 mg**		**No TPO-RA**		**Lus vs. No TPO-RA**			**Ava 40 mg vs. No TPO-RA**		
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**	**Incr. Costs (£)**	**Incr. QALYs**	**ICER (£)**
0	£2,907	3.3628	£2,916	3.3630	£2,283	3.3630	£624	-0.0002	Dominated	£633	0.0000	Dominated
0.036, 4weeks	£2,907	3.3627	£2,916	3.3630	£2,283	3.3628	£624	-0.0001	Dominated	£633	0.0002	£3,081,487
0.072, 4weeks (BC)	£2,907	3.3625	£2,916	3.3629	£2,283	3.3625	£624	0.0000	£84,890,361,589	£633	0.0004	£1,529,560
0.144, 4weeks	£2,907	3.3622	£2,916	3.3629	£2,283	3.3621	£624	0.0002	£4,037,573	£633	0.0008	£762,014
0.072, 2weeks	£2,907	3.3627	£2,916	3.3630	£2,283	3.3628	£624	-0.0001	Dominated	£633	0.0002	£3,081,487
0.072, 6weeks	£2,907	3.3624	£2,916	3.3629	£2,283	3.3623	£624	0.0001	£8,074,763	£633	0.0006	£1,017,245
BC = base case, ICER = incremental cost effectiveness ratio, iDFS = invasive disease-free survival; Incr. = incremental, QALY = quality-adjusted life year												

6.3.2.4 Operational validation efforts on the AG model

The AG conducted the following validation efforts:

- Comparing the clinical outcomes of the AG economic model with those from clinical trials
- Comparing the economic and health outcomes of the AG economic model and the Shionogi economic model.

Comparison of the clinical outcomes from the model with clinical trials

The model outcomes for the primary clinical outcomes (i.e. the proportion of patients who did not receive a platelet transfusion and the proportion of patients that received neither platelet transfusion nor rescue therapy) are compared with the minimum-maximum ranges obtained from the clinical trials (Table 6.28). The model generates outputs within the range of the clinical trial results for lusutrombopag and no TPO-RA. However, for avatrombopag, the model underestimates the clinical trial outcomes for the platelet count < 40,000/µL subgroup and slightly overestimates the clinical trial outcomes for the platelet count 40- 50,000µL subgroup. This gap between the model and trial outcomes can be explained by the fact that in the model the proportions obtained from meta-analyses are used, and for each outcome in each subgroup, a common baseline proportion for the placebo arm was considered, taking account the corresponding placebo proportions from all trials. Since the placebo proportions from ADAPT-1 and ADAPT-2 were different from those in the lusutrombopag trials, this difference is accentuated in the difference between the clinical trial outcomes and the model results based on the meta-analysis results.

Table 6.28: Comparison of model outcomes and the clinical trial outcomes

		% of no TPO-RA patients received no PT	% of lusutrombopag patients received no PT	% of avatrombopag patients received no PT*
Platelet count < 40,000 Subgroup	Model	30.55%	76.93%	57.09%
	Trials (min-max)	(5.3%-54.2%)	[redacted]	(78.9%-82.9%)
Platelet count 40-50,000 Subgroup	Model	38.82%	83.44%	89.92%
	Trials (min-max)	(17.9%-54.5%)	[redacted]	(93.2%-94.8%)
		% of no TPO-RA patients received no PT and no rescue	% of lusutrombopag patients received no PT and no rescue	% of avatrombopag patients received no PT and no rescue *
Platelet count < 40,000 Subgroup	Model	25.20%	69.93%	52.71%
	Trials (min-max)	(5.3%-34.9%)	[redacted]	(65.6%-68.6%)
Platelet count 40-50,000 Subgroup	Model	31.90%	74.17%	86.36%
	Trials (min-max)	(17.9%-40.5%)	[redacted]	(87.9%-88.1%)

*avatrombopag 60 mg is given in the < 40,000 subgroup and avatrombopag 40 mg is given in the 40-50,000 subgroup.
Source: AG model and clinical trials
Abbreviations: PT = platelet transfusion, min = minimum, max = maximum.

Comparison of the clinical outcomes from the AG economic model and Shionogi economic model

For cross-validity, the model outcomes from the AG model and the Shionogi model are compared. The placebo arm platelet transfusion proportions were updated to reflect the lusutrombopag trials in order to improve the comparability (i.e. in the base case, Shionogi model considered 100% platelet transfusion for placebo arm patients). The resulting differences in model outcomes are shown in Table 6.29 below.

The AG model results in less life years and less short-term alive proportions in comparison to the Shionogi model. This is due to the differing surgery mortality inputs for two models.

The platelet transfusion and recue therapy related model outputs differ substantially between Shionogi and AG models. These differences are mostly due to the difference between how the chance node probabilities were obtained. The AG model used formal meta-analysis methods, whereas the Shionogi model used simple pooling.

The QALY difference between the two models is a bit more accentuated in comparison to the life years.

Table 6.29: Differences in model outcomes between the AG and Shionogi models

	AG (<40,000)	**AG (40-50,000)**	**Shionogi model***
Total LYs (discounted)			
Lusutrombopag	7.3961	7.3961	7.7709
Placebo	7.3961	7.3961	7.7496
Total QALYs (discounted)			
Lusutrombopag	3.3627	3.3625	4.0354
Placebo	3.3626	3.3625	4.0236
Proportion receiving no platelet transfusion prior to PEIP			
Lusutrombopag	[redacted]	[redacted]	[redacted]
Placebo	[redacted]		[redacted]
Proportion receiving no rescue therapy and no platelet transfusion			
Lusutrombopag	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]
Proportion not receiving their PEIP within the trial period			
Lusutrombopag	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]
Short-term proportion alive			
Lusutrombopag	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]

*(with actual PT rates from trials used in the placebo arm)
Source: AG economic model and Shionogi economic model
Abbreviations: LYs = life years, PEIP = planned elective invasive procedure, QALYs = quality-adjusted life years.

7. ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES

Given that both avatrombopag and lusutrombopag are taken orally and would be expected to be administered in addition to established clinical practice, no additional change in clinical practice aside from their administration is expected. Indeed, as shown in the cost effectiveness analysis (See Section 6.3.2), there would only be a reduction in the resources currently allocated to this established practice, most notably platelet transfusion.

8. DISCUSSION

8.1 Statement of principle findings

From a comprehensive search, which retrieved 11,305 records, after screening, 35 references pertaining to six studies have been included. The quality of all six studies was at least moderate and both sets of main trials for each of the TPO-RAs, ADAPT-1, ADAPT-2, L-PLUS 1 and L-PLUS 2, were of high quality.

The main finding was that both avatrombopag (for both platelet subgroups) and lusutrombopag, were clearly effective in comparison to no TPO-RA in terms of primary outcome, including that for three of the main trials, ADAPT-1, ADAPT-2 and L-PLUS 2, i.e. avoidance of platelet transfusion or rescue procedure for bleeding.[18, 20] Both avatrombopag and lusutrombopag were also shown to increase the proportion of patients with increased platelet counts or who achieved a particular target i.e. ≥ 20,000/μL above baseline and at least one platelet count >50,000/μL from days 4-8.[18, 19, 21, 52, 56]

Neither avatrombopag nor lusutrombopag were unequivocally better than no TPO-RA in terms of AEs and there was some small amount of evidence to show a higher percentage of deaths with both TPO-RAs.[18, 20]

When the main outcomes of avoidance of the composite outcome no platelets before the elective procedure or rescue therapy or avoidance of platelets only, were analysed according to the subgroups that matched the expected licensed doses of avatrombopag (<40,000/μL for 60 mg or 40,000 to <50,000/μL for 40 mg), both avatrombopag and lusutrombopag were superior to placebo and mostly with a statistically significant difference i.e. 95% confidence intervals did not overlap the point of no difference. The only exception was for the very small JapicCTI-121944 study. However, when the outcome of avoidance of rescue therapy was considered alone, albeit only in those who did not receive platelets before the elective procedure, the lusutrombopag trials were revealed to have a much lower frequency than the ADAPT trials regardless of treatment arm, the explanation for which is not obvious. They also show that there is no statistically significant difference between lusutrombopag and placebo. However, there was a statistically significant difference for avatrombopag in the <40,000/μL subgroup of ADAPT-1 and the 40,000 to <50,000/μL subgroup in ADAPT-2. This did imply an advantage to avatrombopag versus lusutrombopag from the indirect comparison, but which was only statistically significant in the fixed effect analysis of the <40,000/μl subgroup. The proportion of those who received no rescue given receipt of platelets was not available to the AG.

The implications of these results are that both TPO-RAs are effective in reducing platelets prior to the elective procedure. However, there seems to be little difference between them and no TPO-RAs in adverse events including death or in the avoidance of rescue therapy due to bleeding. Neither was there much difference between the two TPO-RAs in any outcome that includes avoidance of platelets and in any of the two main platelet subgroups i.e. <40,000/μL subgroup of ADAPT-1 and the 40,000 to <50,000/μL subgroup. It is interesting to note that this was not the case for the avoidance of rescue therapy given no receipt of platelets: there was some evidence of an advantage to avatrombopag. However, the underlying rate of rescue therapy was much higher in the avatrombopag trials and so this cannot be ruled out as a confounding factor.

When the cost-effectiveness was assessed of both TPO-RAs versus no TPO-RA, it was clear that in terms of quality adjusted life-years there is only a marginal benefit of TPO-RAs over care as usual. When uncertainty is taken into account, both lusutrombopag and avatrombopag have about 50% chance of being more effective than no TPO-RA in terms of QALYs gained. This essentially reduces

the cost effectiveness analysis to a cost minimisation analysis. For both subgroups, no TPO-RA clearly has the lowest costs, even when taking uncertainties into account. Lusutrombopag is about 25% more costly in the <40,000/μL subgroup compared to no TPO-RA, and avatrombopag 28% more costly. For the 40,000 – 50,000/μL subgroup, avatrombopag and lusutrombopag are 28% and 27% more expensive than no TPO-RA, respectively. In the probabilistic sensitivity analysis, it was shown that for all thresholds below £100,000, no TPO-RA had a 100% probability of being cost effective

Various scenario analyses showed that the results are most sensitive to the (currently unknown) price of avatrombopag. If its price were to be 80% below the price of lusutrombopag, avatrombopag would become cost saving in the 40,000 – 50,000/μL subgroup.

A similar pattern is seen for 4 of the 15 other scenario's, "Number of ATDs per platelet transfusion", "Cost of platelet transfusion" and "Underreporting factor for SHOT data platelet transfusion specific mortality". In each of these cases the avatrombopag costs would decrease in the 40,000 – 50,000/μL subgroup to values around 10% more than no TPO-RA, in the most extreme scenarios. However, even then the ICERs would remain very high and clearly out of the range of acceptable ICERs.

8.2 Strengths and limitations of the assessment

Throughout this review, the methods recommended by the Cochrane Collaboration Handbook[9] and the Centre for Reviews and Dissemination (CRD), York[10] were applied in order to reduce the risk of bias and error. This included the search strategy, which was designed to be highly sensitive in order to ensure the lowest risk of missing any relevant studies in either the clinical effectiveness or cost effectiveness sections. Also, all published outcomes in terms of effectiveness and adverse events were extracted. In addition, the AG sought and obtained further data from the companies responsible for each of the interventions in order to inform subgroup analyses necessary to compare them in meta-analyses. All available data were pooled in these meta-analyses and robustness was tested by comparing fixed and random effects analyses as well as sensitivity analyses to test the effect of exclusion of particular studies.

The review was limited initially by lack of much of the data needed to make the comparison between lusutrombopag and avatrombopag in the <40,000/μL and 40,000 to <50,000/μL subgroups. However, this has been largely resolved by the company response to the AG request for clarification.[54, 55] Nevertheless, some of the rescue therapy data for lusutrombopag were not provided in those subgroups. Also, there are inconsistencies in the avatrombopag data, as discussed in Section 8.3. There was also clinical heterogeneity between the lusutrombopag trials as well as between the lusutrombopag and avatrombopag sets of trials. However, statistical heterogeneity was no more than moderate and robustness of outcomes in term of the extent of difference between TPO-RA and no TPO-RA and between both TPO-RAs was demonstrated by sensitivity analyses.

From the cost effectiveness point of view, there were several additional important gaps in the evidence required to conduct the analysis. Most notably, Dova declined to provide a price for avatrombopag. This severely hindered the AG's ability to fairly compare the two treatments in terms of cost effectiveness, as for avatrombopag the same price had to be assumed as lusutrombopag. There was also a lack of consistent reporting and data provision on the content of platelet transfusions, which lead to substantial uncertainty when calculating costs and safety related to platelet transfusion and rescue therapy. This will be discussed further in the next section.

8.3 Uncertainties

There appeared to be a difference in terms of timing of platelet transfusion avoided, the L-PLUS studies specifying prior to the elective procedure and the ADAPT studies specifying up to seven days following randomisation. It is also not clear what the independent contributions of platelet transfusion and rescue procedure are given that nature of the composite outcome.

In the ADAPT trials, all patients received avatrombopag for five days, whereas in the L-PLUS trials, lusutrombopag was administered for between five and seven days depending on platelet count i.e. if the platelet count was at least 50,000/μL with an increase of at least 20,000/μL per litre then no additional dose was given. The implications of this difference are that lusutrombopag was administered on average over a longer period than avatrombopag. However, the implications for clinical practice would depend on the stopping rule. Indeed, it was stated in the EPAR for lusutrombopag that there was "…no clear difference in platelet response for patients without platelet transfusion was found between the group receiving a fixed dosing regimen of 7 days and the group where a stopping criterion was applied." (p.59)[8] However, this same document stated: "The presented data indicate a slightly improved efficacy of lusutrombopag at a fixed 7-day treatment regimen. Conversely, comparative assessment of safety data is uncertain due to the sparsity of data. However, it is considered that the data presented do not implicate a substantial safety issue with regard to a 7-day treatment with lusutrombopag without the application of a stopping criterion." (p. 119) Nevertheless, this same document refers to the absence of a stopping rule in the SmPC.[111] The EPAR for avatrombopag states a fixed time of five days as in the ADAPT trials and so essentially no stopping rule would apply to both drugs in clinical practice. Also, Dova Pharmaceuticals responded to our question regarding this that: "It is expected that all patients who are treated will receive 5 days of dosing. Patients who have been treated in the US have all received 5 days of drug."[55] It therefore seems plausible that should no stopping rule apply that the effectiveness of lusutrombopag might be greater than observed in the L-PLUS trials, but a compromise to safety cannot also be ruled out.

The proportion of those who received no rescue given receipt of platelets was not available to the AG. Shionogi did provide the number of patients who received platelets as rescue in each of the subgroups (Table 5, response to clarification), but they only provided the number of those who received any rescue therapy per trial arm i.e. not in each subgroup.[54] Dova appeared superficially to have provided these numbers in each subgroup, but there was a large discrepancy between the numbers used to inform Table 5.19 and those reported in the response to clarification. For example, the number calculated to receive rescue therapy in the avatrombopag arm of the <40,000/μl subgroup of ADAPT 1 is 71-59 =12. However, the number reported to have received rescue therapy in Table 'Summary of Rescue Therapy – FAS' in the response to clarification is 1.[55] Similarly, the number calculated to receive rescue therapy in the placebo arm of the <40,000/μl subgroup of ADAPT 1 is 26-11 =15, but the corresponding number in the response to clarification is 4.[55]

Although there appeared to be little difference in mortality between each of the TPO-RAs and no TPO-RA, as reported in Table 5.13, follow-up specifically for mortality was unclear and total trial follow-up was short, being no more than five weeks (See Table 5.4). Therefore, longer term outcomes remain uncertain.

In terms of cost effectiveness parameters, one of the biggest uncertainties was the content, and therefore cost, of platelet transfusion. The lack of consistent reporting internationally, as well as between centres, on: definitions such as "units" and "pools", what volume of platelets these correspond to and how this links to UK practice and reference prices, led to substantial uncertainty for this parameter. While the AG were able to estimate a cost based on ATDs through searching UK

guidelines, consulting their clinical expert and using data on the volume of platelets transfused provided by Shionogi in their clarification response, they note that this cost is much smaller than that estimated by Shionogi in their model.[54] As can be seen from scenario analyses surrounding the cost and size of platelet transfusions, assumptions surrounding these aspects have a large impact on the ICER. Given the very small QALY gains associated with these treatments, cost minimisation becomes important. Since the main source of efficacy for these treatments is their ability to avoid platelet transfusions, this is where most of the costs of the drugs are offset. However, the issue is compounded even further, as the other main area where costs can be avoided in the model is a reduction in the number of rescue therapies required, which has a cost also largely dependent on the chosen cost of platelet transfusion. Therefore, the price of platelet transfusion is crucial in determining the price at which these drugs will be cost effective.

An additional source of uncertainty in the model is the effectiveness of the TPO-RA agents in reducing the probability of delays to surgery and the implication this would have in terms of costs and QALYs. The treatment group specific probabilities of delay to surgery were obtained from a single trial (L PLUS 2), which only provided overall probabilities for lusutrombopag and no TPO-RA, which were not separated by subgroup. Furthermore, it was not clear if the reason of surgery postponement was solely due to the thrombocytopenia. Therefore, the AG had to assume that the probability of procedure delay was equal between the two TPO-RAs and equal across subgroups, which may not be a true reflection of reality. Additionally, assumptions had to be made regarding the implication of delays to surgery on costs and utility. The AG assumed a disutility associated with lengthy delays to procedure as they assumed this would impact patients in terms of increased worry and anxiety. However ideally, this assumption would be based on evidence as it is uncertain. The AG also felt it inappropriate to include a sunk cost for cancelled surgeries in the base-case, given that this cost was removed from the reference costs over 10 years ago and under the assumption that surgeon and theatre time would still be efficiently used for other procedures. If there were a cost to the NHS of procedure cancellation or rescheduling, a more substantial disutility associated with delays and the TPO-RA agents are indeed effective in reducing the probability of delay, this would favour the cost-effectiveness of the TPO-RA agents. However, this would probably not be sufficent to make them cost-effective, as the main difference in costs is due to the drug related costs.

8.4 Other relevant factors

There are no other relevant factors to report.

9 CONCLUSIONS

9.1 Implications for service provision

If the aim of service provision is to reduce platelet transfusion prior to elective procedures in those with CLD then both lusutrombopag 3 mg and avatrombopag 60 mg or 40 mg for the <40,000/μL or 40,000 to <50,000/μL subgroups respectively would seem to be able to do that safely. The evidence suggests that avatrombopag might also be able to reduce the need for rescue therapy for bleeding. However, given the large difference between the rates of rescue therapy between the lusutrombopag and avatrombopag trials, it is uncertain what the circumstances are under which this might be observed in clinical practice.

Similarly, from the cost effectiveness point of view, given the lack of difference in long-term QALYs between TPO-RA options and no TPO RA the aim of service provision may become important to the decision. If the aim is to reduce reliance on platelet transfusion, evidence suggests that TPO-RAs are successful in safely achieving this. Therefore, careful consideration must be given to the costs of platelet transfusion versus TPO RA drug costs. If the focus is on long-term QALY benefits, rather than reducing reliance on platelet transfusion, results suggest that the TPO-RA options assessed are not cost effective given current assumptions surrounding costs and effects.

9.2 Suggested research priorities

Given the need to compare the two TPO-RAs and the potential lack of comparability of the extant trials, a head to head trial is warranted. This should ideally measure all relevant outcomes, including risk of platelet transfusion separate to rescue therapy and with a longer follow-up at least of mortality. The trial should be of a size that permits subgroup analysis according to baseline platelet count as well as in terms of CLD type and elective procedure.

Any future trials in this area should focus on consistent collection of data on the content of platelet transfusions in terms of the volume of platelets transfused or consistent and clear definitions such as ATDs so that accurate costs can be calculated. This is particularly important given that the avoidance of platelet transfusion does not seem to translate into differences in QALYs. Therefore, accurate costing is of crucial importance for decision making.

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11 APPENDICES

APPENDIX 1: LITERATURE SEARCH STRATEGIES

Clinical effectiveness, cost effectiveness and safety search strategies

Database/ Resource	Host	Date range	Results	Date Searched
MEDLINE	Ovid	1946 to January week 3 2019	805	24.1.19
MEDLINE Epub Ahead of Print; MEDLINE In-Process & Other Non-Indexed Citations; MEDLINE Daily Update	Ovid	January 23, 2019	89	24.1.19
PubMed	NLM	up to 24 January 2019	255	24.1.19
Embase	Ovid	1974 to 2019 Week 3	1614	24.1.19
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library: Wiley	Issue 1 of 12, January 2019	8	24.1.19
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Library: Wiley	Issue 1 of 12, January 2019	138	24.1.19
KSR Evidence	www.ksrevidence.com	Database last updated 2019 Jan 24	68	24.1.19
Epistemonikos	https://www.epistemonikos .org/en/	up to 24 January 2019	212	24.1.19
Database of Abstracts of Reviews of Effects (DARE)	https://www.crd.york.ac.uk/ CRDWeb/	up to 31 March 2015	19	24.1.19
Health Technology Assessment Database (HTA)	https://www.crd.york.ac.uk/ CRDWeb/	up to 31 March 2015	7	24.1.19
NHS Economic Evaluation Databases (NHS EED)	https://www.crd.york.ac.uk/ CRDWeb/	up to 31 March 2018	11	24.1.19
PROSPERO	https://www.crd.york.ac.uk/ PROSPERO/	up to 24 January 2019	39	24.1.19
Science Citation Index Expanded (SCI)	Web of Science	1988-2019-01-23	722	24.1.19
CINAHL	EBSCO	1982-20190123	122	24.1.19
Latin American and Caribbean Health Sciences (LILACS)	http://lilacs.bvsalud.org/en/	1982-2019/01/24	157	24.1.19
Northern Light Life Sciences Conference Abstracts	Ovid	2010-2019/week 02	227	24.1.19

Transfusion Evidence Library	http://www.transfusionevidencelibrary.com/	up to 23 January 2019	40	23.1.19
RePEc: Research Papers in Economics	http://repec.org/	up to 23 January 2019	14	23.1.19
ClinicalTrials.gov	http://clinicaltrials.gov/ct2/search/advanced	up to 23 January 2019	319	23.1.19
WHO International Clinical Trials Register Portfolio (ICTRP)	http://www.who.int/ictrp/search/en/	up to 23 January 2019	207	23.1.19
US Food & Drug Administration (FDA)	http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm	up to 23 January 2019	4	23.1.19
European Medicines Agency (EMA)	http://www.ema.europa.eu	up to 23 January 2019	2	23.1.19
OAIster	http://oaister.worldcat.org	up to 23 January 2019	37	23.1.19
OpenGrey	www.opengrey.eu/	up to 23 January 2019	41	23.1.19
COPAC	https://copac.jisc.ac.uk/	up to 23 January 2019	90	23.1.19
Total records retrieved			**5247**	
Duplicate records removed			**1729**	
Total records to screen			**3518**	

MEDLINE (Ovid): 1946-2019/January Week 3
MEDLINE Epub Ahead of Print (Ovid): January 22, 2019
MEDLINE In-Process & Other Non-Indexed Citations (Ovid): January 23, 2019
MEDLINE Daily Update (Ovid): January 22, 2019
Searched: 24.1.19

1 (avatrombopag or doptelet or AKR 501 or AKR501 or AS 1670542 or AS1670542 or E 5501 or E5501 or oralE 5501 or oralE5501 or YM 477 or YM477 or 570406-98-3 or 677007-74-8).af. (33)

2 (lusutrombopag or mulpleta or S 888711 or S888711 or 1110766-97-6).af. (14)

3 or/1-2 (46)

4 exp Thrombocytopenia/ (45457)

5 (thrombocytopeni$ or thrombocytopaeni$ or thrombopeni$ or thrombopaeni$ or macrothrombocytopeni$ or macrothrombocytopaeni$).ti,ab,ot,hw. (69081)

6 ((11q or 11q23) adj3 (disorder$ or syndrome$ or delet$ or jacobsen)).ti,ab,ot,hw. (574)

7 (jacobsen adj3 syndrome$).ti,ab,ot,hw. (129)

8 paris trousseau.ti,ab,ot,hw. (30)

9 kasabach merritt.ti,ab,ot,hw. (704)

10 (hemangioma or haemangioma).ti,ab,ot,hw. (32339)

11 (thrombotic adj2 (microangiopath$ or micro angiopath$)).ti,ab,ot,hw. (3354)

12 (hemolytic uremic or haemolytic uremic).ti,ab,ot,hw. (7663)

13 gasser$.ti,ab,ot,hw. (1689)

14 HELLP Syndrome/ (1709)

15 (HELLP adj2 syndrome$).ti,ab,ot,hw. (2561)

16 ((hemolysis or haemolysis) adj2 liver adj2 platelet$).ti,ab,ot,hw. (7)

17 May Hegglin.ti,ab,ot,hw. (221)

18 ((haemolytic or hemolytic) adj2 (anaemi$ or anemi$) adj2 (microangiopathic or micro angiopathic)).ti,ab,ot,hw. (1411)

19 moschcowitz.ti,ab,ot,hw. (107)

20 werlhof.ti,ab,ot,hw. (120)

21 Wiskott-Aldrich Syndrome/ (1428)

22 (wiskott and Aldrich).ti,ab,ot,hw. (3312)

23 (immunodeficiency 2 or immunodeficiency2 or Imd2).ti,ab,ot,hw. (44)

24 ((platelet$ or thrombocyte$) adj3 (defici$ or reduc$ or low or lower or lowest or few or fewer or fewest or decrease or decreases or decreased or defective or destruc$ or destroy$)).ti,ab,ot,hw. (22231)

25 or/4-24 (132417)

26 exp Liver Diseases/ (521414)

27 ((liver$ or hepat$ or intrahepat$) adj2 (disease$ or disorder$ or lesion$)).ti,ab,ot,hw. (163004)

28 (cirrhosis or cirrhoses or cirrhotic).ti,ab,ot,hw. (123945)

29 (chronic adj3 destructive cholangitis).ti,ab,ot,hw. (98)

30 ((fibrosis or fibroses or scar$) adj3 (liver$ or hepat$)).ti,ab,ot,hw. (23356)

31 ((hepatitis or hepatopath$) adj3 (chronic or acute or persistent or long stand$ or long term or recurr$)).ti,ab,ot,hw. (76827)

32 ((liver$ or hepat$ or intrahepat$) adj3 inflam$).ti,ab,ot,hw. (13126)

33 (haemochromatosis or hemochromatosis or bronze$ diabet$ or recklinghausen applebaum or siderochromatosis).ti,ab,ot,hw. (10335)

34 primary biliary cholangitis.ti,ab,ot,hw. (552)

35 ((liver$ or hepat$ or intrahepat$) adj3 carcinoma$).ti,ab,ot,hw. (110103)

36 (hepatocarcinoma or hepatoma$).ti,ab,ot,hw. (30671)

37 or/26-36 (614221)

38 25 and 37 (9693)

39 Receptors, Thrombopoietin/ (1355)

40 ((thrombopoietin$ or c-Mpl) adj3 (agonist$ or agent$ or mimetic$ or receptor$)).ti,ab,ot,hw. (1939)

41 (eltrombopag or promacta or revolade or SB 497115 or SB497115 or 496775-61-2).ti,ab,ot,hw,rn. (631)

42 (romiplostim or nplate or remiplistim or amg 531 or amg531 or 267639-76-9).ti,ab,ot,hw,rn. (521)

43 promegapoietin.ti,ab,ot,hw,rn. (12)

44 Platelet Transfusion/ (6808)

45 ((platelet$ or thrombocyt$) adj3 (transfus$ or infus$ or administ$)).ti,ab,ot,hw. (12351)

46 Splenectomy/ (21173)

47 (splenectom$ or (spleen adj3 (resect$ or remov$ or surg$))).ti,ab,ot,hw. (30967)

48 Splenic Artery/ and Embolization, Therapeutic/ (667)

49 ((spleen or splenic or eria lienalis or lienal) adj3 (embolisation or embolization or embolism or embolus or thrombus or embolotherap$ or therap$ occlus$)).ti,ab,ot,hw. (999)

50 Megakaryocytes/ (7273)

51 ((megakaryocyte$ or karyocyte$) adj3 (stimul$ or maturat$ or produc$)).ti,ab,ot,hw. (1186)

52 Thrombopoiesis/ (848)

53 (thrombopoiesi$ or thrombocytopoies$ or megakaryocytopoies$).ti,ab,ot,hw. (2678)

54 ((platelet$ or thrombocyt$) adj3 (produc$ or formation or stimulat$)).ti,ab,ot,hw. (15525)

55 Portasystemic Shunt, Transjugular Intrahepatic/ (2365)

56 (transjugular intrahepatic portosystemic shunt$ or transjugular intrahepatic porto systemic shunt$ or transjugular intrahepatic portacaval shunt$ or transjugular intrahepatic porta systemic shunt$ or transjugular intrahepatic portasystemic shunt$ or transjugular intrahepatic shunt$ or transjugular intrahepatic stent$ or TIPS or TIPSS).ti,ab,ot,hw. (29852)

57 or/39-56 (96920)

58 38 and 57 (897)

59 3 or 58 (919)

60 exp animals/ not humans/ (4540224)

61 59 not 60 (894)

MEDLINE	**805**
MEDLINE Epub Ahead of Print	**18**
MEDLINE In-Process & Other Non-Indexed Citations	**71**
MEDLINE Daily Update	**0**

PubMed (NLM): up to 24 January 2019

Searched: 24.1.19

#41 (#39 AND #40) 255

#40 pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb] 3121488

#39 (#4 OR #38) 3451

#38 (#26 AND #37) 3428

#37 (#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36) 176154

#36 "Portasystemic Shunt, Transjugular Intrahepatic"[Mesh] OR "transjugular intrahepatic portosystemic shunt"[tiab] OR "transjugular intrahepatic porto systemic shunt"[tiab] OR "transjugular intrahepatic portacaval shunt"[tiab] OR "transjugular intrahepatic porta systemic shunt"[tiab] OR "transjugular intrahepatic portasystemic shunt"[tiab] OR "transjugular intrahepatic shunt"[tiab OR "transjugular intrahepatic stent*"[tiab] OR TIPS[tiab] OR TIPSS[tiab] 29035

#35 (platelet*[tiab] OR thrombocyt*[tiab]) AND (produc*[tiab] OR formation[tiab] OR stimulat*[tiab]) 71046

#34 "Thrombopoiesis"[Mesh] OR thrombopoiesi*[tiab] OR thrombocytopoies*[tiab] OR megakaryocytopoies*[tiab] 2712

#33 "Megakaryocytes"[Mesh] OR (megakaryocyte*[tiab] OR karyocyte*[tiab]) AND (stimul*[tiab] OR maturat*[tiab] OR produc*[tiab]) 4666

#32 (spleen[tiab] OR splenic[tiab] OR "eria lienalis"[tiab] OR lineal[tiab]) AND (embolisation[tiab] OR embolization[tiab] OR embolism[tiab] OR embolus[tiab] OR thrombus[tiab] OR embolotherap*[tiab] OR "therapautic occlusion"[tiab]) 2234

#31 "Splenic Artery"[Mesh] AND "Embolization, Therapeutic"[Mesh] 683

#30 "Splenectomy"[Mesh] OR splenectom*[tiab] OR (spleen[tiab] AND (resect*[tiab] OR remov*[tiab] OR surg*[tiab])) 38387

#29 "Platelet Transfusion"[Mesh] OR ((platelet*[tiab] OR thrombocyt*[tiab]) AND (transfus*[tiab] OR infus*[tiab] OR administ*[tiab])) 47154

#28 eltrombopag[tiab] OR promacta[tiab] OR revolade[tiab] OR "SB 497115"[tiab] OR SB497115[tiab] OR romiplostim[tiab] OR nplate[tiab] OR remiplistim[tiab] OR "amg 531"[tiab] OR amg531[tiab] OR promegapoietin[tiab] 825

#27 "Receptors, Thrombopoietin"[Mesh] OR (thrombopoietin*[tiab] OR c-Mpl[tiab]) AND (agonist*[tiab] OR agent*[tiab] OR mimetic*[tiab] OR receptor*[tiab]) 1980

#26 (#15 AND #25) 11827

#25 (#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24) 649767

#24 (liver*[tiab] OR hepatic[tiab] OR intrahepatic[tiab]) AND carcinoma*[tiab] 75099

#23 haemochromatosis[tiab] OR hemochromatosis[tiab] OR "bronze diabetes"[tiab] OR "bronze diabetic"[tiab] OR "recklinghausen applebaum"[tiab] OR siderochromatosis[tiab] OR "primary biliary cholangitis"[tiab] OR hepatocarcinoma[tiab] OR hepatoma*[tiab] 40197

#22 (liver*[tiab] OR hepatic[tiab] OR intrahepatic[tiab]) AND inflam*[tiab] 57427

#21 (hepatitis[tiab] OR hepatopath*[tiab]) AND (chronic[tiab] OR acute[tiab] OR persistent[tiab] OR "long standing"[tiab] OR "long term"[tiab] OR recurr*[tiab]) 91895

#20 (fibrosis[tiab] OR fibroses[tiab] OR scar*[tiab]) AND (liver*[tiab] OR hepatic[tiab]) 40403

#19 chronic[tiab] AND "destructive cholangitis"[tiab] 118

#18 cirrhosis[tiab] OR cirrhosis[tiab] OR cirrhotic[tiab] 95558

#17 "liver disease"[tiab] OR "liver diseases"[tiab] OR "hepatic disease"[tiab] OR "hepatic diseases"[tiab] OR "intrahepatic disease"[tiab] OR "intrahepatic diseases"[tiab] OR "liver disorder"[tiab] OR "liver disorders"[tiab] OR "hepatic disorder"[tiab] OR "hepatic disorders"[tiab] OR "intrahepatic disorder"[tiab] OR "intrahepatic disorders"[tiab] OR "liver lesion"[tiab] OR "liver lesions"[tiab] OR "hepatic lesion"[tiab] OR "hepatic lesions"[tiab] OR "intrahepatic lesion"[tiab] OR "intrahepatic lesions"[tiab] 108675

#16 "Liver Diseases"[Mesh] 521434

#15 (#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14) 188201

#14 (platelet*[tiab] OR thrombocyte*[tiab]) AND (defici*[tiab] OR reduc*[tiab] OR low[tiab] OR lower[tiab] OR lowest[tiab] OR few[tiab] OR fewer[tiab] OR fewest[tiab] OR decrease[tiab] OR decreases[tiab] OR decreased[tiab] OR defective[tiab] OR destruc*[tiab] OR destroy*[tiab]) 99513

#13 "immunodeficiency 2" OR immunodeficiency2 OR Imd2 46

#12 Moschcowitz[tiab] OR werlhof[tiab] OR "Wiskott-Aldrich Syndrome"[Mesh] OR (wiskott[tiab] AND Aldrich[tiab]) 2664

#11 (haemolytic[tiab] OR hemolytic[tiab]) AND (anaemi*[tiab] OR anemi*[tiab]) AND (microangiopath*[tiab]) 1765

#10 (hemolysis[tiab] OR haemolysis[tiab]) AND liver[tiab] AND platelet*[tiab] 1247

#9 "HELLP Syndrome"[Mesh] OR "HELLP syndrome" OR "HELLP syndromes" 2583

#8 (thrombotic[tiab] AND microangiopath*[tiab]) OR "hemolytic uremic" OR "haemolytic uremic" OR gasser*[tiab] 12074

#7 "jacobsen syndrome" OR "paris trousseau" OR "kasabach merritt" OR "May Hegglin" OR hemangioma[tiab] OR haemangioma[tiab] 17717

#6 (11q[tiab] OR 11q23[tiab]) AND (disorder*[tiab] OR syndrome*[tiab] OR delet*[tiab] OR Jacobsen[tiab]) 1605

#5 "Thrombocytopenia"[Mesh] OR thrombocytopeni*[tiab] OR thrombocytopaeni*[tiab] OR thrombopeni*[tiab] OR thrombopaeni*[tiab] OR macrothrombocytopeni*[tiab] OR macrothrombocytopaeni*[tiab] 73938

#4 (#2 OR #3) 47

#3 lusutrombopag OR mulpleta OR "S 888711" OR S888711 14

#2 avatrombopag OR doptelet OR "AKR 501" OR AKR501 OR "AS 1670542" OR AS1670542 OR "E 5501" OR E5501 OR "oralE 5501" OR oralE5501 OR "YM 477" OR YM477 34

Embase (Ovid): 1974 to 2019 week 3

Searched: 24.1.19

1 avatrombopag/ (64)
2 (avatrombopag or doptelet or AKR 501 or AKR501 or AS 1670542 or AS1670542 or E 5501 or E5501 or oralE 5501 or oralE5501 or YM 477 or YM477 or 570406-98-3 or 677007-74-8).af. (135)
3 lusutrombopag/ (33)
4 (lusutrombopag or mulpleta or S 888711 or S888711 or 1110766-97-6).af. (33)
5 or/1-4 (163)
6 exp thrombocytopenia/ (157171)
7 (thrombocytopeni$ or thrombocytopaeni$ or thrombopeni$ or thrombopaeni$ or macrothrombocytopeni$ or macrothrombocytopaeni$).ti,ab,ot. (87986)
8 ((11q or 11q23) adj3 (disorder$ or syndrome$ or delet$ or jacobsen)).ti,ab,ot. (1015)
9 (jacobsen adj3 syndrome$).ti,ab,ot. (187)
10 paris trousseau.ti,ab,ot. (49)
11 kasabach merritt.ti,ab,ot. (793)
12 (hemangioma or haemangioma).ti,ab,ot. (18275)
13 (thrombotic adj2 (microangiopath$ or micro angiopath$)).ti,ab,ot. (5177)
14 (hemolytic uremic or haemolytic uremic).ti,ab,ot. (7454)
15 gasser$.ti,ab,ot. (1885)
16 (HELLP adj2 syndrome$).ti,ab,ot. (3305)
17 ((hemolysis or haemolysis) adj2 liver adj2 platelet$).ti,ab,ot. (11)
18 May Hegglin.ti,ab,ot. (262)
19 ((haemolytic or hemolytic) adj2 (anaemi$ or anemi$) adj2 (microangiopathic or micro angiopathic)).ti,ab,ot. (2048)
20 moschcowitz.ti,ab,ot. (93)
21 werlhof.ti,ab,ot. (55)
22 (wiskott and aldrich).ti,ab,ot. (2815)
23 (immunodeficiency 2 or immunodeficiency2 or Imd2).ti,ab,ot. (71)
24 ((platelet$ or thrombocyte$) adj3 (defici$ or reduc$ or low or lower or lowest or few or fewer or fewest or decrease or decreases or decreased or defective or destruc$ or destroy$)).ti,ab,ot. (33439)
25 or/6-24 (221567)
26 chronic liver disease/ or liver disease/ or liver cirrhosis/ or liver fibrosis/ or chronic hepatitis/ (244905)
27 ((liver$ or hepat$ or intrahepat$) adj2 (disease$ or disorder$ or lesion$)).ti,ab,ot. (170572)
28 (cirrhosis or cirrhoses or cirrhotic).ti,ab,ot. (134378)
29 ((chronic adj3 nonsuppurative destructive cholangitis) or (chronic adj3 non suppurative destructive cholangitis)).ti,ab,ot. (126)
30 ((fibrosis or fibroses or scar$) adj3 (liver$ or hepat$)).ti,ab,ot. (38165)
31 ((hepatitis or hepatopath$) adj3 (chronic or acute or persistent or long stand$ or long term or recurr$)).ti,ab,ot. (93566)
32 ((liver$ or hepat$ or intrahepat$) adj3 inflam$).ti,ab,ot. (20905)
33 (haemochromatosis or hemochromatosis or bronze$ diabet$ or recklinghausen applebaum or siderochromatosis).ti,ab,ot. (9700)
34 primary biliary cholangitis.ti,ab,ot. (1046)
35 liver cell carcinoma/ (136789)
36 ((liver$ or hepat$ or intrahepat$) adj3 carcinoma$).ti,ab,ot. (122282)
37 (hepatocarcinoma or hepatoma$).ti,ab,ot. (35186)
38 or/26-37 (532951)
39 25 and 38 (13778)

40 thrombopoietin receptor/ (1769)
41 ((thrombopoietin$ or c-Mpl) adj3 (agonist$ or agent$ or mimetic$ or receptor$)).ti,ab,ot. (2199)
42 eltrombopag/ (1783)
43 (eltrombopag or promacta or revolade or SB 497115 or SB497115 or 496775-61-2).ti,ab,ot,hw,rn,tn. (1834)
44 romiplostim/ (1552)
45 (romiplostim or nplate or remiplistim or amg 531 or amg531 or 267639-76-9).ti,ab,ot,hw,rn,tn. (1698)
46 promegapoietin.ti,ab,ot,hw,rn,tn,dj. (25)
47 thrombocyte transfusion/ (17075)
48 ((platelet$ or thrombocyt$) adj3 (transfus$ or infus$ or administ$)).ti,ab,ot. (13882)
49 splenectomy/ (32248)
50 (splenectom$ or (spleen adj2 (resect$ or remov$ or surg$))).ti,ab,ot. (27238)
51 spleen artery/ and exp artificial embolism/ (457)
52 ((spleen or splenic or eria lienalis or lienal) adj3 (embolisation or embolization or embolism or embolus or thrombus or embolotherap$ or therap$ occlus$)).ti,ab,ot. (1536)
53 megakaryocyte/ and (stimulation/ or cell maturation/) (1079)
54 ((megakaryocyte$ or karyocyte$) adj3 (stimul$ or maturat$ or produc$)).ti,ab,ot. (1555)
55 thrombocytopoiesis/ (4137)
56 (thrombopoiesi$ or thrombocytopoies$ or megakaryocytopoies$).ti,ab,ot. (2708)
57 ((platelet$ or thrombocyt$) adj3 (produc$ or formation or stimulat$)).ti,ab,ot. (20991)
58 transjugular intrahepatic portosystemic shunt/ (3426)
59 (transjugular intrahepatic portosystemic shunt$ or transjugular intrahepatic porto systemic shunt$ or transjugular intrahepatic portacaval shunt$ or transjugular intrahepatic porta systemic shunt$ or transjugular intrahepatic portasystemic shunt$ or transjugular intrahepatic shunt$ or transjugular intrahepatic stent$ or TIPS).ti,ab,ot. (35802)
60 or/40-59 (124052)
61 39 and 60 (1558)
62 5 or 61 (1651)
63 animal/ or animal experiment/ (3692962)
64 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot. (4424329)
65 63 or 64 (5722776)
66 exp human/ or human experiment/ (19263219)
67 65 not (65 and 66) (4428740)
68 62 not 67 (1614)

Cochrane Database of Systematic Reviews (CDSR) (Cochrane Library: Wiley): Issue 1 of 12, January 2019

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library: Wiley): Issue 1 of 12, January 2019

Searched: 24.1.19

#1 avatrombopag or doptelet or "AKR 501" or AKR501 or "AS 1670542" or AS1670542 or "E 5501" or E5501 or "oralE 5501" or oralE5501 or "YM 477" or YM477 47

#2 lusutrombopag or mulpleta or "S 888711" or S888711 11

#3 #1 or #2 58

#4 MeSH descriptor: [Thrombocytopenia] explode all trees 1121

#5 (thrombocytopeni* or thrombocytopaeni* or thrombopeni* or thrombopaeni* or macrothrombocytopeni* or macrothrombocytopaeni*):ti,ab,kw 7871

#6 ((11q or 11q23) NEAR/3 (disorder* or syndrome* or delet* or jacobsen)):ti,ab,kw 42

#7 (jacobsen NEAR/3 syndrome*):ti,ab,kw 0

#8 "paris trousseau" 2

#9 "kasabach merritt" 4

#10 (hemangioma or haemangioma):ti,ab,kw 298

#11 (thrombotic NEAR/2 (microangiopath* or micro angiopath*)):ti,ab,kw 70

#12 (hemolytic uremic or haemolytic uremic) 135

#13 (gasser*):ti,ab,kw 100

#14 MeSH descriptor: [HELLP Syndrome] this term only 45

#15 (HELLP NEAR/2 syndrome*):ti,ab,kw 130

#16 ((hemolysis or haemolysis) NEAR/3 platelet*):ti,ab,kw 9

#17 "May Hegglin" 0

#18 ((haemolytic or hemolytic) NEAR/2 (anaemi* or anemi*) NEAR/2 (microangiopathic or micro angiopathic)):ti,ab,kw 16

#19 (moschcowitz):ti,ab,kw 1

#20 (werlhof):ti,ab,kw 0

#21 MeSH descriptor: [Wiskott-Aldrich Syndrome] this term only 6

#22 (wiskott and aldrich):ti,ab,kw 24

#23 ("immunodeficiency 2" or immunodeficiency2 or Imd2):ti,ab,kw 1

#24 ((platelet* or thrombocyte*) NEAR/3 (defici* or reduc* or low or lower or lowest or few or fewer or fewest or decrease or decreases or decreased or defective or destruc* or destroy*)):ti,ab,kw 2416

#25 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 10523

#26 MeSH descriptor: [Liver Diseases] explode all trees 13186

#27 ((liver* or hepat* or intrahepat*) NEAR/2 (disease* or disorder* or lesion*)):ti,ab,kw 7716

#28 (cirrhosis or cirrhoses or cirrhotic):ti,ab,kw 8338

#29 (chronic NEAR/3 destructive cholangitis):ti,ab,kw 1

#30 ((fibrosis or fibroses) NEAR/3 (liver* or hepat*)):ti,ab,kw 1583

#31 ((hepatitis or hepatopath*) NEAR/3 (chronic or acute or persistent or long stand* or long term or recurr*)):ti,ab,kw 9152

#32 ((liver or hepat* or intrahepat*) NEAR/3 inflam*):ti,ab,kw 663

#33 (haemochromatosis or hemochromatosis or bronze* diabet* or recklinghausen applebaum or siderochromatosis):ti,ab,kw 96

#34 primary biliary cholangitis:ti,ab,kw 287

#35 ((liver* or hepat* or intrahepat*) NEAR/3 carcinoma*):ti,ab,kw 3866

#36 (hepatocarcinoma or hepatoma*):ti,ab,kw 172

#37 #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 27420

#38 #25 and #37 787

#39 MeSH descriptor: [Receptors, Thrombopoietin] this term only 45

#40 ((thrombopoietin* or c-Mpl or mpl) NEAR/3 (agonist* or agent* or mimetic* or receptor*)):ti,ab,kw 196

#41 (eltrombopag or promacta or revolade or "SB 497115" or SB497115):ti,ab,kw 198

#42 (romiplostim or nplate or remiplistim or "amg 531" or amg531):ti,ab,kw 157

#43 promegapoietin 0

#44 MeSH descriptor: [Platelet Transfusion] this term only 300

#45 ((platelet* or thrombocyt*) NEAR/3 (transfus* or infus* or administ*)):ti,ab,kw 3034

#46 MeSH descriptor: [Splenectomy] this term only 176

#47 (splenectom* or (spleen NEAR/2 (resect* or remov* or surg*))):ti,ab,kw 617

#48 MeSH descriptor: [Splenic Artery] this term only 18

#49 ((spleen or splenic or eria lienalis or lienal) NEAR/3 (embolisation or embolization or embolism or embolus or thrombus or embolotherap* or "therap* occlus*")):ti,ab,kw 38

#50 MeSH descriptor: [Megakaryocytes] this term only 28

#51 ((megakaryocyte* or karyocyte*) NEAR/3 (stimul* or maturat* or produc*)):ti,ab,kw 27

#52 MeSH descriptor: [Thrombopoiesis] this term only 8

#53 (thrombopoiesi* or thrombocytopoies* or megakaryocytopoies*):ti,ab,kw 89

#54 ((platelet* or thrombocyt*) NEAR/3 (produc* or formation or stimulat*)):ti,ab,kw 848

#55 MeSH descriptor: [Portasystemic Shunt, Transjugular Intrahepatic] this term only94

#56 ("transjugular intrahepatic portosystemic shunt*" or "transjugular intrahepatic porto systemic shunt*" or "transjugular intrahepatic portacaval shunt*" or "transjugular intrahepatic porta systemic shunt*" or "transjugular intrahepatic portasystemic shunt*" or "transjugular intrahepatic shunt*" or "transjugular intrahepatic stent*" or TIPS or TIPSS):ti,ab,kw 1028

#57 #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 5620

#58 #38 and #57 110

#59 #3 or #58 146

CDSR **8**

CENTRAL **138**

KSR Evidence (Internet): Database last updated 2019 Jan 24
www.ksrevidence.com
Searched: 24.1.19

#	Query	Results
1	avatrombopag OR doptelet OR "AKR 501" OR AKR501 OR "AS 1670542" OR AS1670542 OR "E 5501" OR E5501 OR "oralE 5501" OR oralE5501 OR "YM 477" OR YM477 OR lusutrombopag OR mulpleta OR "S 888711" OR S888711 in All text	-
2	thrombocytopeni* OR thrombocytopaeni* OR thrombopeni* OR thrombopaeni* OR macrothrombocytopeni* OR macrothrombocytopaeni* in All text	461
3	(11q OR 11q23) AND (disorder* OR syndrome* OR delet* OR Jacobsen) in All text	-
4	"jacobsen syndrome" OR "paris trousseau" OR "kasabach merritt" OR "May Hegglin" OR hemangioma OR haemangioma in All text	42
5	(thrombotic AND microangiopath*) OR "hemolytic uremic" OR "haemolytic uremic" OR gasser* OR "HELLP syndrome" OR "HELLP syndromes" in All text	46
6	(hemolysis OR haemolysis) AND liver AND platelet* in All text	10

7	(haemolytic OR hemolytic) AND (anaemi* OR anemi*) AND (microangiopath*) in All text	1
8	Moschcowitz OR werlhof OR (wiskott AND Aldrich) in All text	-
9	"immunodeficiency 2" OR immunodeficiency2 OR Imd2 in All text	-
10	(platelet* OR thrombocyte*) AND (defici* OR reduc* OR low OR lower OR lowest OR few OR fewer OR fewest OR decrease OR decreases OR decreased OR defective OR destruc* OR destroy*) in All text	540
11	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10	1027
12	"liver disease" OR "liver diseases" OR "hepatic disease" OR "hepatic diseases" OR "intrahepatic disease" OR "intrahepatic diseases" OR "liver disorder" OR "liver disorders" OR "hepatic disorder" OR "hepatic disorders" OR "intrahepatic disorder" OR "intrahepatic disorders" OR "liver lesion" OR "liver lesions" OR "hepatic lesion" OR "hepatic lesions" OR "intrahepatic lesion" OR "intrahepatic lesions" OR cirrhosis OR cirrhosis OR cirrhotic in All text	994
13	chronic AND "destructive cholangitis" in All text	-
14	(fibrosis OR fibroses OR scar*) AND (liver* OR hepatic) in All text	256
15	(hepatitis OR hepatopath*) AND (chronic OR acute OR persistent OR "long standing" OR "long term" OR recurr*) in All text	488
16	(liver* OR hepatic OR intrahepatic) AND inflam* in All text	165
17	haemochromatosis OR hemochromatosis OR "bronze diabetes" OR "bronze diabetic" OR "recklinghausen applebaum" OR siderochromatosis OR "primary biliary cholangitis" OR hepatocarcinoma OR hepatoma* in All text	29
18	(liver* OR hepatic OR intrahepatic) AND carcinoma* in All text	664
19	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	1885
20	#11 AND #19	68
21	**#1 OR #20**	**68**

Database last updated 24 Jan 2019, 1:06 p.m.

Epistemonikos (Internet): up to 2019 Jan 24
https://www.epistemonikos.org/en/
Searched: 24.1.19

Title/Abstract: avatrombopag OR doptelet OR "AKR 501" OR AKR501 OR "AS 1670542" OR AS1670542 OR "E 5501" OR E5501 OR "oralE 5501" OR oralE5501 OR "YM 477" OR YM477 OR lusutrombopag OR mulpleta OR "S 888711" OR S888711

OR

Title/Abstract: (thrombocytopeni* OR thrombocytopaeni* OR thrombopeni* OR thrombopaeni* OR macrothrombocytopeni* OR macrothrombocytopaeni*) AND ("liver* disease*" OR "hepatic disease*" OR "liver* disorder*" OR "hepatic disorder*" OR "liver* lesion*" OR "hepatic lesion*" OR cirrho* OR fibros* OR "liver* carcinoma*" OR "hepatic carcinoma*")

OR

Title/Abstract: ((platelet* OR thrombocyte*) AND (defici* OR reduc* OR low OR lower OR lowest OR few OR fewer OR fewest OR decrease OR decreases OR decreased OR defective OR destruc* OR destroy*)) AND ("liver* disease*" OR "hepatic disease*" OR "liver* disorder*" OR "hepatic disorder*" OR "liver* lesion*" OR "hepatic lesion*" OR cirrho* OR fibros* OR "liver* carcinoma*" OR "hepatic carcinoma*")

Records retrieved: 212

Database of Abstracts of Reviews of Effects (DARE) (CRD): up to 31 March 2015*
Health Technology Assessment Database (HTA) (CRD): up to 31 March 2018*
NHS Economic Evaluation Databases (NHS EED) (CRD): up to 31 March 2015*
https://www.crd.york.ac.uk/CRDWeb/
Searched: 24.1.19
***DARE and NHS EED have ceased; records were published until 31st March 2015. HTA database records were added until 31st March 2018; updating and addition of new records will resume on the International Network of Agencies for Health Technology Assessment (INAHTA) platform, when it is ready.**

1 (avatrombopag or doptelet or AKR 501 or AKR501 or AS 1670542 or AS1670542 or E 5501 or E5501 or oralE 5501 or oralE5501 or YM 477 or YM477 or 570406-98-3) 2
2 (lusutrombopag or mulpleta or S 888711 or S888711 or 1110766-97-6) 0
3 #1 OR #2 2
4 MeSH DESCRIPTOR Thrombocytopenia EXPLODE ALL TREES 107
5 (thrombocytopeni* or thrombocytopaeni* or thrombopeni* or thrombopaeni* or macrothrombocytopeni* or macrothrombocytopaeni*) 369
6 (11q or 11q23) 0
7 (jacobsen near3 syndrome*) 0
8 (paris trousseau) 0
9 (kasabach merritt) 1
10 (hemangioma or haemangioma) 34
11 (thrombotic near2 (microangiopath* or micro angiopath*)) 0
12 (hemolytic uremic or haemolytic uremic) 14
13 (gasser*) 4
14 MeSH DESCRIPTOR HELLP Syndrome EXPLODE ALL TREES 5
15 (HELLP near2 syndrome*) 11
16 ((hemolysis or haemolysis) near2 liver near2 platelet*) 2
17 (May Hegglin) 0
18 ((haemolytic or hemolytic) near (anaemi* or anemi*)) 18
19 (microangiopath* near thrombotic) 0
20 (moschcowitz or werlhof) 0
21 MeSH DESCRIPTOR Wiskott-Aldrich Syndrome EXPLODE ALL TREES 0
22 (wiskott and Aldrich) 5
23 (immunodeficiency 2 or immunodeficiency2 or Imd2) 1
24 ((platelet* or thrombocyte*) near3 (defici* or reduc* or low or lower or lowest or few or fewer or fewest or decrease or decreases or decreased or defective or destruc* or destroy*)) 24
25 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 467
26 MeSH DESCRIPTOR Liver Diseases EXPLODE ALL TREES 1983
27 ((liver or hepat* or intrahepat*) near (disease* or disorder* or lesion*)) 723
28 (cirrhosis or cirrhoses or cirrhotic) 643
29 (chronic near3 cholangitis) 1
30 ((fibrosis or fibroses or scar*) near3 (liver* or hepat*)) 49

31 ((hepatitis or hepatopath*) near3 (chronic or acute or persistent or long stand* or long term or recurr*)) 547
32 ((liver* or hepat* or intrahepat*) near3 inflam*) 20
33 (haemochromatosis or hemochromatosis or bronze* diabet* or recklinghausen applebaum or siderochromatosis) 37
34 (primary biliary cholangitis) 1
35 ((liver* or hepat* or intrahepat*) near3 carcinoma*) 516
36 (hepatocarcinoma or hepatoma*) 14
37 #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 2427
38 #25 AND #37 36
39 #3 OR #38 37

DARE 19
HTA 7
NHS EED 11

PROSPERO (Internet): up to 24 January 2019
https://www.crd.york.ac.uk/PROSPERO/
Searched 24.1.19

#1 avatrombopag or doptelet or "AKR 501 " or AKR501 or "AS 1670542 " or AS1670542 or "E 5501 " or E5501 or "oralE 5501 " or oralE5501 or "YM 477 " or YM477 or lusutrombopag or mulpleta or "S 888711 " or S888711 3

#2 thrombocytopeni* OR thrombocytopaeni* OR thrombopeni* OR thrombopaeni* OR macrothrombocytopeni* OR macrothrombocytopaeni* 177

#3 (platelet* OR thrombocyte*) AND (defici* OR reduc* OR low OR lower OR lowest OR few OR fewer OR fewest OR decrease OR decreases OR decreased OR defective OR destruc* OR destroy*) 363

#4 #2 OR #3 478

#5 "liver* disease*" OR "hepatic disease*" OR "liver* disorder*" OR "hepatic disorder*" OR "liver* lesion*" OR "hepatic lesion*" OR cirrho* OR fibros* OR "liver* carcinoma*" OR "hepatic carcinoma*" 1205

#6 #4 AND #5 37

#7 #1 OR #6 39

Science Citation Index Expanded (SCI) (Web of Science): 1988-2019-01-23
Searched: 24.1.19

# 38	**722**	**#1 or #37**
# 37	687	#25 and #36
# 36	211,185	#26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35
# 35	170,937	TS=("transjugular intrahepatic portosystemic shunt*" or "transjugular intrahepatic porto systemic shunt*" or "transjugular intrahepatic portacaval shunt*" or "transjugular intrahepatic portal systemic shunt*" or "transjugular intrahepatic portasystemic shunt*" or "transjugular intrahepatic shunt*" or "transjugular intrahepatic stent*" or TIPS or TIPSS)

# 34	15,958	TS=((platelet* or thrombocyt*) NEAR/3 (produc* or formation or stimulat*))
# 33	2,359	TS=(thrombopoiesi* or thrombocytopoies* or megakaryocytopoies*)
# 32	1,088	TS=((megakaryocyte* or karyocyte*) NEAR/3 (stimul* or maturat* or produc*))
# 31	983	TS=((spleen or splenic or "eria lienalis" or lienal) NEAR/3 (embolisation or embolization or embolism or embolus or thrombus or embolotherap* or "therap* occlus*"))
# 30	13,388	TS=(splenectom* or (spleen NEAR/2 (resect* or remov* or surg*)))
# 29	7,879	TS=((platelet* or thrombocyt*) NEAR/3 (transfus* or infus* or administ*))
# 28	780	TS=(romiplostim or nplate or remiplistim or "amg 531" or amg531 or promegapoietin)
# 27	882	TS=(eltrombopag or promacta or revolade or "SB 497115" or SB497115)
# 26	1,591	TS=((thrombopoietin* or c-Mpl) NEAR/3 (agonist* or agent* or mimetic* or receptor*))
# 25	4,437	#16 and #24
# 24	367,240	#17 or #18 or #19 or #20 or #21 or #22 or #23
# 23	148,666	TS=("primary biliary cholangitis") or TS=((liver or hepat* or intrahepat*) NEAR/3 carcinoma*) or TS= (hepatocarcinoma or hepatoma*)
# 22	9,840	TS=(haemochromatosis or hemochromatosis or "bronze* diabet*" or "recklinghausen applebaum" or siderochromatosis)
# 21	16,207	TS=((liver* or hepat* or intrahepat*) NEAR/3 inflam*)
# 20	73,241	TS=((hepatitis or hepatopath*) NEAR/3 (chronic or acute or persistent or "long stand*" or "long term" or recurr*))
# 19	29,320	TS=((fibrosis or fibroses or scar*) NEAR/3 (liver* or hepat*))
# 18	96,017	TS=(cirrhosis or cirrhoses or cirrhotic) or TS= (chronic NEAR/3 "destructive cholangitis")
# 17	121,928	TS=((liver* or hepat* or intrahepat*) NEAR/2 (disease* or disorder* or lesion*))
# 16	98,158	#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
# 15	20,790	TS=((platelet* or thrombocyte*) NEAR/3 (defici* or reduc* or low or lower or lowest or few or fewer or fewest or decrease or decreases or decreased or defective or destruc* or destroy*))
# 14	3,306	TS=(werlhof) or TS=(wiskott and aldrich) or TS=("immunodeficiency 2" or

		immunodeficiency2 or Imd2)
# 13	48	TS=(moschcowitz)
# 12	870	TS=((haemolytic or hemolytic) NEAR/2 (anaemi* or anemi*) NEAR/2 (microangiopathic or "micro angiopathic"))
# 11	170	TS=("May Hegglin")
# 10	272	TS=((hemolysis or haemolysis) NEAR/2 liver NEAR/2 platelet*)
# 9	3,797	TS=(gasser*) or TS=(HELLP NEAR/2 syndrome*)
# 8	10,671	TS=("hemolytic uremic" or "haemolytic uremic")
# 7	3,876	TS=(thrombotic NEAR/2 (microangiopath* or "micro angiopath*"))
# 6	11,949	TS=(hemangioma or haemangioma)
# 5	703	TS=("kasabach merritt")
# 4	189	TS=(jacobsen NEAR/3 syndrome*) OR TS=("paris trousseau" NEAR/3 syndrome*)
# 3	643	TS=((11q or 11q23) NEAR/3 (disorder* or syndrome* or delet* or jacobsen))
# 2	53,278	TS=(thrombocytopeni* or thrombocytopaeni* or thrombopeni* or thrombopaeni* or macrothrombocytopeni* or macrothrombocytopaeni*)
# 1	56	TS=(avatrombopag or doptelet or "AKR 501" or AKR501 or "AS 1670542" or AS1670542 or "E 5501" or E5501 or "oralE 5501" or oralE5501 or "YM 477" or YM477) or TS=(lusutrombopag or mulpleta or "S 888711" or S888711)

CINAHL (EBSCO): 1982-20190123
Searched: 24.1.19

S1	avatrombopag or doptelet or "AKR 501" or AKR501 or "AS 1670542" or AS1670542 or "E 5501" or E5501 or "oralE 5501" or oralE5501 or "YM 477" or lusutrombopag or mulpleta or "S 888711" or S888711	15
S2	(MH "Thrombocytopenia+")	5,320
S3	TI (thrombocytopeni* or thrombocytopaeni* or thrombopeni* or thrombopaeni* or macrothrombocytopeni* or macrothrombocytopaeni*) OR AB (thrombocytopeni* or thrombocytopaeni* or thrombopeni* or thrombopaeni* or macrothrombocytopeni* or macrothrombocytopaeni*)	7,424
S4	TI ((11q or 11q23) N3 (disorder* or syndrome* or delet* or jacobsen)) OR AB ((11q or 11q23) N3 (disorder* or syndrome* or delet* or jacobsen))	33
S5	TI (jacobsen N3 syndrome*) OR AB (jacobsen N3 syndrome*)	8
S6	TI ("paris trousseau" or "kasabach merritt" or "May Hegglin") OR AB ("paris trousseau" or "kasabach merritt" or "May Hegglin")	101

S7	TI (hemangioma or haemangioma) OR AB (hemangioma or haemangioma)	2,028
S8	TI (thrombotic N2 (microangiopath* or "micro angiopath*")) or AB (thrombotic N2 (microangiopath* or "micro angiopath*"))	536
S9	TI ("hemolytic uremic" or "haemolytic uremic" or gasser*) or AB ("hemolytic uremic" or "haemolytic uremic" or gasser*)	824
S10	(MH "HELLP Syndrome")	476
S11	TI (HELLP N2 syndrome*) or AB (HELLP N2 syndrome*)	438
S12	TI ((hemolysis or haemolysis) N2 liver N2 platelet*) or AB ((hemolysis or haemolysis) N2 liver N2 platelet*)	78
S13	TI ((haemolytic or hemolytic) N2 (anaemi* or anemi*) N2 (microangiopathic or micro angiopathic)) or AB ((haemolytic or hemolytic) N2 (anaemi* or anemi*) N2 (microangiopathic or micro angiopathic))	159
S14	TI ((microangiopath* or micro angiopath*) N2 thrombotic) or AB ((microangiopath* or micro angiopath*) N2 thrombotic)	536
S15	TI (moschcowitz or werlhof or (wiskott and Aldrich)) or AB (moschcowitz or werlhof or (wiskott and Aldrich))	93
S16	(MH "Wiskott-Aldrich Syndrome")	52
S17	TI ("immunodeficiency 2" or immunodeficiency2 or Imd2) or AB ("immunodeficiency 2" or immunodeficiency2 or Imd2)	1
S18	TI ((platelet* or thrombocyte*) N3 (defici* or reduc* or low or lower or lowest or few or fewer or fewest or decrease or decreases or decreased or defective or destruc* or destroy*)) or AB ((platelet* or thrombocyte*) N3 (defici* or reduc* or low or lower or lowest or few or fewer or fewest or decrease or decreases or decreased or defective or destruc* or destroy*))	2,419
S19	S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18	14,324
S20	(MH "Liver Diseases+")	55,452
S21	TI ((liver* or hepat* or intrahepat*) N2 (disease* or disorder* or lesion*)) OR AB ((liver* or hepat* or intrahepat*) N2 (disease* or disorder* or lesion*))	14,234
S22	TI (cirrhosis or cirrhoses or cirrhotic) or AB (cirrhosis or cirrhoses or cirrhotic)	7,845
S23	TI (chronic N3 destructive cholangitis) or AB (chronic N3 destructive cholangitis)	3
S24	TI ((fibrosis or fibroses or scar*) N3 (liver* or hepat*)) or AB ((fibrosis or fibroses or scar*) N3 (liver* or hepat*))	2,587
S25	TI ((hepatitis or hepatopath*) N3 (chronic or acute or persistent or "long stand*" or "long term" or recurr*)) or AB ((hepatitis or hepatopath*) N3 (chronic or acute or persistent or "long stand*" or "long term" or recurr*))	6,144
S26	TI ((liver* or hepat* or intrahepat*) N3 inflam*) or AB ((liver* or hepat* or intrahepat*) N3 inflam*)	1,639
S27	TI (haemochromatosis or hemochromatosis or "bronze* diabet*" or "recklinghausen applebaum" or siderochromatosis or "primary biliary cholangitis") or AB (haemochromatosis or hemochromatosis or "bronze* diabet*" or "recklinghausen	813

	applebaum" or siderochromatosis or "primary biliary cholangitis")	
S28	TI ((liver* or hepat* or intrahepat*) N3 carcinoma*) or AB ((liver* or hepat* or intrahepat*) N3 carcinoma*)	9,387
S29	TI (hepatocarcinoma or hepatoma*) or AB (hepatocarcinoma or hepatoma*)	799
S30	S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29	66,144
S31	S19 and S30	972
S32	TI ((thrombopoietin* or c-Mpl) N3 (agonist* or agent* or mimetic* or receptor*)) or AB ((thrombopoietin* or c-Mpl) N3 (agonist* or agent* or mimetic* or receptor))	184
S33	TI (eltrombopag or promacta or revolade or "SB 497115" or SB497115) or AB (eltrombopag or promacta or revolade or "SB 497115" or SB497115)	171
S34	TI (romiplostim or nplate or remiplistim or "amg 531" or amg531 or promegapoietin) or AB (romiplostim or nplate or remiplistim or "amg 531" or amg531 or promegapoietin)	146
S35	(MH "Platelet Transfusion")	1,182
S36	TI ((platelet* or thrombocyt*) N3 (transfus* or infus* or administ*)) or AB ((platelet* or thrombocyt*) N3 (transfus* or infus* or administ*))	1,250
S37	(MH "Splenectomy")	1,354
S38	TI (splenectom* or (spleen N3 (resect* or remov* or surg*))) or AB (splenectom* or (spleen N3 (resect* or remov* or surg*)))	1,636
S39	(MH "Splenic Artery") AND (MH "Embolization, Therapeutic+")	155
S40	TI ((spleen or splenic or "eria lienalis " or lienal) N3 (embolisation or embolization or embolism or embolus or thrombus or embolotherap* or therap* occlus*)) or AB ((spleen or splenic or "eria lienalis " or lienal) N3 (embolisation or embolization or embolism or embolus or thrombus or embolotherap* or therap* occlus*))	234
S41	TI ((megakaryocyte* or karyocyte*) N3 (stimul* or maturat* or produc*)) or AB ((megakaryocyte* or karyocyte*) N3 (stimul* or maturat* or produc*))	28
S42	TI (thrombopoiesi* or thrombocytopoies* or megakaryocytopoies*) or AB (thrombopoiesi* or thrombocytopoies* or megakaryocytopoies*)	67
S43	TI ((platelet* or thrombocyt*) N3 (produc* or formation or stimulat*)) or AB ((platelet* or thrombocyt*) N3 (produc* or formation or stimulat*))	962
S44	(MH "Portasystemic Shunt, Surgical")	895
S45	TI ("transjugular intrahepatic portosystemic shunt*" or "transjugular intrahepatic porto systemic shunt*" or "transjugular intrahepatic portacaval shunt*" or "transjugular intrahepatic porta systemic shunt*" or "transjugular intrahepatic portasystemic shunt*" or "transjugular intrahepatic shunt*" or "transjugular intrahepatic stent*" or TIPS or TIPSS) or AB ("transjugular intrahepatic portosystemic shunt*" or "transjugular intrahepatic porto systemic shunt*" or "transjugular intrahepatic portacaval shunt*" or "transjugular intrahepatic porta systemic shunt*" or "transjugular intrahepatic portasystemic shunt*" or "transjugular intrahepatic shunt*" or "transjugular intrahepatic stent*" or TIPS or TIPSS)	22,430
S46	S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45	28,031

S47	S31 and S46	113
S48	**S1 or S47**	**122**

Latin American and Caribbean Health Sciences (LILACS) (Internet): 1982-2019/01/24
http://lilacs.bvsalud.org/en/
Searched: 24.1.19

((MH:c15.378.140.855 OR MH:c15.378.100.100.970 OR thrombocytopeni* OR thrombocytopaeni* OR thrombopeni* OR thrombopaeni* OR macrothrombocytopeni* OR macrothrombocytopaeni* OR trombocitopeni* OR ((platelet* OR thrombocyte*) AND (defici* OR reduc* OR low OR lower OR lowest OR few OR fewer OR fewest OR decrease OR decreases OR decreased OR defective OR destruc* OR destroy*))) AND (MH:C06.552 or "liver disease" OR "liver diseases" OR "hepatic disease" OR "hepatic diseases" OR "intrahepatic disease" OR "intrahepatic diseases" OR "liver disorder" OR "liver disorders" OR "hepatic disorder" OR "hepatic disorders" OR "intrahepatic disorder" OR "intrahepatic disorders" OR "liver lesion" OR "liver lesions" OR "hepatic lesion" OR "hepatic lesions" OR "intrahepatic lesion" OR "intrahepatic lesions" OR hepatopatias OR cirrhosis OR cirrhoses OR cirrhotic OR cirrose OR cirrosis OR ((liver$ OR hepatic OR intrahepatic) AND carcinoma$))) OR (avatrombopag OR doptelet OR "AKR 501" OR akr501 OR "AS 1670542" OR as1670542 OR "E 5501" OR e5501 OR "oralE 5501" OR orale5501 OR "YM 477" OR ym477 OR lusutrombopag OR mulpleta OR "S 888711" OR s888711)

Search limited to non-Medline databases:
- **LILACS (89)**
- **IBECS (45)**
- **BINACIS (13)**
- **CUMED (4)**
- **MedCarib (4)**
- **LIS -Health Information Locator (1)**
- **Index Psychology - Theses (1)**

Northern Light Life Sciences Conference Abstracts (Ovid): 2010-2019/week 02
Searched: 24.1.19

1 (avatrombopag or doptelet or AKR 501 or AKR501 or AS 1670542 or AS1670542 or E 5501 or E5501 or oralE 5501 or oralE5501 or YM 477 or YM477).af. (15)
2 (lusutrombopag or mulpleta or S 888711 or S888711 or 1110766-97-6).af. (10)
3 1 or 2 (25)
4 exp thrombocytopenia/ (19173)
5 (thrombocytopeni$ or thrombocytopaeni$ or thrombopeni$ or thrombopaeni$ or macrothrombocytopeni$ or macrothrombocytopaeni$).ti,ab,hw. (18543)
6 ((11q or 11q23) adj3 (disorder$ or syndrome$ or delet$ or jacobsen)).ti,ab,hw. (132)
7 (jacobsen adj3 syndrome$).ti,ab,hw. (41)
8 (paris trousseau or kasabach merritt or hemangioma or haemangioma).ti,ab,hw. (2487)
9 (thrombotic adj2 (microangiopath$ or micro angiopath$)).ti,ab,hw. (1515)
10 (hemolytic uremic or haemolytic uremic or gasser$).ti,ab,hw. (643)
11 hellp syndrome/ (410)
12 (HELLP adj2 syndrome$).ti,ab,hw. (415)

13 ((hemolysis or haemolysis) adj2 liver adj2 platelet$).ti,ab,hw. (0)

14 May Hegglin.ti,ab,hw. (10)

15 ((haemolytic or hemolytic) adj2 (anaemi$ or anemi$) adj2 (microangiopathic or micro angiopathic)).ti,ab,hw. (77)

16 (moschcowitz or werlhof or (wiskott and Aldrich)).ti,ab,hw. (468)

17 wiskott-aldrich syndrome/ (460)

18 (immunodeficiency 2 or immunodeficiency2 or Imd2).ti,ab,hw. (0)

19 ((platelet$ or thrombocyte$) adj3 (defici$ or reduc$ or low or lower or lowest or few or fewer or fewest or decrease or decreases or decreased or defective or destruc$ or destroy$)).ti,ab,hw. (1916)

20 or/4-19 (24421)

21 exp Liver Diseases/ (70505)

22 ((liver$ or hepat$ or intrahepat$) adj2 (disease$ or disorder$ or lesion$)).ti,ab,hw. (27653)

23 (cirrhosis or cirrhoses or cirrhotic).ti,ab,hw. (14624)

24 (chronic adj3 destructive cholangitis).ti,ab,hw. (3)

25 ((fibrosis or fibroses or scar$) adj3 (liver$ or hepat$)).ti,ab,hw. (4585)

26 ((hepatitis or hepatopath$) adj3 (chronic or acute or persistent or long stand$ or long term or recurr$)).ti,ab,hw. (8107)

27 ((liver$ or hepat$ or intrahepat$) adj3 inflam$).ti,ab,hw. (1780)

28 (haemochromatosis or hemochromatosis or bronze$ diabet$ or recklinghausen applebaum or siderochromatosis).ti,ab,hw. (1151)

29 primary biliary cholangitis.ti,ab,hw. (230)

30 ((liver$ or hepat$ or intrahepat$) adj3 carcinoma$).ti,ab,hw. (13730)

31 (hepatocarcinoma or hepatoma$).ti,ab,hw. (900)

32 or/21-31 (89117)

33 20 and 32 (2415)

34 thrombopoietin/ (1145)

35 ((thrombopoietin$ or c-Mpl) adj3 (agonist$ or agent$ or mimetic$ or receptor$)).ti,ab,hw. (206)

36 (eltrombopag or promacta or revolade or SB 497115 or SB497115 or 496775-61-2).ti,ab,hw. (279)

37 (romiplostim or nplate or remiplistim or amg 531 or amg531 or 267639-76-9).ti,ab,hw. (256)

38 promegapoietin.ti,ab,hw. (0)

39 ((platelet$ or thrombocyt$) adj3 (transfus$ or infus$ or administ$)).ti,ab,hw. (896)

40 (splenectom$ or (spleen adj3 (resect$ or remov$ or surg$))).ti,ab,hw. (1139)

41 ((spleen or splenic or eria lienalis or lienal) adj3 (embolisation or embolization or embolism or embolus or thrombus or embolotherap$ or therap$ occlus$)).ti,ab,hw. (141)

42 megakaryocytes/ (2226)

43 ((megakaryocyte$ or karyocyte$) adj3 (stimul$ or maturat$ or produc$)).ti,ab,hw. (72)

44 (thrombopoiesi$ or thrombocytopoies$ or megakaryocytopoies$).ti,ab,hw. (114)

45 ((platelet$ or thrombocyt$) adj3 (produc$ or formation or stimulat$)).ti,ab,hw. (944)

46 (transjugular intrahepatic portosystemic shunt$ or transjugular intrahepatic porto systemic shunt$ or transjugular intrahepatic portacaval shunt$ or transjugular intrahepatic porta systemic shunt$ or transjugular intrahepatic portasystemic shunt$ or transjugular intrahepatic shunt$ or transjugular intrahepatic stent$ or TIPS or TIPSS).ti,ab,hw. (2278)

47 or/34-46 (8073)

48 33 and 47 (221)

49 3 or 48 (227)

Transfusion Evidence Library (Internet): up to 23 January 2019
http://www.transfusionevidencelibrary.com/
Searched: 23.1.19

(avatrombopag OR doptelet OR lusutrombopag OR mulpleta) OR ((thrombocytopeni* OR thrombocytopaeni* OR thrombopeni* OR thrombopaeni* OR macrothrombocytopeni* OR macrothrombocytopaeni* OR (platelet* OR thrombocyte*) AND (defici* OR reduc* OR low OR lower OR lowest OR few OR fewer OR fewest OR decrease OR decreases OR decreased OR defective OR destruc* OR destroy*)) AND ("liver disease*" OR "hepatic disease*" OR "liver disorder*" OR "hepatic disorder*" OR "liver lesion*" OR "hepatic lesion*" OR cirrhosis OR cirrhosis OR cirrhotic OR "liver* carcinoma*" OR "hepatic carcinoma*"))

Records retrieved: 40

RePEc (Internet): up to 23 January 2019
http://repec.org/
Searched: 23.1.19

IDEAS search interface

(avatrombopag | doptelet | lusutrombopag | mulpleta | thrombocytopenia | thrombocytopenic | thrombocytopaenia | thrombocytopaenic | thrombopenia | thrombopenic | thrombopaenia | thrombopaenic)

Records retrieved: 14

Clinicaltrials.gov (Internet): up to 23 January 2019
http://clinicaltrials.gov/ct2/search/advanced
Searched: 23.1.19

(avatrombopag OR doptelet OR "AKR 501" OR AKR501 OR "AS 1670542" OR AS1670542 OR "E 5501" OR E5501 OR "oralE 5501" OR oralE5501 OR "YM 477" OR YM477 OR lusutrombopag OR mulpleta OR "S 888711" OR S888711) OR ((thrombocytopenia OR thrombocytopenic OR thrombocytopaenia OR thrombocytopaenic OR thrombopenia OR thrombopenic OR thrombopaenia OR thrombopaenic OR macrothrombocytopenia OR macrothrombocytopenic OR macrothrombocytopaenia OR macrothrombocytopaenic) AND (liver OR hepatic OR intrahepatic OR cirrhosis OR cirrhoses OR cirrhotic))

319 Studies found

WHO International Clinical Trials Register Portfolio (ICTRP) (Internet): up to 23 January 2019
http://www.who.int/ictrp/search/en/
Searched: 23.1.19

Advanced search option

	Results
Intervention: avatrombopag OR doptelet OR AKR 501 OR AKR501 OR AS 1670542 OR AS1670542 OR E 5501 OR E5501 OR oralE 5501 OR oralE5501 OR YM 477 OR YM477 OR lusutrombopag OR mulpleta OR S 888711 OR S888711	(49 records for) **20** trials found
Condition: thrombocytopeni* OR thrombocytopaeni* OR thrombopeni* OR thrombopaeni* OR macrothrombocytopeni* OR macrothrombocytopaenia* *Intervention*: thrombopoietin receptor OR thrombopoietin agonist OR thrombopoietin agent	(25 records for) **25** trials found
Condition: thrombocytopeni* OR thrombocytopaeni* OR thrombopeni* OR thrombopaeni* OR macrothrombocytopeni* OR macrothrombocytopaeni* *Intervention*: eltrombopag OR promacta OR revolade or SB 497115 or SB497115 or 496775-61-2	(234 records for) **97** trials found
Condition: thrombocytopeni* OR thrombocytopaeni* OR thrombopeni* OR thrombopaeni* OR macrothrombocytopeni* OR macrothrombocytopaeni* *Intervention*: romiplostim OR nplate OR remiplistim OR amg 531 OR amg531 OR 267639-76-9 OR promegapoietin	(140 records for) **56** trials found
Condition: thrombocytopeni* OR thrombocytopaeni* OR thrombopeni* OR thrombopaeni* OR macrothrombocytopeni* OR macrothrombocytopaenia* *Intervention*: platelet transfusion OR platelet infusion OR platelet administration OR thrombocyt* transfusion OR thrombocyt* infusion OR thrombocyt* administration	(15 records for) **14** trials found
Condition: thrombocytopeni* OR thrombocytopaeni* OR thrombopeni* OR thrombopaeni* OR macrothrombocytopeni* OR macrothrombocytopaenia* *Intervention*: splenectomy OR spleen resection OR spleen remove OR spleen surgery	(4 records for) **4** trials found
Condition: thrombocytopeni* OR thrombocytopaeni* OR thrombopeni* OR thrombopaeni* OR macrothrombocytopeni* OR macrothrombocytopaenia* *Intervention*: embolisation OR embolism OR thrombus	(1 record for) **1** trial found
Condition: thrombocytopeni* OR thrombocytopaeni* OR thrombopeni* OR thrombopaeni* OR macrothrombocytopeni* OR macrothrombocytopaenia* *Intervention*: megakaryocyte OR karyocyte	(1 record for) **1** trial found

Condition: thrombocytopeni* OR thrombocytopaeni* OR thrombopeni* OR thrombopaeni* OR macrothrombocytopeni* OR macrothrombocytopaenia* *Intervention*: thrombopoiesis OR thrombocytopoies OR megakaryocytopoies	(0 records for) **0** trials found
Condition: thrombocytopeni* OR thrombocytopaeni* OR thrombopeni* OR thrombopaeni* OR macrothrombocytopeni* OR macrothrombocytopaenia* *Intervention*: platelet production OR thrombocyt* production OR platelet formation OR thrombocyt* formation OR platelet stimulation OR thrombocyt* stimulation	(0 records for) **0** trials found
Total	**218**
Total after dedup	**207**

US Food & Drug Administration (FDA) (Internet): up to 23 January 2019
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
Searched 23.1.19

Drugs@FDA searched

Drug Name	**Results**
doptelet (avatrombopag)	1
mulpleta (lusutrombopag)	1
promacta (eltrombopag)	1
nplate (romiplostim)	1
promegapoietin	0
Total	**4**

European Medicines Agency (EMA) (Internet): up to 23 January 2019
http://www.ema.europa.eu
Searched 23.1.19

Medicines; Search; European public assessment reports (EPAR)	**EPARs**
doptelet (avatrombopag)	0
mulpleta (lusutrombopag)	0
revolade (eltrombopag, promacta)	1
nplate (romiplostim)	1

promegapoietin	0
Total	**2**

OAIster (Internet): up to 23 January 2019
http://oaister.worldcat.org
Searched: 23.1.19

(avatrombopag OR doptelet OR lusutrombopag OR mulpleta) OR ((thrombocytopeni* OR thrombocytopaeni* OR thrombopeni* OR thrombopaeni*) AND (liver* OR hepat*) AND (thrombopoietin* receptor* OR thrombopoietin* agonist* OR thrombopoietin* agent* OR eltrombopag OR promacta OR revolade OR romiplostim OR nplate OR platelet transfus* OR platelet infus* OR platelet admin* OR thrombocyt* transf* OR thrombocyt* infus* OR thrombocyt* admin* OR splenectom* OR spleen resect* OR spleen remov* OR spleen surger* OR emboli* OR thrombus OR megakaryocyte* OR karyocyte* OR thrombopoiesis OR thrombocytopoies OR megakaryocytopoies OR platelet produc* OR thrombocyt* produc* OR platelet forma* OR thrombocyt* forma* OR platelet stimul* OR thrombocyt* stimul*))

Records retrieved: 37

OpenGrey (Internet): up to 23 January 2019
www.opengrey.eu/
Searched: 23.1.19

(avatrombopag OR doptelet OR lusutrombopag OR mulpleta) OR ((thrombocytopeni* OR thrombocytopaeni* OR thrombopeni* OR thrombopaeni*) AND ((thrombopoietin* NEAR receptor*) OR (thrombopoietin* NEAR agonist*) OR (thrombopoietin* NEAR agent*) OR eltrombopag OR promacta OR revolade OR romiplostim OR nplate OR (platelet NEAR transfus*) OR (platelet NEAR infus*) OR (platelet NEAR admin*) OR (thrombocyt* NEAR transf*) OR (thrombocyt* NEAR infus*) OR (thrombocyt* NEAR admin*) OR splenectom* OR (spleen NEAR resect*) OR (spleen NEAR remov*) OR (spleen NEAR surger*) OR emboli* OR thrombus OR megakaryocyte* OR karyocyte* OR thrombopoiesis OR thrombocytopoies OR megakaryocytopoies OR (platelet NEAR produc*) OR (thrombocyt* NEAR produc*) OR (platelet NEAR forma*) OR (thrombocyt* NEAR forma*) OR (platelet NEAR stimul*) OR (thrombocyt* NEAR stimul*))

Records retrieved: 41

COPAC (Internet): up to 23 January 2019
https://copac.jisc.ac.uk/
Searched: 23.1.19

Keyword: avatrombopag
Keyword: doptelet
Keyword: lusutrombopag
Keyword: mulpleta
Keyword: thrombocytopeni* liver* thrombopoietin*
Keyword: thrombocytopaeni* liver* thrombopoietin*
Keyword: thrombopeni* liver* thrombopoietin*
Keyword: thrombopaeni* liver* thrombopoietin*
Keyword: thrombocytopeni* hepati* thrombopoietin*

Keyword: thrombocytopaeni* hepati* thrombopoietin*
Keyword: thrombopeni* hepati* thrombopoietin*
Keyword: thrombopaeni* hepati* thrombopoietin*
Keyword: thrombocytopeni* liver* eltrombopag
Keyword: thrombocytopaeni* liver* eltrombopag
Keyword: thrombopeni* liver* eltrombopag
Keyword: thrombopaeni* liver* eltrombopag
Keyword: thrombocytopeni* hepati* eltrombopag
Keyword: thrombocytopaeni* hepati* eltrombopag
Keyword: thrombopeni* hepati* eltrombopag
Keyword: thrombopaeni* hepati* eltrombopag
Keyword: thrombocytopeni* liver* romiplostim
Keyword: thrombocytopaeni* liver* romiplostim
Keyword: thrombopeni* liver* romiplostim
Keyword: thrombopaeni* liver* romiplostim
Keyword: thrombocytopeni* hepati* romiplostim
Keyword: thrombocytopaeni* hepati* romiplostim
Keyword: thrombopeni* hepati* romiplostim
Keyword: thrombopaeni* hepati* romiplostim
Keyword: thrombocytopeni* liver* "platelet transfus*"
Keyword: thrombocytopaeni* liver* "platelet transfus*"
Keyword: thrombopeni* liver* "platelet transfus*"
Keyword: thrombopaeni* liver* "platelet transfus*"
Keyword: thrombocytopeni* hepati* "platelet transfus*"
Keyword: thrombocytopaeni* hepati* "platelet transfus*"
Keyword: thrombopeni* hepati* "platelet transfus*"
Keyword: thrombopaeni* hepati* "platelet transfus*"
Keyword: thrombocytopeni* liver* splenectom*
Keyword: thrombocytopaeni* liver* splenectom*
Keyword: thrombopeni* liver* splenectom*
Keyword: thrombopaeni* liver* splenectom*
Keyword: thrombocytopeni* hepati* splenectom*
Keyword: thrombocytopaeni* hepati* splenectom*
Keyword: thrombopeni* hepati* splenectom*
Keyword: thrombopaeni* hepati* splenectom*
Keyword: thrombocytopeni* liver* "splenic emboli*"
Keyword: thrombocytopaeni* liver* "splenic emboli*"
Keyword: thrombopeni* liver* "splenic emboli*"
Keyword: thrombopaeni* liver* "splenic emboli*"
Keyword: thrombocytopeni* hepati* "splenic emboli*"
Keyword: thrombocytopaeni* hepati* "splenic emboli*"
Keyword: thrombopeni* hepati* "splenic emboli*"
Keyword: thrombopaeni* hepati* "splenic emboli*"
Keyword: thrombocytopeni* liver* megakaryocyte*
Keyword: thrombocytopaeni* liver* megakaryocyte*
Keyword: thrombopeni* liver* megakaryocyte*
Keyword: thrombopaeni* liver* megakaryocyte*

Keyword: thrombocytopeni* hepati* megakaryocyte*
Keyword: thrombocytopaeni* hepati* megakaryocyte*
Keyword: thrombopeni* hepati* megakaryocyte*
Keyword: thrombopaeni* hepati* megakaryocyte*
Records retrieved: 90

Utilities/HRQoL search strategies

Database/ Resource	Host	Date range	Results	Date Searched
MEDLINE	Ovid	1946 to January week 3 2019	569	24.1.19
MEDLINE Epub Ahead of Print; MEDLINE In-Process & Other Non-Indexed Citations; MEDLINE Daily Update	Ovid	January 23, 2019	26	24.1.19
PubMed	NLM	up to 24 January 2019	35	24.1.19
Embase	Ovid	1974 to 2019 Week 3	863	24.1.19
Health Technology Assessment Database (HTA)	https://www.crd.york.ac.uk/CRDWeb/	up to 31 March 2015	70	24.1.19
NHS Economic Evaluation Databases (NHS EED)	https://www.crd.york.ac.uk/CRDWeb/	up to 31 March 2018	110	24.1.19
Science Citation Index Expanded (SCI)	Web of Science	1988-2019-01-23	422	24.1.19
CINAHL	EBSCO	1982-20190123	260	24.1.19
Latin American and Caribbean Health Sciences (LILACS)	http://lilacs.bvsalud.org/en/	1982-2019/01/24	837	24.1.19
Northern Light Life Sciences Conference Abstracts	Ovid	2010-2019/week 02	63	24.1.19
CEA Registry	www.cearegistry.org	up to 23 January 2019	18	23.1.19
ScHARR Health Utilities Database (ScHARRHUD)	www.scharrhud.org/	up to 23 January 2019	0	23.1.19
OAIster	http://oaister.worldcat.org	up to 23 January 2019	73	23.1.19
OpenGrey	www.opengrey.eu/	up to 23 January 2019	1	23.1.19
COPAC	https://copac.jisc.ac.uk/	up to 23 January 2019	104	23.1.19
Total records retrieved			**3451**	
Duplicate records removed			**1022**	
Total records to screen			**2429**	

MEDLINE (Ovid): 1946-2019/January Week 3
MEDLINE Epub Ahead of Print (Ovid): January 22, 2019
MEDLINE In-Process & Other Non-Indexed Citations (Ovid): January 23, 2019
MEDLINE Daily Update (Ovid): January 22, 2019
Searched: 19.1.19

1 quality-adjusted life years/ or quality of life/ (179815)

2 (sf36 or sf 36 or sf-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab,ot. (23334)

3 (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,ot. (1938)

4 (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,ot. (5044)

5 (sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab,ot. (745)

6 (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,ot. (386)

7 (sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab,ot. (488)

8 "health related quality of life".ti,ab,ot. (37648)

9 (Quality adjusted life or Quality-adjusted-life).ti,ab,ot. (11042)

10 "assessment of quality of life".ti,ab,ot. (1664)

11 (euroqol or euro qol or eq5d or eq 5d).ti,ab,ot. (9022)

12 (hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab,ot. (17843)

13 (hye or hyes).ti,ab,ot. (63)

14 health$ year$ equivalent$.ti,ab,ot. (40)

15 (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab,ot. (1339)

16 (quality time or qwb or quality of well being or "quality of wellbeing" or "index of wellbeing" or "index of well being").ti,ab,ot,hw. (817)

17 (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab,ot. (3371)

18 (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab,ot. (12572)

19 (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab,ot. (6642)

20 15d.ti,ab,ot. (1625)

21 (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab,ot. (373)

22 (utilit$ adj3 ("quality of life" or valu$ or scor$ or measur$ or health or life or estimat$ or elicit$ or disease$)).ti,ab,ot. (10844)

23 (utilities or disutili$).ti,ab,ot. (6548)

24 (CLDQ or Chronic Liver Disease Questionnaire$).ti,ab,ot,hw. (161)

25 (LDSI or Liver Disease Symptom Index$).ti,ab,ot,hw. (18)

26 (LDQOL or Liver Disease Quality of Life Questionnaire$).ti,ab,ot,hw. (26)

27 (EORTC QLQ-HCC18 or EORTC QLQ-LMC21).ti,ab,ot,hw. (13)

28 (PLD-Q or Polycystic Liver Disease Questionnaire$).ti,ab,ot,hw. (5)

29 or/1-28 (228242)

30 animals/ not (animals/ and humans/) (4507390)

31 29 not 30 (226165)

32 letter.pt. (1013622)

33 editorial.pt. (479604)

34 historical article.pt. (349760)

35 or/32-34 (1824832)

36 31 not 35 (217667)

37 exp Thrombocytopenia/ (45457)

38 (thrombocytopeni$ or thrombocytopaeni$ or thrombopeni$ or thrombopaeni$ or macrothrombocytopeni$ or macrothrombocytopaeni$).ti,ab,ot,hw. (69081)

39 ((11q or 11q23) adj3 (disorder$ or syndrome$ or delet$ or jacobsen)).ti,ab,ot,hw. (574)

40 (jacobsen adj3 syndrome$).ti,ab,ot,hw. (129)

41 paris trousseau.ti,ab,ot,hw. (30)

42 kasabach merritt.ti,ab,ot,hw. (704)

43 (hemangioma or haemangioma).ti,ab,ot,hw. (32339)

44 (thrombotic adj2 (microangiopath$ or micro angiopath$)).ti,ab,ot,hw. (3354)

45 (hemolytic uremic or haemolytic uremic).ti,ab,ot,hw. (7663)

46 gasser$.ti,ab,ot,hw. (1689)

47 HELLP Syndrome/ (1709)

48 (HELLP adj2 syndrome$).ti,ab,ot,hw. (2561)

49 ((hemolysis or haemolysis) adj2 liver adj2 platelet$).ti,ab,ot,hw. (7)

50 May Hegglin.ti,ab,ot,hw. (221)

51 ((haemolytic or hemolytic) adj2 (anaemi$ or anemi$) adj2 (microangiopathic or micro angiopathic)).ti,ab,ot,hw. (1411)

52 moschcowitz.ti,ab,ot,hw. (107)

53 werlhof.ti,ab,ot,hw. (120)

54 Wiskott-Aldrich Syndrome/ (1428)

55 (wiskott and Aldrich).ti,ab,ot,hw. (3312)

56 (immunodeficiency 2 or immunodeficiency2 or Imd2).ti,ab,ot,hw. (44)

57 ((platelet$ or thrombocyte$) adj3 (defici$ or reduc$ or low or lower or lowest or few or fewer or fewest or decrease or decreases or decreased or defective or destruc$ or destroy$)).ti,ab,ot,hw. (22231)

58 or/37-57 (132417)

59 36 and 58 (595)

MEDLINE	**569**
MEDLINE Epub Ahead of Print	**4**
MEDLINE In-Process & Other Non-Indexed Citations	**22**
MEDLINE Daily Update	**0**

HRQoL free-text terms based on: Figure 4: Common free-text terms for electronic database searching for HSUVs in Papaioannou D, Brazier JE, Paisley S. NICE DSU Technical Support Document 9: the identification, review and synthesis of health state utility values from the literature (Internet), 2011 (accessed: 18.8.11) Available from: http://www.nicedsu.org.uk

PubMed (NLM): up to 24 January 2019

Searched: 24.1.19

#31 #29 AND #30 35

#30 pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb] 3121488

#29 #17 AND #28 827

#28 (#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27) 188201

#27 (platelet*[tiab] OR thrombocyte*[tiab]) AND (defici*[tiab] OR reduc*[tiab] OR low[tiab] OR lower[tiab] OR lowest[tiab] OR few[tiab] OR fewer[tiab] OR fewest[tiab] OR decrease[tiab] OR decreases[tiab] OR decreased[tiab] OR defective[tiab] OR destruc*[tiab] OR destroy*[tiab]) 99513

#26 "immunodeficiency 2" OR immunodeficiency2 OR Imd2 46

#25 Moschcowitz[tiab] OR werlhof[tiab] OR "Wiskott-Aldrich Syndrome"[Mesh] OR (wiskott[tiab] AND Aldrich[tiab]) 2664

#24 (haemolytic[tiab] OR hemolytic[tiab]) AND (anaemi*[tiab] OR anemi*[tiab]) AND (microangiopath*[tiab]) 1765

#23 (hemolysis[tiab] OR haemolysis[tiab]) AND liver[tiab] AND platelet*[tiab] 1247

#22 "HELLP Syndrome"[Mesh] OR "HELLP syndrome" OR "HELLP syndromes" 2583

#21 (thrombotic[tiab] AND microangiopath*[tiab]) OR "hemolytic uremic" OR "haemolytic uremic" OR gasser*[tiab] 12074

#20 "jacobsen syndrome" OR "paris trousseau" OR "kasabach merritt" OR "May Hegglin" OR hemangioma[tiab] OR haemangioma[tiab] 17717

#19 (11q[tiab] OR 11q23[tiab]) AND (disorder*[tiab] OR syndrome*[tiab] OR delet*[tiab] OR Jacobsen[tiab]) 1605

#18 "Thrombocytopenia"[Mesh] OR thrombocytopeni*[tiab] OR thrombocytopaeni*[tiab] OR thrombopeni*[tiab] OR thrombopaeni*[tiab] OR macrothrombocytopeni*[tiab] OR macrothrombocytopaeni*[tiab] 73938

#17 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16) 222519

#16 CLDQ[tiab] OR "Chronic Liver Disease Questionnaire"[tiab] OR "Chronic Liver Disease Questionnaires"[tiab] OR LDSI[tiab] OR "Liver Disease Symptom Index"[tiab] OR "Liver Disease Symptom Indexes"[tiab] OR LDQOL[tiab] OR "Liver Disease Quality of Life Questionnaire"[tiab] OR "Liver Disease Quality of Life Questionnaires"[tiab] OR "EORTC QLQ-HCC18"[tiab] OR "EORTC QLQ-LMC21"[tiab] OR PLD-Q[tiab] OR "Polycystic Liver Disease Questionnaire"[tiab] OR "Polycystic Liver Disease Questionnaires"[tiab] 214

#15 utilities[tiab] OR disutili*[tiab] 6591

#14 HSUV*[tiab] OR "health state* value*"[tiab] OR "health state* preference*"[tiab] OR HSPV*[tiab] 135

#13 QALY*[tiab] OR DALY*[tiab] OR HALY*[tiab] OR YHL[tiab] OR HYES[tiab] OR YPLL[tiab] OR YHLL[tiab] OR qald*[tiab] OR qale*[tiab] OR qtime*[tiab] OR AQoL*[tiab] OR timetradeoff[tiab] OR "time tradeoff"[tiab] OR "time trade-off"[tiab] OR "time trade off"[tiab] OR TTO[tiab] OR "standard gamble"[tiab] OR "willingness to pay"[tiab] OR 15d[tiab] 18990

#12 "Disability adjusted life"[tiab] OR "Disability-adjusted life"[tiab] OR "health adjusted life"[tiab] OR "health-adjusted life"[tiab] OR "years of healthy life"[tiab] OR "healthy years equivalent"[tiab] OR "years of potential life lost"[tiab] OR "years of health life lost"[tiab] 3319

#11 "quality time"[tiab] OR qwb[tiab] OR "quality of well being"[tiab] OR "quality of wellbeing"[tiab] OR "index of wellbeing"[tiab] OR "index of well being"[tiab] 556

#10 hui[tiab] OR hui1[tiab] OR hui2[tiab] OR hui3[tiab] OR hui4[tiab] OR hui-4[tiab] OR hui-1[tiab] OR hui-2[tiab] OR hui-3[tiab] 1335

#9 euroqol[tiab] OR "euro qol"[tiab] OR eq5d[tiab] OR "eq 5d"[tiab] OR hql[tiab] OR hrql[tiab] OR hqol[tiab] OR "h qol"[tiab] OR hrqol[tiab] OR "hr qol"[tiab] OR hye[tiab] OR hyes[tiab] or "health year equivalent"[tiab] OR "health years equivalent"[tiab] 25124

#8 "health related quality of life"[tiab] OR "quality adjusted life"[tiab] OR "quality-adjusted-life"[tiab] OR "assessment of quality of life"[tiab] 49632

#7 sf8[tiab] OR "sf 8"[tiab] OR sf-8[tiab] OR "short form 8"[tiab] OR "shortform 8"[tiab] OR "sf eight"[tiab] OR sfeight[tiab] OR "shortform eight"[tiab] OR "short form eight"[tiab] 501

#6 sf20[tiab] OR "sf 20"[tiab] OR sf-20[tiab] OR "short form 20"[tiab] OR "shortform 20"[tiab] OR "sf twenty"[tiab] OR sftwenty[tiab] OR "shortform twenty"[tiab] OR "short form twenty"[tiab] 377

#5 sf6D[tiab] OR "sf 6D"[tiab] OR sf-6D[tiab] OR "short form 6D"[tiab] OR "shortform 6D"[tiab] OR "sf six D"[tiab] OR sfsixD[tiab] OR "shortform six D"[tiab] OR "short form six D"[tiab] 748

#4 sf12[tiab] OR "sf 12"[tiab] OR sf-12[tiab] OR "short form 12"[tiab] OR "shortform 12"[tiab] OR "sf twelve"[tiab] OR sftwelve[tiab] OR "shortform twelve"[tiab] OR "short form twelve"[tiab] 5072

#3 sf6[tiab] or "sf 6"[tiab] OR "sf-6"[tiab] OR "short form 6"[tiab] OR "shortform 6"[tiab] OR "sf six"[tiab] OR sfsix[tiab] OR "shortform six"[tiab] OR "short form six"[tiab] 1917

#2 sf36[tiab] OR "sf 36"[tiab] OR sf-36[tiab] OR "short form 36"[tiab] OR "shortform 36"[tiab] OR "sf thirtysix"[tiab] OR "sf thirty six"[tiab] OR "shortform thirtysix"[tiab] OR "shortform thirty six"[tiab] OR "short form thirty six"[tiab] OR "short form thirtysix"[tiab] OR "short form thirty six"[tiab] 23445

#1 ("Quality-Adjusted Life Years"[Mesh]) OR "Quality of Life"[Mesh]) 179608

Embase (Ovid): 1974 to 2019 Week 3

Searched: 24.1.19

1 quality adjusted life year/ or quality of life index/ (25499)

2 Short Form 12/ or Short Form 20/ or Short Form 36/ or Short Form 8/ (29766)

3 "International Classification of Functioning, Disability and Health"/ or "ferrans and powers quality of life index"/ or "gastrointestinal quality of life index"/ (2998)

4 (sf36 or sf 36 or sf-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab,ot. (37386)

5 (sf6 or sf 6 or sf-6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab,ot. (2074)

6 (sf12 or sf 12 or sf-12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,ot. (8180)

7 (sf6D or sf 6D or sf-6D or short form 6D or shortform 6D or sf six D or sfsixD or shortform six D or short form six D).ti,ab,ot. (1355)

8 (sf20 or sf 20 or sf-20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,ot. (412)

9 (sf8 or sf 8 or sf-8 or short form 8 or shortform 8 or sf eight or sfeight or shortform eight or short form eight).ti,ab,ot. (819)

10 "health related quality of life".ti,ab,ot. (54017)

11 (Quality adjusted life or Quality-adjusted-life).ti,ab,ot. (16849)

12 "assessment of quality of life".ti,ab,ot. (2629)

13 (euroqol or euro qol or eq5d or eq 5d).ti,ab,ot. (16871)

14 (hql or hrql or hqol or h qol or hrqol or hr qol).ti,ab,ot. (28883)

15 (hye or hyes).ti,ab,ot. (119)

16 health$ year$ equivalent$.ti,ab,ot. (40)

17 (hui or hui1 or hui2 or hui3 or hui4 or hui-4 or hui-1 or hui-2 or hui-3).ti,ab,ot. (2812)

18 (quality time or qwb or "quality of well being" or "quality of wellbeing" or "index of wellbeing" or index of well being).ti,ab,ot,hw. (1083)

19 (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab,ot. (4037)

20 (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab,ot. (21565)

21 (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab,ot. (10142)

22 15d.ti,ab,ot. (2352)

23 (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab,ot. (539)

24 (utilit$ adj3 ("quality of life" or valu$ or scor$ or measur$ or health or life or estimat$ or elicit$ or disease$)).ti,ab,ot. (17247)

25 (utilities or disutili$).ti,ab,ot. (10644)

26 (CLDQ or Chronic Liver Disease Questionnaire$).ti,ab,ot,hw. (343)

27 (LDSI or Liver Disease Symptom Index$).ti,ab,ot,hw. (32)

28 (LDQOL or Liver Disease Quality of Life Questionnaire$).ti,ab,ot,hw. (51)

29 (EORTC QLQ-HCC18 or EORTC QLQ-LMC21).ti,ab,ot,hw. (23)

30 (PLD-Q or Polycystic Liver Disease Questionnaire$).ti,ab,ot,hw. (9)

31 or/1-30 (166039)

32 animal/ or animal experiment/ (3692962)

33 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (6355627)

34 or/32-33 (6355627)

35 exp human/ or human experiment/ (19263219)

36 34 not (34 and 35) (4905535)

37 31 not 36 (163378)

38 letter.pt. (1054787)

39 editorial.pt. (594151)

40 note.pt. (740957)

41 or/38-40 (2389895)

42 37 not 41 (158841)

43 exp thrombocytopenia/ (157171)

44 (thrombocytopeni$ or thrombocytopaeni$ or thrombopeni$ or thrombopaeni$ or macrothrombocytopeni$ or macrothrombocytopaeni$).ti,ab,ot. (87986)

45 ((11q or 11q23) adj3 (disorder$ or syndrome$ or delet$ or jacobsen)).ti,ab,ot. (1015)

46 (jacobsen adj3 syndrome$).ti,ab,ot. (187)

47 paris trousseau.ti,ab,ot. (49)

48 kasabach merritt.ti,ab,ot. (793)

49 (hemangioma or haemangioma).ti,ab,ot. (18275)

50 (thrombotic adj2 (microangiopath$ or micro angiopath$)).ti,ab,ot. (5177)

51 (hemolytic uremic or haemolytic uremic).ti,ab,ot. (7454)

52 gasser$.ti,ab,ot. (1885)

53 (HELLP adj2 syndrome$).ti,ab,ot. (3305)

54 ((hemolysis or haemolysis) adj2 liver adj2 platelet$).ti,ab,ot. (11)

55 May Hegglin.ti,ab,ot. (262)

56 ((haemolytic or hemolytic) adj2 (anaemi$ or anemi$) adj2 (microangiopathic or micro angiopathic)).ti,ab,ot. (2048)

57 moschcowitz.ti,ab,ot. (93)

58 werlhof.ti,ab,ot. (55)

59 (wiskott and aldrich).ti,ab,ot. (2815)

60 (immunodeficiency 2 or immunodeficiency2 or Imd2).ti,ab,ot. (71)

61 ((platelet$ or thrombocyte$) adj3 (defici$ or reduc$ or low or lower or lowest or few or fewer or fewest or decrease or decreases or decreased or defective or destruc$ or destroy$)).ti,ab,ot. (33439)

62 or/43-61 (221567)

63 42 and 62 (863)

HRQoL free-text terms based on: Figure 4: Common free-text terms for electronic database searching for HSUVs in Papaioannou D, Brazier JE, Paisley S. NICE DSU Technical Support Document 9: the identification, review and synthesis of health state utility values from the literature (Internet), 2011 (accessed: 18.8.11) Available from: http://www.nicedsu.org.uk

Health Technology Assessment Database (HTA) (CRD): up to 31 March 2018

NHS Economic Evaluation Databases (NHS EED) (CRD): up to 31 March 2015

https://www.crd.york.ac.uk/CRDWeb/

Searched: 24.1.19

1 MeSH DESCRIPTOR Thrombocytopenia EXPLODE ALL TREES 107
2 (thrombocytopeni* or thrombocytopaeni* or thrombopeni* or thrombopaeni* or macrothrombocytopeni* or macrothrombocytopaeni*) 369
3 (11q or 11q23) 0
4 (jacobsen near3 syndrome*) 0
5 (paris trousseau) 0
6 (kasabach merritt) 1
7 (hemangioma or haemangioma) 34
8 (thrombotic near2 (microangiopath* or micro angiopath*)) 0
9 (hemolytic uremic or haemolytic uremic) 14
10 (gasser*) 4
11 MeSH DESCRIPTOR HELLP Syndrome EXPLODE ALL TREES 5
12 (HELLP near2 syndrome*) 11
13 ((hemolysis or haemolysis) near2 liver near2 platelet*) 2
14 (May Hegglin) 0
15 ((haemolytic or hemolytic) near (anaemi* or anemi*)) 18
16 (microangiopath* near thrombotic) 0
17 (moschcowitz or werlhof) 0
18 MeSH DESCRIPTOR Wiskott-Aldrich Syndrome EXPLODE ALL TREES 0
19 (wiskott and Aldrich) 1
20 (immunodeficiency 2 or immunodeficiency2 or Imd2) 1
21 ((platelet* or thrombocyte*) near3 (defici* or reduc* or low or lower or lowest or few or fewer or fewest or decrease or decreases or decreased or defective or destruc* or destroy*)) 24

HTA 70
NHS EED 110

Science Citation Index Expanded (SCI) (Web of Science): 1988-2019-01-23
Searched: 24.1.19

# 34	**422**	**#15 and #33**
# 33	149,819	#16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32
# 32	206	TS=(CLDQ or "Chronic Liver Disease Questionnaire*" or LDSI or "Liver Disease Symptom Index*" or LDQOL or "Liver Disease Quality of Life Questionnaire*" or "EORTC QLQ-HCC18" or "EORTC QLQ-LMC21" or PLD-Q or "Polycystic Liver Disease Questionnaire*")
# 31	46,426	TI=(utilit*) or TS=(disutili*)
# 30	15,981	TS=(utilit* NEAR/3 ("quality of life" or valu* or scor* or measur* or health or life or estimat* or elicit* or disease*))
# 29	431	TS=(HSUV* or "health state* value*" or "health state* preference*" or HSPV*)
# 28	11,538	TS=(timetradeoff or "time tradeoff" or "time trade-off" or "time trade off" or TTO or "Standard gamble*" or "willingness to pay")
# 27	12,299	TS=(QALY* or DALY* or HALY* or YHL or HYES or YPLL or YHLL or qald* or qale* or qtime* or AQoL*)
# 26	2,703	TS=("Disability adjusted life" or "Disability-adjusted life" or "health adjusted life" or "health-adjusted life" or "years of healthy life" or "healthy years equivalent" or "years of potential life lost" or "years of health life lost")
# 25	846	TS=("quality time" or qwb or "quality of well being" or "quality of wellbeing" or "index of wellbeing" or "index of well being")
# 24	16,492	TS=(hql or hrql or hqol or "h qol" or hrqol or "hr qol" or hye or hyes or "health* year* equivalent*")
# 23	10,202	TS=(("assessment of quality of life") or euroqol or "euro qol" or eq5d or "eq 5d")
# 22	47,488	TS=("health related quality of life" or "Quality adjusted life" or "Quality-adjusted-life")
# 21	443	TS=(sf8 or "sf 8" or sf-8 or "short form 8" or "shortform 8" or "sf eight" or sfeight or "shortform eight" or "short form eight")
# 20	255	TS=(sf20 or "sf 20" or sf-20 or "short form 20" or "shortform 20" or "sf twenty" or sftwenty or "shortform twenty" or "short form twenty")
# 19	886	TS=(sf6D or "sf 6D" or sf-6D or "short form 6D" or "shortform 6D" or "sf six

		D" or sfsixD or "shortform six D" or "short form six D")
# 18	4,401	TS=(sf12 or "sf 12" or "sf-12" or "short form 12" or "shortform 12" or "sf twelve" or sftwelve or "shortform twelve" or "short form twelve")
# 17	9,091	TS=(sf6 or "sf 6" or sf-6 or "short form 6" or "shortform 6" or "sf six" or sfsix or "shortform six" or "short form six")
# 16	23,500	TS=(sf36 or "sf 36 " or sf-36 or "short form 36 " or "shortform 36 " or "sf thirtysix " or "sf thirty six " or "shortform thirtysix " or "shortform thirty six " or "short form thirty six " or "short form thirtysix " or "short form thirty six")
# 15	98,158	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
# 14	20,790	TS=((platelet* or thrombocyte*) NEAR/3 (defici* or reduc* or low or lower or lowest or few or fewer or fewest or decrease or decreases or decreased or defective or destruc* or destroy*))
# 13	3,306	TS=(werlhof) or TS=(wiskott and aldrich) or TS=("immunodeficiency 2" or immunodeficiency2 or Imd2)
# 12	48	TS=(moschcowitz)
# 11	870	TS=((haemolytic or hemolytic) NEAR/2 (anaemi* or anemi*) NEAR/2 (microangiopathic or "micro angiopathic"))
# 10	170	TS=("May Hegglin")
# 9	272	TS=((hemolysis or haemolysis) NEAR/2 liver NEAR/2 platelet*)
# 8	3,797	TS=(gasser*) or TS=(HELLP NEAR/2 syndrome*)
# 7	10,671	TS=("hemolytic uremic" or "haemolytic uremic")
# 6	3,876	TS=(thrombotic NEAR/2 (microangiopath* or "micro angiopath*"))
# 5	11,949	TS=(hemangioma or haemangioma)
# 4	703	TS=("kasabach merritt")
# 3	189	TS=(jacobsen NEAR/3 syndrome*) OR TS=("paris trousseau" NEAR/3 syndrome*)
# 2	643	TS=((11q or 11q23) NEAR/3 (disorder* or syndrome* or delet* or jacobsen))
# 1	53,278	TS=(thrombocytopeni* or thrombocytopaeni* or thrombopeni* or thrombopaeni* or macrothrombocytopeni* or macrothrombocytopaeni*)

HRQoL free-text terms based on: Figure 4: Common free-text terms for electronic database searching for HSUVs in Papaioannou D, Brazier JE, Paisley S. NICE DSU Technical Support Document 9: the identification, review and synthesis of health state utility values from the literature (Internet), 2011 (accessed: 18.8.11) Available from: http://www.nicedsu.org.uk

CINAHL (EBSCO): 1982-20190123
Searched: 24.1.19

S1	(MH "Thrombocytopenia+")	5,320
S2	TI (thrombocytopeni* or thrombocytopaeni* or thrombopeni* or thrombopaeni* or macrothrombocytopeni* or macrothrombocytopaeni*) OR AB (thrombocytopeni* or thrombocytopaeni* or thrombopeni* or thrombopaeni* or macrothrombocytopeni* or macrothrombocytopaeni*)	7,424
S3	TI ((11q or 11q23) N3 (disorder* or syndrome* or delet* or jacobsen)) OR AB ((11q or 11q23) N3 (disorder* or syndrome* or delet* or jacobsen))	33
S4	TI (jacobsen N3 syndrome*) OR AB (jacobsen N3 syndrome*)	8
S5	TI ("paris trousseau" or "kasabach merritt" or "May Hegglin") OR AB ("paris trousseau" or "kasabach merritt" or "May Hegglin")	101
S6	TI (hemangioma or haemangioma) OR AB (hemangioma or haemangioma)	2,028
S7	TI (thrombotic N2 (microangiopath* or "micro angiopath*")) or AB (thrombotic N2 (microangiopath* or "micro angiopath*"))	536
S8	TI ("hemolytic uremic" or "haemolytic uremic" or gasser*) or AB ("hemolytic uremic" or "haemolytic uremic" or gasser*)	824
S9	(MH "HELLP Syndrome")	476
S10	TI (HELLP N2 syndrome*) or AB (HELLP N2 syndrome*)	438
S11	TI ((hemolysis or haemolysis) N2 liver N2 platelet*) or AB ((hemolysis or haemolysis) N2 liver N2 platelet*)	78
S12	TI ((haemolytic or hemolytic) N2 (anaemi* or anemi*) N2 (microangiopathic or micro angiopathic)) or AB ((haemolytic or hemolytic) N2 (anaemi* or anemi*) N2 (microangiopathic or micro angiopathic))	159
S13	TI ((microangiopath* or micro angiopath*) N2 thrombotic) or AB ((microangiopath* or micro angiopath*) N2 thrombotic)	536
S14	TI (moschcowitz or werlhof or (wiskott and Aldrich)) or AB (moschcowitz or werlhof or (wiskott and Aldrich))	93
S15	(MH "Wiskott-Aldrich Syndrome")	52
S16	TI ("immunodeficiency 2" or immunodeficiency2 or Imd2) or AB ("immunodeficiency 2" or immunodeficiency2 or Imd2)	1
S17	TI ((platelet* or thrombocyte*) N3 (defici* or reduc* or low or lower or lowest or few or fewer or fewest or decrease or decreases or decreased or defective or destruc* or destroy*)) or AB ((platelet* or thrombocyte*) N3 (defici* or reduc* or low or lower or lowest or few or fewer or fewest or decrease or decreases or decreased or defective or destruc* or destroy*))	2,419
S18	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17	14,324
S19	(MH "Quality-Adjusted Life Years") OR (MH "Quality of Life+")	100,220

S20	TI (sf36 or "sf 36" or sf-36 or "short form 36" or "shortform 36" or "sf thirtysix" or "sf thirty six" or "shortform thirtysix" or "shortform thirty six" or "short form thirty six" or "short form thirtysix" or "short form thirty six") or AB (sf36 or "sf 36" or sf-36 or "short form 36" or "shortform 36" or "sf thirtysix" or "sf thirty six" or "shortform thirtysix" or "shortform thirty six" or "short form thirty six" or "short form thirtysix" or "short form thirty six")	8,163
S21	TI ("health related quality of life" or "Quality adjusted life" or "Quality-adjusted-life" or "assessment of quality of life") or AB ("health related quality of life" or "Quality adjusted life" or "Quality-adjusted-life" or "assessment of quality of life")	21,631
S22	TI (euroqol or "euro qol" or eq5d or "eq 5d" or hql or hrql or hqol or "h qol" or hrqol or "hr qol" or hye or hyes or "health* year* equivalent*") or AB (euroqol or "euro qol" or eq5d or "eq 5d" or hql or hrql or hqol or "h qol" or hrqol or "hr qol" or hye or hyes or "health* year* equivalent*")	8,536
S23	TI ("quality time" or qwb or "quality of well being" or "quality of wellbeing" or "index of wellbeing" or "index of well being") or AB ("quality time" or qwb or "quality of well being" or "quality of wellbeing" or "index of wellbeing" or "index of well being")	373
S24	TI ("Disability adjusted life" or "Disability-adjusted life" or "health adjusted life or health-adjusted life" or "years of healthy life" or "healthy years equivalent" or "years of potential life lost" or "years of health life lost" or QALY* or DALY* or HALY* or YHL or HYES or YPLL or YHLL or qald* or qale* or qtime* or AQoL*) or AB ("Disability adjusted life" or "Disability-adjusted life" or "health adjusted life or health-adjusted life" or "years of healthy life" or "healthy years equivalent" or "years of potential life lost" or "years of health life lost" or QALY* or DALY* or HALY* or YHL or HYES or YPLL or YHLL or qald* or qale* or qtime* or AQoL*)	4,707
S25	TI (timetradeoff or "time tradeoff" or "time trade-off" or "time trade off" or TTO or "Standard gamble*" or "willingness to pay" or HSUV* or "health state* value*" or "health state* preference*" or HSPV*) or AB (timetradeoff or "time tradeoff" or "time trade-off" or "time trade off" or TTO or "Standard gamble*" or "willingness to pay" or HSUV* or "health state* value*" or "health state* preference*" or HSPV*)	2,360
S26	TI (utilit* N3 ("quality of life" or valu* or scor* or measur* or health or life or estimat* or elicit* or disease*)) or AB (utilit* N3 ("quality of life" or valu* or scor* or measur* or health or life or estimat* or elicit* or disease*))	4,802
S27	TI (utilities or disutili*) or AB (utilities or disutili*)	30,817
S28	TI (CLDQ or "Chronic Liver Disease Questionnaire*" or LDSI or "Liver Disease Symptom Index*" or LDQOL or "Liver Disease Quality of Life Questionnaire*" or "EORTC QLQ-HCC18" or "EORTC QLQ-LMC21" or PLD-Q or "Polycystic Liver Disease Questionnaire*") or AB (CLDQ or "Chronic Liver Disease Questionnaire*" or LDSI or "Liver Disease Symptom Index*" or LDQOL or "Liver Disease Quality of Life Questionnaire*" or "EORTC QLQ-HCC18" or "EORTC QLQ-LMC21" or PLD-Q or "Polycystic Liver Disease Questionnaire*")	53
S29	S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28	140,204
S30	**S18 AND S29**	**260**

HRQoL free-text terms based on: Figure 4: Common free-text terms for electronic database searching for HSUVs in Papaioannou D, Brazier JE, Paisley S. NICE DSU Technical Support

Document 9: the identification, review and synthesis of health state utility values from the literature (Internet), 2011 (accessed: 18.8.11) Available from: http://www.nicedsu.org.uk

Latin American and Caribbean Health Sciences (LILACS) (Internet): 1982-2019/01/24

http://lilacs.bvsalud.org/en/

Searched: 24.1.19

(MH:c15.378.140.855 OR MH:c15.378.100.100.970 OR thrombocytopeni* OR thrombocytopaeni* OR thrombopeni* OR thrombopaeni* OR macrothrombocytopeni* OR macrothrombocytopaeni* OR trombocitopeni* OR ((platelet* OR thrombocyte*) AND (defici* OR reduc* OR low OR lower OR lowest OR few OR fewer OR fewest OR decrease OR decreases OR decreased OR defective OR destruc* OR destroy*)) AND (MH:I01.800 OR MH:K01.752.400.750 OR MH:N06.850.505.400.425.837 OR MH:SP4.011.077.593 OR "Quality of Life" OR "Calidad de Vida" OR "Qualidade de Vida" OR MH:E05.318.740.100.500.700 OR MH:N01.224.935.530.700 OR MH:SP5.006.052.168.144 OR "Quality-Adjusted Life" OR "Años de Vida Ajustados por Calidad de Vida" OR "Anos de Vida Ajustados por Qualidade de Vida" OR euroqol OR "euro qo"l OR eq5d OR "eq 5d" OR "Disability adjusted life" OR "health adjusted life" OR QALY* OR DALY* OR timetradeoff OR "time tradeoff" OR "Standard gamble*" OR "willingness to pay" OR utility OR utilities or disutili*))

Search limited to non-Medline databases:

- **LILACS (444)**
- **IBECS (317)**
- **BINACIS (36)**
- **BBO - Dentistry (30)**
- **CUMED (18)**
- **MedCarib (14)**
- **BDENF - Nursing (1)**

Northern Light Life Sciences Conference Abstracts (Ovid): 2010-2019/week 02

Searched: 24.1.19

1 exp thrombocytopenia/ (19173)

2 (thrombocytopeni$ or thrombocytopaeni$ or thrombopeni$ or thrombopaeni$ or macrothrombocytopeni$ or macrothrombocytopaeni$).ti,ab,hw. (18543)

3 ((11q or 11q23) adj3 (disorder$ or syndrome$ or delet$ or jacobsen)).ti,ab,hw. (132)

4 (jacobsen adj3 syndrome$).ti,ab,hw. (41)

5 (paris trousseau or kasabach merritt or hemangioma or haemangioma).ti,ab,hw. (2487)

6 (thrombotic adj2 (microangiopath$ or micro angiopath$)).ti,ab,hw. (1515)

7 (hemolytic uremic or haemolytic uremic or gasser$).ti,ab,hw. (643)

8 hellp syndrome/ (410)

9 (HELLP adj2 syndrome$).ti,ab,hw. (415)

10 ((hemolysis or haemolysis) adj2 liver adj2 platelet$).ti,ab,hw. (0)

11 May Hegglin.ti,ab,hw. (10)

12 ((haemolytic or hemolytic) adj2 (anaemi$ or anemi$) adj2 (microangiopathic or micro angiopathic)).ti,ab,hw. (77)

13 (moschcowitz or werlhof or (wiskott and Aldrich)).ti,ab,hw. (468)

14 wiskott-aldrich syndrome/ (460)

15 (immunodeficiency 2 or immunodeficiency2 or Imd2).ti,ab,hw. (0)

16 ((platelet$ or thrombocyte$) adj3 (defici$ or reduc$ or low or lower or lowest or few or fewer or fewest or decrease or decreases or decreased or defective or destruc$ or destroy$)).ti,ab,hw. (1916)

17 or/1-16 (24421)

18 (sf36 or sf 36 or sf-36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab,hw. (1251)

19 "health related quality of life".ti,ab,hw. (5026)

20 (Quality adjusted life or Quality-adjusted-life).ti,ab,hw. (313)

21 "assessment of quality of life".ti,ab,hw. (178)

22 (euroqol or euro qol or eq5d or eq 5d).ti,ab,hw. (1122)

23 (hql or hrql or hqol or h qol or hrqol or hr qol or hye or hyes).ti,ab,hw. (5101)

24 health$ year$ equivalent$.ti,ab,hw. (0)

25 (quality time or qwb or quality of well being or "quality of wellbeing" or "index of wellbeing" or "index of well being").ti,ab,hw. (47)

26 (Disability adjusted life or Disability-adjusted life or health adjusted life or health-adjusted life or "years of healthy life" or healthy years equivalent or "years of potential life lost" or "years of health life lost").ti,ab,hw. (99)

27 (QALY$ or DALY$ or HALY$ or YHL or HYES or YPLL or YHLL or qald$ or qale$ or qtime$ or AQoL$).ti,ab,hw. (1738)

28 (timetradeoff or time tradeoff or time trade-off or time trade off or TTO or Standard gamble$ or "willingness to pay").ti,ab,hw. (829)

29 (HSUV$ or health state$ value$ or health state$ preference$ or HSPV$).ti,ab,hw. (48)

30 (utilit$ adj3 ("quality of life" or valu$ or scor$ or measur$ or health or life or estimat$ or elicit$ or disease$)).ti,ab,hw. (1620)

31 (utilities or disutili$).ti,ab,hw. (647)

32 (CLDQ or Chronic Liver Disease Questionnaire$).ti,ab,hw. (24)

33 (LDSI or Liver Disease Symptom Index$).ti,ab,hw. (2)

34 (LDQOL or Liver Disease Quality of Life Questionnaire$).ti,ab,hw. (1)

35 (EORTC QLQ-HCC18 or EORTC QLQ-LMC21).ti,ab,hw. (0)

36 (PLD-Q or Polycystic Liver Disease Questionnaire$).ti,ab,hw. (2)

37 or/18-36 (13027)

38 17 and 37 (63)

HRQoL free-text terms based on: Figure 4: Common free-text terms for electronic database searching for HSUVs in Papaioannou D, Brazier JE, Paisley S. NICE DSU Technical Support Document 9: the identification, review and synthesis of health state utility values from the literature (Internet), 2011 (accessed: 18.8.11) Available from: http://www.nicedsu.org.uk

CEA Registry (Internet): up to 23 January 2019

www.cearegistry.org

Searched: 23.1.19

avatrombopag

doptelet

lusutrombopag

mulpleta

thrombocytopenia
thrombocytopenic
thrombocytopaenia
thrombocytopaenic

Records retrieved: 18

ScHARR Health Utilities Database (ScHARRHUD)(Internet): up to 23 January 2019
www.scharrhud.org/
Searched: 23.1.19

Search terms	**Results**
avatrombopag OR doptelet OR lusutrombopag	0
mulpleta OR thrombocytopenia OR thrombocytopenic	0
thrombocytopaenia OR thrombocytopaenic	0
Total	**0**

OAIster (Internet): up to 23 January 2019
http://oaister.worldcat.org
Searched: 23.1.19

((thrombocytopeni* OR thrombocytopaeni* OR thrombopeni* OR thrombopaeni*) AND (quality of life OR quality-adjusted life OR QALY* OR DALY* OR euroqol OR euro qol OR eq5d OR eq 5d OR health* year* equivalent* OR timetradeoff OR time tradeoff OR utility OR utilities OR disutili*))

Records retrieved: 73

OpenGrey (Internet): up to 23 January 2019
www.opengrey.eu/
Searched: 23.1.19

((thrombocytopeni* OR thrombocytopaeni* OR thrombopeni* OR thrombopaeni*) AND (quality of life OR quality-adjusted life OR QALY* OR DALY* OR euroqol OR euro qol OR eq5d OR eq 5d OR health* year* equivalent* OR timetradeoff OR time tradeoff OR utility OR utilities OR disutili*))

Records retrieved: 1

COPAC (Internet): up to 23 January 2019
https://copac.jisc.ac.uk/
Searched: 23.1.19

Keyword: thrombocytopeni* "quality of life"

Keyword: thrombocytopaeni* "quality of life"
Keyword: thrombopeni* "quality of life"
Keyword: thrombopaeni* "quality of life"
Keyword: thrombocytopeni* "quality adjusted life"
Keyword: thrombocytopaeni* "quality adjusted life"
Keyword: thrombopeni* "quality adjusted life"
Keyword: thrombopaeni* "quality adjusted life"
Keyword: thrombocytopeni* QALY*
Keyword: thrombocytopaeni* QALY*
Keyword: thrombopeni* QALY*
Keyword: thrombopaeni* QALY*
Keyword: thrombocytopeni* euroqol
Keyword: thrombocytopaeni* euroqol
Keyword: thrombopeni* euroqol
Keyword: thrombopaeni* euroqol
Keyword: thrombocytopeni* eq5d
Keyword: thrombocytopaeni* eq5d
Keyword: thrombopeni* eq5d
Keyword: thrombopaeni* eq5d
Keyword: thrombocytopeni* utilit*
Keyword: thrombocytopaeni* utilit*
Keyword: thrombopeni* utilit*
Keyword: thrombopaeni* utilit*
Keyword: thrombocytopeni* disutilit*
Keyword: thrombocytopaeni* disutilit*
Keyword: thrombopeni* disutilit*
Keyword: thrombopaeni* disutilit*

Records retrieved: 104

Resource use/Costs search strategies

Database/ Resource	Host	Date range	Results	Date Searched
MEDLINE	Ovid	1946 to January week 3 2019	1260	24.1.19
MEDLINE Epub Ahead of Print; MEDLINE In-Process & Other Non-Indexed Citations; MEDLINE Daily Update	Ovid	January 23, 2019	159	24.1.19
PubMed	NLM	up to 24 January 2019	163	24.1.19
Embase	Ovid	1974 to 2019 Week 3	4838	24.1.19
Science Citation Index Expanded (SCI)	Web of Science	1988-2019-01-23	1197	24.1.19
CINAHL	EBSCO	1982-20190123	337	24.1.19
Latin American and Caribbean Health Sciences (LILACS)	http://lilacs.bvsalud.org/en/	1982-2019/01/24	458	24.1.19

Northern Light Life Sciences Conference Abstracts	Ovid	2010-2019/week 02	226	24.1.19
OAIster	http://oaister.worldcat.org	up to 23 January 2019	34	23.1.19
OpenGrey	www.opengrey.eu/	up to 23 January 2019	0	23.1.19
COPAC	https://copac.jisc.ac.uk/	up to 23 January 2019	67	23.1.19
ISPOR	https://www.ispor.org	up to 23 January 2019	70	23.1.19
HTAi	https://htai.org/	up to 23 January 2019	0	23.1.19
Total records retrieved			**8809**	
Duplicate records removed			**3451**	
Total records to screen			**5358**	

MEDLINE (Ovid): 1946-2019/January Week 3
MEDLINE Epub Ahead of Print (Ovid): January 22, 2019
MEDLINE In-Process & Other Non-Indexed Citations (Ovid): January 23, 2019
MEDLINE Daily Update (Ovid): January 22, 2019
Searched: 24.1.19

1 exp Employment/ (80218)
2 exp Work/ (59092)
3 Efficiency/ (13088)
4 Absenteeism/ (8634)
5 "Cost of Illness"/ or exp Cost Control/ or Budgets/ or Hospital Costs/ or Health Care Costs/ (102801)
6 "Length of Stay"/ (79691)
7 ((employment or employed or employee$ or unemployment or unemployed) adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing or expenditure$)).ti,ab,ot. (2131)
8 (productivity adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing or expenditure$)).ti,ab,ot. (2775)
9 ((long standing or longstanding or long term or longterm or permanent or employee$) adj2 (absence$ or absent$ or ill$ or sick$ or disab$)).ti,ab,ot,hw. (9797)
10 llsi.ti,ab,ot. (14)
11 (cost$ adj2 (illness or disease$ or sickness$)).ti,ab,ot. (4481)
12 (burden$ adj2 (disease$ or illness or sickness$)).ti,ab,ot,hw. (22023)
13 ((social or societ$ or work$ or employe$ or business$ or communit$ or famil$ or carer$ or caregiver$) adj3 (burden$ or consequenc$ or impact$ or problem$ or productivity or sickness or impairment$)).ti,ab,ot,hw. (90909)
14 ((allowance or status or long-term or pension$ or benefit$) adj2 disab$).ti,ab,ot,hw. (11403)
15 ((unable or inability or incapacit$ or incapab$) adj3 work).ti,ab,ot,hw. (1720)
16 budget$ impact$.ti,ab,ot,hw. (1322)
17 budget$ implicat$.ti,ab,ot,hw. (62)
18 (cost$ saving or cost$ savings or cost$ saved).ti,ab,ot. (17139)
19 (cost$ adj2 contain$).ti,ab,ot. (6659)
20 (cost$ adj2 audit$).ti,ab,ot. (127)
21 resource$ use$.ti,ab,ot,hw. (9087)
22 resource$ utili$.ti,ab,ot,hw. (9019)
23 resource$ usage.ti,ab,ot,hw. (347)
24 (length adj2 stay$).ti,ab,ot,hw. (105746)
25 (hospital$ adj2 stay$).ti,ab,ot,hw. (79212)
26 (duration adj2 stay$).ti,ab,ot,hw. (3195)

27 extended stay$.ti,ab,ot,hw. (179)
28 prolonged stay$.ti,ab,ot,hw. (838)
29 ((hospitali?ation or hospitali?ed or hospital) adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing or expenditure$ or budget$)).ti,ab,ot. (20300)
30 (economic consequenc$ or cost consequenc$).ti,ab,ot. (3699)
31 or/1-30 (543481)
32 exp Thrombocytopenia/ (45457)
33 (thrombocytopeni$ or thrombocytopaeni$ or thrombopeni$ or thrombopaeni$ or macrothrombocytopeni$ or macrothrombocytopaeni$).ti,ab,ot,hw. (69081)
34 ((11q or 11q23) adj3 (disorder$ or syndrome$ or delet$ or jacobsen)).ti,ab,ot,hw. (574)
35 (jacobsen adj3 syndrome$).ti,ab,ot,hw. (129)
36 paris trousseau.ti,ab,ot,hw. (30)
37 kasabach merritt.ti,ab,ot,hw. (704)
38 (hemangioma or haemangioma).ti,ab,ot,hw. (32339)
39 (thrombotic adj2 (microangiopath$ or micro angiopath$)).ti,ab,ot,hw. (3354)
40 (hemolytic uremic or haemolytic uremic).ti,ab,ot,hw. (7663)
41 gasser$.ti,ab,ot,hw. (1689)
42 HELLP Syndrome/ (1709)
43 (HELLP adj2 syndrome$).ti,ab,ot,hw. (2561)
44 ((hemolysis or haemolysis) adj2 liver adj2 platelet$).ti,ab,ot,hw. (7)
45 May Hegglin.ti,ab,ot,hw. (221)
46 ((haemolytic or hemolytic) adj2 (anaemi$ or anemi$) adj2 (microangiopathic or micro angiopathic)).ti,ab,ot,hw. (1411)
47 moschcowitz.ti,ab,ot,hw. (107)
48 werlhof.ti,ab,ot,hw. (120)
49 Wiskott-Aldrich Syndrome/ (1428)
50 (wiskott and Aldrich).ti,ab,ot,hw. (3312)
51 (immunodeficiency 2 or immunodeficiency2 or Imd2).ti,ab,ot,hw. (44)
52 ((platelet$ or thrombocyte$) adj3 (defici$ or reduc$ or low or lower or lowest or few or fewer or fewest or decrease or decreases or decreased or defective or destruc$ or destroy$)).ti,ab,ot,hw. (22231)
53 or/32-52 (132417)
54 31 and 53 (1429)
55 exp animals/ not humans/ (4540224)
56 54 not 55 (1419)

MEDLINE	**1260**
MEDLINE Epub Ahead of Print	**23**
MEDLINE In-Process & Other Non-Indexed Citations	**135**
MEDLINE Daily Update	**1**

PubMed (NLM): up to 24 January 2019

Searched: 24.1.19

#28 #26 AND #27 163

#27 pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb] 3121488

#26 #11 AND #25 2144

#25 (#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24) 551151

#24 "length of stay"[tiab] OR "hospital stay"[tiab] OR "hospital cost"[tiab] OR "hospital costs"[tiab] OR "hospital expenditure"[tiab] OR "hospital budget"[tiab] OR "hospital budgets"[tiab]

OR "economic consequence"[tiab] OR "economic consequences"[tiab] OR "cost consequence"[tiab] OR "cost consequences"[tiab] 118299

#23 "resource use"[tiab] OR "resource utilise"[tiab] OR "resource utilize"[tiab] OR "resource utility"[tiab] OR "resource usage"[tiab] 7846

#22 "cost saving"[tiab] OR "cost savings"[tiab] OR "cost saved"[tiab] OR "costs saved"[tiab] OR "cost contain"[tiab] OR "cost contained"[tiab] OR "cost containment"[tiab] OR "cost audit"[tiab] 22036

#21 "budget impact"[tiab] OR "budget impacts"[tiab] OR "budget implication"[tiab] OR "budget implications"[tiab] 1245

#20 (unable[tiab] OR inability[tiab] OR incapacity[tiab] OR incapable[tiab]) AND work[tiab] 9494

#19 "disability allowance"[tiab] OR "disability benefit"[tiab] OR "disability benefits"[tiab] 865

#18 (social[tiab] OR societ*[tiab] OR work*[tiab] OR community[tiab] OR family[tiab] OR carer*[tiab] OR caregiver*[tiab]) AND burden*[tiab] 55842

#17 "cost of illness"[tiab] OR "cost of disease"[tiab] OR "cost of sickness"[tiab] OR "burden of illness"[tiab] OR "burden of disease"[tiab] OR "burden of sickness"[tiab] 11376

#16 absentee*[tiab] OR "long term illness"[tiab] OR "longterm illness"[tiab] OR "long term sick"[tiab] OR "longterm sick"[tiab] OR "long term sickness"[tiab] OR "longterm sickness"[tiab] OR "long term disabled"[tiab] OR "longterm disabled"[tiab] OR "long term disability"[tiab] OR "longterm disability"[tiab] 9106

#15 employment[tiab] OR employee[tiab] OR unemployment[tiab] OR unemployed[tiab] 76820

#14 "Length of Stay"[Mesh] 79696

#13 "Cost of Illness"[Mesh] OR "Cost Control"[Mesh] OR "Budgets"[Mesh] OR "Hospital Costs"[Mesh] OR "Health Care Costs"[Mesh] 116564

#12 "Employment"[Mesh] OR "Work"[Mesh] OR "Efficiency"[Mesh] OR "Absenteeism"[Mesh] 168671

#11 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10) 188201

#10 (platelet*[tiab] OR thrombocyte*[tiab]) AND (defici*[tiab] OR reduc*[tiab] OR low[tiab] OR lower[tiab] OR lowest[tiab] OR few[tiab] OR fewer[tiab] OR fewest[tiab] OR decrease[tiab] OR decreases[tiab] OR decreased[tiab] OR defective[tiab] OR destruc*[tiab] OR destroy*[tiab]) 99513

#9 "immunodeficiency 2" OR immunodeficiency2 OR Imd2 46

#8 Moschcowitz[tiab] OR werlhof[tiab] OR "Wiskott-Aldrich Syndrome"[Mesh] OR (wiskott[tiab] AND Aldrich[tiab]) 2664

#7 (haemolytic[tiab] OR hemolytic[tiab]) AND (anaemi*[tiab] OR anemi*[tiab]) AND (microangiopath*[tiab]) 1765

#6 (hemolysis[tiab] OR haemolysis[tiab]) AND liver[tiab] AND platelet*[tiab] 1247

#5 "HELLP Syndrome"[Mesh] OR "HELLP syndrome" OR "HELLP syndromes" 2583

#4 (thrombotic[tiab] AND microangiopath*[tiab]) OR "hemolytic uremic" OR "haemolytic uremic" OR gasser*[tiab] 12074

#3 "jacobsen syndrome" OR "paris trousseau" OR "kasabach merritt" OR "May Hegglin" OR hemangioma[tiab] OR haemangioma[tiab] 17717

#2 (11q[tiab] OR 11q23[tiab]) AND (disorder*[tiab] OR syndrome*[tiab] OR delet*[tiab] OR Jacobsen[tiab]) 1605

#1 ("Thrombocytopenia"[Mesh] OR thrombocytopeni*[tiab] OR thrombocytopaeni*[tiab] OR thrombopeni*[tiab] OR thrombopaeni*[tiab] OR macrothrombocytopeni*[tiab] OR macrothrombocytopaeni*[tiab]) 73938

Embase (Ovid): 1974 to 2019 Week 3

Searched: 24.1.19

1 exp employment/ (82835)
2 exp work/ (322925)
3 "cost of illness"/ or cost control/ or hospital cost/ or budget/ or health care cost/ (271582)
4 "length of stay"/ (159635)
5 ((employment or employed or employee$ or unemployment or unemployed) adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing or expenditure$)).ti,ab,ot. (2669)
6 (productivity adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing or expenditure$)).ti,ab,ot. (3897)
7 ((long standing or longstanding or long term or longterm or permanent or employee$) adj2 (absence$ or absent$ or ill$ or sick$ or disab$)).ti,ab,ot. (13272)
8 llsi.ti,ab,ot. (16)
9 (cost$ adj2 (illness or disease$ or sickness$)).ti,ab,ot. (6727)
10 (burden$ adj2 (disease$ or illness or sickness$)).ti,ab,ot. (33235)
11 ((social or societ$ or work$ or employe$ or business$ or communit$ or famil$ or carer$ or caregiver$) adj3 (burden$ or consequenc$ or impact$ or problem$ or productivity or sickness or impairment$)).ti,ab,ot. (111968)
12 ((allowance or status or long-term or pension$ or benefit$) adj2 disab$).ti,ab,ot. (17909)
13 ((unable or inability or incapacit$ or incapab$) adj3 work).ti,ab,ot. (2444)
14 budget$ impact$.ti,ab,ot. (3571)
15 budget$ implicat$.ti,ab,ot. (87)
16 (cost$ saving or cost$ savings or cost$ saved).ti,ab,ot. (28279)
17 (cost$ adj2 contain$).ti,ab,ot. (8302)
18 (cost$ adj2 audit$).ti,ab,ot. (208)
19 resource$ use$.ti,ab,ot. (13699)
20 resource$ utili$.ti,ab,ot. (16372)
21 resource$ usage.ti,ab,ot. (500)
22 (length adj2 stay$).ti,ab,ot. (89167)
23 (hospital$ adj2 stay$).ti,ab,ot. (129616)
24 (duration adj2 stay$).ti,ab,ot. (4967)
25 extended stay$.ti,ab,ot. (269)
26 prolonged stay$.ti,ab,ot. (1306)
27 ((hospitali?ation or hospitali?ed or hospital) adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing or expenditure$ or budget$)).ti,ab,ot. (31590)
28 (economic consequenc$ or cost consequenc$).ti,ab,ot. (4997)
29 or/1-28 (1048603)
30 exp thrombocytopenia/ (157171)
31 (thrombocytopeni$ or thrombocytopaeni$ or thrombopeni$ or thrombopaeni$ or macrothrombocytopeni$ or macrothrombocytopaeni$).ti,ab,ot. (87986)
32 ((11q or 11q23) adj3 (disorder$ or syndrome$ or delet$ or jacobsen)).ti,ab,ot. (1015)
33 (jacobsen adj3 syndrome$).ti,ab,ot. (187)
34 paris trousseau.ti,ab,ot. (49)
35 kasabach merritt.ti,ab,ot. (793)
36 (hemangioma or haemangioma).ti,ab,ot. (18275)
37 (thrombotic adj2 (microangiopath$ or micro angiopath$)).ti,ab,ot. (5177)
38 (hemolytic uremic or haemolytic uremic).ti,ab,ot. (7454)
39 gasser$.ti,ab,ot. (1885)
40 (HELLP adj2 syndrome$).ti,ab,ot. (3305)
41 ((hemolysis or haemolysis) adj2 liver adj2 platelet$).ti,ab,ot. (11)
42 May Hegglin.ti,ab,ot. (262)
43 ((haemolytic or hemolytic) adj2 (anaemi$ or anemi$) adj2 (microangiopathic or micro angiopathic)).ti,ab,ot. (2048)
44 moschcowitz.ti,ab,ot. (93)

45 werlhof.ti,ab,ot. (55)
46 (wiskott and aldrich).ti,ab,ot. (2815)
47 (immunodeficiency 2 or immunodeficiency2 or Imd2).ti,ab,ot. (71)
48 ((platelet$ or thrombocyte$) adj3 (defici$ or reduc$ or low or lower or lowest or few or fewer or fewest or decrease or decreases or decreased or defective or destruc$ or destroy$)).ti,ab,ot. (33439)
49 or/30-48 (221567)
50 animal/ or animal experiment/ (3692962)
51 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot. (4424329)
52 50 or 51 (5722776)
53 exp human/ or human experiment/ (19263219)
54 52 not (52 and 53) (4428740)
55 29 and 49 (4872)
56 55 not 54 (4838)

Science Citation Index Expanded (SCI) (Web of Science): 1988-2018-01-23
Searched: 24.1.19

# 32	**1,197**	**#15 AND #31**
# 31	317,316	#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30
# 30	4,262	TS=("economic consequenc*" or "cost consequenc*")
# 29	19,538	TS=((hospitalisation or hospitalization or hospitalised or hospitalized or hospital) NEAR/3 (economic* or cost or costs or costly or costing or price or prices or pricing or expenditure* or budget*))
# 28	98,595	TS=((length NEAR/2 stay*) or (hospital* NEAR/2 stay*) or (duration NEAR/2 stay*) or "extended stay*" or "prolonged stay*")
# 27	30,484	TS=("resource* use*" or "resource* utili*" or "resource* usage")
# 26	4,197	TS=((cost* NEAR/2 contain*) or (cost* NEAR/2 audit*))
# 25	19,854	TS=("cost* saving" or "cost* savings" or "cost* saved")
# 24	2,054	TS=("budget* impact*" OR "budget* implicat*")
# 23	1,173	TS=((unable or inability or incapacit* or incapab*) NEAR/3 work)
# 22	10,217	TS=((allowance or status or long-term or pension* or benefit*) NEAR/2 disab*)
# 21	106,170	TS=((social or societ* or work* or employe* or business* or communit* or famil* or carer* or caregiver*) NEAR/3 (burden* or consequenc* or impact*

		or problem* or productivity or sickness or impairment*))
# 20	25,333	TS=(burden* NEAR/2 (disease* or illness or sickness*))
# 19	6,982	TS=(cost* NEAR/2 (illness or disease* or sickness*))
# 18	8,744	TS=(("long standing" or longstanding or "long term" or longterm or permanent or employee*) NEAR/2 (absence* or absent* or ill* or sick* or disab*))
# 17	5,598	TS=(productivity NEAR/3 (economic* or cost or costs or costly or costing or price or prices or pricing or expenditure*))
# 16	4,719	TS=((employment or employed or employee* or unemployment or unemployed) NEAR/3 (economic* or cost or costs or costly or costing or price or prices or pricing or expenditure*))
# 15	98,158	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
# 14	20,790	TS=((platelet* or thrombocyte*) NEAR/3 (defici* or reduc* or low or lower or lowest or few or fewer or fewest or decrease or decreases or decreased or defective or destruc* or destroy*))
# 13	3,306	TS=(werlhof) or TS=(wiskott and aldrich) or TS=("immunodeficiency 2" or immunodeficiency2 or Imd2)
# 12	48	TS=(moschcowitz)
# 11	870	TS=((haemolytic or hemolytic) NEAR/2 (anaemi* or anemi*) NEAR/2 (microangiopathic or "micro angiopathic"))
# 10	170	TS=("May Hegglin")
# 9	272	TS=((hemolysis or haemolysis) NEAR/2 liver NEAR/2 platelet*)
# 8	3,797	TS=(gasser*) or TS=(HELLP NEAR/2 syndrome*)
# 7	10,671	TS=("hemolytic uremic" or "haemolytic uremic")
# 6	3,876	TS=(thrombotic NEAR/2 (microangiopath* or "micro angiopath*"))
# 5	11,949	TS=(hemangioma or haemangioma)
# 4	703	TS=("kasabach merritt")

# 3	189	TS=(jacobsen NEAR/3 syndrome*) OR TS=("paris trousseau" NEAR/3 syndrome*)
# 2	643	TS=((11q or 11q23) NEAR/3 (disorder* or syndrome* or delet* or jacobsen))
# 1	53,278	TS=(thrombocytopeni* or thrombocytopaeni* or thrombopeni* or thrombopaeni* or macrothrombocytopeni* or macrothrombocytopaeni*)

CINAHL (EBSCO): 1982-20190123
Searched: 24.1.19

S1	(MH "Thrombocytopenia+")	5,320
S2	TI (thrombocytopeni* or thrombocytopaeni* or thrombopeni* or thrombopaeni* or macrothrombocytopeni* or macrothrombocytopaeni*) OR AB (thrombocytopeni* or thrombocytopaeni* or thrombopeni* or thrombopaeni* or macrothrombocytopeni* or macrothrombocytopaeni*)	7,424
S3	TI ((11q or 11q23) N3 (disorder* or syndrome* or delet* or jacobsen)) OR AB ((11q or 11q23) N3 (disorder* or syndrome* or delet* or jacobsen))	33
S4	TI (jacobsen N3 syndrome*) OR AB (jacobsen N3 syndrome*)	8
S5	TI ("paris trousseau" or "kasabach merritt" or "May Hegglin") OR AB ("paris trousseau" or "kasabach merritt" or "May Hegglin")	101
S6	TI (hemangioma or haemangioma) OR AB (hemangioma or haemangioma)	2,028
S7	TI (thrombotic N2 (microangiopath* or "micro angiopath*")) or AB (thrombotic N2 (microangiopath* or "micro angiopath*"))	536
S8	TI ("hemolytic uremic" or "haemolytic uremic" or gasser*) or AB ("hemolytic uremic" or "haemolytic uremic" or gasser*)	824
S9	(MH "HELLP Syndrome")	476
S10	TI (HELLP N2 syndrome*) or AB (HELLP N2 syndrome*)	438
S11	TI ((hemolysis or haemolysis) N2 liver N2 platelet*) or AB ((hemolysis or haemolysis) N2 liver N2 platelet*)	78
S12	TI ((haemolytic or hemolytic) N2 (anaemi* or anemi*) N2 (microangiopathic or micro angiopathic)) or AB ((haemolytic or hemolytic) N2 (anaemi* or anemi*) N2 (microangiopathic or micro angiopathic))	159
S13	TI ((microangiopath* or micro angiopath*) N2 thrombotic) or AB ((microangiopath* or micro angiopath*) N2 thrombotic)	536
S14	TI (moschcowitz or werlhof or (wiskott and Aldrich)) or AB (moschcowitz or werlhof or (wiskott and Aldrich))	93
S15	(MH "Wiskott-Aldrich Syndrome")	52
S16	TI ("immunodeficiency 2" or immunodeficiency2 or Imd2) or AB ("immunodeficiency 2" or immunodeficiency2 or Imd2)	1

S17	TI ((platelet* or thrombocyte*) N3 (defici* or reduc* or low or lower or lowest or few or fewer or fewest or decrease or decreases or decreased or defective or destruc* or destroy*)) or AB ((platelet* or thrombocyte*) N3 (defici* or reduc* or low or lower or lowest or few or fewer or fewest or decrease or decreases or decreased or defective or destruc* or destroy*))	2,419
S18	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17	14,324
S19	(MH "Employment+")	41,279
S20	(MH "Work+")	5,848
S21	(MH "Absenteeism")	4,010
S22	(MH "Health Care Costs+")	48,268
S23	(MH "Caregiver Burden")	8,374
S24	(MH "Health Facility Costs")	3,920
S25	(MH "Budgets")	8,929
S26	(MH "Cost Control+")	19,262
S27	(MH "Length of Stay")	34,378
S28	TI ((employment or employed or employee* or unemployment or unemployed) N3 (economic* or cost or costs or costly or costing or price or prices or pricing or expenditure*)) or AB ((employment or employed or employee* or unemployment or unemployed) N3 (economic* or cost or costs or costly or costing or price or prices or pricing or expenditure*))	1,289
S29	TI (productivity N3 (economic* or cost or costs or costly or costing or price or prices or pricing or expenditure*)) or AB (productivity N3 (economic* or cost or costs or costly or costing or price or prices or pricing or expenditure*))	1,193
S30	TI ((long standing or longstanding or long term or longterm or permanent or employee*) N2 (absence* or absent* or ill* or sick* or disab*)) or AB ((long standing or longstanding or long term or longterm or permanent or employee*) N2 (absence* or absent* or ill* or sick* or disab*))	4,533
S31	TI (cost* N2 (illness or disease* or sickness*)) or AB (cost* N2 (illness or disease* or sickness*))	2,269
S32	TI (burden* N2 (disease* or illness or sickness*)) or AB (burden* N2 (disease* or illness or sickness*))	9,253
S33	TI ((social or societ* or work* or employe* or business* or communit* or famil* or carer* or caregiver*) N3 (burden* or consequenc* or impact* or problem* or productivity or sickness or impairment*)) or AB ((social or societ* or work* or employe* or business* or communit* or famil* or carer* or caregiver*) N3 (burden* or consequenc* or impact* or problem* or productivity or sickness or impairment*))	43,091
S34	TI ((allowance or status or long-term or pension* or benefit*) N2 disab*) or AB ((allowance or status or long-term or pension* or benefit*) N2 disab*)	4,849
S35	TI ((unable or inability or incapacit* or incapab*) N3 work) or AB ((unable or inability or incapacit* or incapab*) N3 work)	534

S36	TI ("budget* impact*" OR "budget* implicat*") or AB ("budget* impact*" OR "budget* implicat*")	650
S37	TI ("cost* saving" or "cost* savings" or "cost* saved") or AB ("cost* saving" or "cost* savings" or "cost* saved")	6,473
S38	TI ((cost* N2 contain*) or (cost* N2 audit*)) or AB ((cost* N2 contain*) or (cost* N2 audit*))	2,241
S39	TI ("resource* use*" or "resource* utili*" or "resource* usage") or AB ("resource* use*" or "resource* utili*" or "resource* usage")	6,674
S40	TI ((length N2 stay*) or (hospital* N2 stay*) or (duration N2 stay*) or "extended stay*" or "prolonged stay*") or AB ((length N2 stay*) or (hospital* N2 stay*) or (duration N2 stay*) or "extended stay*" or "prolonged stay*")	38,550
S41	TI ((hospitalisation or hospitalization or hospitalised or hospitalized or hospital) N3 (economic* or cost or costs or costly or costing or price or prices or pricing or expenditure* or budget*)) or AB ((hospitalisation or hospitalization or hospitalised or hospitalized or hospital) N3 (economic* or cost or costs or costly or costing or price or prices or pricing or expenditure* or budget*))	8,953
S42	TI ("economic consequenc*" or "cost consequenc*") or AB ("economic consequenc*" or "cost consequenc*")	1,030
S43	S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42	243,749
S44	**S18 AND S43**	**337**

Latin American and Caribbean Health Sciences (LILACS) (Internet): 1982-2019/01/24
Searched: 24.1.19

((MH:c15.378.140.855 OR MH:c15.378.100.100.970 OR thrombocytopeni* OR thrombocytopaeni* OR thrombopeni* OR thrombopaeni* OR macrothrombocytopeni* OR macrothrombocytopaeni* OR trombocitopeni* OR ((platelet* OR thrombocyte*) AND (defici* OR reduc* OR low OR lower OR lowest OR few OR fewer OR fewest OR decrease OR decreases OR decreased OR defective OR destruc* OR destroy*))) AND (MH:N03.219.151.165 OR MH:N03.219.151.400 OR MH: N01.824.245 OR MH:F02.784.692.107 OR MH:I03.946 OR MH:E02.760.400.480 OR "cost of illness" OR "burden of illness" OR "cost saving" OR "cost savings" OR "cost saved" OR "budget impact" OR "resource use" OR "resource utilisation" OR "resource utilization" OR "resource utility" OR "resource usage" OR "costo de enfermedad" OR "efeitos psicossociais da doença" OR "length of stay" OR "hospital stay" OR "tiempo de internación" OR "tempo de internação" OR "health care cost" OR "health care costs" OR "costos de la atención en salud" OR "custos de cuidados de saúde" OR "hospital cost" OR "hospital costs" OR "hospital expenditure" OR "hospital expenditures" OR "economic consequence" OR "economic consequences" OR "cost consequence" OR "cost consequences" OR employment OR employed OR employee* OR unemployment OR unemployed OR empleo OR emprego OR work OR trabajo OR trabalho OR absenteeism OR absentismo OR absenteísmo OR carer* OR caregiver*))

Search limited to non-Medline databases:

- **LILACS (301)**
- **IBECS (106)**

- **BINACIS (25)**
- **BBO - Dentistry (22)**
- **CUMED (17)**
- **MedCarib (3)**
- **BDENF - Nursing (2)**
- **BRISA/RedTESA (2)**
- **Coleciona SUS (2)**

Northern Light Life Sciences Conference Abstracts (Ovid): 2010-2019/week 02
Searched: 24.1.19

1 exp thrombocytopenia/ (19173)
2 (thrombocytopeni$ or thrombocytopaeni$ or thrombopeni$ or thrombopaeni$ or macrothrombocytopeni$ or macrothrombocytopaeni$).ti,ab,hw. (18543)
3 ((11q or 11q23) adj3 (disorder$ or syndrome$ or delet$ or jacobsen)).ti,ab,hw. (132)
4 (jacobsen adj3 syndrome$).ti,ab,hw. (41)
5 (paris trousseau or kasabach merritt or hemangioma or haemangioma).ti,ab,hw. (2487)
6 (thrombotic adj2 (microangiopath$ or micro angiopath$)).ti,ab,hw. (1515)
7 (hemolytic uremic or haemolytic uremic or gasser$).ti,ab,hw. (643)
8 hellp syndrome/ (410)
9 (HELLP adj2 syndrome$).ti,ab,hw. (415)
10 ((hemolysis or haemolysis) adj2 liver adj2 platelet$).ti,ab,hw. (0)
11 May Hegglin.ti,ab,hw. (10)
12 ((haemolytic or hemolytic) adj2 (anaemi$ or anemi$) adj2 (microangiopathic or micro angiopathic)).ti,ab,hw. (77)
13 (moschcowitz or werlhof or (wiskott and Aldrich)).ti,ab,hw. (468)
14 wiskott-aldrich syndrome/ (460)
15 (immunodeficiency 2 or immunodeficiency2 or Imd2).ti,ab,hw. (0)
16 ((platelet$ or thrombocyte$) adj3 (defici$ or reduc$ or low or lower or lowest or few or fewer or fewest or decrease or decreases or decreased or defective or destruc$ or destroy$)).ti,ab,hw. (1916)
17 or/1-16 (24421)
18 ((employment or employed or employee$ or unemployment or unemployed) adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing or expenditure$)).ti,ab,hw. (121)
19 (productivity adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing or expenditure$)).ti,ab,hw. (248)
20 ((long standing or longstanding or long term or longterm or permanent or employee$) adj2 (absence$ or absent$ or ill$ or sick$ or disab$)).ti,ab,hw. (623)
21 (cost$ adj2 (illness or disease$ or sickness$)).ti,ab,hw. (592)
22 (burden$ adj2 (disease$ or illness or sickness$)).ti,ab,hw. (3836)
23 ((social or societ$ or work$ or employe$ or business$ or communit$ or famil$ or carer$ or caregiver$) adj3 (burden$ or consequenc$ or impact$ or problem$ or productivity or sickness or impairment$)).ti,ab,hw. (7569)
24 ((allowance or status or long-term or pension$ or benefit$) adj2 disab$).ti,ab,hw. (802)
25 ((unable or inability or incapacit$ or incapab$) adj3 work).ti,ab,hw. (59)
26 (budget$ impact$ or budget$ implicat$).ti,ab,hw. (1171)
27 (cost$ saving or cost$ savings or cost$ saved or (cost$ adj2 contain$) or (cost$ adj2 audit$)).ti,ab,hw. (4768)
28 (resource$ use$ or resource$ utili$ or resource$ usage).ti,ab,hw. (4055)
29 ((length or hospital$ or duration) adj2 stay$).ti,ab,hw. (11980)
30 (extended stay$ or prolonged stay$).ti,ab,hw. (94)
31 ((hospitali?ation or hospitali?ed or hospital) adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing or expenditure$ or budget$)).ti,ab,hw. (2579)
32 (economic consequenc$ or cost consequenc$).ti,ab,hw. (318)
33 or/18-32 (35882)

34 17 and 33 (226)

OAIster (Internet): up to 23 January 2019
http://oaister.worldcat.org
Searched: 23.1.19

((thrombocytopeni* OR thrombocytopaeni* OR thrombopeni* OR thrombopaeni*) AND (cost of illness OR burden of illness OR cost saving* OR resource use OR resource usage OR length of stay OR hospital stay OR health care cost OR health care costs OR hospital cost* OR economic consequence* OR cost consequence* OR employment OR employed OR employee* OR unemployment OR unemployed OR absenteeism OR carer* OR caregiver*))

Records retrieved: 34

OpenGrey (Internet): up to 23 January 2019
www.opengrey.eu/
Searched: 23.1.19

((thrombocytopeni* OR thrombocytopaeni* OR thrombopeni* OR thrombopaeni*) AND (cost of illness OR burden of illness OR cost saving* OR resource use OR resource usage OR length of stay OR hospital stay OR health care cost OR health care costs OR hospital cost* OR economic consequence* OR cost consequence* OR employment OR employed OR employee* OR unemployment OR unemployed OR absenteeism OR carer* OR caregiver*))

Records retrieved: 0

COPAC (Internet): up to 23 January 2019
https://copac.jisc.ac.uk/
Searched: 23.1.19

Keyword: thrombocytopeni* "cost of illness"
Keyword: thrombocytopaeni* "cost of illness"
Keyword: thrombopeni* "cost of illness"
Keyword: thrombopaeni* "cost of illness"
Keyword: thrombocytopeni* "burden of illness"
Keyword: thrombocytopaeni* "burden of illness"
Keyword: thrombopeni* "burden of illness"
Keyword: thrombopaeni* "burden of illness"
Keyword: thrombocytopeni* "resource use"
Keyword: thrombocytopaeni* "resource use"
Keyword: thrombopeni* "resource use"
Keyword: thrombopaeni* "resource use"
Keyword: thrombocytopeni*; Title words: cost
Keyword: thrombocytopeni*; Title words: costs
Keyword: thrombocytopaeni*; Title words: cost
Keyword: thrombocytopaeni*; Title words: costs
Keyword: thrombopeni*; Title words: cost

Keyword: thrombopeni*; Title words: costs
Keyword: thrombopaeni*; Title words: cost
Keyword: thrombopaeni*; Title words: costs
Keyword: thrombocytopeni*; Title words: economic
Keyword: thrombocytopeni*; Title words: economic s
Keyword: thrombocytopaeni*; Title words: economic
Keyword: thrombocytopaeni*; Title words: economics
Keyword: thrombopeni*; Title words: economic
Keyword: thrombopeni*; Title words: economics
Keyword: thrombopaeni*; Title words: economic
Keyword: thrombopaeni*; Title words: economics
Keyword: thrombocytopeni* "length of stay"
Keyword: thrombocytopaeni* "length of stay"
Keyword: thrombopeni* "length of stay"
Keyword: thrombopaeni* "length of stay"
Keyword: thrombocytopeni* "hospital stay"
Keyword: thrombocytopaeni* "hospital stay"
Keyword: thrombopeni* "hospital stay"
Keyword: thrombopaeni* "hospital stay"
Keyword: thrombocytopeni* "hospital cost"
Keyword: thrombocytopaeni* "hospital cost"
Keyword: thrombopeni* "hospital cost"
Keyword: thrombopaeni* "hospital cost"
Keyword: thrombocytopeni* "hospital costs"
Keyword: thrombocytopaeni* "hospital costs"
Keyword: thrombopeni* "hospital costs"
Keyword: thrombopaeni* "hospital costs"
Keyword: thrombocytopeni* carer*
Keyword: thrombocytopaeni* carer*
Keyword: thrombopeni* carer*
Keyword: thrombopaeni* carer*
Keyword: thrombocytopeni* caregiver*
Keyword: thrombocytopaeni* caregiver*
Keyword: thrombopeni* caregiver*
Keyword: thrombopaeni* caregiver*
Records retrieved: 67

ISPOR (Internet): up to 23 January 2019
https://www.ispor.org/
Searched: 23.1.19

General website search	**Results**
avatrombopag OR doptelet	0

lusutrombopag OR mulpleta	0
thrombocytopenia OR thrombocytopenic OR thrombocytopaenia OR thrombocytopaenic OR thrombopenia OR thrombopenic OR thrombopaenia OR thrombopaenic	27
Total	**27**

Scientific Presentations Database search; Keyword Search	**Results**
avatrombopag	0
doptelet	
lusutrombopag	0
mulpleta	
Titles: thrombocytopenia	44
Titles: thrombocytopenic	22
Titles: thrombocytopaenia	0
Titles: thrombocytopaenic	0
Titles: thrombopenia	0
Titles: thrombopenic	0
Titles: thrombopaenia	0
Titles: thrombopaenic	0
Total	**66**

Overall Total	**93**
Total after removal of duplicate records	**70**

HTAi (Internet): up to 23 January 2019
https://htai.org/
Searched: 23.1.19

avatrombopag
doptelet
lusutrombopag
mulpleta
thrombocytopenia

thrombocytopenic
thrombocytopaenia
thrombocytopaenic
thrombopenia
thrombopenic
thrombopaenia
thrombopaenic

Records retrieved: 0

Economic model: search strategies

Supplementary literature searches were conducted to identify data to help populate the economic model. The search strategies were developed pragmatically, using a targeted rather than extensive approach. Limits included: focussed subject headings; restricted proximity; precise free text terms; fewer databases; and date limits.

PubMed search for NIHR HTA reports with similar economic models

PubMed (NLM): up to 11 April 2019
Searched: 11.4.19

#16 Search (#14 AND #15) 42
#15 Search "Health Technol Assess"[jour] 1233
#14 Search (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #12 OR #13) 763896
#13 Search "platelet transfusion"[tiab] OR "thrombocyte transfusion"[tiab] OR "blood transfusion"[tiab] 40906
#12 Search "Platelet Transfusion"[Mesh] 6869
#10 Search (liver*[tiab] OR hepatic[tiab] OR intrahepatic[tiab]) AND carcinoma*[tiab] 76177
#9 Search (haemochromatosis[tiab] OR hemochromatosis[tiab] OR "bronze diabetes"[tiab] OR "bronze diabetic"[tiab] OR "recklinghausen applebaum"[tiab] OR siderochromatosis[tiab] OR "primary biliary cholangitis"[tiab] OR hepatocarcinoma[tiab] OR hepatoma*[tiab]) 40459
#8 Search (liver*[tiab] OR hepatic[tiab] OR intrahepatic[tiab]) AND inflam*[tiab] 58570
#7 Search (hepatitis[tiab] OR hepatopath*[tiab]) AND (chronic[tiab] OR acute[tiab] OR persistent[tiab] OR "long standing"[tiab] OR "long term"[tiab] OR recurr*[tiab]) 92789
#6 Search ((fibrosis[tiab] OR fibroses[tiab] OR scar*[tiab]) AND (liver*[tiab] OR hepatic[tiab])) 41152
#5 Search chronic[tiab] AND "destructive cholangitis"[tiab] 118
#4 Search cirrhosis[tiab] OR cirrhosis[tiab] OR cirrhotic[tiab] 96549
#3 Search "liver disease"[tiab] OR "liver diseases"[tiab] OR "hepatic disease"[tiab] OR "hepatic diseases"[tiab] OR "intrahepatic disease"[tiab] OR "intrahepatic diseases"[tiab] OR "liver disorder"[tiab] OR "liver disorders"[tiab] OR "hepatic disorder"[tiab] OR "hepatic disorders"[tiab] OR "intrahepatic disorder"[tiab] OR "intrahepatic disorders"[tiab] OR "liver lesion"[tiab] OR "liver lesions"[tiab] OR "hepatic lesion"[tiab] OR "hepatic lesions"[tiab] OR "intrahepatic lesion"[tiab] OR "intrahepatic lesions"[tiab] 110351
#2 Search "Liver Diseases"[Mesh] 525899

#1 Search (("Thrombocytopenia"[Mesh] OR thrombocytopeni*[tiab] OR thrombocytopaeni*[tiab] OR thrombopeni*[tiab] OR thrombopaeni*[tiab] OR macrothrombocytopeni*[tiab] OR macrothrombocytopaeni*[tiab])) 74587

Literature searches to identify rates of procedures with bleeding risk in patients with chronic liver disease

MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to May 17, 2019

Searched: 20.5.19

1 exp *Liver Diseases/ and exp Chronic Disease/ (14897)

2 ((liver$ or hepat$ or intrahepat$) adj2 (disease$ or disorder$ or lesion$ or failure$) adj2 (chronic or refractory or unmanageab$ or uncontrol$ or resistant or persist$ or intractable$ or recurren$ or sustained or permanent$ or unremitting or unrelenting or continual$ or continuous$ or constant$ or unending or unceasing)).ti,ab. (23997)

3 (cirrhosis or cirrhoses or cirrhotic).ti,ab. (93496)

4 ((fibrosis or fibroses or scar$) adj2 (liver$ or hepat$ or intrahepat$)).ti,ab. (21311)

5 or/1-4 (130417)

6 exp Specialties, Surgical/sn, td [Statistics & Numerical Data, Trends] (13407)

7 exp Surgical Procedures, Operative/sn, td [Statistics & Numerical Data, Trends] (105017)

8 exp Liver Diseases/sn [Statistics & Numerical Data] (185)

9 Paracentesis/sn, td or Thoracentesis/ or exp Endoscopy, Gastrointestinal/sn, td or Bronchoscopy/sn, td or Chemoembolization, Therapeutic/sn, td or Portasystemic Shunt, Transjugular Intrahepatic/sn, td or Oral Surgical Procedures/sn, td or Biliary Tract Surgical Procedures/sn, td or Nephrotomy/ or Radiofrequency Ablation/sn, td or Catheter Ablation/sn, td or Laparoscopy/sn, td (8036)

10 ((paracentesis or paracenteses) adj3 (rate or rates or occurrence or reoccurrence or frequen$ or repeat$ or pattern$ or trend$ or episode$ or prevalence or incidence or quantity or amount$ or number or numbers or life time or lifetime or long term or longterm or subsequent$ or repetition$ or reoperat$ or re-operate$ or readmiss$ or readmit$)).ti,ab. (303)

11 ((thoracentesis or thoracenteses or thoracocentesis or thoracocenteses or pleurocentesis or pleurocenteses) adj3 (rate or rates or occurrence or reoccurrence or frequen$ or repeat$ or pattern$ or trend$ or episode$ or prevalence or incidence or quantity or amount$ or number or numbers or life time or lifetime or long term or longterm or subsequent$ or repetition$ or reoperat$ or re-operate$ or readmiss$ or readmit$)).ti,ab. (232)

12 ((endoscop$ or enteroscop$) adj2 (gastrointestinal or balloon$ or push or mucosal or submucosal) adj3 (rate or rates or occurrence or reoccurrence or frequen$ or repeat$ or pattern$ or trend$ or episode$ or prevalence or incidence or quantity or amount$ or number or numbers or life time or lifetime or long term or longterm or subsequent$ or repetition$ or reoperat$ or re-operate$ or readmiss$ or readmit$)).ti,ab. (486)

13 (bronchoscop$ adj2 (gastrointestinal or balloon$ or push or mucosal or submucosal) adj3 (rate or rates or occurrence or reoccurrence or frequen$ or repeat$ or pattern$ or trend$ or episode$ or prevalence or incidence or quantity or amount$ or number or numbers or life time or lifetime or long term or longterm or subsequent$ or repetition$ or reoperat$ or re-operate$ or readmiss$ or readmit$)).ti,ab. (4)

14 ((ethanol or alcohol) adj2 (ablation or inject$) adj3 (rate or rates or occurrence or reoccurrence or frequen$ or repeat$ or pattern$ or trend$ or episode$ or prevalence or incidence or quantity or amount$ or number or numbers or life time or lifetime or long term or longterm or subsequent$ or repetition$ or reoperat$ or re-operate$ or readmiss$ or readmit$)).ti,ab. (242)

15 (chemoemboli?ati$ adj3 (rate or rates or occurrence or reoccurrence or frequen$ or repeat$ or pattern$ or trend$ or episode$ or prevalence or incidence or quantity or amount$ or number or numbers or life time or lifetime or long term or longterm or subsequent$ or repetition$ or reoperat$ or re-operate$ or readmiss$ or readmit$)).ti,ab. (261)

16 ((vascular or cardiac or cardiovascular or heart or blood vessel$) adj2 (catheteri?ation or catherteri?ed) adj3 (rate or rates or occurrence or reoccurrence or frequen$ or repeat$ or pattern$ or trend$ or episode$ or prevalence or incidence or quantity or amount$ or number or numbers or life time or lifetime or long term or longterm or subsequent$ or repetition$ or reoperat$ or re-operate$ or readmiss$ or readmit$)).ti,ab. (735)

17 ((transjugular intrahepatic portosystemic shunt$ or transjugular intrahepatic porto systemic shunt$ or transjugular intrahepatic portacaval shunt$ or transjugular intrahepatic porta systemic shunt$ or transjugular intrahepatic portasystemic shunt$ or transjugular intrahepatic shunt$ or transjugular intrahepatic stent$ or TIPS) adj3 (rate or rates or occurrence or reoccurrence or frequen$ or repeat$ or pattern$ or trend$ or episode$ or prevalence or incidence or quantity or amount$ or number or numbers or life time or lifetime or long term or longterm or subsequent$ or repetition$ or reoperat$ or re-operate$ or readmiss$ or readmit$)).ti,ab. (770)

18 ((dental or tooth or teeth or molar) adj2 (surg$ or operat$ or reoperat$ or soldering or inlay or preparation or pulp extirpation or extraction$ or amputation or resect$ or removal or remove or reimplant$ or replantat$ or reinclusion or extract$) adj3 (rate or rates or occurrence or reoccurrence or frequen$ or repeat$ or pattern$ or trend$ or episode$ or prevalence or incidence or quantity or amount$ or number or numbers or life time or lifetime or long term or longterm or subsequent$ or repetition$ or reoperat$ or re-operate$ or readmiss$ or readmit$)).ti,ab. (673)

19 ((bile or biliary or gall bladder or gallbladder) adj2 (surg$ or operat$ or reoperat$) adj3 (rate or rates or occurrence or reoccurrence or frequen$ or repeat$ or pattern$ or trend$ or episode$ or prevalence or incidence or quantity or amount$ or number or numbers or life time or lifetime or long term or longterm or subsequent$ or repetition$ or reoperat$ or re-operate$ or readmiss$ or readmit$)).ti,ab. (253)

20 ((nephrostom$ or nephrotom$ or pyelostom$ or pyelotom$ or kidney incision$) adj3 (rate or rates or occurrence or reoccurrence or frequen$ or repeat$ or pattern$ or trend$ or episode$ or prevalence or incidence or quantity or amount$ or number or numbers or life time or lifetime or long term or longterm or subsequent$ or repetition$ or reoperat$ or re-operate$ or readmiss$ or readmit$)).ti,ab. (132)

21 ((catheter$ or radiofrequency or radio frequency or electric$) adj2 ablation$ adj3 (rate or rates or occurrence or reoccurrence or frequen$ or repeat$ or pattern$ or trend$ or episode$ or prevalence or incidence or quantity or amount$ or number or numbers or life time or lifetime or long term or longterm or subsequent$ or repetition$ or reoperat$ or re-operate$ or readmiss$ or readmit$)).ti,ab. (1881)

22 ((laparoscop$ or celioscop$ or peritoneoscop$ or pelvic endoscop$ or peritoneoscop$ or videolaparoscop$ or laparoendoscop$) adj3 (rate or rates or occurrence or reoccurrence or frequen$ or repeat$ or pattern$ or trend$ or episode$ or prevalence or incidence or quantity or amount$ or number or numbers or life time or lifetime or long term or longterm or subsequent$ or repetition$ or reoperat$ or re-operate$ or readmiss$ or readmit$)).ti,ab. (5125)

23 or/6-22 (126330)

24 ((surg$ or operat$ or reoperat$ or procedure$ or radiosurg$ or microsurg$ or perioperat$ or intraoperat$ or perisurg$ or intrasurg$ or postoperat$ or postsurg$) adj3 (rate or rates or occurrence or reoccurrence or frequen$ or repeat$ or pattern$ or trend$ or episode$ or prevalence or incidence or quantity or amount$ or number or numbers or life time or lifetime or long term or longterm or subsequent$ or repetition$ or reoperat$ or re-operate$ or readmiss$ or readmit$)).ti,ab. (217981)

25 exp *Hemorrhage/ and exp *Risk/ (355)

26 *Blood Loss, Surgical/ (6090)

27 *postoperative hemorrhage/ (5616)

28 (bleeding or blood loss or blood losses or haemorrhage$ or hemorrhage$).ti,ab. (374472)

29 or/25-28 (376698)

30 24 and 29 (23560)

31 5 and (23 or 30) (1796)

32 exp animals/ not humans/ (4580930)

33 (comment or editorial or historical article or letter).pt. (2057682)

34 31 not (32 or 33) (1757)

35 limit 34 to yr="2009 -Current" (795)

36 "cost of illness"/ or health care costs/ (58162)

37 ((cost$ or burden$) adj2 (illness or disease$ or sickness$ or health care or healthcare)).ti,ab. (56342)

38 36 or 37 (103028)

39 exp *General Surgery/ or (surg$ or operat$ or reoperat$ or procedure$ or radiosurg$ or microsurg$ or perioperat$ or intraoperat$ or perisurg$ or intrasurg$ or postoperat$ or postsurg$).ti,ab. (3262613)

40 5 and 38 and 39 (82)

41 40 not (32 or 33) (81)

42 limit 41 to yr="2009 -Current" (59)

43 35 or 42 (845)

Embase (Ovid): 1974 to 2019 Week 20

Searched: 20.5.19

1 *chronic liver disease/ or *liver cirrhosis/ or *liver fibrosis/ or *chronic hepatitis/ (78147)

2 ((liver$ or hepat$ or intrahepat$) adj2 (disease$ or disorder$ or lesion$ or failure$) adj2 (chronic or refractory or unmanageab$ or uncontrol$ or resistant or persist$ or intractable$ or recurren$ or sustained or permanent$ or unremitting or unrelenting or continual$ or continuous$ or constant$ or unending or unceasing)).ti,ab. (36615)

3 (cirrhosis or cirrhoses or cirrhotic).ti,ab. (136515)

4 ((fibrosis or fibroses or scar$) adj2 (liver$ or hepat$ or intrahepat$)).ti,ab. (34839)

5 or/1-4 (196772)

6 (exp *surgery/ or elective surgery/ or chronic liver disease/dm, su) and (statistics/ or trend study/ or reoperation/ or frequency/) (70352)

7 (exp liver surgery/ or paracentesis/ or thoracocentesis/ or gastrointestinal endoscopy/ or bronchoscopy/ or ablation therapy/ or chemoembolization/ or blood vessel catheterisation/ or transjugular intrahepatic portosystemic shunt/ or exp dental procedure/ or biliary tract surgery/ or exp nephrostomy/ or nephrostomy tube/ or radiofrequency ablation/ or catheter ablation/ or exp laparoscopy/) and (statistics/ or trend study/ or reoperation/ or frequency/) (16383)

8 ((surg$ or operat$ or reoperat$ or procedure$ or radiosurg$ or microsurg$ or perioperat$ or intraoperat$ or perisurg$ or intrasurg$ or postoperat$ or postsurg$) adj3 (rate or rates or occurrence or reoccurrence or frequen$ or repeat$ or pattern$ or trend$ or episode$ or prevalence or incidence or quantity or amount$ or number or numbers or life time or lifetime or long term or longterm or subsequent$ or repetition$ or reoperat$ or re-operate$ or readmiss$ or readmit$)).ti,ab. (311322)

9 ((paracentesis or paracenteses) adj3 (rate or rates or occurrence or reoccurrence or frequen$ or repeat$ or pattern$ or trend$ or episode$ or prevalence or incidence or quantity or amount$ or number or numbers or life time or lifetime or long term or longterm or subsequent$ or repetition$ or reoperat$ or re-operate$ or readmiss$ or readmit$)).ti,ab. (585)

10 ((thoracentesis or thoracenteses or thoracocentesis or thoracocenteses or pleurocentesis or pleurocenteses) adj3 (rate or rates or occurrence or reoccurrence or frequen$ or repeat$ or pattern$ or trend$ or episode$ or prevalence or incidence or quantity or amount$ or number or numbers or life time or lifetime or long term or longterm or subsequent$ or repetition$ or reoperat$ or re-operate$ or readmiss$ or readmit$)).ti,ab. (477)

11 ((endoscop$ or enteroscop$) adj2 (gastrointestinal or balloon$ or push or mucosal or submucosal) adj3 (rate or rates or occurrence or reoccurrence or frequen$ or repeat$ or pattern$ or trend$ or episode$ or prevalence or incidence or quantity or amount$ or number or numbers or life time or lifetime or long term or longterm or subsequent$ or repetition$ or reoperat$ or re-operate$ or readmiss$ or readmit$)).ti,ab. (900)
12 (bronchoscop$ adj2 (gastrointestinal or balloon$ or push or mucosal or submucosal) adj3 (rate or rates or occurrence or reoccurrence or frequen$ or repeat$ or pattern$ or trend$ or episode$ or prevalence or incidence or quantity or amount$ or number or numbers or life time or lifetime or long term or longterm or subsequent$ or repetition$ or reoperat$ or re-operate$ or readmiss$ or readmit$)).ti,ab. (7)
13 ((ethanol or alcohol) adj2 (ablation or inject$) adj3 (rate or rates or occurrence or reoccurrence or frequen$ or repeat$ or pattern$ or trend$ or episode$ or prevalence or incidence or quantity or amount$ or number or numbers or life time or lifetime or long term or longterm or subsequent$ or repetition$ or reoperat$ or re-operate$ or readmiss$ or readmit$)).ti,ab. (327)
14 (chemoemboli?ati$ adj3 (rate or rates or occurrence or reoccurrence or frequen$ or repeat$ or pattern$ or trend$ or episode$ or prevalence or incidence or quantity or amount$ or number or numbers or life time or lifetime or long term or longterm or subsequent$ or repetition$ or reoperat$ or re-operate$ or readmiss$ or readmit$)).ti,ab. (380)
15 ((vascular or cardiac or cardiovascular or heart or blood vessel$) adj2 (catheteri?ation or catherteri?ed) adj3 (rate or rates or occurrence or reoccurrence or frequen$ or repeat$ or pattern$ or trend$ or episode$ or prevalence or incidence or quantity or amount$ or number or numbers or life time or lifetime or long term or longterm or subsequent$ or repetition$ or reoperat$ or re-operate$ or readmiss$ or readmit$)).ti,ab. (1206)
16 ((transjugular intrahepatic portosystemic shunt$ or transjugular intrahepatic porto systemic shunt$ or transjugular intrahepatic portacaval shunt$ or transjugular intrahepatic porta systemic shunt$ or transjugular intrahepatic portasystemic shunt$ or transjugular intrahepatic shunt$ or transjugular intrahepatic stent$ or TIPS) adj3 (rate or rates or occurrence or reoccurrence or frequen$ or repeat$ or pattern$ or trend$ or episode$ or prevalence or incidence or quantity or amount$ or number or numbers or life time or lifetime or long term or longterm or subsequent$ or repetition$ or reoperat$ or re-operate$ or readmiss$ or readmit$)).ti,ab. (1053)
17 ((dental or tooth or teeth or molar) adj2 (surg$ or operat$ or reoperat$ or soldering or inlay or preparation or pulp extirpation or extraction$ or amputation or resect$ or removal or remove or reimplant$ or replantat$ or reinclusion or extract$) adj3 (rate or rates or occurrence or reoccurrence or frequen$ or repeat$ or pattern$ or trend$ or episode$ or prevalence or incidence or quantity or amount$ or number or numbers or life time or lifetime or long term or longterm or subsequent$ or repetition$ or reoperat$ or re-operate$ or readmiss$ or readmit$)).ti,ab. (742)
18 ((bile or biliary or gall bladder or gallbladder) adj2 (surg$ or operat$ or reoperat$) adj3 (rate or rates or occurrence or reoccurrence or frequen$ or repeat$ or pattern$ or trend$ or episode$ or prevalence or incidence or quantity or amount$ or number or numbers or life time or lifetime or long term or longterm or subsequent$ or repetition$ or reoperat$ or re-operate$ or readmiss$ or readmit$)).ti,ab. (326)
19 ((nephrostom$ or nephrotom$ or pyelostom$ or pyelotom$ or kidney incision$) adj3 (rate or rates or occurrence or reoccurrence or frequen$ or repeat$ or pattern$ or trend$ or episode$ or prevalence or incidence or quantity or amount$ or number or numbers or life time or lifetime or long term or longterm or subsequent$ or repetition$ or reoperat$ or re-operate$ or readmiss$ or readmit$)).ti,ab. (220)
20 ((catheter$ or radiofrequency or radio frequency or electric$) adj2 ablation$ adj3 (rate or rates or occurrence or reoccurrence or frequen$ or repeat$ or pattern$ or trend$ or episode$ or prevalence or incidence or quantity or amount$ or number or numbers or life time or lifetime or long term or longterm or subsequent$ or repetition$ or reoperat$ or re-operate$ or readmiss$ or readmit$)).ti,ab. (3513)
21 ((laparoscop$ or celioscop$ or peritoneoscop$ or pelvic endoscop$ or peritoneoscop$ or videolaparoscop$ or laparoendoscop$) adj3 (rate or rates or occurrence or reoccurrence or frequen$ or repeat$ or pattern$ or trend$ or episode$ or prevalence or incidence or quantity or amount$ or number

or numbers or life time or lifetime or long term or longterm or subsequent$ or repetition$ or reoperat$ or re-operate$ or readmiss$ or readmit$)).ti,ab. (8370)
22 or/9-21 (17952)
23 exp *bleeding/ or operative blood loss/ or postoperative hemorrhage/ (287515)
24 (bleeding or blood loss or blood losses or haemorrhage$ or hemorrhage$).ti,ab. (545372)
25 23 or 24 (660304)
26 (or/6-8) and 25 (46987)
27 5 and (22 or 26) (1909)
28 animal/ or animal experiment/ (3761876)
29 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot. (4490245)
30 28 or 29 (5807883)
31 exp human/ or human experiment/ (19651633)
32 30 not (30 and 31) (4495226)
33 27 not 32 (1898)
34 (editorial or letter or note).pt. (2417131)
35 conference$.pt,st,so. (4205445)
36 33 not (34 or 35) (1124)
37 "cost of illness"/ or disease burden/ (27606)
38 exp *health care cost/ (62402)
39 ((cost$ or burden$) adj2 (illness or disease$ or sickness$ or health care or healthcare)).ti,ab,ot. (85720)
40 or/37-39 (158152)
41 exp *surgery/ or (surg$ or operat$ or reoperat$ or procedure$ or radiosurg$ or microsurg$ or perioperat$ or intraoperat$ or perisurg$ or intrasurg$ or postoperat$ or postsurg$).ti,ab. (5124738)
42 5 and 40 and 41 (210)
43 42 not (32 or 34 or 35) (97)
44 36 or 43 (1215)
45 limit 44 to yr="2009 -Current" (589)

NHS Economic Evaluation Databases (NHS EED) (CRD): up to 31 March 2015
Health Technology Assessment Database (HTA) (CRD): up to 31 March 2018

https://www.crd.york.ac.uk/CRDWeb/

Searched: 20.5.19

1 MeSH DESCRIPTOR Liver Diseases EXPLODE ALL TREES 1983

2 (((liver or hepat* or intrahepat*) near (disease* or disorder* or lesion*))) 723

3 ((cirrhosis or cirrhoses or cirrhotic)) 643

4 (((fibrosis or fibroses or scar*) near3 (liver* or hepat*))) 49

5 (((hepatitis or hepatopath*) near3 (chronic or acute or persistent or long stand* or long term or recurr*))) 547

6 #1 OR #2 OR #3 OR #4 OR #5 2378

7 MeSH DESCRIPTOR General Surgery EXPLODE ALL TREES 61

8 MeSH DESCRIPTOR Reoperation EXPLODE ALL TREES 483

9 MeSH DESCRIPTOR Surgical Procedures, Operative EXPLODE ALL TREES 16709

10 ((surg* or operat* or reoperat* or procedure* or radiosurg* or microsurg* or perioperat* or intraoperat* or perisurg* or intrasurg* or postoperat* or postsurg*)) 23205

11 #7 OR #8 OR #9 OR #10 27484

12 #6 AND #11 886

13 * IN NHSEED FROM 2009 TO 2019 8219

14 #12 AND #13 84
15 * IN HTA FROM 2009 TO 2019 8591
16 #12 AND #15 43

CEA Registry (Internet): up to 20 May 2019
www.cearegistry.org
Searched: 20.5.19

chronic liver

13 records retrieved

ScHARR Health Utilities Database (ScHARRHUD)(Internet): up to 20 May 2019
www.scharrhud.org/
Searched: 20.5.19

liver* or hepat* or intrahepat*
15 records retrieved

Literature searches to identify UK mortality data associated with platelet transfusion

MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Update (Ovid): 1946 to May 24, 2019
Searched: 28.5.19

1 Platelet Transfusion/ (6911)
2 ((platelet$ or thrombocyt$) adj3 (transfus$ or infus$ or administ$ or transfer$)).ti,ab. (8619)
3 1 or 2 (12763)
4 exp Mortality/ or exp Death/ (487368)
5 (mortalit$ or death or deaths or dead or died or fatal$ or decease$).ti,ab. (1560525)
6 4 or 5 (1794102)
7 exp United Kingdom/ (352811)
8 (britain or united kingdom or uk or england or scotland or ireland or wales or english or scottish or irish or welsh).ti,ab,in. (1680163)
9 7 or 8 (1873549)
10 3 and 6 and 9 (162)
11 exp animals/ not humans/ (4583131)
12 10 not 11 (160)
13 (comment or editorial or historical article or letter).pt. (2059990)
14 12 not 13 (158)
15 limit 14 to yr="2009 -Current" (93)

Embase (Ovid): 1974 to 2019 Week 21
Searched: 28.5.19

1 thrombocyte transfusion/ (17434)
2 ((platelet$ or thrombocyt$) adj3 (transfus$ or infus$ or administ$ or transfer$)).ti,ab. (14612)
3 1 or 2 (24063)
4 exp mortality/ or exp death/ (1512465)
5 (mortalit$ or death or deaths or dead or died or fatal$ or decease$).ti,ab. (2194505)

6 4 or 5 (2630028)
7 exp United Kingdom/ or exp British citizen/ (401362)
8 (britain or united kingdom or uk or england or scotland or ireland or wales or english or scottish or irish or welsh).ti,ab,in. (2978485)
9 7 or 8 (3130072)
10 3 and 6 and 9 (647)
11 animal/ or animal experiment/ (3766632)
12 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot. (4495229)
13 11 or 12 (5814073)
14 exp human/ or human experiment/ (19680703)
15 13 not (13 and 14) (4499942)
16 (editorial or letter or note or ("conference abstract" or "conference review")).pt. or conference$.so,st. (5886982)
17 10 not (15 or 16) (449)
18 limit 17 to yr="2009 -Current" (295)

Literature searches to identify platelet transfusion refractoriness studies

MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Update (Ovid): 1946 to May 24, 2019

Searched: 28.5.19

2 ((platelet$ or thrombocyt$) adj3 (transfus$ or infus$ or administ$ or transfer$)).ti,ab. (8619)
3 1 or 2 (12763)
4 (refractor$ or resistan$).ti,ab. (1031160)
5 3 and 4 (1180)
6 exp animals/ not humans/ (4583131)
7 5 not 6 (1108)
8 (comment or editorial or historical article or letter).pt. (2059990)
9 7 not 8 (1078)
10 limit 9 to yr="2009 -Current" (367)

Embase (Ovid): 1974 to 2019 Week 21

Searched: 28.5.19

1 *thrombocyte transfusion/ (3846)
2 ((platelet$ or thrombocyt$) adj3 (transfus$ or infus$ or administ$ or transfer$)).ti,ab. (14612)
3 1 or 2 (15782)
4 (refractor$ or resistan$).ti,ab. (1316064)
5 3 and 4 (2192)
6 platelet refractoriness.dq. (18)
7 refractory thrombocytopenia/ (298)
8 or/5-7 (2437)
9 animal/ or animal experiment/ (3766632)
10 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot. (4495229)
11 9 or 10 (5814073)
12 exp human/ or human experiment/ (19680703)
13 11 not (11 and 12) (4499942)

14 (editorial or letter or note or ("conference abstract" or "conference review")).pt. or conference$.so,st. (5886982)
15 8 not (13 or 14) (1253)
16 limit 15 to yr="2009 -Current" (489)

Literature searches to identify chronic liver disease/thrombocytopenia cost of illness studies

MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily Update (Ovid): 1946 to May 28, 2019

Searched: 29.5.19

1 exp *Liver Diseases/ and exp Chronic Disease/ (14897)
2 ((liver$ or hepat$ or intrahepat$) adj2 (disease$ or disorder$ or lesion$ or failure$) adj2 (chronic or refractory or unmanageab$ or uncontrol$ or resistant or persist$ or intractable$ or recurren$ or sustained or permanent$ or unremitting or unrelenting or continual$ or continuous$ or constant$ or unending or unceasing)).ti,ab. (24065)
3 (cirrhosis or cirrhoses or cirrhotic).ti,ab. (93760)
4 ((fibrosis or fibroses or scar$) adj2 (liver$ or hepat$ or intrahepat$)).ti,ab. (21382)
5 or/1-4 (130775)
6 exp *Thrombocytopenia/ (33008)
7 (thrombocytopeni$ or thrombocytopaeni$ or thrombopeni$ or thrombopaeni$ or macrothrombocytopeni$ or macrothrombocytopaeni$).ti,ab. (59374)
8 6 or 7 (67504)
9 "Cost of Illness"/ (25073)
10 ((cost$ or burden$) adj2 illness).ti,ab. (3967)
11 9 or 10 (27504)
12 (5 or 8) and 11 (201)
13 limit 12 to yr="2009 -Current" (149)

Embase (Ovid): 1974 to 2019 Week 21

Searched: 29.5.19

1 *chronic liver disease/ or *liver cirrhosis/ or *liver fibrosis/ or *chronic hepatitis/ (78218)
2 ((liver$ or hepat$ or intrahepat$) adj2 (disease$ or disorder$ or lesion$ or failure$) adj2 (chronic or refractory or unmanageab$ or uncontrol$ or resistant or persist$ or intractable$ or recurren$ or sustained or permanent$ or unremitting or unrelenting or continual$ or continuous$ or constant$ or unending or unceasing)).ti,ab. (36672)
3 (cirrhosis or cirrhoses or cirrhotic).ti,ab. (136679)
4 ((fibrosis or fibroses or scar$) adj2 (liver$ or hepat$ or intrahepat$)).ti,ab. (34905)
5 or/1-4 (197020)
6 exp *thrombocytopenia/ (42771)
7 (thrombocytopeni$ or thrombocytopaeni$ or thrombopeni$ or thrombopaeni$ or macrothrombocytopeni$ or macrothrombocytopaeni$).ti,ab. (90374)
8 6 or 7 (100725)
9 *"cost of illness"/ (5068)
10 ((cost$ or burden$) adj2 illness).ti,ab. (5954)
11 9 or 10 (10092)
12 (5 or 8) and 11 (104)
13 limit 12 to yr="2009 -Current" (90)

NHS Economic Evaluation Databases (NHS EED) (CRD): up to 31 March 2015

https://www.crd.york.ac.uk/CRDWeb/

Searched: 29.5.19

1 MeSH DESCRIPTOR Cost of Illness EXPLODE ALL TREES 673
2 ("cost of illness") IN NHSEED 667
3 #1 OR #2 725
4 MeSH DESCRIPTOR Liver Diseases EXPLODE ALL TREES 1983
5 (((liver or hepat* or intrahepat*) near (disease* or disorder* or lesion*))) IN NHSEED 221
6 ((cirrhosis or cirrhoses or cirrhotic)) IN NHSEED 259
7 (((fibrosis or fibroses or scar*) near3 (liver* or hepat*))) IN NHSEED 9
8 #4 OR #5 OR #6 OR #7 2098
9 MeSH DESCRIPTOR Thrombocytopenia EXPLODE ALL TREES 107
10 ((thrombocytopeni* or thrombocytopaeni* or thrombopeni* or thrombopaeni* or macrothrombocytopeni* or macrothrombocytopaeni*)) IN NHSEED 93
11 #9 OR #10 170
12 (#3 AND (#8 OR #11)) IN NHSEED FROM 2009 TO 2019 9

Citation searches

Science Citation Index (SCI); Google Scholar (GS); PubMed (PM)
Searched: 23.5.19

Included papers	**SCI**	**GS**	**PM**
Terrault N, Chen YC, Izumi N, Kayali Z, Mitrut P, Tak WY, et al. Avatrombopag before procedures reduces need for platelet transfusion in patients with chronic liver disease and thrombocytopenia. Gastroenterology 2018;155(3):705-18.	13	19	4
Terrault NA, Hassanein T, Howell CD, Joshi S, Lake J, Sher L, et al. Phase II study of avatrombopag in thrombocytopenic patients with cirrhosis undergoing an elective procedure. J Hepatol 2014;61(6):1253-9.	23	30	8
Hidaka H, Kurosaki M, Tanaka H, Kudo M, Abiru S, Igura T, et al. Lusutrombopag reduces need for platelet transfusion in patients with thrombocytopenia undergoing invasive procedures. Clin Gastroenterol Hepatol 2019;17(6):1192-1200.	2	5	1
Tateishi R, Seike M, Kudo M, Tamai H, Kawazoe S, Katsube T, et al. A randomized controlled trial of lusutrombopag in Japanese patients with chronic liver disease undergoing radiofrequency ablation. J Gastroenterol 2019;54(2):171-81.	4	9	2
Brown RS, Imawari M, Izumi N, Osaki Y, Bentley R, Baykal T, et al. Lusutrombopag reliably increases platelet counts for up to 3 weeks in chronic liver disease patients with thrombocytopenia undergoing invasive procedures regardless of baseline platelet counts: results from two phase 3 trials. Hepatology 2018;68(Suppl 1):1178A-1179A.	-	0	-
Brown RS, Imawari M, Izumi N, Osaki Y, Ochiai T, Kano T, et al. Lusutrombopag is a safe and efficacious treatment option for thrombocytopenia in patients with chronic liver disease undergoing invasive	-	-	-

procedures: a pooled analysis of two phase 3 trials. Hepatology 2018;68(Suppl 1):1148A.			
Caldwell S, Alkhouri N, Allen LF, Aggarwal K, Vredenburg M, Shah N. Characterization of baseline thrombopoietin levels in patients with chronic liver disease: results from 2 pooled clinical studies in patients with thrombocytopenia and liver disease. Hepatology 2018;68(Suppl 1):487A-488A.	-	0	-
Alkhouri N, Imawari M, Izumi N, Osaki Y, Ochiai T, Bentley R, et al. Use of the thrombopoietin receptor agonist lusutrombopag for management of thrombocytopenia in patients with hepatocellular carcinoma undergoing planned invasive procedures. Hepatology 2018;68(Suppl 1):553A-554A.	-	0	-
Poordad F, Allen LF, Aggarwal K, Vredenburg M, Alkhouri N. Superiority of avatrombopag to placebo in increasing platelet counts and reducing platelet transfusions in patients with chronic liver disease-associated thrombocytopenia undergoing scheduled procedures: pooled analysis of 2 randomized phase 3 studies. Res Pract Thromb Haemost 2018;2(Suppl 1):10.	-	-	-
Poordad F, Allen L, Aggarwal K, Vredenburg M, Tian W, Terrault N. Exploratory analyses of the efficacy of avatrombopag versus placebo from 2 phase 3 studies using alternate baseline platelet count cohorts and an alternate secondary efficacy endpoint. Res Pract Thromb Haemost 2018;2(Suppl 1):9.	-	-	-
Sammy S, Allen LF, Aggarwal K, Vredenburg M, Terrault N. Consistent efficacy of avatrombopag compared to placebo in patients with thrombocytopenia and chronic liver disease undergoing procedures across various disease severities and etiologies. J Hepatol 2018;68(Suppl 1):S752.	-	0	-
Sammy S, Alkhouri N, Allen LF, Aggarwal K, Vredenburg M, Tian W, et al. Efficacy of avatrombopag compared with placebo across various mean baseline platelet count subgroups-pooled data from 2 phase 3 studies. J Hepatol 2018;68(Suppl 1):S751.	-	0	-
Reau NS, Sammy S, Allen LF, Aggarwal K, Vredenburg M, Kim WR. Avatrombopag decreases need for platelet transfusion in patients chronic liver disease and thrombocytopenia undergoing medical procedures with low to high associated bleeding risks. J Hepatol 2018;68(Suppl 1):S751.	-	0	-
Afdhal N, Duggal A, Ochiai T, Motomiya T, Kano T, Nagata T, et al. Platelet response to lusutrombopag, a thrombopoietin receptor agonist, in patients with chronic liver disease and thrombocytopenia undergoing non-emergency invasive procedures: results from a phase 3 randomized, double-blind, placebo-controlled study. Blood 2017;130(Suppl 1):Abstract 291.	-	4	-
Frelinger AL, Koganov ES, Forde EE, Carmichael SL, Michelson AD. Avatrombopag, a novel thrombopoietin receptor agonist, increases platelet counts without increasing platelet activation in patients with thrombocytopenia due to chronic liver disease. Blood 2017;130(Suppl 1):Abstract 290.	-	1	-

Terrault N, Kuter DJ, Izumi N, Kayali Z, Mitrut P, Tak WY, et al. Superiority of avatrombopag to placebo in increasing platelet counts in patients with chronic liver disease-associated thrombocytopenia undergoing scheduled procedures: results from 2, phase 3 randomized studies. Blood 2017;130(Suppl 1):Abstract 18.	-	3	-
Peck-Radosavljevic M, Duggal A, Ochiai T, Motomiya T, Kano T, Nagata T, et al. Lusutrombopag for treatment of thrombocytopenia in patients with chronic liver disease who are undergoing non-emergency invasive procedures: results from an international phase 3, randomized, double-blind, placebo-controlled study (L-PLUS 2). United European Gastroenterol J 2017;5(8):1145.	-	-	-
Izumi N, Osaki Y, Yamamoto K, Kurokawa M, Tanaka K, Kano T, et al. A phase 3, randomized, double-blind, placebo-controlled study of lusutrombopag for thrombocytopenia in patients with chronic liver disease undergoing elective invasive procedures in Japan (L-PLUS 1). Hepatology 2015;62(6):1397A-1398A.	1	4	-
Terrault N, Bibbiani F, Chen YC, Izumi N, Kayali Z, Soto JRL, et al. Superiority of avatrombopag (AVA) to placebo (PBO) for the treatment of chronic liver disease (CLD)-associated thrombocytopenia (TCP) in patients undergoing scheduled procedures: results of 2 randomized, PBO-controlled phase 3 studies. Hepatology 2017;66(Suppl 1):124A-125A.	1	0	-
Izumi N, Tateishi R, Seike M, Kudo M, Tamai H, Kawazoe S, et al. Once-daily oral lusutrombopag, alternative to platelet transfusion in thrombocytopenic patients with chronic liver disease undergoing radiofrequency ablation: results from a phase 2B, randomized, double-blind study. J Hepatol 2014;60(1 Suppl 1):S386.	2	3	-
Terrault N, Hassanein T, Joshi S, Lake JR, Sher LS, Vargas HE, et al. Once-daily oral avatrombopag (E5501) prior to elective surgical or diagnostic procedures in patients with chronic liver disease and thrombocytopenia: results from a phase 2, randomized, double-blind, placebo-controlled study (Study 202). Hepatology 2012;56(Suppl 1):253A-254A.	-	0	-
Poordad F, Vredenburg M, Allen LF, Aggarwal K, Alkhouri N. Superiority of avatrombopag to placebo in increasing platelet counts and reducing platelet transfusions in patients with chronic liver disease-associated thrombocytopenia undergoing scheduled procedures-pooled analysis of 2 randomized phase 3 studies. Gastroenterology 2018;154(6):S529.	-	0	-
Saab S, Allen LF, Aggarwal K, Vredenburg M, Terrault N. Consistent efficacy of avatrombopag compared to placebo in patients with thrombocytopenia and chronic liver disease undergoing procedures across various liver disease severities and etiologies. Gastroenterology 2018;154(6):S1247-S1248.	-	-	-
Saab S, Alkhouri N, Allen LF, Aggarwal K, Vredenburg M, Tian W. Efficacy of avatrombopag compared with placebo across various mean baseline platelet count subgroups: pooled data from 2 phase 3 studies. Gastroenterology 2018;154(6):S1249.	-	-	-

Vredenburg M, Reau N, Allen LF, Aggarwal K, Poordad F. Consistent efficacy of avatrombopag over placebo in the treatment of thrombocytopenia in patients with chronic liver disease undergoing invasive procedures across demographic subgroups: pooled results of two phase 3 studies. Gastroenterology 2018;154(6):S532.	-	0	-
Afdhal NH, Duggal A, Ochiai T, Motomiya T, Kano T, Nagata T, et al. Lusutrombopag for treatment of thrombocytopenia in patients with chronic liver disease who are undergoing non-emergency invasive procedures: results from an international phase 3, randomized, double-blind, placebo-controlled study (L-PLUS 2). Hepatology 2017;66(6):1254A.	-	0	-
Shionogi Inc. Safety and efficacy study of lusutrombopag for thrombocytopenia in patients with chronic liver disease undergoing elective invasive procedures (L-PLUS 2). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2015-2017 [cited 2019 Jan 23]. Available from: https://ClinicalTrials.gov/show/NCT02389621. NLM Identifier: NCT02389621	-	-	-
Eisai Inc. Treatment of thrombocytopenia in patients with chronic liver disease undergoing an elective procedure. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2013-2017 [cited 2019 Jan 23]. Available from: https://ClinicalTrials.gov/show/NCT01976104. NLM Identifier: NCT01976104	-	-	-
Eisai Inc. Treatment of thrombocytopenia in patients with chronic liver disease undergoing an elective procedure. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014-2017 [cited 2019 Jan 23]. Available from: https://ClinicalTrials.gov/show/NCT01972529. NLM Identifier: NCT01972529	-	-	-
Eisai Inc. Once-daily oral avatrombopag tablets used in subjects with chronic liver diseases and thrombocytopenia prior to elective surgical or diagnostic procedures. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2009-2011 [cited 2019 Jan 23]. Available from: https://ClinicalTrials.gov/show/NCT00914927. NLM Identifier: NCT00914927	-	-	-
Eisai Co Ltd. Treatment of thrombocytopenia in patients with chronic liver disease undergoing an elective procedure. JPRN-JapicCTI-142746. In: WHO International Clinical Trials Registry Platform (ICTRP) [Internet]. Geneva: World Health Organization (WHO). 2014 [accessed 23.1.19]. Available from: http://www.clinicaltrials.jp/user/showCteDetailE.jsp?japicId=JapicCTI-142746	-	-	-
Center for Drug Evaluation and Research, US Food & Drug Administration. Doptelet/avatrombopag. Other Review(s) [Internet]: US Food & Drug Administration (FDA), 2017 [accessed 23.1.19] Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210238Orig1s000OtherR.pdf	-	-	-
Center for Drug Evaluation and Research, US Food & Drug Administration. Doptelet (avatrombopag). Drug Approval Package [Internet]. US Food &	-	-	-

Drug Administration (FDA), 2018 [accessed 23.1.19]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210238Orig1s000TOC.cfm			
Center for Drug Evaluation and Research, US Food & Drug Administration. Mulpleta (lusutrombopag). Multi-Discipline Review/Summary, Clinical, Non-Clinical [Internet]: US Food & Drug Administration (FDA), 2017 [accessed 23.1.19] Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210923Orig1s000MultidisciplineR.pdf	-	-	-
Total	**46**	**78**	**15**
Combined Total	**139**		
Combined total after removal of duplicates	**59**		

APPENDIX 2: QUALITY ASSESSMENT

The following criteria from the Cochrane Collaboration 2011 checklist will be used to assess the quality of randomised controlled trials (RCTs). Each study will be assessed as "yes"(i.e. low risk of bias), "no" (i.e. high risk of bias), or "unclear" (i.e. unclear risk of bias):

Domain	Judgement	Criteria	Supporting text
Selection bias			
Random sequence generation	**Low risk of bias**	The investigators describe a random component in the sequence generation process such as: • Referring to a random number table • Using a computer random number generator • Coin tossing • Shuffling cards or envelopes • Throwing dice • Drawing of lots • Minimisation* *Minimisation may be implemented without a random element, and this is considered to be equivalent to being random	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups
	High risk of bias	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: • Sequence generated by odd or even date of birth • Sequence generated by some rule based on date (or day) of admission • Sequence generated by some rule based on hospital or clinic record number Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorisation of participants, for example: • Allocation by judgement of the clinician • Allocation by preference of the participant • Allocation based on the results of a laboratory test or a series of tests • Allocation by availability of the intervention	
	Unclear risk of bias	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'	
Allocation concealment	**Low risk of bias**	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: • Central allocation (including telephone, web-based and pharmacy-controlled randomisation) • Sequentially numbered drug containers of identical appearance • Sequentially numbered, opaque, sealed envelopes	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment

Domain	Judgement	Criteria	Supporting text
	High risk of bias	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: • Using an open random allocation schedule (e.g. a list of random numbers) • Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered) • Alternation or rotation • Date of birth • Case record number • Any other explicitly unconcealed procedure	
	Unclear risk of bias	Insufficient information to permit judgement of 'Low risk' or 'High risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.	
Performance bias			
Blinding of participants and personnel *Assessments should be made for each main outcome (or class of outcomes).*	**Low risk of bias**	Any one of the following: • No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding • Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective
	High risk of bias	Any one of the following: • No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding • Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding	
	Unclear risk of bias	Any one of the following: • Insufficient information to permit judgement of 'Low risk' or 'High risk' • The study did not address this outcome	
Detection bias			
Blinding of outcome assessment *Assessments should be made for each main outcome (or*	**Low risk of bias**	Any one of the following: • No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding • Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective
	High risk of bias	Any one of the following: • No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding	

Domain	Judgement	Criteria	Supporting text
class of outcomes).		• Blinding of outcome assessment, but likely that the blinding could have been broken and the outcome measurement are likely to be influenced by lack of blinding	
	Unclear risk of bias	Any one of the following: • Insufficient information to permit judgement of 'Low risk' or 'High risk' • The study did not address this outcome	
Attrition bias			
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes).*	**Low risk of bias**	Any one of the following: • No missing outcome data • Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias) • Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate • For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size • Missing data have been imputed using appropriate methods	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors
	High risk of bias	Any one of the following: • Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate • For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size • 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation • Potentially inappropriate application of simple imputation	
	Unclear risk of bias	Any one of the following: • Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g. number randomized not stated, no reasons for missing data provided) • The study did not address this outcome	
Reporting bias			
Selective	**Low risk of**	Any of the following:	State how the possibility of selective

Domain	Judgement	Criteria	Supporting text
reporting.	**bias**	• The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way • The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)	outcome reporting was examined by the review authors, and what was found
	High risk of bias	Any one of the following: • Not all of the study's pre-specified primary outcomes have been reported • One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified • One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect) • One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis • The study report fails to include results for a key outcome that would be expected to have been reported for such a study	
	Unclear risk of bias	Insufficient information to permit judgement of 'Low risk' or 'High risk'. It is likely that the majority of studies will fall into this category	
Other bias			
Other sources of bias.	**Low risk of bias**	The study appears to be free of other sources of bias.	State any important concerns about bias not addressed in the other domains in the tool If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry
	High risk of bias	There is at least one important risk of bias. For example, the study: • Had a potential source of bias related to the specific study design used or • Has been claimed to have been fraudulent or • Had some other problem	
	Unclear risk of bias	There may be a risk of bias, but there is either: • Insufficient information to assess whether an important risk of bias exists or • Insufficient rationale or evidence that an identified problem will introduce bias	

APPENDIX 3: TABLE OF EXCLUDED STUDIES WITH RATIONALE

This is not intended to be an exhaustive list of every study examining the intervention. However it should include studies that have passed the first screening but on closer inspection are not deemed to be relevant and/or valid. This should include studies provided in company/sponsor submissions.

Reason for exclusion	Reference
Population	Afdhal N, Giannini E, Tayyab GN, Mohsin A, Lee JW, Andriulli A, et al. Eltrombopag in chronic liver disease patients with thrombocytopenia undergoing an elective invasive procedure: results from ELEVATE, a randomised clinical trial. J Hepatol 2010;52(Suppl 1):S460.
	Afdhal NH, Giannini EG, Tayyab G, Mohsin A, Lee JW, Andriulli A, et al. Eltrombopag before procedures in patients with cirrhosis and thrombocytopenia. N Engl J Med 2012;367(8):716-24.
	Allen R, Bryden P, Grotzinger KM, Stapelkamp C, Woods B. Cost-effectiveness of eltrombopag versus romiplostim for the treatment of chronic immune thrombocytopenia in England and Wales. Value Health 2016;19(5):614-22.
	Berg T, Riordan S, Karamanolis D, Garcia-Samaniego J, Porayko M, Campbell F, et al. ENABLE-ALL: safety and efficacy of eltrombopag in thrombocytopenic hepatitis C virus-infected patients with cirrhosis who withdrew from the ENABLE-1&2 studies. Hepatol Int 2014;8(1 Suppl 1):S172-S173.
	Lopez-Plaza I, Weissfeld J, Triulzi DJ. The cost-effectiveness of reducing donor exposures with single-donor versus pooled random-donor platelets. Transfusion 1999;39(9):925-32.
Intervention	Afdhal N, Dusheiko G, Giannini EG, Chen PJ, Han KH, Moshin A, et al. Final results of ENABLE 1, a phase 3, multicenter study of eltrombopag as an adjunct for antiviral treatment of hepatitis C virus-related chronic liver disease associated with thrombocytopenia. Hepatology 2011;54(Suppl 1):1427A-1428A.
	Afdhal NH, McHutchison JG, Shiffman ML, Rodriguez-Torres M, Dusheiko GM, Sigal S. Eltrombopag raises platelet counts in two weeks in patients with HCV and significant thrombocytopenia. Hepatology 2007;46(4 Suppl 1):252A.
	Ata RMA. The efficacy of eltrombopag in improving thrombocytopenia in patients with chronic liver disease: a meta analysis. Hepatol Int 2013;7(Suppl 1):S541.
	Botros Y, Hafez HA, Fouad R, El Negoly M, Shiha G, Waked I, et al. The effect of eltrombopag (Promecta) on thrombocytopenia in Egyptian patients with chronic hepatitis C. J Gastroenterol Hepatol Res 2016;5(3):2088-92.
	Chen P-J, Han K-H, Dusheiko GM, Campbell FM, Vasey SY, Patwardhan R, et al. Eltrombopag as a supportive agent to enable antiviral therapy in East Asian patients with thrombocytopenia and hepatitis C virus. Paper presented at APASL Liver Week 2013; 6-10 Jun 2013; Singapore: Singapore. 2013.
	Dusheiko G, Afdhal N, Giannini EG, Chen PJ, Han KH, Rodriguez-Torres M, et al. Results of ENABLE 2, a phase 3, multicenter study of

Reason for exclusion	Reference
	eltrombopag and peginterferon alfa-2B treatment in patients with hepatitis C and thrombocytopenia. J Hepatol 2012;56(Suppl 2):S27.
	Dusheiko G, Afdhal NH, Giannini E, Chen PJ, Han KH, Kamel YM, et al. Final results of open-label treatment with eltrombopag during ENABLE 1: a study of eltrombopag as an adjunct for antiviral treatment of hepatitis C virus associated with thrombocytopenia. Blood 2011;118(21):Abstract 2232.
	Eltrombopag (Revolade) and thrombocytopenia in patients with hepatitis C. Hepatotoxic drug; more harms than benefits. Prescrire Int 2015;24(163):208-9.
	Giannini E, Dusheiko G, Afdhal N, Chen P, Han K, Mostafa Kamel Y, et al. Eltrombopag raises platelet counts prior to antiviral therapy in patients with chronic hepatitis C virus infection associated with thrombocytopenia. Haematologica 2012;97(Suppl 1):251.
	GlaxoSmithKline Pharmaceuticals Ltd. TPL104054: eltrombopag to reduce the need for platelet transfusion in subjects with chronic liver disease and thrombocytopenia undergoing elective invasive procedures. (ELEVATE). CTRI/2009/091/000524. In: WHO International Clinical Trials Registry Platform (ICTRP) [Internet]. Geneva: World Health Organization (WHO). 2009 [accessed 23.1.19]. Available from: http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=730
	GlaxoSmithKline SA España. Estudio aleatorizado, doble ciego, controlado con placebo, multicéntrico para evaluar la seguridad y eficacia de eltrombopag para reducir la necesidad de transfusión de plaquetas en sujetos trombocitopénicos con enfermedad hepática crónica que se van a someter a un procedimiento invasivo programado. EUCTR2007-005851-40-ES. In: WHO International Clinical Trials Registry Platform (ICTRP) [Internet]. Geneva: World Health Organization (WHO). 2008 [accessed 23.1.19]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2007-005851-40
	Koganov ES, Carmichael SL, Forde EE, Frelinger AL, Michelson AD. Platelet function in thrombocytopenic patients with chronic liver disease. Blood 2017;130(Suppl 1):Abstract 2314.
	Provan D, Saleh M, Goodison S, Rafi R, Stone N, Hamilton JM, et al. The safety profile of eltrombopag, a novel oral platelet growth factor, in thrombocytopenic patients and healthy subjects. J Clin Oncol 2006;24(18 Suppl):18596.
Comparator	GlaxoSmithKline. Eltrombopag to reduce the need for platelet transfusion in subjects with chronic liver disease and thrombocytopenia undergoing elective invasive procedures. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2008-2009 [cited 2019 Jan 23]. Available from: https://ClinicalTrials.gov/show/NCT00678587. NLM Identifier: NCT00678587
Outcomes	Dova Pharmaceuticals. Avatrombopag for the treatment of thrombocytopenia in adults with chronic liver disease undergoing a procedure. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2018- [cited 2019 Jan 23]. Available from: https://ClinicalTrials.gov/show/NCT03554759. NLM Identifier: NCT03554759
No extractable	Afdhal NH, Theodore D. Eltrombopag for thrombocytopenic patients with chronic HCV infection. Reply. Gastroenterology 2014;147(1):255-6.
	Center for Drug Evaluation and Research, US Food & Drug Administration. Mulpleta (lusutrombopag). Other Review(s) [Internet]: US Food &

Reason for exclusion	Reference
outcomes	Drug Administration (FDA), 2017 [accessed 23.1.19] Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210923Orig1s000OtherR.pdf
	Dova Pharmaceuticals. Avatrombopag for the treatment of thrombocytopenia in adults scheduled for a surgical procedure. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2018- [cited 2019 Jan 23]. Available from: https://ClinicalTrials.gov/show/NCT03326843. NLM Identifier: NCT03326843
	Eisai Co. Ltd. A study to evaluate the efficacy, safety, and pharmacokinetics of once-daily oral avatrombopag in Japanese subjects with chronic liver diseases and thrombocytopenia. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2014-2015 [cited 2019 Jan 23]. Available from: https://ClinicalTrials.gov/show/NCT02227693. NLM Identifier: NCT02227693
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APPENDIX 4: TABLE OF SERIOUS ADVERSE EVENTS

Serious adverse event	Study ID	Trial name	NCT/ other trial number	Lower / Upper platelets (per µL)	Arm name	Follow-up time point (weeks)	No. patients with event (n)	No. patients analyzed (N) or "NR"	% with event or "NR" -
Abdominal pain	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	0	89	0.0
					Placebo 60mg	NR/Unclear	0	48	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	1	58	1.7
					Placebo 40mg	NR/Unclear	0	32	0.0
Abdominal pain lower	Peck-Radosavljevic 2019[20]	L-PLUS 2	NCT02389621	<50,000	Lusutrombopag	NR/Unclear	1	107	0.9
					Placebo	NR/Unclear	0	107	0.0
Abdominal Pain Upper	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	1	89	1.1
					Placebo 60mg	NR/Unclear	0	48	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	58	0.0
					Placebo 40mg	NR/Unclear	0	32	0.0
Acute kidney injury	Peck-Radosavljevic 2019[20]	L-PLUS 2	NCT02389621	<50,000	Lusutrombopag	NR/Unclear	1	107	0.9
					Placebo	NR/Unclear	0	107	0.0
	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	1	89	1.1
					Placebo 60mg	NR/Unclear	0	48	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	58	0.0
					Placebo 40mg	NR/Unclear	0	32	0.0
Acute myocardial infarction	Terrault 2018[18]	ADAPT-2	NCT01976104	<40,000	Avatrombopag 60mg	NR/Unclear	0	70	0.0
					Placebo 60mg	NR/Unclear	0	43	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	57	0.0
					Placebo 40mg	NR/Unclear	1	33	3.0
Acute respiratory	Terrault 2018[18]	ADAPT-2	NCT01976104	<40,000	Avatrombopag 60mg	NR/Unclear	0	70	0.0
					Placebo 60mg	NR/Unclear	0	43	0.0

Serious adverse event	Study ID	Trial name	NCT/ other trial number	Lower / Upper platelets (per µL)	Arm name	Follow-up time point (weeks)	No. patients with event (n)	No. patients analyzed (N) or "NR"	% with event or "NR" -
failure				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	1	57	1.8
					Placebo 40mg	NR/Unclear	0	33	0.0
Anaemia	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	1	89	1.1
					Placebo 60mg	NR/Unclear	0	48	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	58	0.0
					Placebo 40mg	NR/Unclear	0	32	0.0
	Peck-Radosavljevic 2019[20]	L-PLUS 2	NCT02389621	<50,000	Lusutrombopag	NR/Unclear	1	107	0.9
					Placebo	NR/Unclear	0	107	0.0
Anaphylactic transfusion reaction	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	0	89	0.0
					Placebo 60mg	NR/Unclear	1	48	2.1
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	58	0.0
					Placebo 40mg	NR/Unclear	0	32	0.0
Ascites	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	1	89	1.1
					Placebo 60mg	NR/Unclear	0	48	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	58	0.0
					Placebo 40mg	NR/Unclear	0	32	0.0
Asthma	Hidaka 2018[19]	L-PLUS 1	JapicCTI-132323	<50,000	Lusutrombopag	NR/Unclear	0	48	0.0
					Placebo	NR/Unclear	1	48	2.1
Azotaemia	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	1	89	1.1
					Placebo 60mg	NR/Unclear	0	48	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	58	0.0
					Placebo 40mg	NR/Unclear	0	32	0.0
Cardiac arrest	Peck-Radosavljevic 2019[20]	L-PLUS 2	NCT02389621	<50,000	Lusutrombopag	NR/Unclear	1	107	0.9
					Placebo	NR/Unclear	0	107	0.0

Serious adverse event	Study ID	Trial name	NCT/ other trial number	Lower / Upper platelets (per µL)	Arm name	Follow-up time point (weeks)	No. patients with event (n)	No. patients analyzed (N) or "NR"	% with event or "NR" -
Cardiac ventricular thrombosis	Peck-Radosavljevic 2019[20]	L-PLUS 2	NCT02389621	<50,000	Lusutrombopag	NR/Unclear	1	107	0.9
					Placebo	NR/Unclear	0	107	0.0
Cellulitis	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	0	89	0.0
					Placebo 60mg	NR/Unclear	0	48	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	1	58	1.7
					Placebo 40mg	NR/Unclear	0	32	0.0
Chronic hepatic failure	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	0	89	0.0
					Placebo 60mg	NR/Unclear	0	48	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	1	58	1.7
					Placebo 40mg	NR/Unclear	0	32	0.0
Circulatory collapse	Peck-Radosavljevic 2019[20]	L-PLUS 2	NCT02389621	<50,000	Lusutrombopag	NR/Unclear	0	107	0.0
					Placebo	NR/Unclear	1	107	0.9
Clostridium difficile infection	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	0	89	0.0
					Placebo 60mg	NR/Unclear	0	48	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	1	58	1.7
					Placebo 40mg	NR/Unclear	0	32	0.0
Clostridium test positive	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	0	89	0.0
					Placebo 60mg	NR/Unclear	1	48	2.1
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	58	0.0
					Placebo 40mg	NR/Unclear	0	32	0.0
Coma hepatic	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	0	89	0.0
					Placebo 60mg	NR/Unclear	0	48	0.0
				40,000 -	Avatrombopag 40mg	NR/Unclear	1	58	1.7

Serious adverse event	Study ID	Trial name	NCT/ other trial number	Lower / Upper platelets (per µL)	Arm name	Follow-up time point (weeks)	No. patients with event (n)	No. patients analyzed (N) or "NR"	% with event or "NR" -
				50,000	Placebo 40mg	NR/Unclear	0	32	0.0
Dehydration	Peck-Radosavljevic 2019[20]	L-PLUS 2	NCT02389621	<50,000	Lusutrombopag	NR/Unclear	0	107	0.0
					Placebo	NR/Unclear	1	107	0.9
Diarrhoea	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	1	89	1.1
					Placebo 60mg	NR/Unclear	0	48	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	58	0.0
					Placebo 40mg	NR/Unclear	1	32	3.1
Encephalopathy	Peck-Radosavljevic 2019[20]	L-PLUS 2	NCT02389621	<50,000	Lusutrombopag	NR/Unclear	0	107	0.0
					Placebo	NR/Unclear	1	107	0.9
Epistaxis	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	0	89	0.0
					Placebo 60mg	NR/Unclear	1	48	2.1
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	58	0.0
					Placebo 40mg	NR/Unclear	0	32	0.0
Fluid retention	Peck-Radosavljevic 2019[20]	L-PLUS 2	NCT02389621	<50,000	Lusutrombopag	NR/Unclear	1	107	0.9
					Placebo	NR/Unclear	0	107	0.0
Gastrointestinal haemorrhage	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	1	89	1.1
					Placebo 60mg	NR/Unclear	0	48	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	58	0.0
					Placebo 40mg	NR/Unclear	0	32	0.0
Generalised oedema	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	0	89	0.0
					Placebo 60mg	NR/Unclear	1	48	2.1
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	58	0.0
					Placebo 40mg	NR/Unclear	0	32	0.0
Haematemesis	Terrault 2018[18]	ADAPT-1	NCT0197252	<40,000	Avatrombopag 60mg	NR/Unclear	1	89	1.1

Serious adverse event	Study ID	Trial name	NCT/ other trial number	Lower / Upper platelets (per µL)	Arm name	Follow-up time point (weeks)	No. patients with event (n)	No. patients analyzed (N) or "NR"	% with event or "NR" -
			9		Placebo 60mg	NR/Unclear	0	48	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	58	0.0
					Placebo 40mg	NR/Unclear	0	32	0.0
		ADAPT-2	NCT01976104	<40,000	Avatrombopag 60mg	NR/Unclear	1	70	1.4
					Placebo 60mg	NR/Unclear	0	43	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	57	0.0
					Placebo 40mg	NR/Unclear	0	33	0.0
Haemorrhagic anaemia	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	1	89	1.1
					Placebo 60mg	NR/Unclear	0	48	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	58	0.0
					Placebo 40mg	NR/Unclear	0	32	0.0
Hepatic cirrhosis	Peck-Radosavljevic 2019[20]	L-PLUS 2	NCT02389621	<50,000	Lusutrombopag	NR/Unclear	1	107	0.9
					Placebo	NR/Unclear	0	107	0.0
Hepatic encephalopathy	Peck-Radosavljevic 2019[20]	L-PLUS 2	NCT02389621	<50,000	Lusutrombopag	NR/Unclear	1	107	0.9
					Placebo	NR/Unclear	2	107	1.9
	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	1	89	1.1
					Placebo 60mg	NR/Unclear	1	48	2.1
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	58	0.0
					Placebo 40mg	NR/Unclear	0	32	0.0
		ADAPT-2	NCT01976104	<40,000	Avatrombopag 60mg	NR/Unclear	0	70	0.0
					Placebo 60mg	NR/Unclear	1	43	2.3
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	57	0.0
					Placebo 40mg	NR/Unclear	0	33	0.0
Hepatocellular	Peck-Radosavljevic	L-PLUS 2	NCT0238962	<50,000	Lusutrombopag	NR/Unclear	0	107	0.0

Serious adverse event	Study ID	Trial name	NCT/ other trial number	Lower / Upper platelets (per µL)	Arm name	Follow-up time point (weeks)	No. patients with event (n)	No. patients analyzed (N) or "NR"	% with event or "NR" -
carcinoma	2019[20]		1		Placebo	NR/Unclear	2	107	1.9
Hyperkalaemia	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	1	89	1.1
					Placebo 60mg	NR/Unclear	0	48	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	58	0.0
					Placebo 40mg	NR/Unclear	0	32	0.0
Hypertensive crisis	Peck-Radosavljevic 2019[20]	L-PLUS 2	NCT02389621	<50,000	Lusutrombopag	NR/Unclear	0	107	0.0
					Placebo	NR/Unclear	1	107	0.9
Hypokalemia	Peck-Radosavljevic 2019[20]	L-PLUS 2	NCT02389621	<50,000	Lusutrombopag	NR/Unclear	0	107	0.0
					Placebo	NR/Unclear	1	107	0.9
Hyponatraemia	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	1	89	1.1
					Placebo 60mg	NR/Unclear	0	48	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	1	58	1.7
					Placebo 40mg	NR/Unclear	0	32	0.0
Hypotension	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	1	89	1.1
					Placebo 60mg	NR/Unclear	0	48	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	58	0.0
					Placebo 40mg	NR/Unclear	0	32	0.0
Ileus paralytic	Terrault 2018[18]	ADAPT-2	NCT01976104	<40,000	Avatrombopag 60mg	NR/Unclear	0	70	0.0
					Placebo 60mg	NR/Unclear	0	43	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	1	57	1.8
					Placebo 40mg	NR/Unclear	0	33	0.0
Multiorgan failure	Peck-Radosavljevic 2019[20]	L-PLUS 2	NCT02389621	<50,000	Lusutrombopag	NR/Unclear	1	107	0.9
					Placebo	NR/Unclear	0	107	0.0
Multiple Organ	Terrault 2018[18]	ADAPT-1	NCT0197252	<40,000	Avatrombopag 60mg	NR/Unclear	0	89	0.0

Serious adverse event	Study ID	Trial name	NCT/ other trial number	Lower / Upper platelets (per µL)	Arm name	Follow-up time point (weeks)	No. patients with event (n)	No. patients analyzed (N) or "NR"	% with event or "NR" -
dysfunction syndrome			9		Placebo 60mg	NR/Unclear	0	48	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	1	58	1.7
					Placebo 40mg	NR/Unclear	0	32	0.0
		ADAPT-2	NCT01976104	<40,000	Avatrombopag 60mg	NR/Unclear	0	70	0.0
					Placebo 60mg	NR/Unclear	0	43	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	57	0.0
					Placebo 40mg	NR/Unclear	1	33	3.0
Muscle spasms	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	0	89	0.0
					Placebo 60mg	NR/Unclear	0	48	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	1	58	1.7
					Placebo 40mg	NR/Unclear	0	32	0.0
Myalgia	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	1	89	1.1
					Placebo 60mg	NR/Unclear	0	48	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	58	0.0
					Placebo 40mg	NR/Unclear	0	32	0.0
Nausea	Peck-Radosavljevic 2019[20]	L-PLUS 2	NCT02389621	<50,000	Lusutrombopag	NR/Unclear	0	107	0.0
					Placebo	NR/Unclear	1	107	0.9
Oesophageal varices haemorrhage	Hidaka 2018[19]	L-PLUS 1	JapicCTI-132323	<50,000	Lusutrombopag	NR/Unclear	0	48	0.0
					Placebo	NR/Unclear	1	48	2.1
	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	0	89	0.0
					Placebo 60mg	NR/Unclear	0	48	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	1	58	1.7
					Placebo 40mg	NR/Unclear	0	32	0.0
Platelet count	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	0	89	0.0

Serious adverse event	Study ID	Trial name	NCT/ other trial number	Lower / Upper platelets (per µL)	Arm name	Follow-up time point (weeks)	No. patients with event (n)	No. patients analyzed (N) or "NR"	% with event or "NR" -
decreased			9		Placebo 60mg	NR/Unclear	1	48	2.1
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	58	0.0
					Placebo 40mg	NR/Unclear	0	32	0.0
Pneumonia	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	1	89	1.1
					Placebo 60mg	NR/Unclear	0	48	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	58	0.0
					Placebo 40mg	NR/Unclear	0	32	0.0
Portal vein thrombosis	Hidaka 2018[19]	L-PLUS 1	JapicCTI-132323	<50,000	Lusutrombopag	NR/Unclear	1	48	2.1
					Placebo	NR/Unclear	0	48	0.0
	Peck-Radosavljevic 2019[20]	L-PLUS 2	NCT02389621	<50,000	Lusutrombopag	NR/Unclear	1	107	0.9
					Placebo	NR/Unclear	0	107	0.0
Post procedural haemorrhage	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	1	89	1.1
					Placebo 60mg	NR/Unclear	1	48	2.1
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	58	0.0
					Placebo 40mg	NR/Unclear	0	32	0.0
Post-operative fever/plural effusion	Hidaka 2018[19]	L-PLUS 1	JapicCTI-132323	<50,000	Lusutrombopag	NR/Unclear	0	48	0.0
					Placebo	NR/Unclear	1	48	2.1
Procedural haemorrhage	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	0	89	0.0
					Placebo 60mg	NR/Unclear	1	48	2.1
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	58	0.0
					Placebo 40mg	NR/Unclear	0	32	0.0
Procedural pain	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	1	89	1.1
					Placebo 60mg	NR/Unclear	0	48	0.0

Serious adverse event	Study ID	Trial name	NCT/ other trial number	Lower / Upper platelets (per µL)	Arm name	Follow-up time point (weeks)	No. patients with event (n)	No. patients analyzed (N) or "NR"	% with event or "NR" -
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	58	0.0
					Placebo 40mg	NR/Unclear	0	32	0.0
Pyrexia	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	0	89	0.0
					Placebo 60mg	NR/Unclear	1	48	2.1
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	58	0.0
					Placebo 40mg	NR/Unclear	1	32	3.1
Sepsis	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	0	89	0.0
					Placebo 60mg	NR/Unclear	0	48	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	1	58	1.7
					Placebo 40mg	NR/Unclear	0	32	0.0
Splenic haemorrhage	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	1	89	1.1
					Placebo 60mg	NR/Unclear	0	48	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	58	0.0
					Placebo 40mg	NR/Unclear	0	32	0.0
Splenic infarction	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	1	89	1.1
					Placebo 60mg	NR/Unclear	0	48	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	58	0.0
					Placebo 40mg	NR/Unclear	0	32	0.0
Splenomegaly	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	1	89	1.1
					Placebo 60mg	NR/Unclear	0	48	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	58	0.0
					Placebo 40mg	NR/Unclear	0	32	0.0
Stress polycythaemia	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	1	89	1.1
					Placebo 60mg	NR/Unclear	0	48	0.0

Serious adverse event	Study ID	Trial name	NCT/ other trial number	Lower / Upper platelets (per µL)	Arm name	Follow-up time point (weeks)	No. patients with event (n)	No. patients analyzed (N) or "NR"	% with event or "NR" -
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	58	0.0
					Placebo 40mg	NR/Unclear	0	32	0.0
Syncope	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	1	89	1.1
					Placebo 60mg	NR/Unclear	0	48	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	58	0.0
					Placebo 40mg	NR/Unclear	0	32	0.0
Transfusion reaction	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	0	89	0.0
					Placebo 60mg	NR/Unclear	3	48	6.3
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	58	0.0
					Placebo 40mg	NR/Unclear	0	32	0.0
Upper gastrointestinal haemorrhage	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	1	89	1.1
					Placebo 60mg	NR/Unclear	0	48	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	1	58	1.7
					Placebo 40mg	NR/Unclear	0	32	0.0
Urinary tract infection	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	0	89	0.0
					Placebo 60mg	NR/Unclear	0	48	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	1	58	1.7
					Placebo 40mg	NR/Unclear	0	32	0.0
Urticaria	Hidaka 2018[19]	L-PLUS 1	JapicCTI-132323	<50,000	Lusutrombopag	NR/Unclear	0	48	0.0
					Placebo	NR/Unclear	1	48	2.1
Vertigo	Terrault 2018[18]	ADAPT-1	NCT01972529	<40,000	Avatrombopag 60mg	NR/Unclear	1	89	1.1
					Placebo 60mg	NR/Unclear	0	48	0.0
				40,000 - 50,000	Avatrombopag 40mg	NR/Unclear	0	58	0.0
					Placebo 40mg	NR/Unclear	0	32	0.0

Serious adverse event	Study ID	Trial name	NCT/ other trial number	Lower / Upper platelets (per µL)	Arm name	Follow-up time point (weeks)	No. patients with event (n)	No. patients analyzed (N) or "NR"	% with event or "NR" -
Vessel perforation	Peck-Radosavljevic 2019[20]	L-PLUS 2	NCT02389621	<50,000	Lusutrombopag	NR/Unclear	1	107	0.9
					Placebo	NR/Unclear	0	107	0.0
Vomiting	Peck-Radosavljevic 2019[20]	L-PLUS 2	NCT02389621	<50,000	Lusutrombopag	NR/Unclear	0	107	0.0
					Placebo	NR/Unclear	1	107	0.9

APPENDIX 5: FOREST PLOTS OF EACH INTERVENTION VERSUS PLACEBO

Proportion of subjects who required neither platelet transfusion prior to the primary invasive procedure and nor rescue therapy for bleeding from randomization (risk ratio scale)

Proportion of subjects who required no platelet transfusion prior to the primary invasive procedure (risk ratio scale)

Proportion of subjects who required no rescue therapy for bleeding (risk ratio scale)

Proportion of subjects who required neither platelet transfusion prior to the primary invasive procedure and nor rescue therapy for bleeding from randomization (odds ratio scale)

Proportion of subjects who required no platelet transfusion prior to the primary invasive procedure (odds ratio scale)

Proportion of subjects who required no rescue therapy for bleeding (odds ratio scale)

APPENDIX 6: DETAILS OF THE BAYESIAN META-ANALYSIS

WinBUGS code for the meta-analysis of the baseline arms for absolute effects (e.g. placebo arm baseline proportions of the patients who had no platelet transfusion prior to surgery for patients who had platelet count less than 40,000/μL)

```
# Binomial likelihood, logit link

# Baseline random effects model

model{                    # *** PROGRAM STARTS

for (i in 1:ns){          # LOOP THROUGH STUDIES

   r[i] ~ dbin(p[i],n[i])          # Likelihood

   logit(p[i]) <- mu[i]                    # Log-odds of response

   mu[i] ~ dnorm(m,tau.m)     # Random effects model

 }

mu.new ~ dnorm(m,tau.m)          # predictive dist. (log-odds)

m ~ dnorm(0,.0001)          # vague prior for mean

var.m <- 1/tau.m            # between-trial variance

tau.m <- pow(sd.m,-2)   # between-trial precision = (1/between-trial variance)

sd.m ~ dunif(0,5)           # vague prior for between-trial SD

#sd.m <- dunif(0,0.5)   #less vague prior for between-trial SD for circumventing numerical instability in the presence of zero cells

#tau.m ~ dgamma(0.001,0.001)  #gamma distributed prior

#sd.m <- sqrt(var.m)  #gamma distributed prior

logit(R) <- m               # posterior probability of response

logit(R.new) <- mu.new      # predictive probability of response

}

#Data

list(ns=5)  # ns=number of studies

#in sparse networks or several trials having zero cells, correction by adding 0.5 to the numerator and 1 to the denominator can be applied.

r[]     n[]     #     Study ID

1       19      #     1

15      68      #     2
```

```
1       6       #       3
26      48      #       4
22      43      #       5
END
```

WinBUGS code for the random-effects meta-analysis to obtain the binomial probabilities to be used in the electronic model (e.g. treatment-specific proportions of the patients who had no platelet transfusion prior to surgery for patients who had platelet count less than 40,000/μL)

```
# Binomial likelihood, logit link
# Random effects model for multi-arm trials
model{                          # *** PROGRAM STARTS
for(i in 1:ns){                 # LOOP THROUGH STUDIES
   w[i,1] <- 0    # adjustment for multi-arm trials is zero for control arm
   delta[i,1] <- 0           # treatment effect is zero for control arm
   mu[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
   for (k in 1:na[i]) {            # LOOP THROUGH ARMS
      r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
      logit(p[i,k]) <- mu[i] + delta[i,k]  # model for linear predictor
      rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
#Deviance contribution
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))
         +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))        }
#  summed residual deviance contribution for this trial
   resdev[i] <- sum(dev[i,1:na[i]])
   for (k in 2:na[i]) {            # LOOP THROUGH ARMS
# trial-specific LOR distributions
      delta[i,k] ~ dnorm(md[i,k],taud[i,k])
# mean of LOR distributions (with multi-arm trial correction)
      md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]
# precision of LOR distributions (with multi-arm trial correction)
      taud[i,k] <- tau *2*(k-1)/k
```

```
# adjustment for multi-arm RCTs
      w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])
# cumulative adjustment for multi-arm trials
      sw[i,k] <- sum(w[i,1:k-1])/(k-1)
    }
  }
totresdev <- sum(resdev[])          # Total Residual Deviance
d[1]<-0      # treatment effect is zero for reference treatment
# vague priors for treatment effects
for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
sd ~ dunif(0,5)     # vague prior for between-trial SD
#sd.m <- dunif(0,0.5)   #less vague prior for between-trial SD for circumventing numerical instability in the presence of zero cells
tau <- pow(sd,-2)   # between-trial precision = (1/between-trial variance)
# Provide estimates of treatment effects T[k] on the natural (probability) scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k in 1:nt) { logit(T[k]) <- A + d[k]  }
}                              # *** PROGRAM ENDS
#Data
# ns= number of studies; nt=number of treatments; meanA and precA are obtained from meta-analysis of the baseline arms for absolute effects
#in sparse networks or several trials having zero cells, correction by adding 0.5 to the numerator and 1 to the denominator can be applied.
list(ns=5, nt=3, meanA=-0.9979, precA=1.140) #RE of all 5 RCTs
```

r[,1]	n[,1]	r[,2]	n[,2]	t[,1]	t[,2]	na[]	# Study ID
4	7	1	6	2	1	2	
12	15	1	19	2	1	2	
31	54	15	68	2	1	2	
71	90	26	48	3	1	2	

```
58      70      22      43      3       1       2
END
```

WinBUGS code for the fixed-effects meta-analysis to obtain the binomial probabilities to be used in the electronic model (e.g. treatment-specific proportions of the patients who had no platelet transfusion prior to surgery for patients who had platelet count less than 40,000/μL)

```
# Binomial likelihood, logit link
# Fixed effects model
model{ # *** PROGRAM STARTS
for(i in 1:ns){ # LOOP THROUGH STUDIES
 mu[i] ~ dnorm(0,.0001) # vague priors for all trial baselines
 for (k in 1:na[i]) { # LOOP THROUGH ARMS
 r[i,k] ~ dbin(p[i,k],n[i,k]) # binomial likelihood
 logit(p[i,k]) <- mu[i] + d[t[i,k]] - d[t[i,1]] # model for linear predictor
 rhat[i,k] <- p[i,k] * n[i,k] # expected value of the numerators
 dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k])) #Deviance contribution
 + (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) - log(n[i,k]-rhat[i,k])))
 }
 resdev[i] <- sum(dev[i,1:na[i]]) # summed residual deviance contribution for this trial
 }
totresdev <- sum(resdev[]) #Total Residual Deviance
d[1]<-0 # treatment effect is zero for reference treatment
for (k in 2:nt){ d[k] ~ dnorm(0,.0001) } # vague priors for treatment effects

# Provide estimates of treatment effects T[k] on the natural (probability) scale
# Given a Mean Effect, meanA, for 'standard' treatment A,
# with precision (1/variance) precA
A ~ dnorm(meanA,precA)
for (k in 1:nt) { logit(T[k]) <- A + d[k]  }
}                               # *** PROGRAM ENDS
#Data
```

ns= number of studies; nt=number of treatments; meanA and precA are obtained from meta-analysis of the baseline arms for absolute effects

#in sparse networks or several trials having zero cells, correction by adding 0.5 to the numerator and 1 to the denominator can be applied.

list(ns=5, nt=3, meanA=-0.9979, precA=1.140) #FE of all 5 RCTs

r[,1]	n[,1]	r[,2]	n[,2]	t[,1]	t[,2]	na[]	#	Study ID
4	7	1	6	2	1	2		
12	15	1	19	2	1	2		
31	54	15	68	2	1	2		
71	90	26	48	3	1	2		
58	70	22	43	3	1	2		

END

WinBUGS output for the fixed-effects and random-effects meta-analyses conducted to obtain the binomial probabilities to be used in the electronic model (e.g. treatment-specific proportions of the patients who had no platelet transfusion prior to surgery for patients who had platelet count less than 40,000/μL)

Random effects:

node	mean	sd	MC error	2.50%	median	97.50%	start	Sample
T[1]	0.3001	1.73E-01	5.63E-04	0.05472	0.269	0.6982	30001	100000
T[2]	0.7585	2.15E-01	9.31E-04	0.1992	0.8242	0.9926	30001	100000
T[3]	0.5614	2.70E-01	9.46E-04	0.04327	0.5873	0.9774	30001	100000
d[2]	2.6	1.271	0.006792	0.2003	2.479	5.489	30001	100000
d[3]	1.349	1.403	0.004838	-1.686	1.346	4.359	30001	100000
tau	227.7	9209	117.2	0.05228	0.5646	94.85	30001	100000
totresdev	10.29	4.432	0.02536	3.43	9.685	20.57	30001	100000

	Dbar	Dhat	pD	DIC
r	45.268	35.598	9.67	5.49E+01
total	45.268	35.598	9.67	5.49E+01

Fixed effects

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
T[1]	0.3855	0.1279	3.98E-01	0.1629	0.3773	0.6522	30001	100000
T[2]	0.8288	0.09496	3.69E-01	0.5942	0.8484	0.9559	30001	100000
T[3]	0.8855	0.07547	4.11E-01	0.6912	0.9039	0.9767	30001	100000
d[2]	2.226	0.3734	0.002102	1.5120	2.2190	2.9750	30001	100000

d[3]	2.752	0.479	0.004095	1.8650	2.7310	3.7450	30001	100000
totresdev	13.79	3.82E+00	0.0161	8.37	13.11	23.04	30001	100000

	Dbar	Dhat	pD	DIC
r	45.268	38.195	7.073	5.23E+01
total	45.268	38.195	7.073	5.23E+01

APPENDIX 7: PSA parameters

Table 1: Parameters varied in PSA on general characteristics, efficacy, mortality, and safety.

Parameter varied in PSA	Condition / Comparison	Trials / Subgroup	Base Value (SE)	Distribution (α, β)	95% CI: lower limit - upper limit
General					
Age (years)	All trials and conditions pooled		58.55 (0.39)	N (58.55, 0.39)	57.8 - 59.3
Proportion male			62.68%	B (487, 290)	59.25% - 66.04%
Proportion Child Pugh A			57.46% (0.11)	Conditional Beta Distribution	
Proportion Child Pugh B			38.93% (0.08)		
Proportion Child Pugh C			3.611% (0.01)		
Efficacy					
Proportion not receiving platelet transfusion prior to PEIP	AVA	< 40	0.571	WinBUGS CODA	
	LUSU		[redacted]		
	PBO		[redacted]		
	AVA	40 - < 50	0.899		
	LUSU		[redacted]		
	PBO		[redacted]		
Proportion requiring rescue therapy	AVA	< 40	0.077		
	LUSU		[redacted]		
	PBO		[redacted]		
	AVA	40 - < 50	0.040		
	LUSU		[redacted]		
	PBO		[redacted]		
Proportion procedure not performed	LUSU	Pooled (L-PLUS 2 only)	[redacted]	B (3, 49)	0.01 – 0.13
	PBO		[redacted]	B (3, 34)	0.02 – 0.19

Mortality					
Mortality due to platelet transfusion	Assumed to be the same for all patients in all subgroups		4.6*10-6	B (4.60, 999995.40)	1.4*10-6 - 9.7*10-6
Mortality due to surgery			0.019 (0.077)	B (0.04, 2.17)	0.00 - 0.25
Safety					
Number of ATDs per transfusion	Assumed the same for all patients (based on all patients in all LUSU trials pooled)		[redacted]	[redacted]	[redacted]
Transfusion AE % Pneumo			3.95*10-05	B (25.00, 632861.39)	2.6*10-05 – 5.6*10-05
Transfusion AE % FAHR (major)			7.38*10-05	B (25.00, 338559.21)	4.8*10-05 – 1.05*10-04
Transfusion AE % Bacteria			6.34*10-08	B (25.00, 394026225.00)	4.1*10-08 –9.1*10-08
Transfusion AE % HAV			6.34*10-08	B (25.00, 394026225.00)	4.1*10-08 –9.1*10-08
Transfusion AE % HBV			6.3*10-08	B (25.00, 394026225.00)	4.1*10-08 –9.1*10-08
Transfusion AE % HEV			6.34*10-07	B (25.00, 39402577.50)	4.1*10-07 –9.1*10-07
Transfusion AE % Parvovirus			6.34*10-08	B (25.00, 394026225.00)	4.1*10-08 –9.1*10-08
Proportion experiencing bleeding	AVA	< 40	0.044	WinBUGS CODA	
	LUSU		[redacted]		
	PBO		[redacted]		
	AVA	40 - < 50	0.021		
	LUSU		[redacted]		
	PBO		[redacted]		
Proportion experiencing PVT	AVA	< 40	0.012		
	LUSU		[redacted]		
	PBO		[redacted]		
	AVA	40 - < 50	0.002		
	LUSU		[redacted]		
	PBO		[redacted]		
Source: AG model.					

Abbreviations: PSA = probabilistic sensitivity analysis, SE = standard error, CI = confidence interval, AVA = avatrombopag, LUSU = lusutrombopag, PBO = placebo, ATD = adult therapeutic dose, FAHR = febrile, allergic or hypotensive reactions, HAV = hepatitis A virus, HBV = hepatitis B virus, HEV = hepatitis E virus.

Table 2: Parameters varied in PSA on utilities and costs.

Parameter varied in PSA	Base Value (SE)	Distribution (α, β)	95% C.I.: lower limit - upper limit
Utilities			
Utility, chronic liver disease, Sullivan	0.54 (0.051)	*B* (51.86, 43.56)	0.44 - 0.64
Utility, chronic liver disease, Scalone	0.80 (0.007)	*B* (2372.01, 589.30)	0.79 - 0.82
Disutility, transfusion-related reaction NICE	0.10 (0.02)	*B* (22.50, 202.50)	0.06 - 0.14
Disutility, portal vein thrombosis, Jugrin	0.03 (0.01)	*B* (24.28, 812.79)	0.02 - 0.04
Disutility, major bleed, Jugrin	0.40 (0.08)	*B* (15.08, 22.90)	0.25 - 0.55
Disutility, minor bleed, Jugrin	0.12 (0.02)	*B* (21.95, 157.97)	0.08 - 0.17
Duration, transfusion-related reaction	4.00 (0.80)	*Γ* (25.00, 0.16)	2.59 - 5.20
Duration, portal vein thrombosis	1.00 (0.20)	*Γ* (25.00, 0.04)	0.65 - 1.30
Duration, major bleed	1.00 (0.20)	*Γ* (25.00, 0.04)	0.65 - 1.30
Duration, minor bleed	1.00 (0.20)	*Γ* (25.00, 0.04)	0.65 - 1.30
Proportion of bleeds, major	0.30 (0.06)	*B* (17.50, 40.83)	0.19 - 0.42
Proportion of patients with transfusion related reaction	0.00 (0.00)	*B* (25.00, 218826.45)	0.00 - 0.00
Disutility, Transfusion related acute lung injury	0.40 (0.08)	*B* (15.00, 22.50)	0.25 - 0.56
Disutility, Hepatitis A Virus (HAV)	0.03 (0.01)	*B* (24.25, 784.08)	0.02 - 0.04
Disutility, Hepatitis B Virus (HBV)	0.16 (0.03)	*B* (21.00, 110.25)	0.10 - 0.23
Disutility, Hepatitis C Virus (HCV)	0.46 (0.09)	*B* (13.50, 15.85)	0.29 - 0.64
Disutility, Human Immunodeficiency Virus (HIV)	0.50 (0.10)	*B* (12.50, 12.50)	0.31 - 0.69
Disutility, Parvovirus B19 (P-B19)	0.03 (0.01)	*B* (24.25, 784.08)	0.02 - 0.04

Disutility, Prion disease (CJD)			0.00 (0.00)	*B* (0.00, 0.00)	0.00 - 0.00
Disutility, Severe allergic reactions			0.40 (0.08)	*B* (15.00, 22.50)	0.25 - 0.56
Costs					
Cost of platelet transfusion, NHS reference costs, daycase			£499.20 (99.84)	*Γ* (25.00, 19.97)	£323.05 - £649.26
Cost of platelet transfusion, NHS reference costs, elective inpatient			£971.06 (194.21)	*Γ* (25.00, 38.84)	£628.42 - £1,262.97
Cost of platelet transfusion, NICE TA293, initial			£57.72 (11.54)	*Γ* (25.00, 2.31)	£37.35 - £75.07
Cost of platelet transfusion, NICE TA293, units			£230.39 (46.08)	*Γ* (25.00, 9.22)	£149.10 - £299.65
Cost of platelet transfusion, NICE TA293, follow-up			£262.00 (52.40)	*Γ* (25.00, 10.48)	£169.55 - £340.76
Cost of platelet transfusion, Stokes, admin cost first unit			£61.37 (12.27)	*Γ* (25.00, 2.45)	£39.72 - £79.82
Cost of platelet transfusion, Stokes, admin cost subsequent units			£40.31 (8.06)	*Γ* (25.00, 1.61)	£26.09 - £52.43
Cost of platelet transfusion, NHS Blood and Transplant Pricing Proposals, Cost per unit, apheresis			£219.30 (43.86)	*Γ* (25.00, 8.77)	£141.92 - £285.22
Number of platelet transfusions prior to surgery	< 40	AVA	1.00 (0.20)	*Γ* (25.00, 0.04)	0.70 - 1.40
		LUSU	[redacted]	[redacted]	[redacted]
		PBO (all trials pooled)	[redacted]	[redacted]	[redacted]
		PBO (AVA trials pooled)	1.12 (0.22)	*Γ* (25.00, 0.04)	0.72 - 1.45
		PBO (LUSU trials pooled)	[redacted]	[redacted]	[redacted]
	40 - <50	AVA	1.00 (0.20)	*Γ* (25.00, 0.04)	0.65 - 1.30
		LUSU	[redacted]	[redacted]	[redacted]
		PBO (all trials pooled)	[redacted]	[redacted]	[redacted]
		PBO (AVA trials pooled)	1.06 (0.21)	*Γ* (25.00, 0.04)	0.69 - 1.38
		PBO (LUSU trials pooled)	[redacted]	[redacted]	[redacted]
Adverse event cost, portal vein thrombosis			£958.95 (191.79)	*Γ* (25.00, 38.36)	£620.58 - £1,247.22
1208 M0626, Proportion of patients, Percutaneous radiofrequency ablation (RFA)			[redacted]	The frequency and unit costs of the surgeries from each trial are sampled using beta distribution for the proportions (using the event and nonevent	
1208 M0626, Proportion of patients, Endoscopic variceal ligation			[redacted]		

1208 M0626, Proportion of patients, Endoscopic injection sclerotherapy	[redacted]	numbers) and gamma distribution for the unit cost of the surgeries, assuming a SE/mean ratio of 0.2
1208 M0626, Proportion of patients, Transcatheter arterial chemoembolisation	[redacted]	
1208 M0626, Proportion of patients, Liver biopsy	[redacted]	
1208 M0626, Proportion of patients, Dental extraction	[redacted]	
1208 M0626, Proportion of patients, Vascular catheterisation	[redacted]	
1208 M0626, Proportion of patients, Argon plasma coagulation	[redacted]	
1208 M0626, Proportion of patients, Percutaneous ethanol injection therapy	[redacted]	
1208 M0626, Proportion of patients, Endoscopy w/wo polypectomy/biopsy	[redacted]	
1208 M0626, Proportion of patients, Percutaneous RFA/microwave coagulation therapy	[redacted]	
1208 M0626, Proportion of patients, Paracentesis	[redacted]	
1208 M0626, Proportion of patients, Other liver procedures	[redacted]	
1208 M0626, Proportion of patients, Other gastrointestinal procedures	[redacted]	
1208 M0626, Proportion of patients, Others	[redacted]	
L PLUS 1, Proportion of patients, Percutaneous radiofrequency ablation (RFA)	[redacted]	
L PLUS 1, Proportion of patients, Endoscopic variceal ligation	[redacted]	
L PLUS 1, Proportion of patients, Endoscopic injection sclerotherapy	[redacted]	
L PLUS 1, Proportion of patients, Transcatheter arterial chemoembolisation	[redacted]	
L PLUS 1, Proportion of patients, Liver biopsy	[redacted]	
L PLUS 1, Proportion of patients, Dental extraction	[redacted]	
L PLUS 1, Proportion of patients, Vascular catheterisation	[redacted]	
L PLUS 1, Proportion of patients, Argon plasma coagulation	[redacted]	
L PLUS 1, Proportion of patients, Percutaneous ethanol injection therapy	[redacted]	
L PLUS 1, Proportion of patients, Endoscopy w/wo polypectomy/biopsy	[redacted]	
L PLUS 1, Proportion of patients, Percutaneous RFA/microwave	[redacted]	

coagulation therapy		
L PLUS 1, Proportion of patients, Paracentesis	[redacted]	
L PLUS 1, Proportion of patients, Other liver procedures	[redacted]	
L PLUS 1, Proportion of patients, Other gastrointestinal procedures	[redacted]	
L PLUS 1, Proportion of patients, Others	[redacted]	
L PLUS 2, Proportion of patients, Percutaneous radiofrequency ablation (RFA)	[redacted]	
L PLUS 2, Proportion of patients, Endoscopic variceal ligation	[redacted]	
L PLUS 2, Proportion of patients, Endoscopic injection sclerotherapy	[redacted]	
L PLUS 2, Proportion of patients, Transcatheter arterial chemoembolisation	[redacted]	
L PLUS 2, Proportion of patients, Liver biopsy	[redacted]	
L PLUS 2, Proportion of patients, Dental extraction	[redacted]	
L PLUS 2, Proportion of patients, Vascular catheterisation	[redacted]	
L PLUS 2, Proportion of patients, Argon plasma coagulation	[redacted]	
L PLUS 2, Proportion of patients, Percutaneous ethanol injection therapy	[redacted]	
L PLUS 2, Proportion of patients, Endoscopy w/wo polypectomy/biopsy	[redacted]	
L PLUS 2, Proportion of patients, Percutaneous RFA/microwave coagulation therapy	[redacted]	
L PLUS 2, Proportion of patients, Paracentesis	[redacted]	
L PLUS 2, Proportion of patients, Other liver procedures	[redacted]	
L PLUS 2, Proportion of patients, Other gastrointestinal procedures	[redacted]	
L PLUS 2, Proportion of patients, Others	[redacted]	
ADAPT, Proportion of patients, Percutaneous radiofrequency ablation (RFA)	[redacted]	
ADAPT, Proportion of patients, Endoscopic variceal ligation	[redacted]	
ADAPT, Proportion of patients, Endoscopic injection sclerotherapy	[redacted]	
ADAPT, Proportion of patients, Transcatheter arterial chemoembolisation	[redacted]	

ADAPT, Proportion of patients, Liver biopsy	[redacted]	
ADAPT, Proportion of patients, Dental extraction	[redacted]	
ADAPT, Proportion of patients, Vascular catheterisation	[redacted]	
ADAPT, Proportion of patients, Argon plasma coagulation	[redacted]	
ADAPT, Proportion of patients, Percutaneous ethanol injection therapy	[redacted]	
ADAPT, Proportion of patients, Endoscopy w/wo polypectomy/biopsy	[redacted]	
ADAPT, Proportion of patients, Percutaneous RFA/microwave coagulation therapy	[redacted]	
ADAPT, Proportion of patients, Paracentesis	[redacted]	
ADAPT, Proportion of patients, Other liver procedures	[redacted]	
ADAPT, Proportion of patients, Other gastrointestinal procedures	[redacted]	
Cost, Percutaneous radiofrequency ablation (RFA)	£2,309.03 (461.81)	
Cost, Endoscopic variceal ligation	£4,202.11 (840.42)	
Cost, Endoscopic injection sclerotherapy	£2,410.75 (482.15)	
Cost, Transcatheter arterial chemoembolisation	£2,921.50 (584.30)	
Cost, Liver biopsy	£1,546.72 (309.34)	
Cost, Dental extraction	£680.04 (136.01)	
Cost, Vascular catheterisation	£1,125.62 (225.12)	
Cost, Argon plasma coagulation	£4,202.11 (840.42)	
Cost, Percutaneous ethanol injection therapy	£2,921.50 (584.30)	
Cost, Endoscopy w/wo polypectomy/biopsy	£1,213.27 (242.65)	
Cost, Percutaneous RFA/microwave coagulation therapy	£2,309.03 (461.81)	
Cost, Paracentesis	£1,090.43 (218.09)	
Cost, Other liver procedures	£2,921.50 (584.30)	
Cost, Other gastrointestinal procedures	£4,202.11 (840.42)	
Cost, Others	£2,309.03 (461.81)	

Costs Pneumo	£2,640 (527.93)	
Costs FAHR (major)	£1,134 (226.85)	
Costs Bacteria	£2,024 (404.79)	
Costs HAV	£6,488 (1297.60)	
Costs HBV	£8,971 (1794.20)	
Costs HEV	£6,488 (1297.60)	
Costs Parvovirus	£1,095 (219.00)	

Source: AG model.
Abbreviations: PSA = probabilistic sensitivity analysis, SE = standard error, CI = confidence interval, AVA = avatrombopag, LUSU = lusutrombopag, PBO = placebo, FAHR = febrile, allergic or hypotensive reactions, HAV = hepatitis A virus, HBV = hepatitis B virus, HEV = hepatitis E virus.

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Avatrombopag and lusutrombopag for treating thrombocytopenia in people with chronic liver disease needing an elective procedure

ERRATUM TABLE

This document contains errata in the AG report due to economic model errors identified by the AG. The model errors hardly changed the incremental results.

The table below lists the page to be replaced in the original document and the nature of the change:

Page nr:	**Change:**
4	"For the 40,000 – 50,000/µL subgroup, avatrombopag and lusutrombopag are 24% and 26% more expensive than no TPO-RA, respectively." Changed to "For the 40,000 – 50,000/µL subgroup, avatrombopag and lusutrombopag are 28% and 27% more expensive than no TPO-RA, respectively." Following model corrections
8	"For the 40,000 – 50,000/µL subgroup, avatrombopag and lusutrombopag are 24% and 26% more expensive than no TPO-RA, respectively." Changed to "For the 40,000 – 50,000/µL subgroup, avatrombopag and lusutrombopag are 28% and 27% more expensive than no TPO-RA, respectively." Following model corrections and model results updated in Table 1.4 And "If its price were to be 70% below the price of lusutrombopag, avatrombopag would become cost saving in the 40,000 – 50,000/µL subgroup." Changed to "If its price were to be 80% below the price of lusutrombopag, avatrombopag would become cost saving in the 40,000 – 50,000/µL subgroup."
9	"For the 40,000 – 50,000/µL subgroup, avatrombopag and lusutrombopag are 24% and 26% more expensive than no TPO-RA, respectively." Changed to "For the 40,000 – 50,000/µL subgroup, avatrombopag and lusutrombopag are 28% and 27% more expensive than no TPO-RA, respectively." Following model corrections
10	"For the 40,000 – 50,000/µL subgroup, avatrombopag and lusutrombopag are 24% and 26% more expensive than no TPO-RA, respectively." Changed to "For the 40,000 – 50,000/µL subgroup, avatrombopag and lusutrombopag are 28% and 27% more expensive than no TPO-RA, respectively." And "If its price were to be 70% below the price of lusutrombopag, avatrombopag

	would become cost saving in the 40,000 – 50,000/µL subgroup." Changed to "If its price were to be 80% below the price of lusutrombopag, avatrombopag would become cost saving in the 40,000 – 50,000/µL subgroup." Following model corrections
77	Footnote added to Table 6.3 to clarify discrepancy between model values and those values provided in the table. This footnote reads as follows "* Discrepancies between the values seen in this table and in the model are due to differences in the number of iterations used to calculate the values. The values presented in the table were obtained from the WINBUGS output summary from 100,000 iterations (after a burn-in of 30,000 iterations). In the excel model we use 2,000 iterations from the WINBUGS to provide values for the PSA of the model"
79	"Therefore, the AG assumed a pooled estimate of [redacted] ATDs per transfusion across all transfusions given in the model." Changed to "Therefore, the AG assumed a pooled estimate of [redacted] ATDs per transfusion across all transfusions given in the model." And Table 6.4 updated following model corrections
80	"By combining this with the probability of a transfusion reaction, we find an overall mortality due to platelet transfusion of 0.000458% (see Table 6.5)." changed to "By combining this with the probability of a transfusion reaction, we find an overall mortality due to platelet transfusion of 0.0004592% (see Table 6.5)." and "Therefore in scenario analyses underreporting factors were included for transfusion related mortality to adjust the base-case estimate of 0.000458%" changed to "Therefore in scenario analyses underreporting factors were included for transfusion related mortality to adjust the base-case estimate of 0.0004592%"
81	Mortality due to platelet transfusion value of 0.000458% corrected to 0.0004592% and references added for SHOT reports 2012-17
82	"([redacted] units, calculated by the AG, the details are explained under the *platelet transfusion* section)" changed to "([redacted] units, calculated by the AG, the details are explained under the *platelet transfusion* section)"

	following model correction
83	Footnote added to Table 6.6 to clarify discrepancy between model values and those values provided in the table. This footnote reads as follows "* Discrepancies between the values seen in this table and in the model are due to differences in the number of iterations used to calculate the values. The values presented in the table were obtained from the WINBUGS output summary from 100,000 iterations (after a burn-in of 30,000 iterations). In the excel model we use 2,000 iterations from the WINBUGS to provide values for the PSA of the model"
84	"The disutility of 0.1 for a duration of four weeks was multiplied with the incidence of 0.0114%, which equated to a total QALY decrement of 0.00000086." changed to "The disutility of 0.1 for a duration of four weeks was multiplied with the incidence of 0.0114%, which equated to a total QALY decrement of 0.000000876."
86	"This was multiplied by the estimate of [redacted] ATDs per transfusion" changed to "This was multiplied by the estimate of [redacted] ATDs per transfusion" following model corrections
87	"the AG cost of platelet transfusion of [redacted] was used in the base-case." Changed to "the AG cost of platelet transfusion of [redacted] was used in the base-case." following model corrections Reference added for Whiting et al (2015) Clarification added to explain the calculation of transfusion related reaction costs, so that "Costs associated with treating transfusion-related AEs were taken from the report by Whiting et al (2015), with costs inflated from 2013 to 2019, see Table 6.8." became "Costs associated with treating transfusion-related AEs were taken from the report by Whiting et al (2015), [108] with costs inflated from 2013 to 2019, see Table 6.8. These costs were multiplied by the incidences of transfusion related reactions estimated from the SHOT data. [93-97] [108] This resulted in an estimated cost of treating transfusion related reactions of £0.22 per transfusion. This was added to the cost of platelet transfusion, creating a base-case total cost of platelet transfusion of [redacted]."
88	Table 6.8 Number of ATDs transfused per platelet transfusion value amended from [redacted] to [redacted] and Cost of platelet transfusion (base case) amended from [redacted] to [redacted] following model corrections

92	"The calculation of the AG base-case assumption of each platelet transfusion containing [redacted] ATDs was explained in the *platelet transfusion* Section of 6.3.1.4." changed to "The calculation of the AG base-case assumption of each platelet transfusion containing [redacted] ATDs was explained in the *platelet transfusion* Section of 6.3.1.4."
93	Following model corrections and clarification added for the inclusion of the cost of treating transfusion related reactions within the cost of platelet transfusion (and the cost of platelet transfusion is amended following model corrections), so that "In the AG base-case the cost of platelet transfusion is calculated from Stokes et al. 2018, while the unit cost of an ATD of platelets (obtained from apheresis) is taken from the NHSBT pricing proposals.[110] This resulted in a cost per platelet transfusion of [redacted]." Became "In the AG base-case the cost of platelet transfusion is calculated from Stokes et al. 2018, while the unit cost of an ATD of platelets (obtained from apheresis) is taken from the NHSBT pricing proposals.[110] The cost of treating transfusion related reactions was estimated at £0.22 per transfusion, using costs from Whiting et al. (2015) and incidences from the SHOT data. [93-97] [108] This resulted in a cost per platelet transfusion of [redacted]." And the cost of platelet transfusion was amended so that "However, in the face of uncertainty surrounding what would actually be given in UK practice, the AG cost of platelet transfusion of [redacted] was used in the base-case" Became "However, in the face of uncertainty surrounding what would actually be given in UK practice, the AG cost of platelet transfusion of [redacted] was used in the base-case"
95	Table 6.9 Results amended following model corrections
96	Discussion of deterministic model results amended following model correction so that "In the 40,000- 50,000/µL subgroup, avatrombopag 40 mg is the next cheapest option after no TPO-RA, with an incremental cost of £552 and an incremental QALY of 0.00044, resulting in an ICER around £1,250,00 compared to no TPO-RA. Lusutrombopag is the most expensive option in this subgroup but provides a lower QALY gain than avatrombopag 40 mg, with an incremental QALY gain of -0.00042. Lusutrombopag is therefore dominated by avatrombopag in the 40,000-50,000/µL subgroup." Became

	"In the 40,000- 50,000/µL subgroup, lusutrombopag is the next cheapest option after no TPO-RA, with an incremental cost of £624 and an incremental QALY of 0.000000007, resulting in an ICER over £84,000,000,000 compared to no TPO-RA. Avatrombopag 40 mg is the most expensive option in this subgroup but provides a higher QALY gain, with an incremental QALY gain of 0.00041 over lusutrombopag. This results in an ICER of £21,947 for avatrombopag 40mg versus lusutrombopag." And Table 6.10 results updated following model corrections
97	Table 6.11 results updated following model corrections and text updated to reflect changed results, so that "Disaggregated cost results, displayed in Table 6.10, show that, while the costs of platelet transfusion, AE management and rescue therapy are higher for no TPO-RA than for lusutrombopag and avatrombopag, the combined difference is still substantially lower than the drug costs for lusutrombopag and avatrombopag." Became "Disaggregated cost results, displayed in Table 6.10, show that, while the costs of platelet transfusion, AE management and rescue therapy are higher for no TPO-RA than for lusutrombopag and avatrombopag (except for AE costs in the 40,000-50,000/µL subgroup), the combined difference is still substantially lower than the drug costs for lusutrombopag and avatrombopag." And Table 6.12 results updated following model corrections
98	Text updated to reflect changes in probabilistic results following model corrections so that "Lusutrombopag is more expensive than no TPO-RA by £589 (i.e. 25% more expensive) and more effective by 0.0002 QALYs, resulting in an ICER just below £3,500,000. Avatrombopag 60 mg is slightly more expensive than lusutrombopag and slightly less effective (-0.0001 QALYS) and is therefore dominated. In the 40,000- 50,000/µL subgroup, no TPO-RA is again the cheapest option. However, lusutrombopag is the next cheapest and most effective, with an incremental cost of £623 and incremental QALYs of 0.0004. Avatrombopag 40 mg is £10 more expensive than lusutrombopag and -0.0004 QALYs less effective and is therefore dominated by lusutrombopag." became "Lusutrombopag is more expensive than no TPO-RA by £600 (i.e. 25% more expensive) and more effective by 0.0001 QALYs, resulting in an ICER of approximately £4,000,000. Avatrombopag 60 mg is slightly more expensive than lusutrombopag and slightly less effective and is therefore dominated. In the 40,000-50,000/µL subgroup, no TPO-RA is again the cheapest option. Lusutrombopag is the next cheapest and most effective, with an incremental cost of £626 and incremental QALYs of 0.0004. Avatrombopag 40 mg is £10 more expensive than lusutrombopag and -0.0005 QALYs less effective and is therefore dominated by

	lusutrombopag." And clarification is added to explanation of the cost-effectiveness plane with "it appears that approximately half of the iterations suggest the avatrombopag is less effective than no TPO-RA." Becoming "it appears that approximately half of the iterations suggest the avatrombopag is less effective than no TPO-RA (orange points)." And Figure 6.4 updated following model corrections
99	Figure 6.5 and Figure 6.6 updated following model corrections
100	Figure 6.7 updated following model corrections
101	Text updated following model corrections, so that "In this scenario analysis, the prices of avatrombopag were lowered, in increments of 10%, by 10-70% from the assumed price of £800. Results displayed in Table 6.13 below show that these drug price reductions slowly reduce the incremental costs and ICER comparing avatrombopag with no TPO-RA. At an 70% price reduction, avatrombopag 40mg dominates no TPO-RA in the 40,000-50,000/μL subgroup." became "In this scenario analysis, the prices of avatrombopag were lowered, in increments of 10%, by 10-80% from the assumed price of £800. Results displayed in Table 6.13 below show that these drug price reductions slowly reduce the incremental costs and ICER comparing avatrombopag with no TPO-RA. At an 80% price reduction, avatrombopag 40mg dominates no TPO-RA in the 40,000-50,000/μL subgroup and the ICER is within the NICE threshold for avatrombopag 60mg in the <40,000/μL subgroup."
102	Table 6.13 results updated following model corrections
103	Text updated following model corrections to reflect updated results, so that "However, none of the assumed number of ATDs result in a cost effective option, with an ICER of £447,779 for avatrombopag 40 mg versus no TPO-RA being the lowest ICER observed in these scenarios." Became "However, none of the assumed number of ATDs result in a cost effective option, with an ICER of £631,735 for avatrombopag 40 mg versus no TPO-RA being the lowest ICER observed in these scenarios."

	And Table 6.14 results updated following model corrections
104	AG base-case cost of platelet transfusion updated from [redacted] to [redacted] and text updated following model corrections to reflect updated results, so that "However, none reduced the ICER sufficiently for it to be considered cost effective, with the lowest ICER being £437,329 for avatrombopag 40 mg versus lusutrombopag." Became "However, none reduced the ICER sufficiently for it to be considered cost effective, with the lowest ICER being £620,415 for avatrombopag 40 mg versus lusutrombopag." And Table 6.15 results updated following model corrections
105	AG base-case cost of platelet transfusion updated from [redacted] to [redacted] and Table 6.16 results updated following model corrections
106	Table 6.17 results updated following model corrections
107	Table 6.18 results updated following model corrections
108	Table 6.19 results updated following model corrections
109	Table 6.20 results updated following model corrections
110	Incidences of platelet transfusion related deaths which result from different underreporting factors corrected, so that "(corresponding to incidences of platelet transfusion related deaths of 0.046% and 1.148%)" Became "(corresponding to incidences of platelet transfusion related deaths of 0.00046% and 0.023%)" And Table 6.21 results updated following model corrections
111	Table 6.22 results updated following model corrections
112	Text updated to reflect updated results, so that "The biggest impact was seen for lusutrombopag versus no TPO-RA in the 40-50,000 subgroup with the ICER dropping by approximately £6,000,000, however this could be expected as this is the largest ICER by a factor of 5, as compared to the next largest ICER." became "The biggest impact was seen for lusutrombopag versus no TPO-RA in the 40-50,000 subgroup with the ICER approximately halving, however this could be expected as this is the comparison with by far the smallest incremental QALYs, and therefore an increase (even a small one) makes a large impact on the very large

	ICER." And Table 6.23 results updated following model corrections
113	Table 6.24 results updated following model corrections
114	Table 6.25 results updated following model corrections
115	Table 6.26 results updated following model corrections
116	Text updated to reflect updated results, so that "A 0 disutility results in dominated ICERs for avatrombopag 60 mg versus no TPO-RA in the <40,000/µL subgroup and lusutrombopag versus no TPO-RA in the 40-50,000µL subgroup and ICERs over £12,000,000 for the remaining two comparisons versus no TPO-RA." Became "A 0 disutility results in dominated ICERs for avatrombopag 60 mg versus no TPO-RA in the <40,000/µL subgroup, dominated ICERs for both treatments versus no TPO-RA in the 40-50,000µL subgroup and an ICER over £30,000,000 for the remaining comparison versus no TPO-RA in the <40,000/µL subgroup." And Table 6.27 results updated following model corrections
122	"For the 40,000 – 50,000/µL subgroup, avatrombopag and lusutrombopag are 24% and 26% more expensive than no TPO-RA, respectively." Changed to "For the 40,000 – 50,000/µL subgroup, avatrombopag and lusutrombopag are 28% and 27% more expensive than no TPO-RA, respectively." And "If its price were to be 70% below the price of lusutrombopag, avatrombopag would become cost saving in the 40,000 – 50,000/µL subgroup." Changed to "If its price were to be 80% below the price of lusutrombopag, avatrombopag would become cost saving in the 40,000 – 50,000/µL subgroup." Following model corrections

ID1520 Avatrombopag And Lusutrombopag For Treating Severe Thrombocytopenia in People with Chronic Liver Disease Needing an Elective Procedure

Shionogi: Consultee Response to the Assessment Group Report

Executive Summary

Shionogi disagrees with the Assessment Group (AG) analyses suggesting that lusutrombopag is not effective and the conclusion that lusutrombopag is not a cost-effective treatment option to the NHS within its licensed indication i.e. "treatment of severe thrombocytopenia for adult patients with chronic liver disease (CLD) undergoing invasive procedures".

Shionogi present a revised base case which incorporates several AG preferences but disputes a number of key points with respect to health benefits, model structure, conditional probabilities, and cost inputs.

The revised base case results demonstrate that lusutrombopag remains cost-effective when compared to platelet transfusion, even at the lower NICE willingness-to-pay (WTP) threshold, although it was no longer found to be dominant as in the submitted Shionogi base case.

Two further aspects of the economic analysis previously described in the original submission are also presented: a consideration of the effect of reduced length of stay on procedure costs, and the benefit of the prolonged therapeutic window allowing multiple procedures following one course of lusutrombopag (as observed in the pivotal trials).

Length of stay scenario results show that one-day, half-day reductions and quarter-day in planned elective invasive procedure (PEIP) inpatient stay length resulted in lusutrombopag being estimated to be dominant compared to platelet transfusion.

Scenarios of multiple procedures being undertaken (as observed in the pivotal clinical trials) were presented in the Shionogi submission, but were unfortunately ignored by the AG. Revised scenarios are presented with some AG changes to the base model and demonstrate that lusutrombopag is still dominant in the tested scenarios.

Improved Health Outcomes

Shionogi demonstrated the benefit associated to lusutrombopag through 3 RCTs and a meta-analysis. Lusutrombopag (3mg once a day for 7 days) is statistically and significantly increasing platelet count compared to SoC (platelet transfusion), and this finding was also retrieved in the responder rates ([redacted], for a sustained median period of 17.3 days versus 1.8 days, respectively. Consequently, more patients avoided platelet transfusions in the lusutrombopag arms in a strong statistical and significant manner ([redacted]. Furthermore, with the meta-analysis lusutrombopag critically showed a statistical reduction in bleeding event ([redacted]. Of note, a post-marketing study in Japan jets a 94% avoidance of platelet transfusion, somewhat as felt by the AG. Moreover, a recent study (Ishikawa et al 2019) investigating the repeated use of lusutrombopag did show similar efficacy to the main RCTs with no new adverse event and no treatment refractoriness.

Individual Patient Data from clinical trials are used to inform the decision-tree model with conditional probabilities, enhancing predictions thereby. Related to this, the AG model ignores the conditional probability approach submitted by Shionogi on the basis that avatrombopag data were not available to match this approach. Shionogi request that the AG make use of the approach and data submitted when considering lusutrombopag.

Absolutely crucial to the analysis is the correct consideration of bleeding events and the consequences thereof. Despite clear evidence from the lusutrombopag meta-analysis showing a reduction in bleeding events, the AG modified the model structure arbitrarily to exclude the associated clinical benefit on mortality and instead assigned the same chance of surgical related mortality to lusutrombopag and platelet transfusion arms.

Shionogi therefore request that the AG should reinstate the mortality risk for bleeding into their model structure to correctly capture the benefit of lusutrombopag treatment.

Moreover, the AG calculation estimating the incidence associated to "pneumological" adverse events sourced from the SHOT report, established from the general population, is not corresponding to any observed incidence of these events following platelet transfusion for CLD patients. Reference publications in CLD patient are endorsing a wider scale of this adverse event; thereby Shionogi deem wise to use the very conservative incidence rate previously validated by clinical experts and presented in the base model.

Costs

Shionogi agrees with the AG perspective that there is notable uncertainty surrounding what constitutes the content and cost of platelet transfusions particularly in transnational context, and it appears that there is no exact content measure for one bag when dealing with biological products with short half-life.

Nonetheless, the AG and Shionogi have different perspective towards the number of units transfused in clinical practice in this patient population for this setting. Shionogi highlight a number of points related to platelet transfusion within NHS practice. While Shionogi understand the AG preferred cost per ATD, the number of ATDs i.e. one ATD per patient per procedure; this is not reflecting mainstream clinical practice for CLD patient undergoing an invasive procedure.

The full NICE NG24 guideline itself is considering that platelet dosing in liver disease patients being of higher doses as 2 adult units or more. This information is corroborated via a Multiregional Audit of Blood Component use in cirrhotic patient indicating a larger use of platelet unit than one unit as main clinical practice, invalidating thus the AG proposition for one unit per patient per procedure as main stream clinical practice to manage severe thrombocytopenia in CLD patient that are undergoing invasive procedures.

Shionogi demonstrate also clearly that contrary to AG assertion, sunk costs for delayed or cancelled procedures remain in the latest NHS Reference Costs and remain appropriate for inclusion in the economic model. This point is key to a fair costing analysis of the decision problem.

In summary, Shionogi request that the AG and Committee acknowledge that, in patients with severe TCP and CLD, post-procedural complications are anticipated outside the therapeutic window for a single ATD thus indicating further infusions; this is in addition to the fact that majority of these patients will require more than one ATD in each transfusion episode, as reflected in the AG base case cost of transfusion.

As a result, Shionogi request that the AG increase the platelet transfusion costs within the model to reflect that the procedural and post-procedural transfusions are frequently indicated in this population and that additional administration costs will be incurred by this, as well as additional platelet costs.

Additional critical considerations

In this discussion, important is to consider from a patient perspective the unacceptability to receive someone else blood, and theoretically been exposed to communicable disease, when a medication could be safer, more efficacious, and help them save out of pocket money with an oral treatment administrated at home.

An additional unquantifiable lusutrombopag potential benefit not captured in the QALY framework compared to platelet transfusion is the plausible short to long-term immune risk of alloimmunisation that can theoretically jeopardise the chance of a successful liver transplant outcomes should patients on the waiting list become platelet refractory via heavy peripheral induced thrombocytopenia conveyed through repeated use of platelet transfusions.

The Handbook of Transfusion Medicines first commandment is that "Transfusion should only be used when the benefits outweigh the risk and there are no appropriate alternatives".

The AG report is notably silent on the ethical implications of the continued use of blood products given the availability of licensed pharmaceutical alternatives. Shionogi request that the Committee explicitly consider this in their decision making; in addition, Shionogi note that some minorities are unable to receive platelet transfusions, and a decision to restrict use of TPO-RAs would adversely affect such groups.

On a process terms, the manufacturer of avatrombopag have not provided a proposed price and until they do so, and it is not for the AG or the Committee to suggest a list price for an intervention. Shionogi propose that avatrombopag is not considered by the Committee at the appraisal meeting.

Furthermore, the AG used a post hoc analysis of based on two subgroups (< 40,000/µL and 40,000 – 50,000/µL platelet count) as their base case. This data-cut was driven by avatrombopag dosing requirements and these subgroups do not reflect the lusutrombopag marketing authorisation, NICE Final scope, trial randomisation or clinical guidelines.

Shionogi therefore feel that this analysis is inappropriate. Were the Committee not to recommend lusutrombopag as a result of considering the methodological approach adopted by the AG, this would be unreasonable in the light of the evidence submitted to NICE. Shionogi therefore request that all analyses utilising lusutrombopag trial data remain based on the lusutrombopag license and trial design.

Conclusion

Shionogi trust that the Committee will consider their objections to key AG assumptions and will consider that the revised Shionogi base case continues to demonstrate that lusutrombopag is the cost-effective option within its licensed indication.

Lusutrombopag availability and use in the CLD patient population would help after platelet count check prior to the procedure to reduce clinical practice variation and help implement and get to the objective in CLD patient to only require 1 ATD (as per the guideline objective) if and only necessary.

Response to individual points

Whilst the gold standard has traditionally been platelet transfusion, there are several disadvantages with this approach. It involves transfusion of blood products, which can be associated with costly transfusion reactions, and become less effective over time due to allosensitization. In addition, platelet transfusions do not ensure a haemostatic platelet level, especially when the risk of bleeding is high meaning that exogenous platelets often do not last for the duration of the procedure, never mind for the entire risk period for bleeding, which could extend up to 1-week post-procedure. Thus, platelet transfusions lack clear efficacy and their potential for side effects leads to a need for alternative management options, such as lusutrombopag. Lusutrombopag can provide more predictable and reliable increases in platelet count which last for a significantly longer period of time than current standard of care.

A. Improved health outcomes

About Lusutrombopag:

The AG concluded that there are no significant improvements and benefit associated with the use of lusutrombopag compared to standard-of-care (i.e. platelet transfusion) for chronic liver disease (CLD) patient undergoing invasive procedures. Shionogi strongly dispute this assessment.

Shionogi submitted three RCTs in this setting and a meta-analysis, showing that lusutrombopag strongly increases platelet count prior to CLD patient with severe thrombocytopenia (<50x 10^9/L) undergo a surgery. The responder criteria were defined as an increase platelet count of ≥ 20 × 10^9/L with platelet count reaching the guideline threshold of ≥ 50 × 10^9/L.

Overall, the responder rates were approximately 68% vs. 11% with lusutrombopag and platelet transfusion, respectively. The Odds Ratio (OR) for responder ([redacted] shows the level of efficacy associated to lusutrombopag that is also sustained for a median period of 17.3 days versus 1.8 days with the platelet transfusion arm.

The RCTs demonstrated that CLD patients in the lusutrombopag arms managed to avoid platelet transfusion ([redacted]) thus enabling more procedure to be performed from a platelet count perspective. Furthermore, the meta-analysis showed a statistical reduction in bleeding event ([redacted]in favour to lusutrombopag.

About the standard of care, platelet transfusions:

It is reported that one platelet unit in the UK corresponds to one adult therapeutic dose (ATD) and that in typical 70 Kg adult patient, one ATD would give an immediate rise in platelet count of 20-40 x 10^9/L. For information, in the lusutrombopag L-PLUS 2 trials, mean patient weight was about 77 Kg.

This anticipated platelet count increase with one transfused ATD is not observed in CLD patient with severe thrombocytopenia undergoing invasive procedures. Literature reports that CLD patients have an acute disappearance of transfused platelets from the circulation (Aster RH), explaining current clinical practice with more than two platelet units use to reach a platelet threshold.

1. Exclusion of Conditional Probabilities Data is Unreasonable

The AG report states "The AG was unable to trace back the numbers used to calculate bleeding event efficacy to the lusutrombopag trials' CSRs. On clarification request, Shionogi provided data for the number of bleeding events in each trial and treatment group. However, these numbers did not suggest that lusutrombopag substantially reduced the odds of bleeding from the individual RCTs, as it was implemented in the original Shionogi submission model. In addition, these conditional probabilities were not available for avatrombopag. The small number of WHO grade 2 bleeding events and the rescue events seen in the trials led to concerns surrounding the confidence that can be placed in conditional probabilities based on such data." Grade 2 bleed are significant.

Shionogi would like to remind that the clarification questions were by subgroups and as per say, the requested group were smaller than the original dataset supporting the licensed indication. The subgroup analyses were likely not powered to detect the statistical reduction in bleeds.

It is also commonly admitted, that conditional probability data are methodologically more robust for decision tree models as they account for the sequential nature of events in a way that unconditional probability data do not. It is notable that the AG express concern regarding the small number of events informing this approach yet expressed no such concern when applying their arbitrary splitting of the lusutrombopag trial data to fit the avatrombopag dosing regimen.

Conditional probability data for lusutrombopag (and platelet transfusion) should not be excluded from consideration on the basis that equivalent data for avatrombopag were not made available to the AG. Separate analyses may be conducted between platelet transfusion and avatrombopag with unconditional probability data if absolutely necessary, however any cost-effectiveness comparisons between platelet transfusion and lusutrombopag should make use of the best available data. Were the Committee not to recommend lusutrombopag as a result of allowing the AG to discard the submitted conditional probability data, such a decision would be unreasonable in the light of the evidence submitted to NICE and the unquantifiable benefit that are outside the QALY framework.

2. The AG Model Does Not Appropriately Consider Bleeding and potential Bleeding-Related Mortality in the Model

a. Bleeding event

The AG decided to model bleeding events as a surgical complication rather than a separate event, considering that only bleeding requiring rescue therapy would have impact on the incremental cost-effectiveness ratio.

By doing so the AG has ignored the evidence from the trials plus meta-analysis where lusutrombopag resulted in a statistically significant reduction in any bleeding events ([redacted] submission p.41).

Nonetheless, lining to the AG perspective (pooled from the avatrombopag and lusutrombopag data), about 30% of grade 2 bleeding events are grade 3 and in needs of additional procedure, the base case analysis is altered in this sense (Table 2).

It should also be considered that patient with grade 3 bleeds not only receive a rescue therapy but have also a longer Length of Stay (LOS) at hospital (LOS) prior to discharge, and that element is not captured in the AG modelling approach.

It is noteworthy to add that bleeding events grade 2 (e.g. hematoma, purpura, haemoptysis or haematuria) are usually not requiring rescue therapy or additional procedures, however, these typically require a "watch and wait" period prior to hospital discharge. This would result to an increases LOS or further healthcare resources use; therefore, a scenario analysis is presented in Table 4.

b. Bleeding related to mortality

Moreover, the AG assumed that patients receiving lusutrombopag experience the same mortality risk as platelet transfusion patients during surgery. This AG assumption is arbitrary, and the AG have no evidence on which to ignore this potential benefit of lusutrombopag treatment.

It should also be noted that a suggestion that further large clinical trials be undertaken to provide further evidence on these serious-but-infrequent events would now be inherently unethical, given the demonstrated benefits of the treatment and the known complications of platelet transfusion.

In addition, it should be noted that surgery is not the only possible cause of a bleeding event, as patients may experience bleeding from oesophageal and gastric varices associated with their liver disease (Bieker et al); lusutrombopag is not licensed to address such bleeding but given its

mechanism of action, it is not inappropriate to exclude the possibility of a reduction in all-cause bleeds.

Shionogi request that the AG should therefore reinstate the mortality risk for bleeding. It is not unreasonable to consider that where there is a bleed and major bleed there is a mortality risk.

Shionogi also note that the AG appear to have used surgical-related mortality obtained from the trial mortality data, rather than a probability of mortality from bleeding obtained from Takaki *et al*. 2012, used by Shionogi; Shionogi note that their preferred literature source provides for much larger patient numbers upon which to base the risks of bleeding-related morality. Takaki *et al*. 2012 reported the risk of death from haemorrhages 0.83% (substantially lower than the alternative values identified in the literature of 6.00% and 20.00% values reported in Lo *et al*. 2010 and Triantos *et al*. 2014). The data from Takaki *et al*. 2012 were based a lower proportion of major bleeds than the AG suggested was appropriate with 16 major and 105 minor haemorrhages (13.2%), making it a conservative source for bleeding-related mortality. This was also validated by clinical and economic experts.

3. The "pneumological" adverse events set by the AG is not reflecting the incidence in CLD patients with platelet transfusion

The AG calculation for the incidence of "pneumological" adverse events (0.004%) sourced from the SHOT report (general population) is not corresponding to any observed incidence with the use of platelet transfusion in clinical practice for CLD patients. The AG analysis estimates the pneumological adverse events being the same to a typical patient with severe thrombocytopenia. Slichter et al (2006) estimated the incidence of those in CLD patient to 3%. As per the Shionogi submission, in a conservative manner, clinical experts validated an incidence of 1.10% sourced from the Van Eerd et al. study.

B. Costings

The AG states that there is uncertainty surrounding the content and costs of platelet transfusions. Shionogi certainly agrees with this statement; however, Shionogi disagrees with the AG's analysis of the costs associated with platelet transfusion, the number of platelet units required, and the latest cost of platelet unit from the last NHSBT pricing proposal.

4. Use of Platelet Transfusion in Current NHS Practice: Severe Thrombocytopenia in Chronic Liver Disease is Distinct, Multiple ATDs Per Procedure are Common

The AG Report quotes the United Kingdom Blood Services *Handbook of Transfusion Medicine* for a number of points relating to platelet transfusion in NHS practice.

Shionogi would first like to note that the *Handbook* itself contains a statement on pre-operative platelets which highlights why the specific population of patients relevant to this appraisal is distinct to the overall norm addressed by their recommendations:[3]

> "Patients who also have impaired blood coagulation (e.g. **liver disease**, oral anticoagulants) or are on antiplatelet drugs, such as aspirin or clopidogrel, are at **higher risk** of perioperative bleeding and **specialist advice** should be sought if major surgery cannot be delayed." (emphasis added)

The AG Report also quotes the NICE Guidance on Blood Transfusion (NG24). The summary guidelines state "do not routinely give more than a single dose of platelets in a transfusion", however the full guidelines for NG24 provide further evidence underpinning the summary recommendation; specifically, the following text in the full guidelines expands on the "routine" part of the summary recommendation:[4]

> "**The GDG** considered dosing of platelets in platelet function disorders, **such as thrombocytopenia**, and **agreed that higher doses e.g. a dose of 2 adult units** may be **considered** in the presence of **bleeding** or as prophylaxis in advance of major surgery'" (NG24 – Full Guideline – Page 234, 18 May 2015; emphasis added)

In relation to the usual platelet count thresholds used to determine the necessity of platelet transfusion, the distinct population addressed in this appraisal would also require special consideration, as NG24 also states:

> "Consider a higher threshold (for example 50–75x10^9 per litre) for patients with a **high risk of bleeding** who are having **invasive procedures** or surgery, after taking into account:
>
> - the specific procedure the patient is having
> - the cause of the thrombocytopenia
> - whether the patient's platelet count is falling
> - any coexisting causes of abnormal haemostasis"

For the rescue bleeding recommendation in NG24, the full guidelines state:[4]

> "The GDG considered specific requirements for patients who had **severe thrombocytopenia** and **bleeding in a critical site** and agreed that higher doses of platelet transfusions may be needed to provide timely and effective haemostasis.
>
> Based on the above rationale and economic considerations, the GDG recommended that higher doses of platelet transfusions, whilst not the standard treatment, may be considered in patients with **severe thrombocytopenia and bleeding from a critical site**." (NG24 – Full Guideline – Page 235, 18 May 2015; emphasis added)

Shionogi request that the AG and Committee recognise that people with severe thrombocytopenia and chronic liver disease represent a distinct population with higher bleeding risks. Use of more than one ATD indeed may not be routine across the broad spectrum of conditions for which platelet transfusions are indicated, as reflected in the *Handbook* and in NG24, but people with severe thrombocytopenia and CLD are a population with distinct risks and needs.

As noted in the company submission, Shionogi had been advised by UK clinical experts that patients with severe TCP and CLD would typically receive multiple bags of platelets; Shionogi were therefore surprised by the AG base case assumption, based on the general recommendations from the *Handbook* and NG24, that only one ATD would be used in typical practice.

Shionogi retrieved an Audit from the British Society of Gastroenterology, confirming that the median platelet unit used prior to an invasive procedure is not one unit. Moreover, in rescue therapy, patient could more than often receive 2 to 5 ATD units.

In addition, in order to reconcile the conflicting advice given to the AG and to Shionogi, Shionogi re-consulted a number of clinical experts to explore this issue further. These experts took issue with the AG base case and reiterated their advice that multiple bags are often used in practice; however, in explaining further it became apparent that the initial Shionogi model might have miss a key detail when costing. Specifically, clinical experts stated that, at a very minimum, patients would receive one ATD before the procedure and a second ATD during the procedure or later (e.g. 6 hours post-procedure), with many patients receiving more than this.

This information allows the reconciliation of the AG approach (many patients, though not a majority, receive one ATD per transfusion) with Shionogi's submission base case that on average three ATDs are used as a result of a procedure.

Indeed, this information reveals that Shionogi's initial costing approach of one transfusion administration cost to cover three ATDs was in fact conservative as separate infusions of each of the three ATDs at various timepoints would incur repeated administration costs.

A further relevant consideration is that "many hospitals do not store platelets on site and the time for transfer from the blood centre must be factored into local protocols." This time for transfer can be in the order of several hours and in patients with severe TCP and CLD, platelet counts may not ever rise above the suggested threshold for triggering the order of further platelets.

In summary Shionogi request that the AG and Committee acknowledge that, in patients with severe TCP and CLD, post-procedural complications are anticipated outside the therapeutic window for a single ATD thus indicating further infusions; this is in addition to the fact that some patients will require more than one ATD in each transfusion episode, as reflected in the AG base case cost of transfusion. As a result, Shionogi request that the AG increase the platelet transfusion costs within

the model to reflect the procedural and post-procedural transfusions are frequently indicated in this population and that additional administration costs will be incurred by this, as well as additional platelet costs.

5. Cost per bag

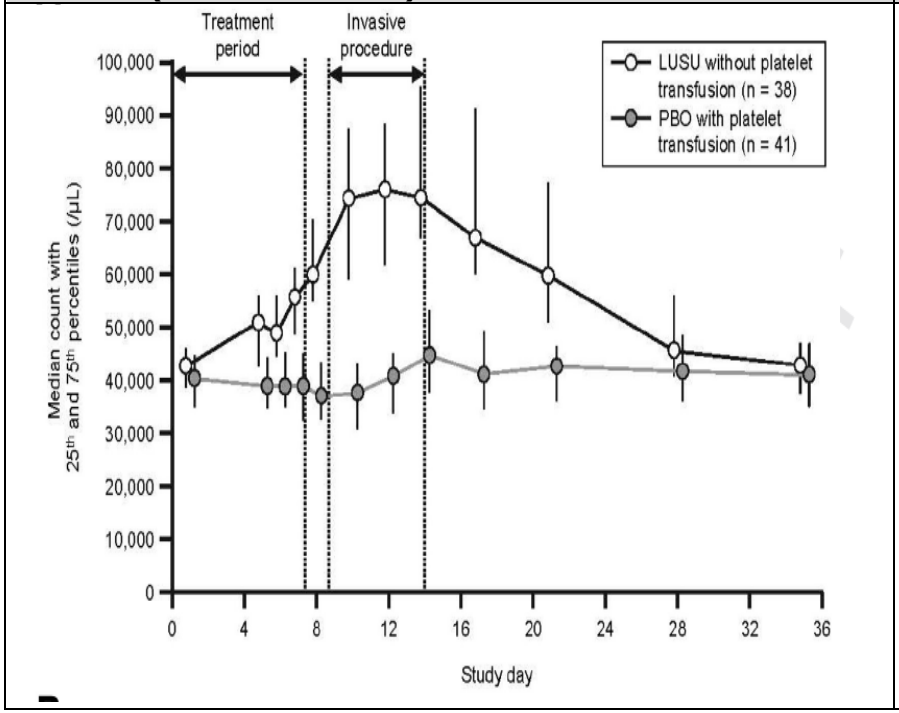
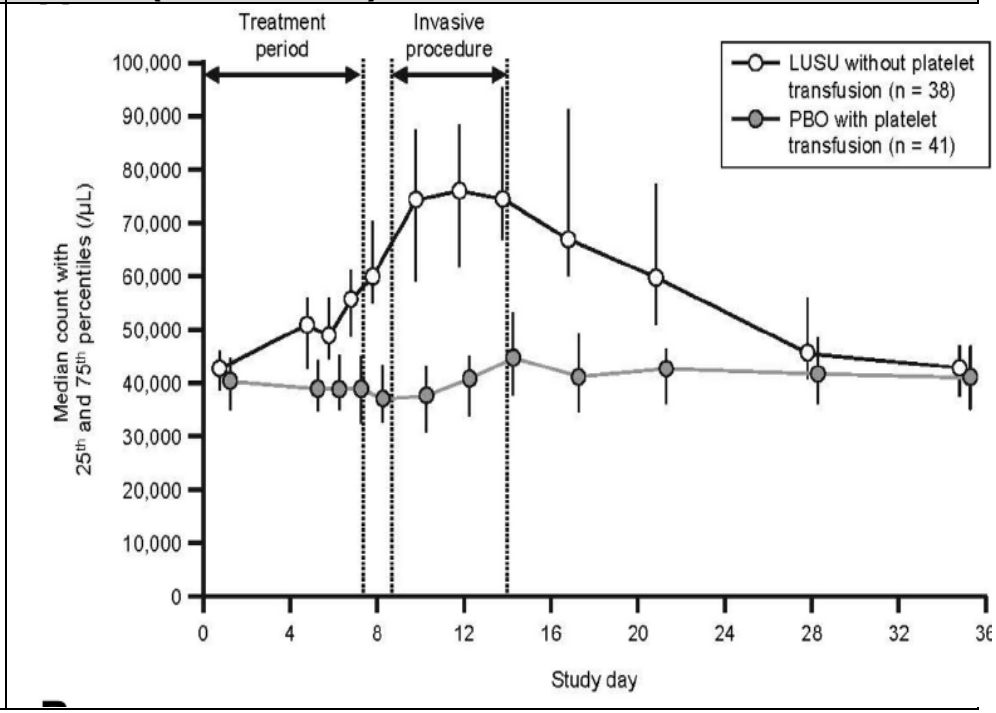
Shionogi agrees with the AG perspective that there is considerable uncertainty surrounding what constitutes the content and cost of platelet transfusions in international context. A typical platelet unit life is about 5 days and the amount of platelet in bag is decreasing from day 3, which should lead to a CCI (Count correction indices).

We understand from the literature and clinical experts that platelets vanish faster in CLD patient compare to typical patient (Aster RH). The physiopathology has not been entirely elucidated and there is several clinical and biological theory to this effect.

The point is that usual platelet transfusion (ATD or unit or bag) in CLD patient do not raise satisfactorily platelet count as anticipated by guideline in the UK with non CLD patient.
For instance, it has been suggested that one ATD is immediately rising platelet count by $20x10^9$/L to $40x10^9$/L (Southend Hospital Guidelines). From the clinical trials and with the AG calculation of [redacted] ATD, the observed effect in terms of platelet count is negligible and perhaps illustrate the result of adhering to clinical guideline in a clinical trial context. The change in platelet count presented in the figure 1 below (from L-PLUS1 and L-PLUS2) are illustrating the modest efficacy of the administered platelet transfusion with an average platelet rise of [redacted] $x10^9$/L.

As described in Shionogi's base case analysis, UK NHS routine practice is to administer on average 3 ATD units should clinicians increase platelet count by the anticipated level of one ATD per patient. Implying that the calculated cost of £244.15 for one unit (AG cost) should be considered by 3 units.

Figure 1: Platelet count change during the L-PLUS 1 & 2 follow-up period (35 days)

L-PLUS 1 (Hidaka et al. 2018)	L-PLUS 2 (Peck et al 2018)
	

6. Sunk Costs Remain Appropriate and Have Not Been Removed from NHS Reference Costs

With respect to the sunk cost proposed by Shionogi, the AG Report states "This cost was subsequently removed from the NHS reference costs, suggesting it was no longer considered appropriate practice to cost this." (page 70).

Shionogi had initially sourced this cost from the recent paper Cookson 2017, however, in development of the submission Shionogi noted this was a secondary source and therefore referenced back to the original NHS Reference Cost used by Cookson (2009/2010 WA14Z: 'planned procedure not carried out').

Following the AG challenge to the inclusion of sunk costs, Shionogi have now revisited this issue in more details. This has revealed that the original HRG Code was removed because it was replaced by two separate HRG Codes (WA14A & WA14B), which differed by the cause of the delay: whether for medical or patient reasons, or whether for other or unspecified reasons. Subsequent redesign of the HRG subchapters to split the old WA subchapter into new subchapters WH and WJ resulted in these codes being relabelled WH50A & WH50B. Therefore, the AG suggestion that this cost is no longer appropriate is not accurate, and the current NHS Reference Costs are presented below in Table 1 for both total HRG and for Elective Inpatients – cancellation due to insufficient platelet levels is covered by HRG WH50A, as this is a medical cancellation (NHS reference costs).

Table 1. Sunk costs in the current NHS Reference Costs

		Total			Elective Inpatient		
Currency	Currency Description	Activity	Unit Cost	Total Cost	Activity	Unit Cost	Total Cost
WH50A	Procedure Not Carried Out, for Medical or Patient Reasons	120,806	£406	£49,082,452	18,722	£617	£11,549,801
WH50B	Procedure Not Carried Out, for Other or Unspecified Reasons	153,724	£431	£66,183,177	37,578	£599	£22,510,773

Source: National Schedule of Reference Costs Year: 2017–18 - All NHS trusts and NHS foundation trusts - HRG Data

It should be noted that the sunk costs in the current year reference costs are ~20–30% of the average procedure costs used by the AG model of £1,976.98. Therefore, the inclusion of a sunk cost does not make the assumption that the entire surgery slot is wasted, but rather demonstrates that there is a quantifiable cost to the NHS associated with the cancellation of the procedure in spite of the surgeon and theatre team being able to find other activities to undertake.

The AG states: "If there were a cost to the NHS of procedure cancellation or rescheduling, a more substantial disutility associated with delays and the TPO-RA agents are indeed effective in reducing the probability of delay, this would favour the cost-effectiveness of the TPO-RA agents" (page 124). The presence of these costs in the current year NHS Reference Costs suggests that they are highly relevant to current NHS practice and costing. Shionogi reaffirm that any economic model addressing the Decision Problem for this appraisal must include the sunk cost of procedures not carried out and at least the differences in proportion of cancellation observed in the L-PLUS RCTs which are anticipated to be extremely conservative.

7. Shionogi Revised Base Case Economic Model Results

Given the responses made above, Shionogi have prepared a revised model base case where the following AG changes have been implemented:

- Removal of the chance node for death due to surgery delay
- The cost per platelet transfusion **£244.15** (AG cost) plus administration from Stoke et al.
- The pooled baseline characteristics provided by the AG in Table 6.2
- Overall mortality due to platelet transfusion set to 0.000458%
- The assumption that 100% of patients in the platelet transfusion arm received platelet transfusions was removed and replaced with the pooled data from the lusutrombopag clinical trials (78.43%), in line with the AG preferred approach (although the AG data were pooled across comparator trials and split by avatrombopag-derived subgroups)
- The proportion of bleeds assumed to be major was set to 30%

- The incidence of surgical procedures used by the AG was implemented
- Adverse event incidence and cost inputs from the SHOT database used by the AG were implemented except for "pneumological adverse event"

The revised economic model should still consider the points as described above:

- Conditional probabilities for lusutrombopag and platelet transfusion as used in the original Shionogi model
- Distinct mortality risk associated to bleeding from Takaki et al.
- "Pneumological adverse event" reset to the conservative estimate of 1.10%
- The base case number of ATDs and number of administrations was set to 3 (as previously reasoned above)
- Sunk cost from cancelled/delayed elective invasive procedures updated to **£406.29** (WH50A – Procedure Not Carried Out, for Medical or Patient Reasons. Source: National Schedule of Reference Costs Year: 2017–18 - All NHS trusts and NHS foundation trusts - HRG Data)[2]

The revised Shionogi base case analysis for this appraisal is presented in Table 2. The base case results demonstrate that lusutrombopag remains cost-effective when compared to platelet transfusion, even at the lower NICE willingness-to-pay (WTP) threshold, although it was no longer found to be dominant as in the submitted Shionogi base case.

Table 2. Revised Shionogi Base Case analysis results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Life years	ICER (£/QALY)
Platelet transfusion	£3,031.98	3.9500			7.5308	
Lusutrombopag	£3,070.37	3.9540	£38.38	0.0040	7.5375	£9,599.36

Additional cost-effectiveness perspectives

The cost-effectiveness scenario described below with reduced length of stay analysis and the option to multiple procedures were described in the original Shionogi submission.

8. Reduced Length of Hospital Stays Scenario Analysis

A reduction of length of hospital stays was described in the original Shionogi lusutrombopag submission as part of the innovation section.

As lusutrombopag has shown the possible potential to reduce the number of bleeding events (as per AG pooled data and the Shionogi meta-analysis) after invasive procedures to varying degrees, its use may allow clinicians to discharge patients earlier from hospital than patients who receive platelet transfusions.

In addition, clinicians indicate that even grade 2 bleeds are associated to a period of observation ("watch and wait") prior to discharge. This increases length of stay and often require further healthcare resources use. As hospital stays incur costs, a reduction in the length of hospital stays from lusutrombopag use would create cost savings for the NHS.

In this situation, average length of stays and the excess bed day cost for each of the planned elective inpatient procedures (PEIPs) included in the model were identified from the NHS reference costs (Table 3). It was assumed that an excess bed day cost represented the marginal cost of a one day bed stay, and therefore the cost savings from reducing the length of inpatient stays could be calculated by deducting the cost of an excess bed day from the cost of a procedure. For procedures where an excess bed day cost was not available in the NHS Reference Costs (those which had the shortest lengths of stay), it was assumed that length of stay (and thus cost) for these procedures were unchanged.

Table 3. Cost of excess bed days obtained from the NHS reference costs 2017–18

Type of PEIP	Currency code	Elective inpatient cost	Average length of stay	Elective inpatient excess bed day costs	Procedure cost assuming a reduction of inpatient stay by		
					One day	Half a day	Quarter of a day
Percutaneous radiofrequency ablation (RFA)	YG01B	£2,309	1.42	£301	£2,008	£2,159	£2,234
Endoscopic variceal ligation	FF04D	£4,202	2	£438	£3,764	£3,983	£4,093
Endoscopic injection sclerotherapy	FE11D	£2,411	1.89	£523	£1,888	£2,150	£2,280
Transcatheter arterial chemoembolisation	GA13B	£2,922	1.68	£279	£2,643	£2,783	£2,852
Liver biopsy	YG10Z	£1,547	1.28	N/A (assumed £0)	£1,547	£1,547	£1,547
Dental extraction	CD07A	£680	1	N/A (assumed £0)	£680	£680	£680
Vascular catheterisation	YR42A	£1,126	1.19	N/A (assumed £0)	£1,126	£1,126	£1,126
Argon plasma coagulation	FF04D	£4,202	2	£438	£3,764	£3,983	£4,093
Percutaneous ethanol injection therapy	GA13B	£2,922	1.68	£279	£2,643	£2,783	£2,852
Endoscopy w/wo polypectomy/biopsy	FE20Z	£1,213	1.04	N/A (assumed £0)	£1,213	£1,213	£1,213
Percutaneous RFA/microwave coagulation therapy	YG01B	£2,309	1.42	£301	£2,008	£2,159	£2,234
Paracentesis	YG06Z	£1,090	1.21	N/A (assumed £0)	£1,090	£1,090	£1,090
Other liver procedures	GA13B	£2,922	1.68	£279	£2,643	£2,783	£2,852
Other gastrointestinal procedures	FF04D	£4,202	2	£438	£3,764	£3,983	£4,093
Others	YG01B	£2,309	1.42	£301	£2,008	£2,159	£2,234

Results for three scenarios were estimated, where all patients who received lusutrombopag were assumed to have a reduction in the length of inpatient stay for their PEIP by one day, half a day, and a quarter of day. The cost-effectiveness results for each of these scenarios are presented in Table 4, Table 5 and Table 6, respectively. As the cost-effectiveness results show, one-day, half-day and quarter-day reductions in PEIP inpatient stay length resulted in lusutrombopag being estimated to be dominant compared to platelet transfusion.

Table 4. One-day reduction in bed days scenario analysis results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Life years	ICER (£/QALY)
Platelet transfusion	£3,031.98	3.9500				-
Lusutrombopag	£2,913.74	3.9540	-£118.24	0.0040	0.0067	Dominant

Table 5. Half-day reduction in bed days scenario analysis results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Life years	ICER (£/QALY)
Platelet transfusion	£3,031.98	3.9500				-
Lusutrombopag	£2,992.22	3.9540	-£39.76	0.0040	0.0067	Dominant

Table 6. Quarter-day reduction in bed days scenario analysis results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Life years	ICER (£/QALY)
Platelet transfusion	£3,031.98	3.9500				-
Lusutrombopag	£3,031.26	3.9540	-£0.73	0.0040	0.0067	Dominant

9. Multiple Procedures: Revised Scenario Analyses

It should be noted that the licensed indication for lusutrombopag is: "Treatment of severe thrombocytopenia in adult patients with chronic liver disease undergoing invasive **procedures**".

Note: this is a different indication to avatrombopag licensed for one invasive procedure.

With one course of lusutrombopag, the typical 2-3 weeks platelet elevation could facilitate multiple interventions in the same patient. As an example, 10-12 dental extractions are not infrequent in CLD patient and could be performed in two sessions saving important number of scarce platelet units. In this situation or similar situation with EVL (Endoscopic Variceal Ligation), the saving to the NHS could amount [redacted], 6 platelet units saved in two sessions apart performed within the elevated platelet count window.

As reported in the Shionogi's submission, of the [redacted] patients treated with lusutrombopag from all studies in severe thrombocytopenic patients with chronic liver disease, [redacted] had a second or subsequent invasive procedure (up to [redacted]) on a different day during the study period with only one lusutrombopag treatment course.

The economic case presented in the Shionogi submission did include a scenario analysis that considers multiple procedures undertaken following a single course of treatment with lusutrombopag.

Scenario analysis results where multiple procedures undertaken following a single course of treatment with lusutrombopag were rerun using the revised base case version of the model presented above and are presented below in Table 7. In all of the tested scenario analyses, lusutrombopag was dominant compared to platelet transfusion.

Table 7. Multiple procedures scenario analyses results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Life years	ICER (£/QALY)
	Two procedures (costs adjusted only)					
Platelet transfusion	£5,943.16	3.9500	-	-	7.5308	-
Lusutrombopag	£5,047.34	3.9540	-£895.82	0.0040	7.5375	Dominant
	Three procedures (costs adjusted only)					
Platelet transfusion	£8,854.34	3.9500	-	-	7.5308	-
Lusutrombopag	£7,024.32	3.9540	-£1,830.02	0.0040	7.5375	Dominant
	Four procedures (costs adjusted only)					
Platelet transfusion	£11,765.52	3.9500	-	-	7.5308	-
Lusutrombopag	£9,001.30	3.9540	-£2,764.22	0.0040	7.5375	Dominant

This scenario was not addressed by the AG in their report. Shionogi request that it be made clear to the Committee that in this scenario, lusutrombopag remains the dominant technology as shown above. Failure to consider the impact of this scenario in Committee decision making would be unreasonable in the light of the evidence submitted to NICE.

C. Issues not captured in the cost per QALY framework

Number of benefits associated to TPO-RAs (lusutrombopag) are unquantifiable making the cost per QALY framework relatively insensitive to degree of unmet medical need, equity consideration, patient dignity, religious, cultural or societal ground, patient preference and experience, patient medical loss of chance, blood supply issue, service provision, NHS opportunity to recast treatment and patient pathway. The innovative nature of lusutrombopag is also indicated by an MHRA positive Promising Innovative Medicine (PIM) designation.

10. Continued Use of Platelet Transfusion Should be Considered Unethical, Given Availability of Licensed Medical Alternatives

The United Kingdom Blood Services *Handbook of Transfusion Medicine* is quoted by the AG Report for a number of points of detail; however, the first chapter of the *Handbook* is entitled "Transfusion ten commandments" and deals with the general principals of transfusion medicine. Shionogi request that the attention of the Committee is drawn to the "first commandment" given in the *Handbook*:

> "Transfusion should only be used when the benefits outweigh the risks and there are no appropriate alternatives."

Shionogi note that this statement was not directly addressed in the AG Report. When appropriate, licensed, alternatives to platelet transfusion are available for patients with severe thrombocytopenia and chronic liver disease who require procedures, the question of whether no thrombopoietin receptor agonist (TPO-RA) remains a viable option for NHS practice, must be addressed by the Committee. If a strategy based solely on platelet transfusion is now considered unethical in these

patients, the decision of the Committee must be explicitly framed in this context. Shionogi would note that AG report Conclusions section states:

> "If the aim of service provision is to reduce platelet transfusion prior to elective procedures in those with CLD then both lusutrombopag 3 mg and avatrombopag … would seem to be able to do that safely" (AG Report page 127)
>
> "Similarly, from the cost effectiveness point of view … the aim of service provision may become important to the decision. If the aim is to reduce reliance on platelet transfusion, evidence suggests that TPO-RAs are successful in safely achieving this." (AG Report page 125)

11. Patient preference to avoid transfusions

Firstly, patients will experience non-health-related improvements in QoL, associated with avoidance of a procedure which is invasive and 'distasteful' (the idea of having someone else's blood pumped into their bodies) plus a certain sense of dignity loss. Patient are also anxious of communicable disease such as Creutzfeldt Jacob prion disease and unknow plus untested pathogen (e.g. Norovirus) as of today which may uncover epidemiological breakthrough few years down the line.

Second, there may be out-of-pocket cost savings (e.g. personal travel, childcare costs, etc.) for patients, associated with a reduction in time spent at hospital for transfusion administration.

Both arguments contribute to a patient preference to avoid transfusions, which needs to be considered by NICE, above and beyond cost-effectiveness as measured by cost per QALYs.

12. Equity and equality considerations

Shionogi note that some groups of patients are unable to utilise blood products on religious ground, for example Jehovah's Witnesses, and request that the Committee address this question in their considerations.

The health technology in consideration may be able to reduce unwanted local variation in clinical excellence, allowing an efficient use of the scarce platelet units.

13. No Price for Avatrombopag Precludes a Meaningful Multiple Technology Appraisal

Having been placed into the MTA process, Shionogi would like to express their concern at the approach taken by the AG in conducting pricing analyses on avatrombopag in the AG Report.

The manufacturer of avatrombopag have not provided a proposed price and until they do so, and it is not for the AG or the Committee to suggest a list price for an intervention. Shionogi propose that avatrombopag is not considered by the Committee at the appraisal meeting

Shionogi would again note that had this appraisal been scheduled under the Single Technology Appraisal process, it is likely that lusutrombopag would have qualified for the Fast Track Appraisal process.

14. Subgroup analysis applied to lusutrombopag data

The AG used a post hoc analysis of based on two subgroups (< 40,000/μL and 40,000 – 50,000/μL platelet count) as their base case. This data-cut was driven by avatrombopag dosing requirements and these subgroups do not reflect the lusutrombopag marketing authorisation, NICE Final scope, trial randomisation or clinical guidelines. Shionogi therefore feel that this subgroup analysis result in practice with smaller data cut that are less conservative and associated with greater uncertainty.

It is of particular note, that the Final NICE Scope states that guidance will only be issued in accordance with the market authorisation. While Shionogi cooperated with the AG at the Clarification Question stage and provided post hoc data, lusutrombopag dosing is not dependent on baseline platelet count and the L-PLUS studies were neither designed nor powered for these subgroups.

As a result, Shionogi request that the AG re-do all analyses considering both the no TPO-RA and lusutrombopag arms from the lusutrombopag trials in line with the trial design and resultant marketing authorisation. To use complicated dosing strategies of a comparator product as the basis for removing the randomisation and powering of the lusutrombopag RCTs seems unreasonable and is not in line with the NICE Final Scope.

Were the Committee not to recommend lusutrombopag as a result of considering the methodological approach adopted by the AG, this would be unreasonable in the light of the evidence submitted to NICE.

15. Supply of platelet units

Platelet are scarce resource and should be preserved to patient for whom there is no therapeutic alternative. The storage, the supply and the half-life of platelet are a challenge to the NHS. Platelet needs storage at 22 degrees, with continuous movement, and supply are often complex as described by JPAC (Joint UK Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee), where usual availability is often restricted to certain hours (11am to 4pm) putting physicians to timely access challenges.

A further relevant consideration is that "many hospitals do not store platelets on site and the time for transfer from the blood centre must be factored into local protocols." This time for transfer can be in the order of several hours.

16. Potential medical/prognosis loss of chance

An additional unquantifiable lusutrombopag potential benefit not captured in the QALY framework compared to platelet transfusion is the plausible short to long-term immune risk of alloimmunisation (Stoy et al 2018) that can theoretically jeopardise the chance of a successful liver transplant outcomes should patients on the waiting list become platelet refractory via heavy peripheral induced thrombocytopenia conveyed through repeated use of platelet transfusions.

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Avatrombopag and lusutrombopag for treating thrombocytopenia in people with chronic liver disease needing an elective procedure

Addendum 1

Produced by	Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University
Authors	Nigel Armstrong, Health Economist, KSR Ltd Nasuh Büyükkaramikli, Health Economics Researcher, EUR Hannah Penton, Health Economics Researcher, EUR Rob Riemsma, Reviews Manager, KSR Ltd Pim Wetzelaer, Health Economics Researcher, EUR Vanesa Huertas Carrera, Systematic Reviewer, KSR Ltd Stephanie Swift, Systematic Reviewer, KSR Ltd Thea Drachen, Systematic Reviewer, KSR Ltd Heike Raatz, Systematic Reviewer, KSR Ltd Steve Ryder, Health Economist, KSR Ltd Dhwani Shah, Health Economist, KSR Ltd Titas Buksnys, Health Economist, KSR Ltd Gill Worthy, Statistician, KSR Ltd Steven Duffy, Information Specialist, KSR Ltd Maiwenn Al, Health Economics Researcher, EUR Jos Kleijnen, Director, KSR Ltd, Professor of Systematic Reviews in Health Care, Maastricht University

Correspondence to	Nigel Armstrong, Kleijnen Systematic Reviews Unit 6, Escrick Business Park Riccall Road, Escrick York, UK YO19 6FD
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Declared competing interests of the authors

None.

1. Pairwise comparison of lusutrombopag versus established clinical management without thrombopoietin receptor agonists

In this addendum, the assessment group (AG) analyses the cost-effectiveness of lusutrombopag versus established clinical management without thrombopoietin receptor agonists (no TPO-RA), for treating thrombocytopenia in people with CLD requiring surgery.

Unlike avatrombopag, the licensed dose for lusutrombopag is not divided into subgroups dependent on the baseline platelet count. As there is no price communicated for avatrombopag, this addendum includes the results of the additional, cost-effectiveness analyses, comparing lusutrombopag versus no TPO-RA for the whole group of patients, based on the direct evidence from the trials identified comparing lusutrombopag versus no TPO-RA.

These analyses are conducted by the AG to facilitate the decision making of the committee, and these analyses were not provided in the original report [1], since they did not fall under the scope of the original decision problem, which was a multiple technology appraisal.[2]

After these analyses, a narrative summary on additional modelling considerations on the long-term impact for the lusutrombopag treatment is provided.

1.1 Updates in the economic model

The AG model from the original report is updated for the pairwise comparison of lusutrombopag versus no TPO-RA.[1] First, these updates to the original model are reported.

1.1.1 Patient population

The patient population considered is CLD patients with severe thrombocytopenia (platelet count <50,000/μL), who are scheduled to undergo a planned invasive procedure. The patient population is not divided into subgroups passed on platelet count.

1.1.2 Interventions

Lusutrombopag is administered orally, once daily at a dose of 3 mg for up to seven days, starting the first administration a minimum of nine days prior to the scheduled procedure.

Standard of care entails that patients are given a platelet transfusion if platelet counts fail to reach ≥ 50,000/μL on the day of the scheduled procedure.

1.1.3 Model structure

The AG model structure is not changed.

1.1.4 AG Input parameters

Baseline characteristics

The baseline characteristics of the AG model is not changed, the pooled baseline characteristics were calculated by the AG from the three included lusutrombopag trials (L-PLUS 1, L-PLUS 2, and the Phase 2b trial) and two avatrombopag trials (ADAPT-1 and ADAPT-2).

Based on the characteristics of patients in all trials pooled, patients were of mean age 85.6 years (SD: 10.8 years), 62.7% of the patients were male, and patients were categorised as Child-Pugh A, B, or C in proportions of 57.5%, 38.9%, and 3.6%, respectively.

Efficacy

The efficacy inputs of the model are updated using the data from the lusutrombopag trials (L-PLUS 1, L-PLUS 2, and the Phase 2b trial)[3,4,5] on the number of patients in each treatment arm who:

- Did not require platelet transfusion prior to invasive procedure
- Did not require rescue therapy given there was no platelet transfusion prior to invasive procedure

From these data, for each outcome, a direct treatment comparison was performed using Bayesian meta-analysis methods to obtain estimates for the proportions/probabilities of each of the above outcomes.

First, the proportions for the no TPO-RA group (all trials pooled) were obtained in a separate Bayesian meta-analysis. These values were used to inform the baseline probabilities for the natural history, i.e. for no TPO-RA. They were then combined in a Bayesian evidence synthesis model with odds ratios estimated using a logit function in order to calculate the corresponding probabilities for lusutrombopag. Due to the clinical heterogeneity in the trials (international vs Japanese or different type of the procedures), random effects models were used.

The first chance node in the model requires the probability or proportion of patients who require platelet transfusion prior to planned elective invasive procedure (PEIP). In the base-case, the proportion of patients in each treatment arm (for each subgroup) not requiring platelet transfusion prior to PEIP was estimated from the posterior distribution parameter estimates of the Bayesian meta-analysis, derived from the baseline placebo proportions and the ORs obtained from the random effects model, using the number of patients that received platelet transfusion before PEIP as provided in Tables 5.13 and 5.15 of the original AG report.[1] These proportions were then subtracted from 1 to find the proportion of patients in each treatment arm who *do not* require platelet transfusion prior to PEIP.

The model inputs for the second chance node, the proportion of PEIPs not performed within the trial period, were not changed. As provided in Table 11-3 of the L-PLUS 2 CSR, [redacted] and [redacted] of lusutrombopag and no TPO-RA patients respectively did not receive their planned procedure within the trial period.[5] The implications for not receiving the planned procedure were not changed.

The third chance node in the model requires the probability of a patient not requiring a rescue therapy. This is also obtained by the meta-analysis of the data from the lusutrombopag trials, on the proportion of patients, who did not require rescue therapy among the patients who did not receive platelet transfusion prior to PEIP. The overview of the clinical inputs used in the lusutrombopag vs no TPO-RA comparison is provided in Table 1 below.

Table 1: Overview of input parameters for clinical efficacy

	Mean (95% CI)	**Mean (95% CI)**	**Source**
Treatment	No TPO-RA	Lusutrombopag	

Proportion requiring platelet transfusion prior to surgery (RE)**	0.681 (0.3164, 0.9082)	0.149 (0.007, 0.767)	Meta-analysis
Proportion procedure not performed (unchanged)	[redacted]	[redacted]	L-PLUS 2
Proportion requiring rescue procedure (RE) **	0.158 (0.004, 0.6825)	0.0756 (0.0006, 0.4943)	Meta-analysis
** Note that these values presented in the table were obtained from the WINBUGS output summary from 100,000 iterations (after a burn-in of 30,000 iterations). In the excel model we use 2,000 iterations from the WINBUGS to provide values for the PSA of the model. Source: Direct treatment comparisons performed by the AG (where applicable, data as provided otherwise) using data provided by the company in the original CS, as well as in response to clarification questions.[6,7] Abbreviations: CI = credible interval; RE = Random Effects.			

Mortality

The mortality inputs of the economic model remained the same.

Safety

In terms of the safety related model inputs, only the incidence of PVT and Grade 2 and above bleeding events in each treatment arm were updated. These values are estimated from the posterior distribution parameter estimates of the WinBUGS code, derived from the baseline placebo proportions and the ORs obtained from the random effects model. The overview of the safety inputs used in the lusutrombopag vs no TPO-RA comparison is provided in Table 2 below.

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Table 2: Overview of input parameters for the incidence of AEs

AE	**AE incidence**		**Source**
Treatment	Placebo	Lusutrombopag	
Treatment-emergent AEs			
Portal vein thrombosis Mean (95% CI)*	0.017 (0.0000, 0.162)	0.02044 (0.0000, 0.2035)	Meta-analysis
Surgery-related AEs			
Bleeding Events (Grade 2 and 3) Mean (95% CI)*	0.0352 (0.009, 0.09)	0.0288 (0.003, 0.11)	Meta-analysis
Proportion of grade 3 bleeding events (unchanged)	30% (6/20)		Pooled from all trials
Platelet transfusion-related AEs (unchanged)			
Pneumological	0.0039500%		SHOT reports

FAHR (major)	0.0073831%	2012-2017
Bacteria	0.0000063%	
HAV	0.0000063%	
HBV	0.0000063%	
HEV	0.0000634%	
Parvovirus	0.0000063%	

* Note that these values presented in the table were obtained from the WINBUGS output summary from 100,000 iterations (after a burn-in of 30,000 iterations). In the excel model we use 2,000 iterations from the WINBUGS to provide values for the PSA of the model.
Source: Direct treatment comparisons performed by the AG using data provided by the company in the original CS, as well as in response to clarification questions, and otherwise as indicated.[6,7]
Abbreviations: AE= adverse event; CI = credibility interval; FAHR = febrile, allergic and hypotensive reactions; HAV = hepatitis A virus; HBV = hepatitis B virus; HEV = hepatitis E virus.

Utilities

The utility inputs of the economic model remained the same.

Costs

Costs were attributed to any platelet transfusions, procedures and rescue therapies given, drug acquisition and administration and AE monitoring.

- Drug acquisition costs

These inputs in the economic model remained the same.

- Platelet transfusion costs

The estimated costs of a platelet transfusion consist of 1) the costs of the platelets, and 2) the costs of the administration of the platelets. This estimate is multiplied with the number of platelet transfusions a patient receives prior to the PEIP.

The number of platelet transfusions were re-calculated from the data provided in response to the clarification letter, for each treatment arm, for the whole thrombocytopenic population.

These updated model inputs are presented in Table 3.

- Cost of the planned elective invasive procedures

This input in the model remained the same.

- Rescue procedure costs

The assumptions on these inputs remained the same.

- Transfusion related AE costs

These inputs in the economic model remained the same.

Table 3: Updated model input parameters for costs

	Value	Source
Platelet transfusion		
Average number of platelet transfusions for patients on lusutrombopag, who were transfused prior to procedure	[redacted]	Calculated from data provided by the company in response to clarification questions.[6]
Average number of platelet transfusions for patients on no TPO-RA, who were transfused prior to procedure	[redacted]	Calculated from data provided by the company in response to clarification questions.[6]
Source: As indicated in column 'Source'.		

1.2 Results from the pairwise comparison economic model

1.2.1 AG model pairwise lusutrombopag vs no TPO-RA comparison, deterministic cost-effectiveness analysis results

Base-case deterministic model results from the AG model, for the pairwise direct comparison of the cost-effectiveness of Lusutrombopag versus No TPO-RA are shown in Table 4 below.

Table 4: Deterministic base-case discounted AG model results

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER (£/QALY)
No TPO-RA	£2,300	7.396	3.363				
Lusutrombopag	£2,903	7.396	3.363	£603	0.00002	0.00018	£3,364,212
ICER = incremental cost effectiveness ratio, Incr. = incremental, LYGs = life years gained, QALYs = quality-adjusted life years.							

Similar to the results in the original report, no TPO-RA treatment incurred the lowest costs and QALYs. Lusutrombopag resulted in an incremental cost compared to no TPO-RA of £603 and incremental QALYs of 0.00018 (which is equivalent to a gain of 1.5 quality-adjusted life hour), resulting in a deterministic ICER around £3,400,000.

Since the incremental QALYs are extremely small, incremental cost due to lusutrombopag resulted in extremely high ICERs.

Table 5: Disaggregated costs

Disaggregated costs	Drug costs	Platelet transfusion costs	AE costs	PEIP costs	Rescue therapy costs	Total costs
no TPO-RA	£0	£252	£16	£1,977	£55	£2,300

Lusutrombopag	£800	£81	£19	£1,977	£25	£2,903
ICER = incremental cost effectiveness ratio, Incr. = incremental, LYGs = life years gained, QALYs = quality-adjusted life years.						

Table 6: Disaggregated QALYs

Disaggregated QALYs	QALY Decrement				Total long-term disc. QALYs
	Platelet transfusion	Bleeding	Rescue Therapy	AEs	
No TPO-RA	0.0000006	0.0000805	0.0000001	0.0000093	3.3625
Lusutrombopag	0.0000002	0.0000632	0.0000001	0.0000112	3.3627

Disaggregated cost results, displayed in Table 5, show that, while the costs of platelet transfusion and rescue therapy are higher for no TPO-RA than for lusutrombopag (except for negligible differences in the AE costs), the combined difference is still substantially lower than the drug costs for lusutrombopag. This results in incremental costs of over £600 for lusutrombopag versus no TPO-RA. In the face of such small incremental QALYs, this incremental cost has a large impact on the ICER.

The incremental QALY results are mostly due to the differences in the QALY decrements due to bleeding, which cause small differences but it led to high ICERs).

1.2.1 AG model pairwise lusutrombopag vs no TPO-RA comparison, probabilistic cost-effectiveness analysis results

Table 7: PSA results

Technologies	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
no TPO-RA	£2,208	3.5683			
Lusutrombopag	£2,809	3.5685	£601	0.0002	£3,208,995
ICER = incremental cost effectiveness ratio, Incr. = incremental, LYGs = life years gained, QALYs = quality-adjusted life years.					

The probabilistic results, displayed in Table 7, follow the same pattern as the deterministic results. Lusutrombopag is more expensive than no TPO-RA by £601 (i.e. 25% more expensive) and more effective by 0.0002 QALYs, resulting in an ICER of approximately £3,200,000.

The cost effectiveness scatterplots (Figure 1) show that, for the majority of iterations, lusutrombopag is more costly and more effective than no TPO-RA. However, it can also be seen that a substantial proportion of iterations fall in the NW quadrant, where the treatment is more expensive but less effective than no TPO-RA. This indicates that given the uncertainties in the model, the treatments can be regarded as having equivalent effectiveness in terms of QALYs.

The CEACs in turn (Figure 2) show that for all threshold ICERs up to £100,000, no TPO-RA has a 100% probability of being most cost-effective.

Figure 1: Cost effectiveness plane

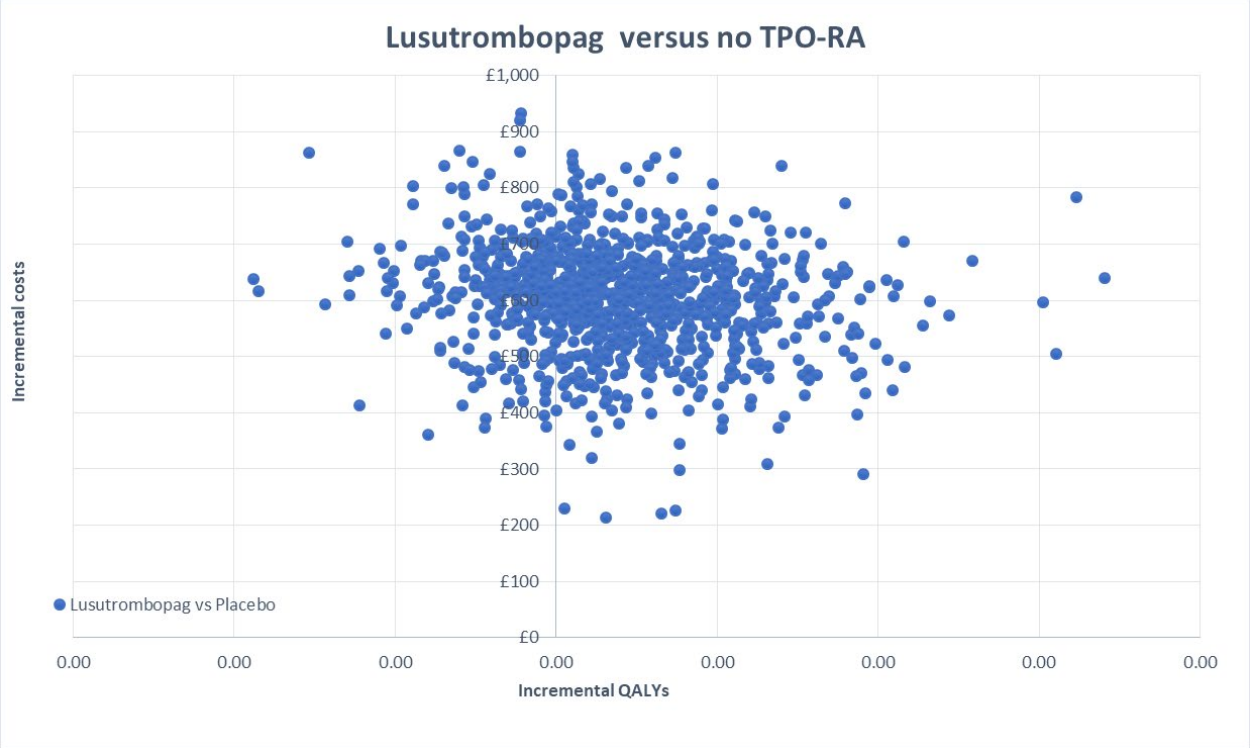
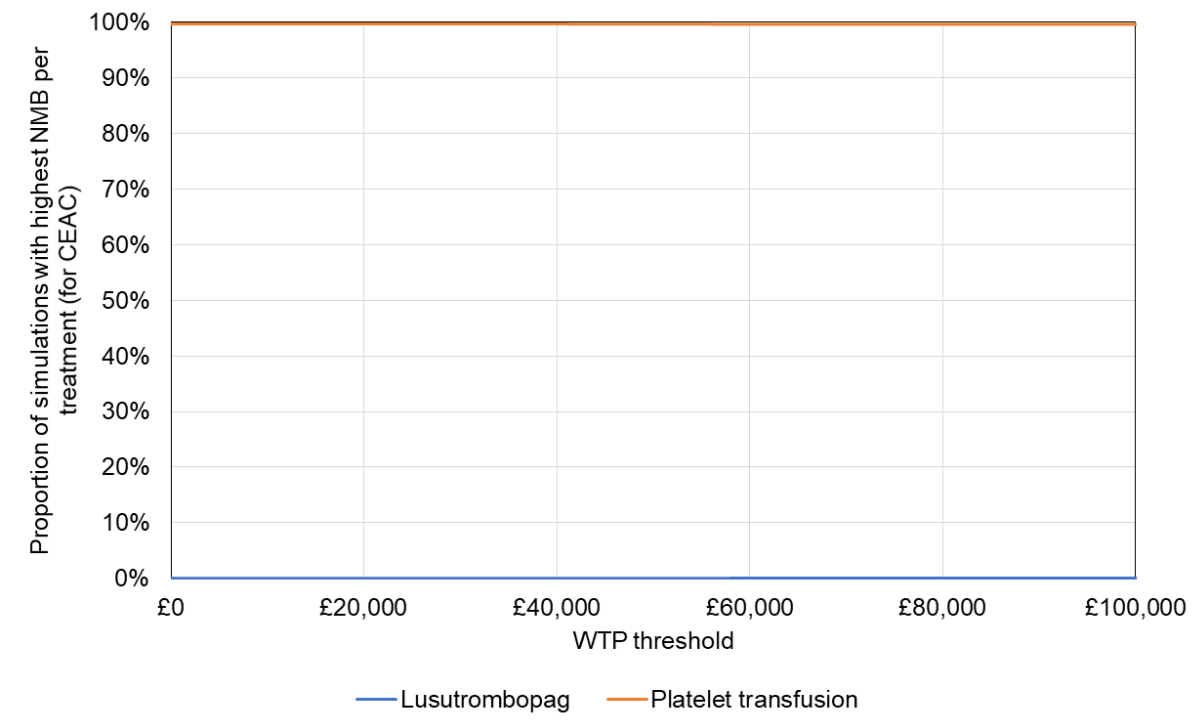


Figure 2: Cost effectiveness acceptability curve



1.2.3 Scenario analysis results

The AG conducted a series of scenario analyses for the pairwise comparison of lusutrombopag versus no TPO-RA. In comparison to the scenario analysis list in the original report, in this addendum only

the "number of adult therapeutic dose (ATDs) per platelet transfusion" scenario was explored, because it was the only scenario that had a substantial impact on the incremental results are investigated. We skip the PT transfusion cost scenarios, because by increasing the number of ATD units, the cost of PT transfudion increases automatically.

1. Number of ATDs per platelet transfusion
2. Sunk costs due to the postponed procedure

1.2.3.1 Number of ATDs per platelet transfusion

Given the uncertainty surrounding the number of ATDs per platelet transfusion, we explored scenarios surrounding this variable are important. As shown in Table 8 below, the assumption of one ATD per transfusion results in the highest ICER as this results in the lowest cost for platelet transfusion and therefore the biggest incremental cost difference between the treatment and no TPO-RA.

Table 8: Scenario analysis – Number of ATDs per platelet transfusion

No. ATDs	no TPO-RA		Lusutrombopag		Lus vs. no TPO-RA		
	Costs (£)	QALYs	Costs (£)	QALYs	Incr. Costs (£)	Incr. QALYs	ICER (£)
[redacted]	[redacted]	3.363	[redacted]	3.363	[redacted]	0.0002	£3,471,665
[redacted] (AG BC)	£2,300	3.363	£2,903	3.363	£603	0.0002	£3,364,212
[redacted]	[redacted]	3.363	[redacted]	3.363	[redacted]	0.0002	£2,539,397
3 (Sh BC)	[redacted]	3.363	[redacted]	3.363	[redacted]	0.0002	£1,607,130

AG = assessment group, ATD = adult therapeutic dose, BC = base-case, ICER = incremental cost effectiveness ratio, Incr. = incremental, QALY = quality-adjusted life year, Sh = Shionogi

The Shionogi base-case of three ATDs per transfusion (equivalent to treating ATDs as the assumed units in the Shionogi model) provides the lowest ICER versus no TPO-RA. However, none of the assumed number of ATDs result in a cost effective option, with an ICER around £1,607,000 for lusutrombopag versus no TPO-RA, being the lowest ICER observed in these scenarios.

1.2.3.2 Sunk costs due to the postponed procedure

In this scenario, a sunk cost of £617 is provided, which is based on the 2017/2018 NHS reference costs with the updated code (code: WH50A, Procedure Not Carried Out, for Medical or Patient Reasons) for elective inpatients.[8] This value is provided by the company in response to the AG report. This cost is assigned if the procedure is postponed. In this scenario we assumed that all treatments that were postponed were postponed due to the platelet count related reasons, even though it was not clear from the clinical study report of the L-PLUS 2 trial. The cost-effectiveness analysis results of this scenario is given in Table 9.

From Table 9, it can be seen that incorporating the sunk costs slightly decreased the incremental costs and the ICER.

Table 9: Scenario analysis: sunk costs for postponed operation

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER (£/QALY)
No TPO-RA	£2,352	7.396	3.363				
Lusutrombopag	£2,937	7.396	3.363	£585	0.00002	0.00018	£3,267,779

ICER = incremental cost effectiveness ratio, Incr. = incremental, LYGs = life years gained, QALYs = quality-adjusted life years.

2. Additional modelling considerations

Refractoriness

In the literature it has been noted that, when platelet transfusions are given repeatedly to a patient over the long term, they can become less effective over time, as patients become refractory. Therefore, in the case where we expect patients to receive multiple procedures over their remaining lifetime, the literature would suggest that the platelet transfusions received could become less effective, necessitating larger transfusions, or could stop raising platelet counts altogether. However, the AG could not identify sufficient evidence on refractoriness in this population in order to model it in an evidenced based manner. In order to model this process effectively the AG would require evidence for the follow:

- The percentage of patients who would be expected to become refractory
- The rate at which refractoriness would occur (for each successive procedure, how much larger would the required dose of platelets need to be and at what point would clinicians switch to alternative techniques such as human leukocyte antigen (HLA)-matched platelets, splenic artery embolization, splenectomy and TIPPS)
- How many procedures would this population be expected to receive over their remaining lifetime

The AG consulted with their clinical expert on these issues during the model design phase.[9] When asked how many elective invasive procedures he would expect thrombocytopenic CLD patients to receive over the course of their illness, the expert stated that he would expect this population to receive 1-2 procedures only. Given that 1 is already modelled, we would therefore only expect that some of the patients in the model would receive a second. The clinician also stated that we would expect between 5-10% of this population to become refractory to platelet transfusion, but given the rarity in clinical practice he could not provide more detail on the process of refractoriness. When asked what a clinicians strategy would be to a patient showing signs of refractoriness he stated that it was difficult to know, given that relatively few patients require more than one or two procedures and he had seen only a tiny number where there was no response to platelet transfusion. He stated that if the first transfusion failed to increase levels sufficiently, a clinician may give a second, but if this did not work he would not give more. When asked at what point clinicians would turn to alternative strategies, such as HLA matched platelets, he responded that he had never had to do this. Additionally, the company provided evidence from the Thrombocytopenia in Chronic Liver Disease report produced by Method Analytics (2018), showing that out of 4,556 patients in the HES inpatient data from April 2012 to March 2017, the percentage of patients receiving splenic artery embolization, splenectomy and TIPPS as second line treatments due to platelet refractoriness was [redacted]%, [redacted]% and [redacted]% respectively.[10] This information collectively suggests that extreme refractoriness affects a small percentage of patients.

An assumption would also have to be made about the effectiveness of successive administrations of lusutrombopag over the long term, for which no evidence is available. It would be inappropriate to only assume refractoriness for platelet transfusion, due to a lack of evidence available for the intervention.

Given the many uncertainties, due to a lack of evidence in this population, the AG did not feel that analysis regarding refractoriness due to multiple procedures would be in any way evidence based. Additionally, the responses from the clinical expert suggest that the impact of these analyses would be

small as we would not expect more than 1 additional procedure in this population and only a small percentage would be expected to become refractory, even if refractoriness were expected to occur between the first and second procedure.

Bleeding and other long-term consequences of lusutrombopag treatment

The AG model considered bleeding as an adverse event. The probabilities used in the company model could not be traced back by the AG, taking the WHO bleeding scores as presented in the Table 39 of the company submission appendix into consideration, which reported no Grade 3 bleeding events in L-PLUS 2. Furthermore, this evidence was not in line how the company modelled the rescue operation (which is conditional on the bleeding event). Therefore, bleeding related adverse events as provided in response to the clarification letter (Question A1.f) are incorporated to the AG model as treatment related adverse events. The utility decrements for these bleeding related events are incorporated in the model.

Furthermore, the clinical evidence from the trials were on "rescue operations due to bleeding". The AG is not aware of any evidence to suggest that there is any residual problem following a rescue therapy, e.g. disability due to bleeding. For the effect of delay/modification in operation, the AG was only able to speculate beyond what is the disutility due to anxiety. The likelihood of the cancellation of a surgery is deemed to be very low by our clinical expert, and also it cannot be known if this would be different between treatment arms.[9]

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NICE Dossier:

DOPTELET® (avatrombopag) for Thrombocytopenia in Patients With Chronic Liver Disease

1 PRODUCT INFORMATION AND DISEASE DESCRIPTION

1.1 Place of Product in Therapy

1.1.1 Disease Description

Thrombocytopenia is a condition characterized by low blood PLT CT (Hod and Schwartz, 2008). It can arise from various conditions; it can be idiopathic, immune-related, or the result of a specific disorder such as CLD (Mayo Clinic, 2017) (Afdhal et al., 2008; Peck-Radosavljevic, 2017). Regardless of etiology, severe TCP is associated with an increased risk of bleeding (Mayo Clinic, 2017). In general, major *spontaneous* bleeding does not occur until the PLT CT reaches $<10 \times 10^9$/L (Maan et al., 2015).

Thrombocytopenia is a common blood disorder in individuals with CLD undergoing procedures (Afdhal et al., 2008; Peck-Radosavljevic, 2017). In patients with CLD, mild or moderate TCP rarely leads to bleeding during procedures (eg, liver biopsy and liver transplant) and usually does not interfere with treatment. However, severe TCP can be associated with significant morbidity, and therefore can complicate medical management and the scheduling of procedures in patients with advanced liver disease (Afdhal et al., 2008). As DOPTELET is indicated for treatment of TCP in patients with CLD who are scheduled to undergo a procedure, the remaining sections of the dossier will provide data specific to this patient population.

1.1.1.1 Clinical Presentation

Thrombocytopenia can often be silent, without any signs or symptoms. Mild TCP is usually asymptomatic and is often discovered incidentally based on results of a complete blood count during a routine office visit (NIH, 2012). The main symptom of more severe TCP is bleeding—it can occur inside the body (internal bleeding) or underneath the skin (external bleeding)—which can appear suddenly or over time (Hod and Schwartz, 2008; NIH, 2012). In patients with CLD, TCP is usually identified as a reduced PLT CT during a routine complete blood count (Gangireddy et al., 2014).

In a retrospective analysis of a US administrative claims database, 56,445 patients were identified to have a diagnosis code of CLD from January 2000 to December 2003. Among the CLD patients with a TCP diagnosis code, 27.8% had a bleeding event, compared with 10.0% in those without a TCP diagnosis code (Poordad et al., 2012). A strong correlation between the mean PLT CT and bleeding event in patients with TCP was observed ($P<.007$); no such correlation was observed among those without TCP ($P=.614$) (Poordad et al., 2012).

People with CLD and severe TCP (PLT CT $<50 \times 10^9$/L) are at an increased risk of bleeding if they undergo a procedure, with the risk dependent on the characteristics of the patient and

the procedure itself. There is a higher risk with the lowest PLT CTs (<50 × 10^9/L), Child-Pugh stage C, and alcoholic cirrhosis (Peck-Radosavljevic, 2017). Bleeding occurred in 20% of patients who underwent a procedure; all of whom had severe TCP (Giannini et al., 2010).

An Italian retrospective study of oral surgery in patients with cirrhosis awaiting liver transplant found that postextraction bleeding was significantly associated with PLT CT (*P*=.04) (Cocero et al., 2017). Nonemergency patients with PLT CTs ≤40 × 10^9/L were given a preoperative platelet transfusion. Of 1,183 extractions carried out in 318 patients, there was a 3.1% rate of severe bleeding, with 12 severe bleeding episodes requiring surgical repair in 10 patients. These rates included emergency patients with PLT CTs as low as 25 × 10^9/L who did not receive a preprocedure platelet transfusion. For patients with severe TCP (≤40 × 10^9/L), the rate of severe bleeding was 6%. The authors concluded that PLT CTs ≤40 × 10^9/L represented a significant risk factor for bleeding during oral surgery (Cocero et al., 2017).

In a similar study in Finland, there was a 9% rate of bleeding in 134 patients awaiting liver transplant undergoing tooth extraction, despite preprocedural transfusions of platelets, fresh frozen plasma, and tranexamic acid. Although people with bleeding tended to have a lower PLT CT than those without bleeding, this difference was not statistically significant (114 × 10^9/L vs 136 × 10^9/L; *P*=.48) (Helenius-Hietala et al., 2016).

1.1.1.2 Economic Burden

Cost of TCP

Managing TCP in patients with CLD imposes substantial economic burden. Patients with CLD with severe TCP experience treatment costs related to multiple platelet transfusions, transfusion-related complications, additional staffing and hospital charges, and delays in planned medical procedures (Brown, 2007). These patients frequently undergo medical procedures for diagnosis and treatment, some of which are invasive. The risk of bleeding complications can cause postponement of necessary procedures and therapy, interfere with planned medical care, and significantly add to health care costs in these patients (Afdhal and Esteban, 2007; Poordad, 2007).

Thrombocytopenia and its associated complications can increase both direct and indirect costs (Table 4). Direct costs include the price of platelet transfusions, blood monitoring, and medical staff needed for transfusions; possible hospitalization resulting from inadequate therapy for TCP or from TCP-related complications arising from medically necessary procedures; and any additional treatments needed to restore PLT CT. In approximately 30% of the patients, platelet transfusions may result in complications that can prolong treatment and further raise costs (Brown, 2007).

CLD = chronic liver disease; HCV = hepatitis C virus; PLT CT = platelet count; TCP = thrombocytopenia.

Source: Brown (2007).

A normal uncomplicated procedure (eg, dental extraction) may require additional monitoring and therapy to prevent or treat TCP. The total increase of cost may range from $5,000 to $11,000 (Table 1), representing a 10-fold increase compared with costs in patients without TCP. Additional costs may be incurred if complications occur or aggressive therapy is needed to treat low PLT CT (Brown, 2007).

Table 1. Potential Increases in Costs for Routine Procedures in Thrombocytopenic Patients With CLD Receiving Platelet Transfusion

Supplemental Procedures Due to TCP	Estimated Additional Costs, $
2- to 3-day hospitalization	4,000-9,000
1-2 platelet transfusion	500-1,000
Complete blood count monitoring (twice daily)	300-1,000
More aggressive treatment for TCP, bleeding, or other complications	Unknown
Total	**4,800-11,000**

CLD = chronic liver disease; TCP = thrombocytopenia.

Source: Brown (2007).

In a retrospective analysis of data from an integrated, longitudinal database of medical and pharmacy claims and laboratory results in a US commercial health insurance plan, 7,905 patients with chronic HCV infection were identified by diagnostic code, and medical resource use was determined by comparing outpatient visits, emergency department visits, and inpatient hospital stays for patients with HCV with (n = 305) or without (n = 7,600) TCP. During the study period (January 2001 through December 2003), patients with HCV with TCP had a greater incidence of the following events, compared with those without TCP (Poordad et al., 2011):

- Bleeding events (27.3% vs 9.9%)
- Platelet transfusions (8.5% vs <1%)
- Liver-disease–related ambulatory visits (10.4 vs 4.4; odds ratio [OR] = 2.3; *P*<.001)
- Emergency department visits (OR = 8.6; 95% confidence interval [CI], 5.4-13.7; *P*<.01)
- Inpatient hospital stays (OR = 17.7; 95% CI, 11.9-26.3; *P*<.01)

Patients with HCV with TCP also had significantly higher overall health care costs ($37,924 vs $12,174; *P*<.001) and liver-disease–related costs ($14,569 vs $4,107; *P*<.001) than patients without TCP (Poordad et al., 2011).

A separate analysis of data from the same administrative claims database used in the study by Poordad et al. (2012) compared health care resource utilization and costs for patients with or without TCP. Data from 56,445 patients with CLD from January 2000 to December

2003 were analyzed. Results indicated that, compared with patients without TCP, those with TCP (Poordad et al., 2012):

- Had >2.5 times the annual number of liver-disease–related ambulatory visits (3.63 vs 1.42; OR = 2.6; *P*<.01)
- Were 13 times more likely to have a liver-related inpatient stay (OR = 13.0; *P*<.01)
- Were nearly 4 times more likely to have a liver-disease–related emergency department visit (OR = 3.9; *P*<.01)
- Had 3.5-fold greater mean annual overall medical care cost ($43,562 vs $12,271; *P*<.01)
- Had 7-fold greater annual liver-disease–related medical care cost ($9,938 vs $1,417; *P*<.01)

Cost of Platelet Transfusions

Costs of platelet transfusion, the standard of care for TCP, are significant. Platelets must be stored at room temperature and have a shelf life of only approximately 4 days (Kurokawa and Ohkohchi, 2017). The somewhat unpredictable nature of the demand, shipping, and timing problems can result in platelet shortages. The low supply/shortage issue requires extra time and effort from staff at blood banks and hospitals. On the other hand, high supply with unforeseen low demand causes an excess amount of platelets, resulting in platelet wastage and a significant logistic and financial burden—it was reported that in 2006, nearly 11% of platelet supplies were wasted due to expiration issues in the US (Fontaine et al., 2009). In a study of Stanford University Medical Center and Stanford Blood Center, costs due to platelet expiration were $25,410 and $142,423 per quarter in 2008 at the two institutions, respectively (Fontaine et al., 2009). A reduced reliance on platelet transfusions in the treatment of TCP may therefore help hospitals avoid platelet inventory management issues, saving both time and capital.

Refractoriness, inadequate response to platelet transfusion, generally occurs after multiple transfusions (Kerkhoffs et al., 2008; Maan et al., 2015).

To calculate an estimate of the cost of a platelet transfusion in patients with CLD and TCP, the cost estimates of platelet collection, platelet transfusion, adverse events (AEs) from platelet transfusion, and development of immune refractoriness to platelet transfusion should be summed (Barnett et al., 2018). The total direct cost of a platelet transfusion in this special population in the US is estimated to range between $5,258 and $13,117, with the midpoint being $9,188 (Table 2) (Barnett et al., 2018). Notably, the total cost estimate presented here does not include patient co-pays, or indirect and intangible costs, although these costs may be substantial.

Table 2. Expected Total Direct Cost of a Platelet Transfusion in the United States for Patients With CLD (Including Platelet Collection, Platelet Transfusion, Adverse Events, Refractoriness)

Cost Element	Cost Estimate (2017 US $)
Platelet collection	$428
Platelet transfusion	$3,723-$4,436
Adverse events from platelet transfusion	$233-$675
Refractoriness to platelet transfusion	$874-$7,578
Total direct costs	**$5,258-$13,117** **Midpoint = $9,188**

CLD = chronic liver disease; US = United States.

Source: Barnett, et al. (2018).

1.1.2 Approaches to Treatment

Standard of Care

Platelet transfusion is considered the gold standard for the treatment of TCP, reducing the risk of bleeding (Poordad, 2007). Although the criteria for defining TCP vary and formal guidelines on when to consider platelet transfusion, particularly in patients with CLD, are lacking, platelet transfusion is often initiated in patients with PLT CT <50 × 10^9/L in general (Brown, 2007). Besides as a treatment option, platelet transfusion may provide prophylactic benefit in patients with PLT CT <50 × 10^9/L on the day of the procedures (Dova, 2018; Hayashi et al., 2014).

Risks Associated With Platelet Transfusion

Although platelet transfusion can increase PLT CT, this treatment option is associated with many risks and complications (Table 3), most of which are not caused by platelets themselves but rather other contaminants (Murphy and Vassallo, 2010).

Table 3. Complications of Platelet Transfusion

Cause	Complication
Contaminating leukocytes	▪ Alloimmunization to class I human leukocyte antigen antigens ▪ Refractoriness to platelet transfusion ▪ FNHTR ▪ Cytokine formation ▪ Transmission of cytomegalovirus ▪ Graft-versus-host disease
Contaminating red blood cells	▪ Rh alloimmunization ▪ Parasites (eg, malaria, babesiosis)
Contaminating plasma and associated contents	▪ Contaminating microorganisms: – Bacteria – Viruses (HBV, HCV, HIV, human T-cell lymphotropic virus, West Nile virus) – Parasites (*Trypanosoma cruzi*/Chagas disease, *Babesia microti*) ▪ Human prion disease ▪ Plasma proteins ▪ Minor and major allergic reactions ▪ ABO antibody-mediated hemolysis ▪ Transfusion-related acute lung injury
Platelets	▪ FNHTR ▪ Refractoriness to platelet transfusion ▪ Post-transfusion purpura

FNHTR = febrile nonhemolytic transfusion reaction; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus.

Sources: Bihl et al. (2007); Murphy and Vassallo (2010).

The most common complication of platelet transfusion is refractoriness, occurring in approximately 50% of patients receiving repeated platelet transfusion (Kerkhoffs et al., 2008). It can be defined as a post-transfusion platelet increment that is less than expected (Hod and Schwartz, 2008). People receiving regular platelet transfusions become "refractory" to platelets, whereby transfused platelets are destroyed, reducing the effectiveness of future platelet transfusions (Poordad, 2007). Platelet refractoriness arises from immune and nonimmune causes (Hod and Schwartz, 2008).

- Immune causes include alloimmunization to human leukocyte antigen and/or platelet-specific antigens due to prior exposure from pregnancy, transfusions, and/or transplant (Hod and Schwartz, 2008).
- Nonimmune causes include fever, sepsis, splenomegaly, disseminated intravascular coagulation, bleeding, venoocclusive disease, graft-versus-host disease, and medications (Hod and Schwartz, 2008) or nonimmune platelet consumption associated with splenomegaly or disseminated intravascular coagulation (Poordad, 2007).

- Factors of transfusion service, such as storage of platelet product and ABO compatibility, may also affect refractoriness. No single factor is a good predictor of response in a given patient (Hod and Schwartz, 2008).

Platelet refractoriness can increase the clinical and economic burden of managing patients using platelet transfusions. Patients who are refractory become unresponsive to future platelet transfusions (Mohanty, 2009), which are used to manage bleeding in patients with low PLT CTs, resulting in worse clinical outcomes for these patients, such as an increased risk of bleeding and decreased survival (Stanworth et al., 2015). Platelet transfusion–refractory patients use eight-fold more platelet products, stay in hospital more than twice as long, and have hospitalization costs nearly three times higher than those of their nonrefractory counterparts, creating a significant economic burden (Juskewitch et al., 2017). Alloimmunized refractory patients require human leukocyte antigen–matched platelet transfusions, which also increases treatment costs (Poordad, 2007).

Other complications and limitations of platelet transfusion include febrile nonhemolytic transfusion reactions (FNHTRs), allergic transfusion reactions (ATRs), hemolytic transfusion reactions, and transfusion-transmitted infections (TTI).

- **Febrile nonhemolytic transfusion reactions (FNHTRs):** defined as rise of body temperature by ≥1°C within the first 4 hours of transfusion and temperature normalization within 48 hours, if transfusion of a bacterially contaminated blood product can be excluded and if no signs of hemolysis are found (Kiefel, 2008). Besides the typical rigor and chill, FNHTRs may appear asymptomatic and are not accurately documented. Therefore, the true incidence is unclear—up to 22% have been reported in the literature, depending on study criteria (Kiefel, 2008).
- **Allergic transfusion reactions (ATRs):** common complications of platelet transfusion, occurring in 1% to 3% of patients (Kacker et al., 2013). Allergic transfusion reactions can be minor (e.g., urticaria with or without pruritus) or severe (eg, anaphylactic reactions that result in systemic symptoms, such as dyspnea, wheezing, hypotension, tachycardia, loss of consciousness, shock, and in rare cases death) (Kacker et al., 2013). In addition to the clinical adverse effects, ATRs also increase health care expenditures by prolonging the time required by health care professionals for the transfusion procedure and the evaluation of ATRs and by requiring additional resources to address ATRs directly. Mild ATRs can be managed by antihistamines, and severe ATRs can lead to hospitalization (Kacker et al., 2013). Manipulation of platelets by concentrating or washing to reduce ATRs is time-consuming and costly and may reduce the corrected PLT CT increment (Kacker et al., 2013).
- **Hemolytic transfusion reactions:** In ABO major incompatible platelet transfusions, when an O recipient receives A, B, or AB platelet product, anti-A or

anti-B antibodies in the recipient may reduce platelet increments. Although hemolytic transfusion reactions are very rare, they may be severe or even fatal (Kiefel, 2008).

- **Transfusion-transmitted infections (TTIs)**: Platelets are stored at room temperature, so there is an increased risk of bacterial TTI with platelet transfusion, which has a high 28% overall mortality rate (Estcourt et al., 2017). However, bacterial TTI is rare in countries that have introduced bacterial screening, such as the United Kingdom (since 2010) and the US (draft guidance since 2015) (AABB, 2015; Estcourt et al., 2017). Prior to 2015 in the US, sepsis from bacterially contaminated platelets represented the most frequent infection complication from any blood product (Kaufman et al., 2015). Bacterial screening does not preclude the increased risk of viral TTI such as human immunodeficiency virus and hepatitis associated with platelet transfusion.

Although prophylactic platelet transfusions are often given to people with CLD and TCP prior to procedures, their effectiveness is limited. Platelet transfusion does not always ensure maintenance of platelet levels, which may affect bleeding outcomes in these patients (Poordad, 2007).

Unmet Needs

In light of the limitations of transfusion, better approaches are clearly needed for the treatment of TCP associated with CLD. Ideally, therapies should increase PLT CT (thereby decreasing the need for platelet transfusions), demonstrate clinical effectiveness in most patients, have minimal toxicity, and be cost-effective (Poordad, 2007).

2 CLINICAL EVIDENCE

2.1 Study Summaries

The avatrombopag clinical development program consists of 24 sponsor-initiated studies in patients and healthy volunteers, including phase 1, phase 2, and phase 3 studies, with a total of more than 1,100 participants exposed to one or more doses of avatrombopag. These trials used multiple avatrombopag formulations, doses, and short-term and chronic dosing regimens across multiple patient populations and clinical indications (Dova data on file, 2017c).

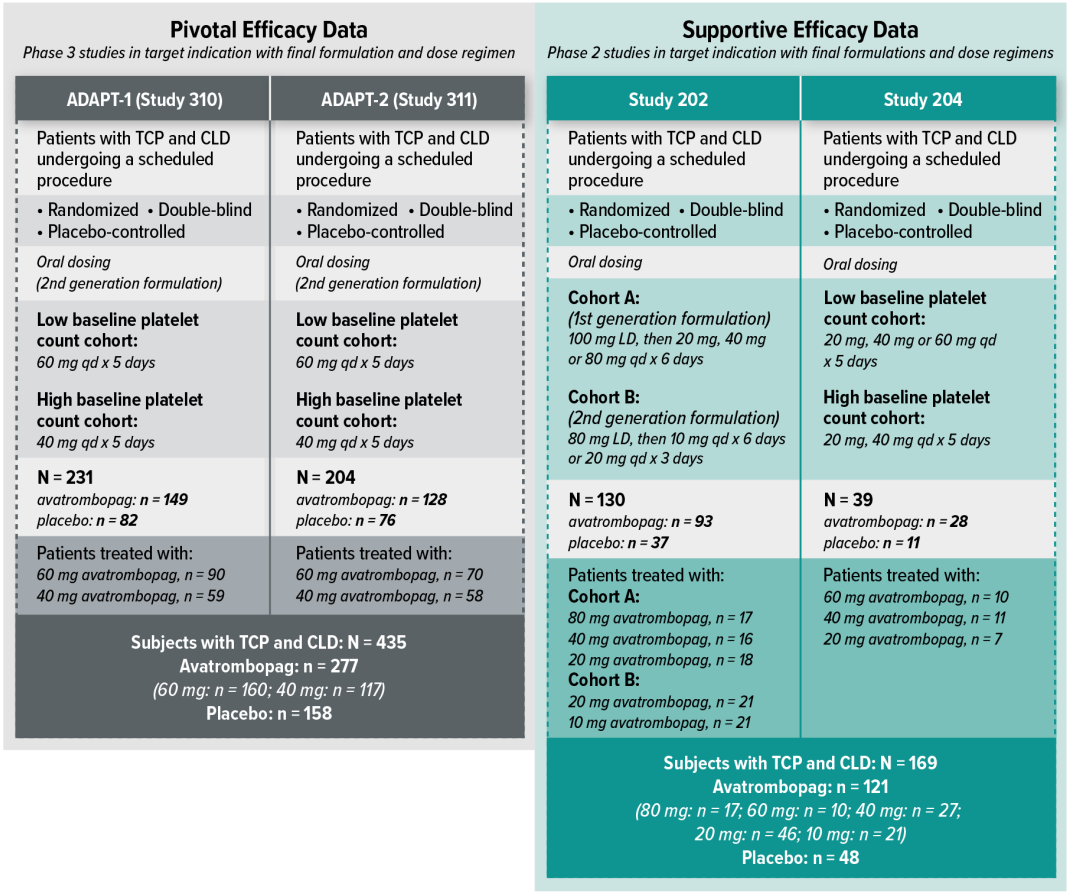
The efficacy and safety of avatrombopag in patients with CLD, who are scheduled to undergo a procedure, have been demonstrated in two phase 2 and two identical phase 3 clinical trials (ADAPT-1 and ADAPT-2) (Table 4 and Figure 1). Clinical trial summaries and evidence table summaries are presented for the two phase 3 trials; the phase 2 trials are summarized in the evidence table only. Note that one of the phase 2 studies (Study 204) is conducted in Japan, and the two phase 2 studies used different doses from the final formulation.

Table 4. Overview of Avatrombopag Clinical Trials in Patients With CLD With TCP Prior to Elective Procedures

Study Identifiers (NCT and Protocol Numbers)	Official Title	Phase	References
NCT01972529 (ADAPT-1)	A randomized, global, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of once-daily oral avatrombopag for the treatment of adults with thrombocytopenia associated with liver disease prior to an elective procedure	Phase 3	DOPTELET (avatrombopag) prescribing information (2018)
NCT01976104 (ADAPT-2)	A randomized, global, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of once-daily oral avatrombopag for the treatment of adults with thrombocytopenia associated with liver disease prior to an elective procedure	Phase 3	DOPTELET (avatrombopag) prescribing information (2018)
NCT00914927	A phase 2, randomized, multicenter, placebo-controlled, double-blind, parallel-group study to evaluate the efficacy, safety, and population pharmacokinetics of once-daily oral E5501 tablets used up to 7 days in patients with CLDs and thrombocytopenia prior to elective surgical or diagnostic procedures	Phase 2	Terrault et al. (2014)
NCT02227693 E5501-J081-204 (Study 204)	A randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy, safety, and pharmacokinetics of once-daily oral avatrombopag in Japanese subjects with CLDs and thrombocytopenia	Phase 2	ClinicalTrials.gov NCT02227693

CLD = chronic liver disease; NCT = National Clinical Trial Number; TCP = thrombocytopenia.

Figure 1. Summary of Efficacy Studies With Avatrombopag in Patients With CLD and TCP Undergoing Procedures



CLD = chronic liver disease; qd = once daily; LD = loading dose; TCP = thrombocytopenia.

Note: Data are the full analysis set.

Source: Dova data on file (2017c).

2.1.1 TCP Summary of Phase 3 Clinical Trials With Avatrombopag

ADAPT-1 and ADAPT-2 evaluated avatrombopag versus placebo in patients with CLD who had severe TCP (<50 × 10^9/L) prior to a procedure. Because both trials were identical in terms of study design and inclusion/exclusion criteria, summary information for ADAPT-1 and ADAPT-2 has been combined in the following sections and details of each trial are presented separately in the evidence table (Table 18).

2.1.1.1 Objective, Location, and Study Start and Completion Dates

Primary objective: To confirm that avatrombopag is superior to placebo in removing the need for platelet transfusions or any rescue procedure for bleeding after randomization

and up to 7 days following procedure in patients with CLD who have TCP (Terrault et al., 2018).

Secondary objectives (Terrault et al., 2018)**:**

- To confirm that avatrombopag is superior to placebo in achieving a PLT CT ≥50 × 10^9/L on procedure day in the proposed target population
- To confirm that avatrombopag is superior to placebo in elevating PLT CT from baseline on procedure day in the proposed target population
- To evaluate the safety of avatrombopag in the proposed target population

Location: 75 sites in 20 countries (ADAPT-1); 74 sites in 16 countries (ADAPT-2) (Terrault et al., 2018)

Completion date: January 26, 2017 (ADAPT-1); January 30, 2017 (ADAPT-2) (Dova data on file, 2017c)

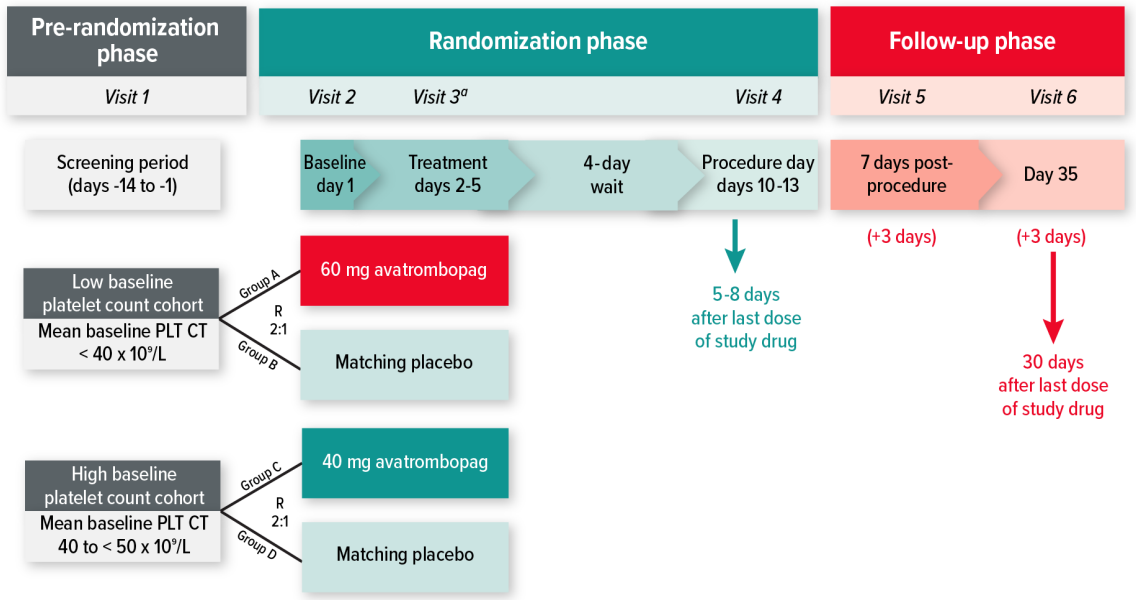
2.1.1.2 Trial Design, Randomization, and Blinding Procedures

Study design: Phase 3, global, multicenter, randomized, double-blind, placebo-controlled, parallel-group study (Terrault et al., 2018)

This study consisted of three phases (Figure 2):

- Prerandomization phase
- Randomization phase
- Follow-up phase

Figure 2. ADAPT-1 and ADAPT-2 Study Design



PLT CT = platelet count; R = randomization.

Note: PLT CT was measured on two separate occasions, during the screening period and at baseline, and must have been performed at least 1 day apart, with neither PLT CT >60 × 10^9/L. The mean of these two PLT CTs (mean baseline PLT CT <50 × 10^9/L) was used for entry criteria and determination of baseline PLT CT.

[a] Visit 3 occurred on day 4 (± 1 day) during the treatment period.

[b] PLT CT was assessed on procedure day: patients received platelet transfusion if PLT CT <50 × 10^9/L.

Sources: Terrault et al. (2018).

Prerandomization: The prerandomization phase included a screening visit that took place from day −14 through day −1 (Terrault et al., 2018). Platelet counts were measured on two separate occasions, during the screening period and at baseline, to be performed at least 1 day apart, with neither PLT CT >60 × 10^9/L. The mean of these two PLT CTs (mean baseline PLT CT <50 × 10^9/L) was used for entry criteria.

During prerandomization, patients were divided into the following two cohorts according to mean baseline PLT CT (Terrault et al., 2018):

- Low baseline PLT CT cohort (Cohort 1): <40 × 10^9/L
- High baseline PLT CT cohort (Cohort 2): 40 to <50 × 10^9/L

Within each cohort, participants were further stratified by risk of bleeding associated with the procedure (low, moderate, and high) (Table 5) and by hepatocellular carcinoma (HCC) status (yes or no) (Terrault et al., 2018).

Table 5. Levels of Risk Associated With Procedures in ADAPT-1 and ADAPT-2

Risk of Bleeding Associated With Procedure	Procedure
Low risk	▪ Paracentesis ▪ Thoracentesis ▪ Gastrointestinal endoscopy with or without plans for biopsy, colonoscopy, polypectomy, or variceal banding
Moderate risk	▪ Liver biopsy ▪ Bronchoscopy with or without plans for biopsy ▪ Ethanol ablation therapy or chemoembolization for hepatocellular carcinoma
High risk	▪ Vascular catheterization (including right-side procedures in patients with pulmonary hypertension) ▪ Transjugular intrahepatic portosystemic shunt ▪ Dental procedures ▪ Renal biopsy ▪ Biliary interventions ▪ Nephrostomy tube placement ▪ Radiofrequency ablation ▪ Laparoscopic interventions

Note: Level of risk was based on expert input and consensus guidelines for periprocedural management of coagulation status and hemostasis risk in percutaneous image-guided interventions (Malloy et al., 2009).

Source: Dova data on file (2015).

Randomization: The randomization phase included the baseline period (visit 2), treatment period (visit 3), and procedure day period (5-8 days after the last dose of study drug [visit 4 on study days 10-13]) (Terrault et al., 2018). Within each cohort and each stratum, patients were randomized in a 2:1 ratio to receive either avatrombopag (40 mg or 60 mg) or placebo once daily for 5 days, followed by a 4-day wait period before the procedure (Terrault et al., 2018). On procedure day (day 10-13, visit 4), PLT CTs were assessed. Participants with PLT CTs ≥50 × 10^9/L could undergo their scheduled procedure, and those with PLT CTs <50 × 10^9/L received a platelet transfusion before their procedure, at the discretion of the physician.

The procedure for those patients whose preprocedural PLT CT was high (>200 × 10^9/L on visit 4/procedure day) could be delayed at the discretion of the investigator until PLT CTs were <200 × 10^9/L.

Patients could receive a platelet transfusion preprocedure as well as postprocedure for bleeding events. The following rescue procedures could be used specifically for bleeding (Dova data on file, 2015):

- Platelet transfusion
- Fresh frozen plasma
- Cryoprecipitate
- Vitamin K (phytonadione)
- Desmopressin
- Recombinant factor VIIa
- Aminocaproic acid
- Tranexamic acid
- Whole blood transfusion
- Packed red cell transfusion
- Surgical intervention or interventional radiology

Follow-up: The follow-up phase included the following two visits: 7 days after procedure day (visit 5) and 30 days after receiving the last dose of study drug (visit 6) (Terrault et al., 2018).

2.1.1.3 Setting and Inclusion and Exclusion Criteria

Setting: Study drug or matching placebo tablets were taken orally, once daily, and with a meal at home.

Key inclusion criteria:

- ≥18 years of age at screening with CLD
- Mean baseline PLT CT <50 × 10^9/L; PLT CTs were measured on two separate occasions, during screening and at baseline, and at least 1 day apart, with neither PLT CT >60 × 10^9/L
- Scheduled to undergo a permitted procedure and would otherwise require a platelet transfusion, per investigator's opinion
- Model for End-Stage Liver Disease (MELD) score ≤24 at screening
- If taking inhibitors of P-glycoprotein, except for verapamil, dose was required to be stable for 7 days before screening

Key exclusion criteria:

- A history of arterial or venous thrombosis (partial or complete)
- Thrombosis (partial or complete) in the main portal vein, portal vein branches, or any part of the splenic mesenteric system at screening
- Portal vein blood flow velocity rate <10 cm per second at screening

- Hepatic encephalopathy that cannot be effectively treated
- Hepatocellular carcinoma (HCC), with Barcelona Clinic Liver Cancer (BCLC) staging classification C or D
- Platelet transfusion or receipt of blood products containing platelet within 7 days of screening (however, packed red blood cells were permitted)
- Heparin, warfarin, nonsteroidal anti-inflammatory drugs, aspirin, verapamil, antiplatelet therapy with ticlopidine or glycoprotein IIb/IIIa antagonists (eg, tirofiban), or erythropoietin-stimulating agents within 7 days of screening or interferon within 14 days of screening

2.1.1.4 Baseline Patient Characteristics and Demographics

The treatment groups were balanced with respect to baseline demographic variables (Table 6 and Table 7) (Terrault et al., 2018).

In ADAPT-1, mean age for the overall study sample was approximately 56 years, and most patients were male (68.4%). Most patients were white (55.4%), followed by Korean (18.6%), Chinese (10.4%), and other Asian ethnicities (9.5%). Mean baseline PLT CTs were 31 × 10^9/L in cohort 1 and 45 × 10^9/L in cohort 2 (Dova data on file, 2017g).

Similarly, in ADAPT-2, the mean age for the overall study sample was approximately 58 years, and most patients were male (62.3%). Most patients were white (64.2%), followed by Japanese (24.5%). Mean baseline PLT CTs were 33 × 10^9/L in cohort 1 and 44 × 10^9/L in cohort 2. Most patients did not have HCC (Dova data on file, 2017b).

In both trials, the distribution of procedures by bleeding risk category was comparable between treatment groups (Table 8). Most participants had low-risk procedures in the combined avatrombopag and placebo groups (61.4% and 59.7%, respectively) (Dova data on file, 2017c).

Table 6. ADAPT-1 Baseline Demographics

Category	Low PLT CT Cohort <40 × 10^9/L		High PLT CT Cohort 40 to <50 × 10^9/L	
	PBO (n = 48)	AVA 60 mg (n = 90)	PBO (n = 34)	AVA 40 mg (n = 59)
Age, years	55.1 (11.02)	55.6 (9.12)	57.8 (11.05)	57.5 (10.06)
Male, n (%)	32 (66.7)	65 (72.2)	24 (70.6)	37 (62.7)
Race				
White	28 (58.3)	50 (55.6)	19 (55.9)	31 (52.5)
Black or African American	0	3 (3.3)	0	2 (3.4)
Asian	18 (37.5)	32 (35.6)	15 (44.1)	24 (40.7)
Other	2 (4.2)	1 (1.1)	0	0
Missing	0	4	0	2
Body mass index, kg/m^2	27.3 (7.08)	27.9 (5.48)	27.8 (7.36)	28.1 (5.49)
Baseline PLT CT, × 10^9/L	30.7 (7.12)	31.1 (7.30)	44.9 (3.11)	44.3 (2.76)
HCC status (yes), n (%)	11 (22.9)	21 (23.3)	7 (20.6)	17 (28.8)
MELD score	11.1 (3.37)	11.1 (3.33)	10.4 (2.74)	11.5 (3.75)
Child-Pugh score	6.4 (1.25)	6.5 (1.33)	6.3 (1.32)	6.7 (1.60)
CLD etiology				
Alcoholic liver disease	7 (14.6)	13 (14.4)	2 (5.9)	11 (18.6)
Chronic viral hepatitis	30 (62.5)	50 (55.6)	27 (79.4)	36 (61.0)
NASH	4 (8.3)	6 (6.7)	0	4 (6.8)
Other	7 (14.6)	20 (22.2)	5 (14.7)	6 (10.2)
Missing	0	1	0	2

AVA = avatrombopag; CLD = chronic liver disease; HCC = hepatocellular carcinoma; MELD = Model for End-Stage Liver Disease; NASH = nonalcoholic steatohepatitis; PBO = placebo; PLT CT = platelet count.

Note: Data are the full analysis set and are mean (standard deviation) unless otherwise stated. Percentages are based on the total number of patients with nonmissing values in the relevant treatment group.

Source: Dova data on file (2017d); Terrault et al. (2018).

Table 7. ADAPT-2: Baseline Demographics

Category	Low PLT CT Cohort <40 × 10^9/L		High PLT CT Cohort 40 to <50 × 10^9/L	
	PBO (n = 43)	AVA 60 mg (n = 70)	PBO (n = 33)	AVA 40 mg (n = 58)
Age, years	57.3 (11.98)	58.6 (14.18)	59.2 (10.31)	57.9 (11.11)
Male, n (%)	27 (62.8)	50 (71.4)	17 (51.5)	33 (56.9)
Race				
White	27 (62.8)	40 (57.1)	24 (72.7)	40 (69.0)
Black or African American	2 (4.7)	2 (2.9)	0	2 (3.4)
Asian	10 (23.3)	25 (35.7)	8 (24.2)	12 (20.7)
Other	4 (9.3)	3 (4.3)	0	4 (6.9)
Missing	0	0	1	0
Body mass index, kg/m^2	28.3 (6.48)	27.1 (6.11)	26.8 (6.95)	27.8 (5.03)
Baseline PLT CT, × 10^9/L	32.5 (6.22)	32.7 (5.24)	44.5 (3.10)	44.3 (3.58)
HCC status (yes), n (%)	14 (32.6)	21 (30.0)	11 (33.3)	15 (25.9)
MELD score	11.4 (3.08)	11.1 (3.25)	10.5 (3.61)	11.0 (4.07)
Child-Pugh score	6.7 (1.41)	6.5 (1.49)	6.9 (1.73)	6.6 (1.51)
CLD etiology				
Alcoholic liver disease	7 (16.3)	12 (17.1)	5 (15.2)	6 (10.3)
Chronic viral hepatitis	26 (60.5)	34 (48.6)	18 (54.5)	29 (50.0)
NASH	5 (11.6)	10 (14.3)	5 (15.2)	6 (10.3)
Other	5 (11.6)	14 (20.0)	5 (15.2)	17 (29.3)

AVA = avatrombopag; CLD = chronic liver disease; HCC = hepatocellular carcinoma; MELD = Model for End-stage Liver Disease; NASH = nonalcoholic steatohepatitis; PBO = placebo; PLT CT = platelet count.

Note: Data are the full analysis set and are mean (standard deviation) unless otherwise stated. Percentages are based on the total number of patients with nonmissing values in the relevant treatment group.

Source: Dova data on file (2017a); Terrault et al. (2018).

Table 8. Combined ADAPT-1 and ADAPT-2: Summary of Scheduled Procedures by Bleeding Risk

	Low PLT CT Cohort <40 × 10^9/L		High PLT CT Cohort 40 to <50 × 10^9/L		Combined Treatment Group Totals		
Procedure Bleeding Risk	**PBO (n = 91) n (%)**	**AVA 60 mg (n = 160) n (%)**	**PBO (n = 67) n (%)**	**AVA 40 mg (n = 117) n (%)**	**PBO (n = 158) n (%)**	**AVA (n = 277) n (%)**	**Overall Total (N = 435) n (%)**
Low	48 (60.0)	96 (63.6)	38 (59.4)	66 (58.4)	86 (59.7)	162 (61.4)	248 (60.8)
Moderate	17 (21.3)	21 (13.9)	12 (18.8)	20 (17.7)	29 (20.1)	41 (15.5)	70 (17.2)
High	15 (18.8)	34 (22.5)	14 (21.9)	27 (23.9)	29 (20.1)	61 (23.1)	90 (22.1)

AVA = avatrombopag; n = number of patients in specified group; PBO = placebo; PLT CT = platelet count.

Note: Percentages are based on the total number of patients with nonmissing values in the relevant treatment group.

Source: Dova data on file (2017c).

2.1.1.5 Dropout Rates

A total of 435 patients were randomized in both studies, with 277 randomized to avatrombopag and 158 to placebo(Terrault et al., 2018). In ADAPT-1, study discontinuation rates were higher in the avatrombopag group compared with placebo in cohort 2 (PLT CT 40 to <50 × 10^9/L), and similar for both treatment groups in cohort 1 (PLT CT <40 × 10^9/L). The most common reason for discontinuation was withdrawal of consent (1 patient in the placebo group in cohort 1, 2 patients in the avatrombopag group in cohort 1, and 1 patient in the avatrombopag group in cohort 2 withdrew consent).

In ADAPT-2, study discontinuation rates were higher in the placebo group compared with the avatrombopag group in cohort 1, and similar for both treatment groups in cohort 2. The most common reasons for discontinuation were loss to follow-up and withdrawal of consent.

2.1.1.6 Treatments and Interventions

In both trials, patients in cohort 1 (PLT CT <40 × 10^9/L) were randomized to the following treatment groups:

- 60 mg avatrombopag one time daily on days 1 to 5
- Matching placebo one time daily on days 1 to 5

Patients in cohort 2 (PLT CT 40 to <50 × 10^9/L) were randomized as follows:

- 40 mg avatrombopag one time daily on days 1 to 5
- Matching placebo on time daily on days 1 to 5

2.1.1.7 Clinical Outcome Measures

Primary endpoint: The proportion of patients who do *not* require a platelet transfusion, or any rescue procedure for bleeding, up to 7 days following a procedure (Terrault et al., 2018)

Secondary endpoints (Terrault et al., 2018):

- Proportion of patients who achieve the target PLT CT ≥50 × 10^9/L on procedure day prior to undergoing a procedure
- Change from baseline in PLT CT on procedure day prior to undergoing a procedure

Exploratory endpoints (Dova data on file, 2015):

- Platelet count and change from baseline in PLT CT at each visit
- Severity of bleeding events assessed by World Health Organization (WHO) bleeding grade

Efficacy Results

Efficacy results for avatrombopag are described below and presented for ADAPT-1 and ADAPT-2 separately and combined as a pooled analysis set. The primary analysis of the individual and pooled phase 3 studies was conducted on the full analysis set, defined as all randomized patients. A "responder" is any patient who did not require a platelet transfusion or any rescue bleeding treatment or procedure. Patients with missing information for the primary efficacy endpoint owing to early withdrawal or other reasons were conservatively considered as having received a transfusion for the primary analysis and therefore were considered "nonresponders" (Dova data on file, 2017c).

Both ADAPT-1 and ADAPT-2 met their primary and secondary endpoints, demonstrating the superiority of avatrombopag over placebo in increasing the proportion of patients not requiring a platelet transfusion or rescue procedure for bleeding and in increasing PLT CTs (Terrault et al., 2018).

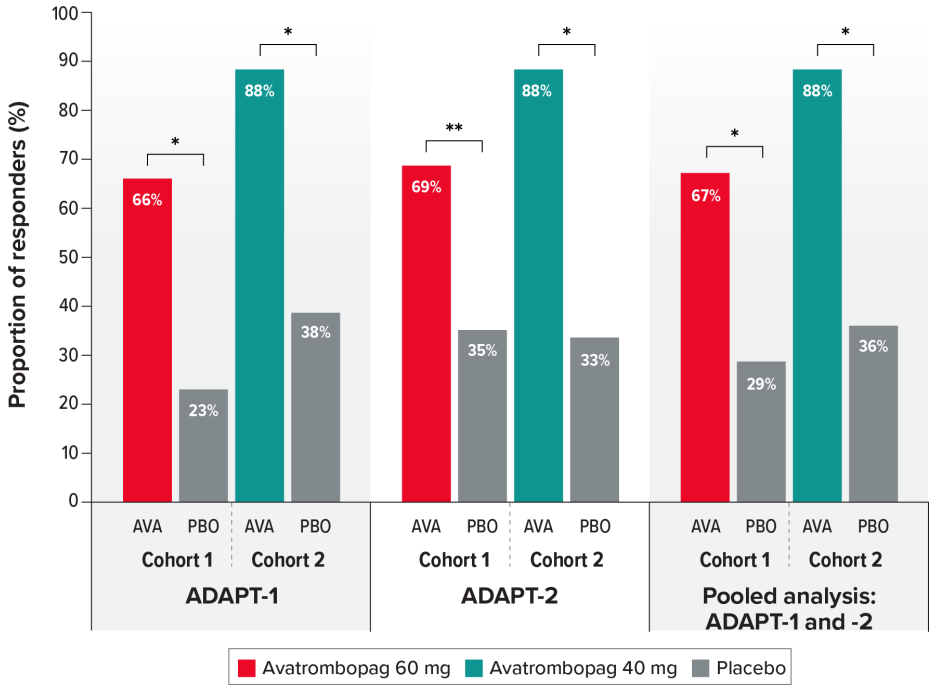
Primary Efficacy Endpoint

The proportion of patients without platelet transfusion or any rescue procedure for bleeding was statistically significantly higher in the avatrombopag groups than in the placebo groups in both trials (Figure 3 and Table 9).

In ADAPT-1, responder rates with avatrombopag were significantly higher than placebo in both the low baseline PLT CT cohort treated with avatrombopag 60 mg (cohort 1: 66% vs 23%; $P<.0001$) and the high baseline PLT CT cohort treated with avatrombopag 40 mg (cohort 2: 88% vs 38%; $P<.0001$). The efficacy of avatrombopag was confirmed in ADAPT-2, which also showed a significantly higher proportion of responders with avatrombopag compared with placebo in both the low baseline PLT CT cohort (69% vs 35%; $P=.0006$) and the high baseline PLT CT cohort (88% vs 33%; $P<.0001$) (Figure 3 and Table 9) (Terrault et al., 2018).

The pooled efficacy analysis of both trials determined that significantly more patients treated with avatrombopag did not require a platelet transfusion (or rescue procedure) compared with those treated with placebo across all baseline PLT CT cohorts (cohort 1: 67% vs 29%; cohort 2: 88% vs 36%; $P<.0001$ for all) (Dova data on file, 2017c).

Figure 3. ADAPT-1 and ADAPT-2: Proportion of Patients Not Requiring a Platelet Transfusion or Any Rescue Procedure for Bleeding



* *P*<.0001, AVA vs PBO; ** *P*=.0006, AVA vs PBO.

AVA = avatrombopag; PBO = placebo.

Notes: Data are from the full analysis set. Responders were defined as the patients not requiring a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following a scheduled procedure.

Values represent the difference of proportion (ie, proportion of responders for avatrombopag minus proportion of responders for placebo).

Sources: Dova data on file (2017c); Terrault et al. (2018).

Table 9. Primary Efficacy Results in ADAPT-1 and ADAPT-2

	Baseline PLT CTs and Treatment Arms											
	ADAPT-1				ADAPT-2				ADAPT-1 + ADAPT-2			
	Cohort 1 <40 × 10^9/L		Cohort 2 40 to <50 × 10^9/L		Cohort 1 <40 × 10^9/L		Cohort 2 40 to <50 × 10^9/L		Cohort 1 <40 × 10^9/L		Cohort 2 40 to <50 × 10^9/L	
Endpoint	**AVA 60 mg (n = 90)**	**PBO (n = 48)**	**AVA 40 mg (n = 59)**	**PBO (n = 34)**	**AVA 60 mg (n = 70)**	**PBO (n = 43)**	**AVA 40 mg (n = 58)**	**PBO (n = 33)**	**AVA 60 mg (n = 160)**	**PBO (n = 91)**	**AVA 40 mg (n = 117)**	**PBO (n = 67)**
% of patients not requiring platelet transfusion or rescue procedure	65.6%	22.9%	88.1%	38.2%	68.6%	34.9%	87.9%	33.3%	66.9%	28.6%	88.0%	35.8%
P value[a]	<.0001		<.0001		.0006		<.0001		<.0001		<.0001	

AVA = avatrombopag; PBO = placebo; PLT CT = platelet count; SD = standard deviation.

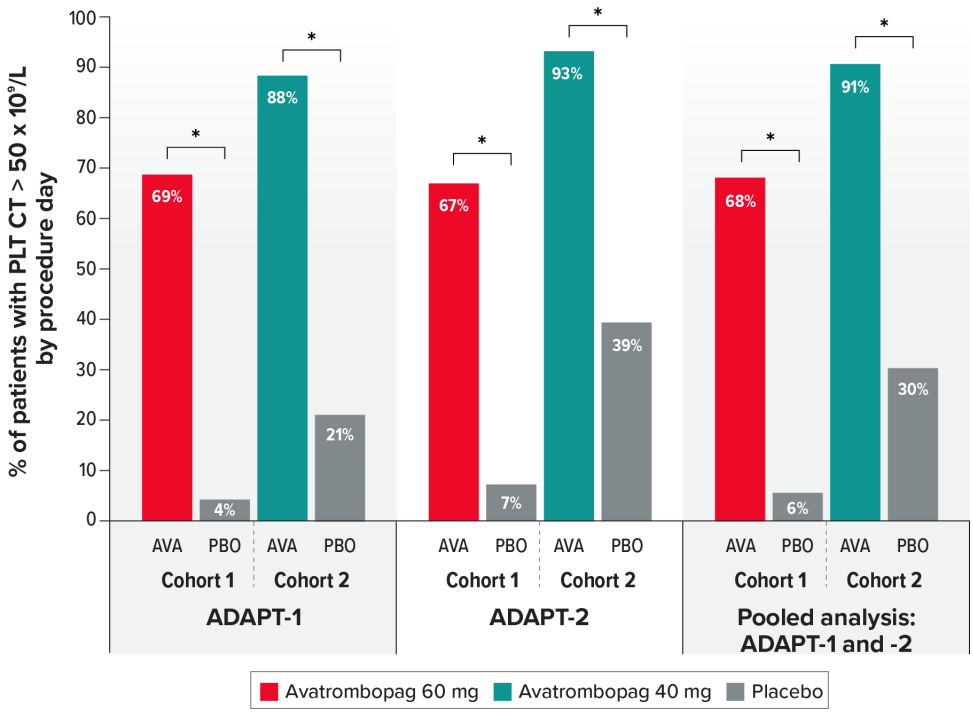
[a] Cochran-Mantel-Haenszel.

Sources: Dova data on file (2017c); Terrault et al. (2018).

Secondary Efficacy Endpoint

In both ADAPT-1 and ADAPT-2, in both cohorts and in the pooled analysis, a significantly higher proportion of patients treated with avatrombopag successfully achieved the target PLT CT threshold of 50 × 10^9/L by procedure day compared with placebo (*P*<.0001 for all) (Figure 4) (Terrault et al., 2018).

Figure 4. ADAPT-1 and ADAPT-2: Proportion of Patients With PLT CT ≥50 × 10^9/L by Procedure Day



* *P*<.0001, AVA vs PBO.

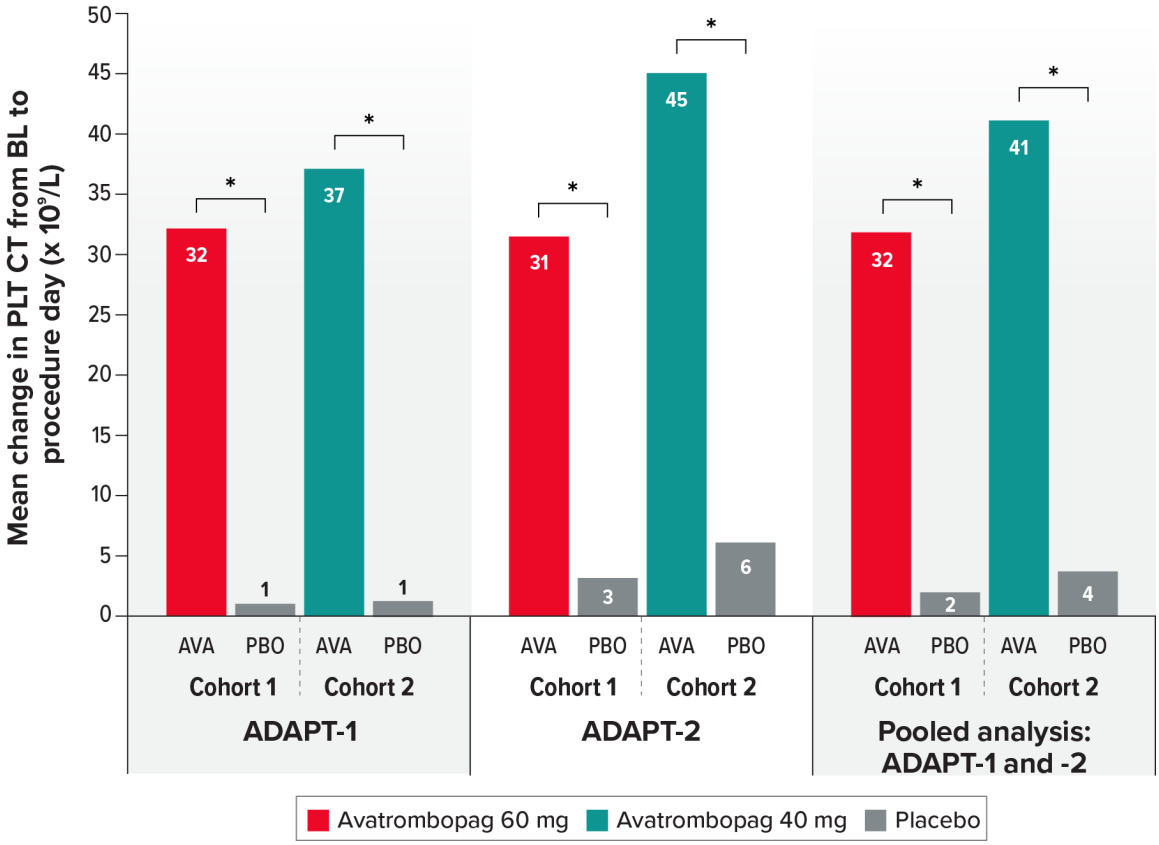
AVA = avatrombopag; PBO = placebo; PLT CT = platelet count.

Note: Data are from the full analysis set. Patients with missing PLT CTs on procedure day were conservatively considered as not having achieved the target PLT CT in the analysis and were considered nonresponders.

Sources: Dova data on file (2017c); Terrault et al. (2018).

The magnitude of change in mean PLT CT from baseline to procedure day was significantly larger in patients treated with avatrombopag compared with placebo in all baseline cohort groups and in the pooled analysis (*P*<.0001 for all) (Figure 5) (Terrault et al., 2018).

Figure 5. ADAPT-1 and ADAPT-2: Mean Change in PLT CT From Baseline to Procedure Day



* *P*<.0001, AVA vs PBO.

AVA = avatrombopag; BL = baseline; PBO = placebo; PLT CT = platelet count.

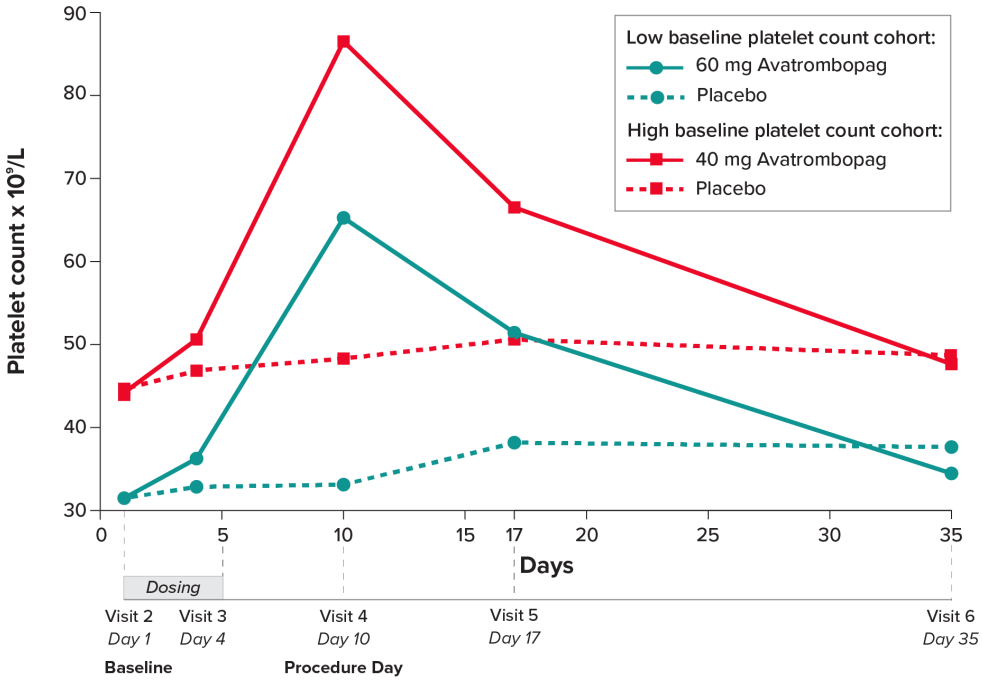
Note: Data are for the full analysis set. Last observation carried forward was used for patients with missing PLT CT on the procedure day.

Sources: Dova data on file (2017c); Terrault et al. (2018).

Exploratory Efficacy Endpoint

Platelet count over time: In both ADAPT-1 and ADAPT-2 trials, mean PLT CT in the avatrombopag treatment groups in both cohorts started to increase on day 4 of treatment (visit 3), peaked at day 10 to day 13 (visit 4, procedure day; 5-8 days from the last avatrombopag dose), and returned to baseline values by day 35 (visit 6, follow-up) (Figure 6) (Dova data on file, 2017c).

Figure 6. Pooled Analysis of Mean PLT CT by Treatment Group Over Time



PLT CT = platelet count.

Source: Terrault et al. (2018).

Of note, across both studies, only 3 patients treated with avatrombopag reached PLT CTs ≥200 × 10^9/L at any visit over the course of the study with the recommended dosing regimens (Terrault et al., 2018).

Safety Results

The primary safety data for avatrombopag consists of pooled safety data from ADAPT-1 and ADAPT-2. The safety analysis set included 430 patients who had received at least one dose of study drug and had one postdose safety assessment. Safety data were pooled and summarized into four treatment groups (Dova data on file, 2017c):

- Low baseline PLT CT cohort:
  - 60 mg avatrombopag group
  - Matching placebo group
- High baseline PLT CT cohort:
  - 40 mg avatrombopag group
  - Matching placebo group

Overall, the safety profile for avatrombopag was comparable to placebo, with no new or unexpected safety signals. In addition, there were no data to suggest an increased risk for hepatotoxicity, (Dova data on file, 2017c).

Table 10 presents the incidence of treatment-emergent adverse event (TEAEs) in the safety analysis set (Dova data on file, 2017c).

- The incidence of overall TEAEs was similar between patients in the combined avatrombopag and placebo treatment groups (54% vs 55%).
- Most TEAEs were of mild to moderate severity, with a similar percentage of patients experiencing TEAEs of grade 3 or above with avatrombopag and placebo (11% vs 10%).
- The percentage of patients with serious TEAEs was also similar in the combined avatrombopag and placebo treatment groups (7% vs 9%).
- Three (0.7%) treatment-emergent deaths were reported during the studies—two deaths with avatrombopag and one with placebo; all were assessed as unrelated to the study drug.
- Only 2 (0.7%) patients receiving avatrombopag had TEAEs leading to study drug withdrawal, and no patients in either group required other drug dose adjustments.
- Rates of study discontinuation due to a TEAE were similar between the avatrombopag and placebo groups (0.4% vs 0.6%).

The most common TEAEs (≥3%) that occurred in the combined avatrombopag and placebo treatment groups included pyrexia (10% vs 9%), abdominal pain (7% vs 6%), nausea (7% vs 7%), headache (6% vs 6%), fatigue (4% vs 3%), and peripheral edema (3% vs 2%) (Table 10) (DOPTELET (avatrombopag) prescribing information, 2018). No consistent pattern of AEs was identified between avatrombopag and placebo treatment groups or between the 60 mg and 40 mg avatrombopag treatment groups to suggest any dose-related toxicities. Overall, avatrombopag was well-tolerated in both dose groups, with an AE profile that was similar to that of placebo (Dova data on file, 2017c).

Table 10. Treatment-Emergent Adverse Events in ≥3% of Patients in ADAPT-1 and ADAPT-2

	Low Baseline PLT CT Cohort <40 × 10^9/L		High Baseline PLT CT Cohort 40 to <50 × 10^9/L		Combined Treatment Group Totals	
Preferred Term	**PBO (n = 91) %**	**AVA 60 mg (n = 159) %**	**PBO (n = 65) %**	**AVA 40 mg (n = 115) %**	**PBO (n = 156) %**	**AVA (n = 274) %**
Pyrexia	9%	11%	9%	8%	9%	10%
Abdominal pain	7%	6%	6%	7%	6%	7%
Nausea	8%	6%	6%	7%	7%	7%
Headache	8%	4%	5%	7%	6%	6%
Fatigue	4%	4%	2%	3%	3%	4%
Edema, peripheral	2%	3%	2%	4%	2%	3%

AVA = avatrombopag; PBO = placebo; PLT CT = platelet count; TEAE = treatment-emergent adverse event.

Source: DOPTELET (avatrombopag) prescribing information (2018).

Treatment-Emergent Bleeding Events

The overall incidence of TEAEs in the bleeding events category was low and similar in both treatment groups (WHO grade 1-4: 11% vs 12%,). Three percent (7/274) of patients treated with avatrombopag had a bleeding event of WHO grade 2 to 4 from randomization to 7 days after the procedure. Four percent (6/156) of patients treated with placebo had a WHO of grade 2 to 4 from randomization to 7 days after the procedure (Dova data on file, 2017c).

Treatment-Emergent Thromboembolic Events

There was one (0.4%) treatment-emergent portal vein thrombosis event reported in a patient treated with 40 mg of avatrombopag on study day 18 that was considered possibly related to avatrombopag (Dova data on file, 2017c).

The dose selection of avatrombopag in the two phase 3 trials focused on providing a predictable increase in PLT CT, while minimizing the number of patients with PLT CTs >200 × 10^9/L, which has been associated with a risk of thromboembolic events (Afdhal et al., 2012; Dova data on file, 2017c).

3 DOSSIER APPENDICES

3.1 Evidence Tables

Table 11. Evidence Table of Clinical Studies

Trial Name	Sample Size, Treatments, and Length of Follow-up	Study Design and Inclusion/Exclusion Criteria	Endpoints	Results
ADAPT-1 NCT01972529	Cohort 1: Lower baseline PLT CT cohort (<40 × 10^9/L) N = 138 ▪ 60 mg avatrombopag, n = 90 ▪ Placebo, n = 48 Cohort 2: Higher baseline PLT CT cohort (40 to <50 × 10^9/L) N = 93 ▪ 40 mg avatrombopag, n = 59 ▪ Placebo, n = 34 **Length of follow-up:** 5 days of treatment and follow-up for up to 30 days after last dose of study drug	**Study design:** Phase 3, global, multicenter, randomized, double-blind, placebo-controlled, parallel-group study **Inclusion criteria:** ▪ ≥ 18 years of age at screening with CLD ▪ Mean baseline PLT CT <50 × 10^9/L; PLT CTs were measured on two separate occasions, during screening and at baseline, and at least 1 day apart, with neither PLT CT >60 × 10^9/L ▪ Scheduled to undergo a permitted procedure and would otherwise require a platelet transfusion, per investigator's opinion ▪ MELD score ≤24 at screening ▪ If taking inhibitors of P-glycoprotein, except for verapamil, dose was required to be stable for 7 days before screening **Exclusion criteria:** ▪ A history of arterial or venous thrombosis (partial or complete)	**Primary endpoints:** ▪ Proportion of patients without platelet transfusion or any rescue procedure for bleeding **Secondary endpoints:** ▪ Proportion of patients who achieve PLT CT of ≥50 × 10^9/L on the procedure day ▪ Change from baseline in PLT CT on the procedure day	**Key results:** Primary efficacy results **Secondary endpoint results:** The proportion patients who achieved a PLT CT of ≥50 × 10^9/L on procedure day (*P*<.0001 in both cohorts): ▪ 68.9% for 60 mg avatrombopag vs 4.2% for placebo in cohort 1 ▪ 88.1% for 40 mg avatrombopag vs 20.6% for placebo in cohort 2 The observed mean change from baseline of PLT CT on the procedure day (*P*<.0001 in both the cohorts): ▪ Cohort 1: – 60 mg avatrombopag group: 31.9 × 10^9/L – Placebo: 1.1 × 10^9/L ▪ Cohort 2: – 40 mg avatrombopag group: 37.1 × 10^9/L – Placebo: 0.9 × 10^9/L **Safety results:**

Outcome	Cohort 1 Baseline Platelet Count <40 × 10^9/L		Cohort 2 Baseline Platelet Count 40 to <50 × 10^9/L	
	Placebo (n = 48)	Avatrombopag 60 mg (n = 90)	Placebo (n = 34)	Avatrombopag 40 mg (n = 59)
Responder	11 (22.9%)	59 (65.6%)	13 (38.2%)	52 (88.1%)
Nonresponder	32 (66.7%)	26 (28.9%)	19 (55.9%)	4 (6.8%)
Missing	5 (10.4%)	5 (5.6%)	2 (5.9%)	3 (5.1%)
Difference of response rate (95% CI)	42.6 (27.2-58.1)		49.9 (31.6-68.2)	
P value	<.0001		<.0001	

Trial Name	Sample Size, Treatments, and Length of Follow-up	Study Design and Inclusion/Exclusion Criteria	Endpoints	Results
		▪ Thrombosis (partial or complete) in the main portal vein, portal vein branches, or any part of the splenic nasoenteric system at screening ▪ Portal vein blood flow velocity rate <10 cm per second at screening ▪ Hepatic encephalopathy that cannot be effectively treated ▪ HCC, with BCLC staging classification C or D ▪ Platelet transfusion or receipt of blood products containing platelet within 7 days of screening ▪ Heparin, warfarin, NSAIDs, aspirin, verapamil, and antiplatelet therapy with ticlopidine or glycoprotein IIb/IIIa antagonists (eg, tirofiban) within 7 days of screening ▪ Use of erythropoietin-stimulating agents within 7 days of screening ▪ Use of interferon within 14 days of screening		▪ The incidence rates of TEAEs, treatment-related TEAEs, and TEAEs with CTCAE grade 3 or above were similar between the avatrombopag and the placebo groups. ▪ There were a total of 84 (57.1%) patients in the avatrombopag groups and 49 (61.3%) patients in the placebo groups that reported any TEAEs during the study. ▪ Most adverse events were mild to moderate. The most commonly reported TEAEs for avatrombopag (≥5%) were abdominal pain, pyrexia, headache, and nausea (across both cohorts).

<table>
<tr><th>Trial Name</th><th>Sample Size, Treatments, and Length of Follow-up</th><th>Study Design and Inclusion/Exclusion Criteria</th><th>Endpoints</th><th>Results</th></tr>
<tr>
<td>ADAPT-2
NCT01976104</td>
<td>Lower baseline PLT CT cohort (<40 × 10^9/L) N = 113
▪ 60 mg avatrombopag, n = 70
▪ Placebo, n = 43

Higher baseline PLT CT cohort (40 to <50 × 10^9/L) N = 91
▪ 40 mg avatrombopag, n = 58
▪ Placebo, n = 33

Length of follow-up:
5 days of treatment and follow-up for up to 30 days after last dose of study drug</td>
<td>Study design:
Same as ADAPT-1
Inclusion criteria:
Same as ADAPT-1
Exclusion criteria:
Same as ADAPT-1</td>
<td>Primary endpoints:
Same as ADAPT-1
Secondary endpoints:
Same as ADAPT-1</td>
<td>Key results:
Primary efficacy results
<table>
<tr><th></th><th colspan="2">Cohort 1
Baseline PLT CT
<40 × 10^9/L</th><th colspan="2">Cohort 2
Baseline PLT CT
40 to <50 × 10^9/L</th></tr>
<tr><th>Outcome</th><th>Placebo (n = 43)</th><th>Avatrombopag 60 mg (n = 70)</th><th>Placebo (n = 33)</th><th>Avatrombopag 40 mg (n = 58)</th></tr>
<tr><td>Responder</td><td>15 (34.9%)</td><td>48 (68.6%)</td><td>11 (33.3%)</td><td>51 (87.9%)</td></tr>
<tr><td>Nonresponder</td><td>25 (58.1%)</td><td>20 (28.6%)</td><td>21 (63.6%)</td><td>6 (10.3%)</td></tr>
<tr><td>Missing</td><td>3 (7.0%)</td><td>2 (2.9%)</td><td>1 (3.0%)</td><td>1 (1.7%)</td></tr>
<tr><td>Difference of response rate (95% CI)</td><td colspan="2">33.7 (15.8-51.6)</td><td colspan="2">54.6 (36.5-72.7)</td></tr>
<tr><td>P value</td><td colspan="2">.0006</td><td colspan="2"><.0001</td></tr>
</table>
Secondary endpoint results:
The proportion patients who achieved a PLT CT of ≥50 × 10^9/L on procedure day (P<.0001 in both cohorts):
▪ 65.7% for 60 mg avatrombopag vs 7.0% for placebo in cohort 1
▪ 93.1% for 40 mg avatrombopag vs 39.4% for placebo in cohort 2

The observed mean change from baseline of PLT CT on the procedure day (P<.0001 in both the cohorts):
▪ Cohort 1:
– 40 mg avatrombopag group: 30.4 × 10^9/L
– Placebo: 3.0 × 10^9/L
▪ Cohort 2:
– 60 mg avatrombopag group: 44.9 × 10^9/L
– Placebo: 5.7 × 10^9/L

Safety results:
▪ The incidence rates of TEAEs, treatment-related TEAEs, and TEAEs with CTCAE grade 3 or above were similar between the</td>
</tr>
</table>

<table>
<tr><th>Trial Name</th><th>Sample Size, Treatments, and Length of Follow-up</th><th>Study Design and Inclusion/Exclusion Criteria</th><th>Endpoints</th><th>Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td>avatrombopag and the placebo groups.
▪ There were a total of 64 (50.4%) patients in the avatrombopag groups and 37 (48.7%) patients in the placebo groups who reported any TEAEs during the study.
▪ Most adverse events were mild to moderate. The most commonly reported TEAEs for avatrombopag (≥5%) were pyrexia and nausea (across both cohorts).</td></tr>
<tr><td>Study 202
Terrault et al. (2014)
NCT00914927</td><td>Cohort A (1st-generation formulation)
N = 67
▪ Avatrombopag 100 mg loading dose plus 20 mg on days 2-7, n = 18
▪ Avatrombopag 100 mg loading dose plus 40 mg on days 2-7, n = 16
▪ Avatrombopag 100 mg loading dose plus 80 mg on days 2-7, n = 17
▪ Placebo, n = 16

Cohort B (2nd-generation formulation)
N = 63
▪ Avatrombopag 80 mg loading dose plus 10 mg on days 2-7, n = 21
▪ Avatrombopag 80 mg loading dose plus 20 mg on days 2-4, n = 21
▪ Placebo, n = 21

Length of follow-up:
8 days of treatment and follow-up for up to 30 days after last dose of study drug</td><td>Study design:
Phase 2, multicenter, randomized, placebo-controlled, double-blind, parallel-group study

Inclusion criteria:
▪ ≥18 years old
▪ CLD secondary to viral hepatitis NASH or alcoholic liver disease
▪ MELD score ≤24
▪ Two independent baseline PLT CT ranging from 10 to 58 × 10^9/L
▪ A procedure scheduled 1-4 days after the last dose of avatrombopag or placebo
▪ Life expectancy ≥3 months

Exclusion criteria:
▪ Presence of any primary hematologic disorder
▪ Idiopathic thrombocytopenic purpura of any cause
▪ A history of arterial or</td><td>Primary endpoints:
▪ Achievement of PLT CT increase of ≥20 × 10^9/L from baseline and >50 × 10^9/L at least once during days 4-8

Exploratory endpoints:
▪ Proportion of patients achieving a PLT CT >75 × 10^9/L or >100 × 10^9/L at least once from days 4-8</td><td>Key efficacy results:
▪ In the ITT population, the proportion of responders among all avatrombopag-treated patients was 48.4%, compared with 8.1% in the placebo group (P<.0001).

Proportion of patients achieving primary endpoint (ITT population) in cohort A
<table><tr><th></th><th>Placebo</th><th colspan="4">Avatrombopag</th></tr><tr><th></th><th></th><th>20 mg</th><th>40 mg</th><th>80 mg</th><th>Total</th></tr><tr><td>Response, n (%)</td><td>1 (6.3)</td><td>7 (38.9)</td><td>5 (31.3)</td><td>13 (76.5)</td><td>25 (49.0)</td></tr><tr><td>95% CI</td><td>0.2-30.2</td><td>17.3-64.3</td><td>11.0-58.7</td><td>50.1-93.2</td><td>34.8-63.4</td></tr><tr><td>Vs placebo</td><td></td><td>.0425</td><td>.1719</td><td><.0001</td><td>.0005*</td></tr></table>* Global test using chi-square test.

Proportion of patients achieving primary endpoint (ITT population) in cohort B
<table><tr><th></th><th>Placebo</th><th colspan="3">Avatrombopag</th></tr><tr><th></th><th></th><th>10 mg</th><th>20 mg</th><th>Total</th></tr><tr><td>Response, n (%)</td><td>2 (9.5)</td><td>9 (42.9)</td><td>11 (52.4)</td><td>20 (47.6)</td></tr><tr><td>95% CI</td><td>1.2-30.4</td><td>21.8-66.0</td><td>29.8-74.3</td><td>32.0-63.6</td></tr><tr><td>Vs placebo</td><td></td><td>0.0325</td><td>0.0063</td><td>0.0093*</td></tr></table>* Global test using chi-square test.

▪ The proportion of patients with a PLT CT >75 × 10^9/L prior to procedure:
– 22.2%-41.2% for cohort A in the avatrombopag group vs 6.3% in</td></tr>
</table>

Trial Name	Sample Size, Treatments, and Length of Follow-up	Study Design and Inclusion/Exclusion Criteria	Endpoints	Results
		venous thrombosis		the placebo group – 14.3%-33.3% for cohort B in the avatrombopag group vs 0% in the placebo group ▪ A PLT CT of >100 × 10^9/L prior to procedure occurred in 0%-17.6% of patients treated with avatrombopag vs 0% in the placebo group. **Safety results:** ▪ The overall incidence of adverse events was similar between the avatrombopag and placebo groups. ▪ Nausea, fatigue, and headache were the most common adverse events in patients receiving avatrombopag or placebo (occurring in >2 patients in any treatment group). ▪ 17.2% of avatrombopag-treated patients and 10.8% of placebo patients had SAEs; in both groups, most SAEs were due to complications of cirrhosis.

Trial Name	Sample Size, Treatments, and Length of Follow-up	Study Design and Inclusion/Exclusion Criteria	Endpoints	Results
Study 204 NCT00914927	N = 39 Once-daily dosing for 5 days: ▪ Avatrombopag 20 mg group: 1 × 20 mg avatrombopag and 2 × placebo ▪ Avatrombopag 40 mg group: 2 × 20 mg avatrombopag and 1 × placebo ▪ Avatrombopag 60 mg group: 3 × 20 mg avatrombopag tablets ▪ Placebo group: 3 × placebo **Procedure day:** Scheduled procedure at the discretion of the investigator if PLT CT ≤200 × 10^9/L after efficacy assessment and 5-8 days after last dose	Phase 2 double-blind, placebo-controlled, parallel-group randomized controlled trial June 23, 2014, to April 1, 2015 21 sites in Japan	**Primary:** Proportion of patients with PLT CT ≥50 × 10^9/L and changes from baseline ≥20 × 10^9/L at visit 4 (day 10 [+3]) **Secondary:** Proportion of patients with PLT CT ≥50 × 10^9/L, ≥75 × 10^9/L, ≥150 × 10^9/L, and ≥200 × 10^9/L at each visit; PLT CT and change from baseline in PLT CT at each visit	**Key efficacy results:** ▪ In the combined efficacy analysis, responder rates were higher with avatrombopag (20 mg, 28.6%; 40 mg, 63.6%; 60 mg, 40.0%) compared with placebo (9.1%). Rates were statistically significant in the avatrombopag 40 mg (*P*=.004) and 60 mg (*P*=.024) groups. ▪ The proportion of patients with PLT CT ≥50 × 10^9/L at visit 4 (procedure day) was also higher in all the combined avatrombopag treatment groups (20 mg, 71.4%; 40 mg, 81.8%, and 60 mg, 50.0%) compared with placebo (9.1%). The treatment difference was significant in the 20-mg (*P*=.012) and 40-mg (*P*=.001) groups but not in the 60-mg group (*P*=.063). Increased PLT CT was shown in all avatrombopag treatment groups over the course of the study. The increase in mean PLT CT was noted starting on day 4 (visit 3) and peaked on procedure day at approximately 1.3-1.9 times the respective baseline PLT CT in avatrombopag-treated patients. By 7 days postprocedure (visit 5), PLT CTs had already decreased in all 3 combined avatrombopag treatment groups; by day 35 (visit 6), they had returned to baseline levels.

BCLC = Barcelona Clinic Liver Cancer; CI = confidence interval; CLD = chronic liver disease; CTCAE = Common Terminology Criteria for Adverse Events; HCC = hepatocellular carcinoma; ITT = intent-to-treat; MELD = Model for End-Stage Liver Disease; NASH = nonalcoholic steatohepatitis; NSAID = nonsteroidal anti-inflammatory drug; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

3.2 Systematic Literature Review

Table A-1 through Table A-2 present the literature search strategies conducted on April 4, 2019, in the PubMed, Embase, Cochrane Library database, and Biosis databases, respectively. Table A-5 presents the summary of the results of these searches. No limits regarding data or language of publication were applied for the literature searches.

Table A-1. Clinical Review: PubMed Literature Search Strategy (Conducted April 4, 2019) Limits: Humans; No comments, letters, editorials, case reports, or phase I clinical trials

Search No.	Search Terms	No. of Records
Population		
#1	"Thrombocytopenia"[MeSH] OR thrombocytopenia*[Text Word] OR thrombocytopaenia*[Text Word] OR thrombopenia*[Text Word] OR "thrombopoietin deficiency"[Text Word] OR (("Thrombopoietin"[MeSH] OR "thrombopoietin"[Text Word] OR "megakaryocyte colony stimulating factor"[Text Word] OR "megakaryocyte growth and development factor"[Text Word] OR "thrombocytopoietin"[Text Word] OR "mpl ligand"[Text Word] OR "myeloproliferative leukemia virus oncogene ligand"[Text Word] OR "thrombocytopoiesis-stimulating factor"[Text Word] OR "thrombocytopoiesis stimulating factor"[Text Word] OR "c-mpl ligand"[Text Word] OR "MGDF factor"[Text Word]) AND ("deficiency"[Subheading] OR deficienc*[Text Word])) OR low platelet count*[Text Word]	73,261
#2	"Hepatic Insufficiency"[MeSH] OR "liver insufficiency"[Text Word] OR "hepatic insufficiency"[Text Word] OR "Liver Failure"[MeSH] OR "liver failure"[Text Word] OR "hepatic failure"[Text Word] OR "End Stage Liver Disease"[MeSH] OR "end stage liver disease"[Text Word] OR chronic liver disease*[Text Word] OR chronic liver dysfunction*[Text Word] OR ((liver disease*[Title/Abstract] OR liver dysfunction*[Title/Abstract]) AND chronic[Title]) OR "Hepatitis C, Chronic"[MeSH] OR "chronic hepatitis C"[Text Word] OR "chronic hep C"[Text Word] OR ("HCV"[Text Word] AND "chronic"[Text Word]) OR "Hepatitis"[MeSH] OR hepatitis[Text Word] OR "Liver Cirrhosis"[MeSH] OR "liver cirrhosis"[Text Word] OR "liver cirrhoses"[Text Word] OR "hepatic cirrhoses"[Text Word] OR "hepatic cirrhosis"[Text Word] OR "liver fibrosis"[Text Word] OR "liver fibroses"[Text Word] OR "cirrhosis of the liver"[Text Word]	351,079
#3	"Platelet Transfusion"[MeSH] OR platelet transfusion*[Text Word] OR ("platelet"[Text Word] AND "transfusion"[Text Word]) OR ("plasma"[Text Word] AND "transfusion"[Text Word]) OR "Avatrombopag"[Text Word] OR "Eltrombopag"[Text Word] OR "Lusutrombopag"[Text Word] OR "Romiplostim"[Text Word]	27,065
#4	#1 AND #2 AND #3	264

Search No.	Search Terms	No. of Records
Exclusions		
#5	"Animals"[MeSH] NOT "Humans"[MeSH]	4,567,050
#6	"Comment"[Publication Type] OR "Letter"[Publication Type] OR "Editorial"[Publication Type] OR "Case Reports"[Publication Type] OR "Clinical Trial, Phase I"[Publication Type] OR "case study"[Title] OR "case studies"[Title] OR case report*[Title] OR "case series"[Title]	3,617,651
Total		
#7	#4 NOT (#5 OR #6)	**194**

Table A-2. Clinical Review: Embase Literature Search Strategy (Conducted April 4, 2019) Limits: Humans; No comments, letters, editorials, case reports, phase I clinical trials, or conference abstracts

Search No.	Search Terms	No. of Records
Population		
#1	('thrombocytopenia'/exp OR thrombocytopenia*:de,ab,ti OR thrombocytopaenia*:de,ab,ti OR thrombopenia*:de,ab,ti OR 'thrombopoietin deficiency':de,ab,ti OR (('thrombopoietin'/exp OR 'thrombopoietin':de,ab,ti OR 'megakaryocyte colony stimulating factor':de,ab,ti OR 'megakaryocyte growth and development factor':de,ab,ti OR 'thrombocytopoietin':de,ab,ti OR 'mpl ligand':de,ab,ti OR 'myeloproliferative leukemia virus oncogene ligand':de,ab,ti OR 'thrombocytopoiesis-stimulating factor':de,ab,ti OR 'thrombocytopoiesis stimulating factor':de,ab,ti OR 'c-mpl ligand':de,ab,ti OR 'mgdf factor':de,ab,ti) AND deficienc*:de,ab,ti) OR ((low NEXT/1 platelet NEXT/1 count*):de,ab,ti)) AND [embase]/lim	153,713
#2	('liver failure'/exp OR 'liver insufficiency':de,ab,ti OR 'hepatic insufficiency':de,ab,ti OR 'liver failure':de,ab,ti OR 'hepatic failure':de,ab,ti OR 'end stage liver disease'/exp OR 'end stage liver disease':de,ab,ti OR ((chronic NEXT/1 liver NEXT/1 disease*):de,ab,ti) OR ((chronic NEXT/1 liver NEXT/1 dysfunction*):de,ab,ti) OR ((((liver NEXT/1 disease*):ti,ab) OR ((liver NEXT/1 dysfunction*):ti,ab)) AND chronic:ti) OR 'chronic hepatitis c'/exp OR 'chronic hepatitis c':de,ab,ti OR 'chronic hep c':de,ab,ti OR ('hcv':de,ab,ti AND 'chronic':de,ab,ti) OR 'hepatitis'/exp OR hepatitis:de,ab,ti OR 'liver cirrhosis'/exp OR 'liver cirrhosis':de,ab,ti OR 'liver cirrhoses':de,ab,ti OR 'hepatic cirrhoses':de,ab,ti OR 'hepatic cirrhosis':de,ab,ti OR 'liver fibrosis':de,ab,ti OR 'liver fibroses':de,ab,ti OR 'cirrhosis of the liver':de,ab,ti) AND [embase]/lim	445,084
#3	('thrombocyte transfusion'/exp OR ((platelet NEXT/1 transfusion*):de,ab,ti) OR ('platelet':de,ab,ti AND 'transfusion':de,ab,ti) OR ('plasma':de,ab,ti AND 'transfusion':de,ab,ti) OR 'avatrombopag':de,ab,ti OR 'eltrombopag':de,ab,ti OR 'lusutrombopag':de,ab,ti OR 'romiplostim':de,ab,ti) AND [embase]/lim	47,354
#4	#1 AND #2 AND #3	1,125
Exclusions		
#5	'animal'/exp NOT 'human'/exp AND [embase]/lim	3,591,050

Search No.	Search Terms	No. of Records
#6	(comment*:ti OR letter:it OR editorial:it OR 'case report'/exp OR 'phase 1 clinical trial'/exp OR 'conference paper':it OR 'conference abstract':it OR 'case study':ti OR 'case studies':ti OR ((case NEXT/1 report*):ti) OR 'case series':ti) AND [embase]/lim	6,535,157
Total		
#7	#4 NOT (#5 OR #6)	**489**

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

ID1520 Avatrombopag and lusutrombopag for treating thrombocytopenia in people with chronic liver disease needing an elective procedure

Company evidence submission for lusutrombopag

April 2019

File name	Version	Contains confidential information	Date
ID1520_Lusutrombopag MTA_12.04.19_v1	**1**	Yes	12.04.19

Contents

Tables and figures

Abbreviations

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
BMI	Body mass index
CI	Confidence interval
CLD	Chronic liver disease
CMH	Cochran-Mantel-Haenszel
CPI	Consumer Price Index
CSR	Clinical study report
DSU	Decision Support Unit
EIS	endoscopic injection sclerotherapy
EMA	European Medicines Agency
EU	European Union
EVL	endoscopic variceal ligation
FAS	Full analysis set
FDA	Food and Drugs Administration
FFP	Fresh-frozen plasma
HLA	Human leukocyte antigen
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ITC	Indirect treatment comparison
ITT	Intention to treat
IVRS	Interactive voice response system
IWRS	Interactive web response system
LUSU	Lusutrombopag
MCT	Microwave coagulation therapy
MIMS	Monthly Index of Medical Specialities
N/A	Not applicable
NAFLD	Non-alcoholic fatty liver disease
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
NR	Not reported
OR	Odds ratio
PIM	Promising Innovative Medicine
PMDA	Pharmaceuticals and Medical Devices Agency
PP	Per-protocol
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services

PT	Platelet transfusion
PVT	Portal vein thrombosis
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RFA	radiofrequency ablation
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
TACE	Transcatheter arterial chemoembolization
TACO	Transfusion associated circulatory overload
TPO	Thrombopoietin
TRALI	Transfusion-related acute lung injury
TSD	Technical Support Document
UKMi	UK Medicines Information
WHO	World Health Organisation
WTP	Willingness-to-pay

1 Executive Summary

Severe Thrombocytopenia in chronic liver disease patients undergoing planned invasive procedures and clinical need

- Chronic liver disease (CLD) encompasses several long-term liver diseases such as viral hepatitis and alcoholic liver disease, and is generally characterised by gradual, irreversible liver damage and multiple comorbid complications. With appropriate treatment, the majority of patients can survive their CLD,[1] however, management of both CLD and any comorbid conditions frequently requires pharmacological therapies and invasive procedures, the latter being an essential part of clinical management.
- Thrombocytopenia is a reduction in the number of circulating platelets in the blood, often defined as a platelet count <150,000/μL blood.[2] Regardless of the aetiology of CLD, thrombocytopenia and CLD are often comorbid, with thrombocytopenia developing in up to 76% of CLD patients.[2, 3]
- Thrombocytopenia is considered a major contributory factor to an increased risk of bleeding during and after invasive diagnostic and therapeutic procedures, such as those required to effectively manage patients with CLD. Furthermore, severe thrombocytopenia, defined as a platelet count <50,000/μL and occurring in 1–2.6% of the CLD population,[2, 4, 5] is associated with an increased risk of potentially serious bleeding events during or after an invasive procedure.[6] Severe thrombocytopenia in CLD may delay or prevent the diagnostic and therapeutic procedures critical to the care of this patient population, potentially exacerbating the condition of a patient or increasing their morbidity and mortality.[3, 7]
- Between 2017–2018, Hospital Episode Statistics (diagnosis codes K70-K77) showed 45,565 admissions with a primary diagnosis of liver disease in England.[8]

Platelet transfusion

- In the UK, platelet transfusion is the standard of care, and only non-surgical treatment option available, for the management of severe thrombocytopenia associated with CLD in patients undergoing planned invasive procedures,[9] and lusutrombopag is the only licensed pharmaceutical treatment option available for this indication in the European Union (EU) and UK. Surgical treatments include splenectomy and splenic artery embolisation, but these are not considered as treatments for elective surgery.[10]
- Whilst platelet transfusion is a valid treatment option when used appropriately,[9] it can be associated with a number of complications including transfusion-related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), allergic and febrile non-haemolytic reactions and risk of infection.
- Challenges associated with platelet transfusion include a limited platelet life span (3–4 days before re-dosing required), and relatively high cost.[7] Furthermore, the haematological effect of platelets is short lived with a progressive decline in platelet increments reported 1 hour and 18–24 hours post-transfusion.[11]
- Accordingly, platelet transfusions may not prevent post-procedural bleeding or bleeding associated with repeat procedures, and further transfusions may be required.[12, 13]
- Patients may become platelet refractory after multiple platelet transfusions.[7] Patients with CLD typically require multiple procedures to manage their progressive liver disease and other health conditions; development of platelet refractoriness from multiple platelet transfusions reduces the options available to provide prophylactic treatment to reduce risk of bleeding prior to a given invasive procedure.[15] This would be a particular concern for patients requiring liver transplant, where antibody-antigen cross-matching will be tested for.[14]
- Given the limitations associated with the current clinical management of this patient population, and the lack of other licensed pharmacological treatments, there is a substantial unmet medical, ethical and economic need in this population. These patients commonly receive platelet transfusions to reduce the risk of procedural bleeding, to treat secondary bleeding complications and to allow repeat procedures, and can thus be exposed repeatedly to the risks associated with these transfusions, with unwanted clinical variation.[16]

Lusutrombopag

- Lusutrombopag is the first and only pharmacological treatment for the management of severe thrombocytopenia in CLD patients undergoing planned invasive procedures in the EU and UK. Lusutrombopag has recently received marketing authorisation from the European Commission (18th February 2019) and is licensed for "the treatment of severe thrombocytopenia in adult patients with chronic liver disease undergoing invasive procedures".[17] Lusutrombopag 3 mg is administered orally once daily for 7 days prior to the planned invasive procedure.
- Lusutrombopag is an orally active, small-molecule thrombopoietin (TPO) receptor agonist that targets the c-Mpl TPO cell surface receptor on megakaryocytes to stimulate platelet production.[18]
- Two pivotal Phase 3 randomised clinical trials (RCTs), L-PLUS 1 and L-PLUS 2, and a Phase 2b RCT, provide evidence that lusutrombopag is efficacious in the treatment of CLD patients with severe thrombocytopenia undergoing a planned invasive procedure, which is in line with the marketing authorisation and anticipated position of lusutrombopag in the clinical pathway.[19-22]
- In L-PLUS 1, L-PLUS 2, and a Phase 2b study, lusutrombopag was shown to increase the platelet count of patients above a 50,000/μL threshold, thereby reducing the need for platelet transfusions and permitting a broader "procedure window" in which to undertake planned invasive procedures, in comparison to treatment with placebo and platelet transfusion.[19-22]
- In L-PLUS 1, significantly more patients met the primary endpoint, of not requiring platelet transfusion prior to the planned invasive procedure (mandated at 50,000/μL), in the lusutrombopag group (79.2%) than the placebo group (12.5%; p<0.0001).[19] A sensitivity analysis using the per-protocol population of L-PLUS 1 demonstrated that the number of patients reaching the primary endpoint was significantly greater in the lusutrombopag group ([redacted] than placebo group ([redacted]).[19]
- Similarly, the primary endpoint was met in L-PLUS 2, with significantly more patients not requiring platelet transfusion prior to the planned invasive procedure and no rescue therapy for bleeding from randomisation through seven days after the procedure in the lusutrombopag group (64.8%) than in the placebo group (29.0%; p<0.0001).[20, 21, 23] A sensitivity analysis using the per-protocol population of L-PLUS 2 demonstrated that the number of patients reaching the primary endpoint was significantly greater in the lusutrombopag group (72.5%) than placebo group (20.2%, p<0.0001).[20, 21]
- Results from the Phase 2b trial were consistent with L-PLUS 1 and L-PLUS 2; 81.3% of patients in the lusutrombopag group and 20.0% of patients in the placebo group did not require pre-operative platelet transfusion, the primary endpoint.[22]
- The proportion of patients requiring platelet transfusion was lower in the lusutrombopag group than in the placebo group in both L-PLUS 1 (lusutrombopag, [redacted]%; placebo, [redacted]%) and L-PLUS 2 (lusutrombopag, 31.5%; placebo, 68.2%).[19, 24] In patients who received a platelet transfusion, the average dose transfused per patient was also less in the lusutrombopag group than in the placebo group (L-PLUS 1, [redacted] units versus [redacted] units; L-PLUS 2, [redacted] versus [redacted] platelets transfused).
- Significantly more patients met the responder criterion (defined as achieving platelet count of ≥ 50,000/μL with an increase of ≥ 20,000/μL from baseline) in the lusutrombopag group than in the placebo group in both L-PLUS 1 (lusutrombopag, 77.1%; placebo, 6.3%; p<0.0001) and L-PLUS 2 (lusutrombopag, 64.8%; placebo, 13.1%; p<0.0001).[19, 20, 23, 24] Similarly, higher proportions of patients in the lusutrombopag arm (68.8%) than the placebo arm (6.7%) met the responder criteria in the Phase 2b study.[22]
- Data from the re-analysis of L-PLUS 1 reported in the SmPC and presented in Appendix C.4.1, demonstrates that for all patients (with and without platelet transfusion), the duration of platelet count increase was significantly greater in the lusutrombopag arm (21.1 days) than placebo arm (3.4 days, p=0.0197).[25] Similarly, for L-PLUS 2, the duration of maintenance of platelet count increase was significantly longer in the lusutrombopag arm (15.1 days) than in the placebo arm (1.0 days, p=0.0002) (Table 17).[20, 21, 23]
- In a pooled analysis of the Phase 2b study, L-PLUS 1 and L-PLUS 2, the incidences of overall adverse events were comparable between the lusutrombopag and placebo groups.[26] Serious nonfatal adverse events occurred at a lower rate in patients treated with lusutrombopag (4%) than in patients treated with placebo (7%).[26] Three (1.8%) subjects treated with lusutrombopag 3 mg and 4 (2.4%) treated with placebo had a thrombotic event.[26]

Innovation

- As the first licensed pharmacological therapy in this indication, lusutrombopag offers a number of clinical benefits over the current standard of care, and has been shown to consistently and sustainably raise platelet counts in severely thrombocytopenic CLD patients undergoing planned invasive procedures.[26] This has been acknowledged through receipt of a positive Promising Innovative Medicine (PIM) designation.
- By raising platelet counts above 50,000/μL for approximately 3 weeks in the majority of patients, the use of platelet transfusions can be avoided not only for the initial planned procedure but for any additional procedures that might be needed during the time platelet counts remain above 50,000/μL.[13, 26]
- Lusutrombopag is also associated with a number of benefits that may not be captured within the NICE cost-utility framework. Patients treated with lusutrombopag are expected to be less likely to require repeated, invasive platelet transfusion and its associated risks, reducing potential worry for patients and carers.[7] Lusutrombopag additionally provides a pharmaceutical treatment option for patients who are platelet refractory. Additionally, lusutrombopag may also reduce inequalities by providing a licensed pharmaceutical treatment option for certain social and religious groups, who may be unable to receive transfusions.
- Lusutrombopag is administered orally, and therefore has the potential to reduce the pre-operative treatment burden attributable to platelet transfusions experienced by patients in addition to making more beds available; hospital attendance would be required by fewer patients the day before an invasive procedure to receive a platelet transfusion, and patients may be discharged from the hospital setting sooner post-operatively. Finally, lusutrombopag may be able to reduce unwanted local variation in clinical quality and efficiency.

Comparative effectiveness

- No indirect treatment comparison (ITC) was presented for lusutrombopag vs avatrombopag; There were important and potentially clinically meaningful differences in the design of the avatrombopag trials compared to that of lusutrombopag. Avatrombopag is not licensed within the UK or used within the NHS, and there is uncertainty regarding the final indication of this product.

Cost-effectiveness

- A *de novo* model was developed to assess lusutrombopag for CLD patients with severe thrombocytopenia undergoing planned invasive procedures. A short-term (decision tree) model presents an ICER based on the QALY benefit demonstrated during the 35-day clinical trial period; a long-term (Markov) model presents an ICER based on QALY benefit and mortality over a lifetime time horizon.
- The base case of the model compared lusutrombopag to platelet transfusion, the current standard of care, with efficacy data based on the pooled lusutrombopag trials (Phase 2b, L-PLUS 1 and L-PLUS 2). Additional inputs, including mortality estimates, utility values and costs were derived from the literature.
- The model was constructed from a UK NHS and Personal Social Services (PSS) perspective, and where appropriate, costs and outcomes were annually discounted at 3.5%.
- Economic modelling indicates that lusutrombopag is cost saving, and delivers increased QALYs; total costs were estimated to be £172 lower with lusutrombopag than with platelet transfusion, and lusutrombopag was projected to yield 0.0147 more QALYs than platelet transfusion. The ICER for lusutrombopag versus platelet transfusion was therefore dominant. Given a WTP threshold of £20,000/QALY, the probability of being cost-effective was 81%; at a willingness-to-pay (WTP) threshold of £30,000/QALY, the probability of being cost-effective was 87%.

Conclusion

- There is a clear unmet need for CLD patients with severe thrombocytopenia undergoing planned invasive procedures, and the current standard of care, platelet transfusion, is associated with a number of limitations, as acknowledged through a positive PIM designation.
- Lusutrombopag has been demonstrated to reduce the need for platelet transfusion; by raising platelet counts above 50,000/μL for approximately 3 weeks on average, the use of platelet transfusions can be avoided not only for the initial planned procedure but may also be avoided for any additional procedures that might be needed during the time platelet counts remain above

50,000/μL.[13, 26]

- Lusutrombopag has been demonstrated to be cost-saving for the treatment of severe thrombocytopenia in patients with CLD, with an 81% probability of being cost-effective at a WTP threshold of £20,000/QALY.
- Lusutrombopag therefore represents a valuable new treatment option for the NHS benefiting patient and payer alike and, given that it meets the criteria for a Fast-Track Appraisal, it is hoped that a positive recommendation will be made as rapidly as possible, irrespective of the Multiple Technology Appraisal process.

2 Background

2.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication. The decision problem for this appraisal is outlined 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	Adult patients with thrombocytopenia associated with chronic liver disease needing an elective procedure.	Adult patients with severe thrombocytopenia associated with chronic liver disease needing a planned invasive procedure.	Lusutrombopag is indicated for use in individuals with severe thrombocytopenia associated with chronic liver disease needing a planned invasive procedure.
Intervention	Avatrombopag Lusutrombopag	Lusutrombopag	As per the scope.
Comparator(s)	Established clinical management without avatrombopag and lusutrombopag (including, but not limited to platelet transfusion).	Established clinical management without lusutrombopag.[9]	There is no direct head-to-head clinical evidence between lusutrombopag and avatrombopag, and it was not deemed appropriate to perform an indirect treatment comparison. There were a number of differences between the lusutrombopag and avatrombopag clinical trials when considering a number of important factors. These included, but are not limited to, determination of primary and secondary endpoints, as well as other study design aspects, including imaging. Furthermore,

			avatrombopag is not licensed in Europe, it is unclear what the final license will be, and is not considered standard of care in UK clinical practice.
Outcomes	The outcome measures to be considered include: • platelet count • response rate • number of platelet transfusions • number of blood transfusions • return to operating theatre • need for rescue treatments • use of concurrent treatments • bleeding score • mortality • adverse effects of treatment • health-related quality of life	The outcome measures included are: • platelet count • response rate • number of platelet transfusions • need for rescue treatments • use of concurrent treatments • bleeding score • mortality • adverse effects of treatment	Excluded outcomes (number of blood transfusions, return to operating theatre and health-related quality of life) not available from the lusutrombopag clinical evidence base.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year The 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.	As per the scope.	As per the scope.
Special considerations including issues related to equity or	N/A	Religious groups Platelet refractory patients	Lusutrombopag may reduce inequalities as the first pharmaceutical treatment option available to help raise platelet counts in CLD

equality			with severe thrombocytopenia prior to planned procedures in patients who are platelet refractory and for certain social and religious groups (for example, Jehovah's Witnesses), who may be unable to receive transfusions.

Abbreviations: NICE, National Institute for Health and Care Excellence; NHS, National Health Service.
Source: NICE final scope.[27]

2.2 Description of the technology being appraised

A brief overview of lusutrombopag is provided in Table 2.

Table 2. Lusutrombopag

UK approved name and brand name	Lusutrombopag
Mechanism of action	Lusutrombopag is an orally active thrombopoietin (TPO) receptor agonist. Lusutrombopag acts on the haematopoietic stem cells and on the transmembrane domain of human TPO receptors expressed in megakaryocytes, to stimulate the megakaryocytes to proliferate and differentiate via the same signal transduction pathway for up-regulating production activated by endogenous TPO, thus leading to thrombocytopoiesis (platelet generation).
Marketing authorisation	Lusutrombopag has recently received marketing authorisation from the EMA on 18th February 2019. Lusutrombopag received PMDA approval in Japan in September 2015, for managing thrombocytopenia associated with CLD in patients undergoing a planned invasive procedure, and received FDA approval in the US on July 31st 2018.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Lusutrombopag is indicated for the treatment of severe thrombocytopenia in adult patients with chronic liver disease undergoing invasive procedures.
Method of administration and dosage	Lusutrombopag is administered orally; the recommended dose is 3 mg once daily for 7 days. The invasive procedure should be performed from day 9 after the start of lusutrombopag treatment.
Additional tests or investigations	Platelet count should be measured prior to the procedure. This is not specific to lusutrombopag, but is advisable for any potential treatment for this indication.
List price and average cost of a course of treatment	The NHS list price of lusutrombopag is £800 per 7-day treatment course.
Patient access scheme (if applicable)	None

Abbreviations: EMA, European medicines agency; PMDA; Pharmaceuticals and Medical Devices Agency; TPO, thrombopoietin.
Source: Lusutrombopag Summary of Product Characteristics[25]; Shionogi & Co Ltd, 2015.[28]

2.3 Health condition and position of the technology in the treatment pathway

Summary of Health Condition and Position of the Technology

- Chronic liver disease (CLD) encompasses several long-term liver diseases such as viral hepatitis and alcoholic liver disease.[29]
- Between 2017–2018, there were 45,565 admissions with a primary diagnosis of liver disease in England;[8] up to 76% of CLD patients develop comorbid thrombocytopenia, and 1–2.6% of those develop severe thrombocytopenia (platelet count <50,000/µL).[2, 4, 5]
- Patients with CLD often require invasive diagnostic and therapeutic procedures to effectively manage their condition, and severe thrombocytopenia is considered a major contributory risk factor to bleeding during and after such procedures.[6, 7]
- Severe thrombocytopenia in CLD may delay or prevent diagnostic and therapeutic procedures critical to the care of this patient population, potentially exacerbating the condition of a patient or increasing their morbidity and mortality.[3, 7]
- There are no reimbursed pharmacological treatments available for this indication and there is a substantial unmet need in this population.
- The current standard of care is platelet transfusion; prophylactic use of platelet transfusion can be associated with a number of issues including the risk of adverse events and a limited effectiveness in CLD patients.[7, 30]
- Lusutrombopag is an oral TPO receptor agonist that targets the c-Mpl TPO cell surface receptor on megakaryocytes to stimulate platelet production,[18] which is administered for 7 days from 9 days prior to the planned invasive procedure.
- It is anticipated that lusutrombopag will reduce the requirement for platelet transfusion both before and after the invasive procedure, reducing the requirement for costly, potentially ineffective platelet transfusion.

An overview of severe thrombocytopenia in chronic liver disease (CLD) and the position of lusutrombopag in the treatment pathway is provided in the following sections.

2.3.1 Thrombocytopenia in patients with CLD

CLD encompasses several long-term liver diseases of diverse aetiology. CLD is generally characterised by gradual, irreversible liver damage and multiple comorbid complications. Aetiologies include viral disease (e.g. hepatitis B, hepatitis C), alcoholic fatty liver disease, metabolic disorders (e.g. non-alcoholic fatty liver disease [NAFLD]) or autoimmune disorders (e.g. primary sclerosing cholangitis).[29] The rate of liver damage can be slowed through adoption of lifestyle modifications or appropriate medical and surgical management. With appropriate treatment, the majority of patients can survive their CLD,[1] however, management of comorbid conditions often requires pharmacological therapies and surgical procedures.

Thrombocytopenia is a reduction in the number of circulating platelets in the blood, often defined as a platelet count <150,000/µL blood.[2] Regardless of the aetiology of CLD, thrombocytopenia and CLD are often comorbid, with thrombocytopaenia developing in up to 76% of CLD patients.[2, 3] Although thrombocytopenia may be common in this population, severe thrombocytopenia, defined as a platelet count <50,000/µL, is rarer, occurring in 1–2.6% of the CLD population.[2, 4, 5] The precise incidence is unclear due to variation in severity of liver disease and the laboratory threshold used to determine thrombocytopenia.[31] The origin of thrombocytopenia in CLD patients is multifactorial and includes decreased platelet production due to decreased levels of the haematopoietic growth factor thrombopoietin (TPO), suppression of platelet production in the

bone marrow, splenic sequestration of platelets in the presence of splenomegaly, and increased platelet destruction.[3, 7, 31]

2.3.2 Increased risk of bleeding during invasive procedures with severe thrombocytopenia

Severe thrombocytopenia is considered a major contributory factor to an increased risk of bleeding during and after invasive diagnostic and therapeutic procedures, such as those required to effectively manage patients with CLD.[6, 7] Such procedures include liver biopsy and endoscopic variceal ligation;[32, 33] Whilst the risk of bleeding varies depending on the diagnostic or surgical procedure, patient characteristics, and clinician skill, patients with CLD-associated severe thrombocytopenia are generally considered to have an increased risk of potentially serious bleeding events during or after an invasive procedure, and this risk is increased with platelet transfusion.[6, 34] Giannini (2010) evaluated the risk of procedure-related bleeding complications in thrombocytopenic advanced liver disease patients awaiting liver transplantation (n=102, platelet count <150,000/μL), and demonstrated that bleeding complications occurred in 31% of patients with severe platelet count (defined as <75,000/μL (n=32) and none with patients who had a platelet count >75,000/μL.[32]

2.3.3 Burden of disease

Between 2017–2018, Hospital Episode Statistics showed 45,565 admissions with a primary diagnosis of liver disease in England (diagnosis codes K70–K77).[8] Despite the high incidence of thrombocytopenia in patients with CLD, severe thrombocytopenia is estimated to occur in 1–2.6% of the CLD patient population.[2, 4, 5]

Severe thrombocytopenia in CLD may delay or prevent the diagnostic and therapeutic procedures critical to the care of this patient population, potentially exacerbating the condition of a patient or increasing their morbidity and mortality.[3, 7] Severe thrombocytopenia may also delay or prevent routine diagnostic or therapeutic procedures unrelated to CLD, for example dental care in pre-transplant patients.[35]

2.3.4 Current clinical management

For CLD patients undergoing a planned invasive procedure with severe thrombocytopenia in the UK, the recommended standard of care is platelet transfusion, as described in NICE Guideline 24 (NG24; Blood transfusions).[9] Additional guidance, for example that from the British Society for Haematology,[36] determine clinical practice, however no guidance is specific to the CLD patient population. An NHS audit has highlighted that local guidelines are also available in certain hospitals, however this is not consistent across the UK, and their uptake and usage varies in clinical practice.[16] Prior to the approval of lusutrombopag, platelet transfusion was the only non-surgical treatment option available for CLD patients with thrombocytopenia .[6] Surgical treatment options available for thrombocytopenic CLD patients include splenectomy and splenic artery embolisation, however neither of these are a practical treatment option in the lusutrombopag-indicated patient population.[10] Although other TPO receptor agonists are available, lusutrombopag is the only approved pharmaceutical treatment option in Europe and the UK for use in CLD patients with severe thrombocytopenia undergoing planned invasive procedures.

Whilst platelet transfusion is a valid treatment option when used appropriately, it can be associated with a number of complications including transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), allergic and febrile non-haemolytic

reactions and risk of infection which will impact upon patient quality of life. Platelet transfusion-related TRALIs occur with an incidence of 1.1% per unit of platelet transfused,[37] with a mortality rate of 5–10%, and are typically caused by the presence of antibodies against HLA or HNA molecules.[38] Additionally, prophylactic platelet transfusion has been observed to be associated with thrombosis and poor outcomes, including mortality.[39] Furthermore, there are a number of challenges associated with platelet transfusion including limited life span in the blood (3–4 days before re-dosing required), limited shelf-life, high cost, and the haematological effect of platelets is short lived with a progressive decline in platelet increments reported 1 hour and 18–24 hours post-transfusion.[7, 11] Accordingly, platelet transfusions may not prevent post-procedural bleeding or bleeding associated with repeat procedures, and further transfusions may be required.[12, 40] However, refractory thrombocytopenia may develop after multiple platelet transfusions in 20–40% of patients; such patients may be unable to receive platelet transfusion.[7, 41, 42] This becomes a particular concern in patients requiring liver transplant, where antibody-antigen cross-matching will be tested for;[14] development of platelet refractoriness with multiple platelet transfusions may reduce the chance of an appropriate donor being sourced. Patients with more advanced CLD require multiple procedures to manage their progressive liver disease and overall general health, including liver biopsy, radiofrequency ablation (RFA), trans-arterial chemoembolisation (TACE), and endoscopic variceal ligation;[32, 33] development of platelet refractoriness due to the multiple required platelet transfusions reduces the options available to treat spontaneous, uncontrolled bleeding or bleeding with major surgical procedures.[15]

Furthermore, evidence indicates that prophylactic use of platelet transfusions in CLD patients with severe thrombocytopenia may not effectively raise the platelet count in this population, due to the splenic sequestration that is thought to be present in the majority of patients.[30] Clinical trial data suggest that treatment with platelet transfusion may result in a limited increase in platelets with short-term maintenance of the effect (Section 3).[21] This is consistent with studies of other TPO receptor agonists, including romiplostim, avatrombopag and eltrombopag.[15, 43, 44] Additionally, this patient population is subject to the risks of fluid overload following platelet transfusion, leading to TACO when large numbers of units are transfused.[45]

Currently, only one TPO receptor agonist, lusutrombopag (Shionogi) is indicated for the treatment of severe thrombocytopenia associated with CLD in patients undergoing planned invasive procedures in Europe and the UK. Given the limitations associated with the current clinical management of this patient population specific to the use of platelet transfusion, and the lack of other existing licensed pharmacological treatments, lusutrombopag addresses a substantial unmet need in this population.

Lusutrombopag

Lusutrombopag is an orally active, small-molecule TPO receptor agonist that targets the c-Mpl TPO cell surface receptor on megakaryocytes to stimulate platelet production.[18] TPO receptor agonists upregulate platelet production by stimulating the differentiation of haematopoietic stem cells and megakaryocyte progenitor cells to megakaryocytes.[6 20] Lusutrombopag is administered for 7 days, to be initiated at least 9 days before a planned invasive procedure.[25] Therefore, lusutrombopag is suitable for prophylaxis of bleeding and not suitable when haemostasis is needed on an emergency basis. Lusutrombopag was approved by the Food and Drugs Administration (FDA) on 31 July 2018 for the treatment of thrombocytopenia in adult patients with CLD scheduled to undergo a procedure, and the European Commission on 18th February 2019 for the treatment of severe thrombocytopenia in adult patients with CLD undergoing invasive procedures.[17, 46]

Lusutrombopag is licensed in the EU and UK for "the treatment of severe thrombocytopenia in adult patients with chronic liver disease undergoing invasive procedures".[25] In line with this licence, the target patient population for lusutrombopag considered in this submission is patients who have severe thrombocytopenia (defined as a platelet count <50,000/μL) associated with CLD undergoing a planned invasive procedure, the study population included in the registration pivotal studies.

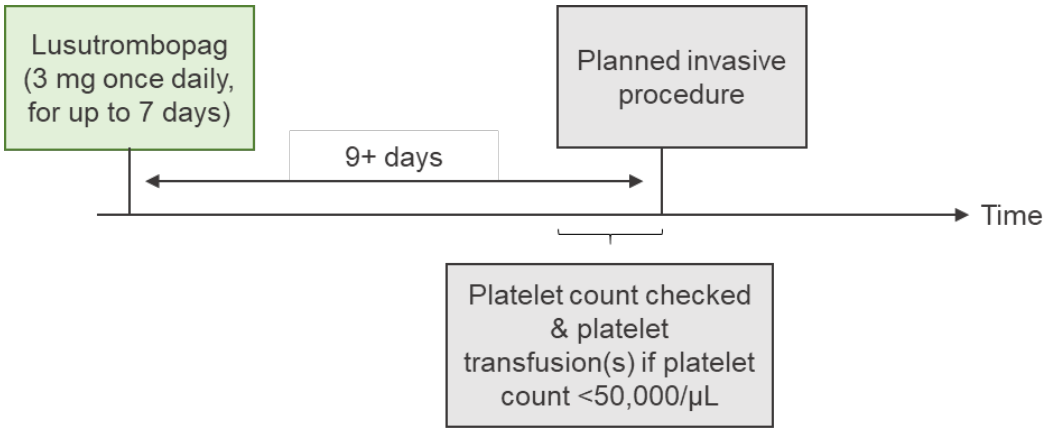
Avatrombopag

Avatrombopag is an orally administered TPO receptor agonist that, similar to lusutrombopag, targets the c-Mpl thrombopoietin receptor to stimulate platelet production.[47] It is approved in the US for the treatment of thrombocytopenia in patients with CLD who are scheduled to undergo a medical procedure (FDA approval 21 May 2018).[46] Avatrombopag does not currently have a marketing authorisation in the EU or UK.[47] It is currently being studied in several indications, including in people with thrombocytopenia associated with chronic liver disease requiring elective surgery.[47] However, a phase 3 trial (NCT03326843) for patients in this indication was recently terminated.[48]

Proposed use and positioning of lusutrombopag

The proposed positioning of lusutrombopag is shown in Figure 1. Lusutrombopag administration (3 mg once daily, for 7 days) should be initiated prior to the planned invasive procedure, which can be performed from day 9 after treatment with lusutrombopag is commenced. It is anticipated that lusutrombopag will alleviate the requirement for platelet transfusion before the planned invasive procedure and will reduce the need for platelet transfusion during and after the invasive procedure due to its efficacy in raising platelet counts.

Figure 1. Proposed positioning of lusutrombopag



Under the current standard of care, the platelet count of patients due to undergo a planned invasive procedure will be checked prior to the procedure. Patients with a platelet count <50,000/μL may receive two or four platelet transfusions prior to the procedure, and in response to bleeding events during or after the invasive procedure. Lusutrombopag administration (3 mg once daily for 7 days) is initiated prior to the planned invasive procedure, which can be performed from day 9 after treatment with lusutrombopag is commenced.

2.4 Innovation

Prior to the approval of lusutrombopag, platelet transfusion was the only non-surgical treatment option available for the management of severe thrombocytopenia associated with CLD in patients undergoing planned invasive procedures. Non-emergency use of platelet transfusion is

subject to a number of limitations that can complicate the clinical management of thrombocytopenic patients with CLD and have significant health consequences, as well as increasing healthcare costs (Section 2.3.4).[7] The innovative nature of lusutrombopag is indicated by the positive Promising Innovative Medicine (PIM) designation.[49]

As the first licensed pharmacological therapy in this indication, lusutrombopag offers a number of clinical benefits over the current standard of care, namely platelet transfusions, providing a clinically meaningful, consistent and durable increase in platelet count in patients undergoing a range of planned invasive procedures.[26] A seven day course of lusutrombopag 3 mg increases platelet counts thereby reducing the need for platelet transfusion; by raising platelet counts above 50,000/μL for approximately 19 days (Section 3.5.4), the use of platelet transfusions can be avoided not only for the initial planned procedure but for any additional procedures that might be needed during the time platelet counts remain above 50,000/μL, providing the opportunity to change clinical practice;[13, 26] Of the 220 patients treated with lusutrombopag across all of the clinical studies in severely thrombocytopenic patients with CLD, 52 patients (23.6%) underwent invasive procedures more than once, 44 of whom (20.0%) had a second or subsequent invasive procedure on a different day during the study period.[13] Given that this is over 20% of patients, it further reinforces that the maintenance of platelet levels following a 7 day course of lusutrombopag is clinically valuable. Additionally, lusutrombopag is well tolerated; in a pooled analysis of twenty clinical trials, patients treated with lusutrombopag experienced fewer serious adverse events (fatal and non-fatal) compared with placebo-treated patients.[26]

Lusutrombopag is also associated with a number of benefits that may not be captured within the NICE cost-utility framework:

- Lusutrombopag provides the reassurance for patients that they will be less likely to require repeated, invasive platelet transfusion with the associated risks; this would reduce potential side effects of platelet transfusion, such as TRALI and TACO, and any associated worry, providing improvements in the quality of life of patients.[7]
- Use of lusutrombopag may plausibly reduce the long-term risk of jeopardising liver transplant outcomes should patients become platelet refractory through repeated use of platelet transfusions.
- Lusutrombopag is administered orally, and therefore has the potential to reduce the pre-operative treatment burden attributable to platelet transfusions experienced by patients in addition to making more beds available; hospital attendance might be required by fewer patients the day before an invasive procedure to receive a platelet transfusion, and patients may be discharged from the hospital setting sooner post-operatively. This may further reduce the social visibility of the disease, permitting patients to retain their dignity, and provide patients with greater independence.
- Lusutrombopag may be able to reduce unwanted local variation in clinical quality and efficiency.[16]

As evidenced above, the introduction of lusutrombopag as a clinically efficacious and well-tolerated therapy represents an opportunity to address the significant unmet need in severely thrombocytopenic patients with CLD undergoing planned elective invasive procedures.

2.5 Equality considerations

Lusutrombopag may reduce inequalities as the first pharmaceutical treatment option available to help raise platelet counts in CLD with severe thrombocytopenia prior to planned elective invasive

procedures in patients who are platelet refractory and for certain social and religious groups (for example, Jehovah's Witnesses), who may be unable to receive transfusions.

3 Clinical effectiveness

Summary of Clinical Effectiveness

- A systematic literature review was conducted, and 3 relevant studies were captured:
- Two key Phase 3 clinical trials (L-PLUS 1 and L-PLUS 2), and one Phase 2b trial[19-22]
- All three clinical trials achieved their primary endpoints:
  - In L-PLUS 1, significantly more patients who received lusutrombopag required no preoperative platelet transfusion than patients treated with placebo (lusutrombopag, 79.2%; placebo, 12.5%).[19] A sensitivity analysis using the per-protocol population of L-PLUS 1 demonstrated that the number of patients reaching the primary endpoint was significantly greater in the lusutrombopag group (78.3%) than placebo group (11.4%, p<0.0001).[19]
  - In L-PLUS 2, significantly more patients treated with lusutrombopag (64.8%) required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomisation through 7 days after the procedure, in comparison to placebo (29.0%).[20, 21] A sensitivity analysis using the per-protocol population of L-PLUS 2 demonstrated that the number of patients reaching the primary endpoint was significantly greater in the lusutrombopag group (72.5%) than placebo group (20.2%, p<0.0001).[20, 21]
  - The Phase 2b trial met its primary endpoint, with results consistent with L-PLUS 1 and L-PLUS 2; 81.3% of patients in the lusutrombopag group and 20.0% of patients in the placebo group did not require pre-operative platelet transfusion.[22]
- A significantly greater proportion of patients met the responder criterion in the lusutrombopag group versus placebo in both L-PLUS 1 (lusutrombopag, 77.1%; placebo, 6.3%; p<0.0001) and L-PLUS 2 (lusutrombopag, 64.8%; placebo, 13.1%; p<0.0001).[19, 20, 23, 50] In the Phase 2b trial, higher proportions of patients in the lusutrombopag arm (68.8%) than the placebo arm (6.7%) met the responder criteria.[22]
- Data from the re-analysis of L-PLUS 1 reported in the SmPC and presented in Appendix C.4.1, demonstrates that for all patients (with and without platelet transfusion), the duration of platelet count increase was significantly greater in the lusutrombopag arm (21.1 days) than placebo arm (3.4 days, p=0.0197). Similarly, for L-PLUS 2, the duration of maintenance of platelet count increase was significantly longer in the lusutrombopag arm (15.1 days) than in the placebo arm (1.0 days, p=0.0002) (Table 17).[20, 21, 23] The proportion of patients requiring platelet transfusion was less in the lusutrombopag group than in the placebo group in both L-PLUS 1 (lusutrombopag, 20.8%; placebo, 85.4%) and L-PLUS 2 (lusutrombopag, 31.5%; placebo, 68.2%).[19, 50] The dose transfused was also less in the lusutrombopag group than in the placebo group.
- In the pooled controlled studies (Phase 2b, L-PLUS 1 and L-PLUS 2), the incidences of overall adverse events were comparable between the lusutrombopag and placebo groups.[26]
- Serious nonfatal adverse events occurred at a lower rate in patients treated with lusutrombopag (4.1%) than in patients treated with placebo (7.1%).[26]
- In the pooled controlled studies, 3 (1.8%) subjects treated with lusutrombopag 3 mg and 4 (2.4%) treated with placebo had a thrombotic event.[26]

3.1 Relevant clinical effectiveness evidence

A systematic literature review (SLR) was conducted in June 2018, and updated in February 2019, to identify relevant clinical trials for lusutrombopag (Appendix B). The clinical effectiveness evidence for lusutrombopag for severe thrombocytopenia associated with CLD in patients undergoing planned invasive procedures is primarily from two Phase 3 clinical trials (L-PLUS 1 and L-PLUS 2) with additional supportive evidence from a Phase 2b trial (Izumi 2014). A summary of L-PLUS 1, L-PLUS 2 and the Phase 2b trial is provided in Table 3.

The clinical evidence presented in support of this submission is principally provided by L-PLUS 1 and L-PLUS 2. Both clinical trials were Phase 3, multicentre, randomised, double-blind, placebo-controlled trials in thrombocytopenic patients with CLD and a platelet count <50,000/μL at screening. In both studies, patients received either lusutrombopag 3 mg orally administered once daily for up to seven days, or a placebo equivalent.

The population studied in the lusutrombopag clinical trials presented herein were performed in a narrower population (patients with CLD who have *severe* thrombocytopenia) than the final scope for this appraisal.[27] However, this population is in line with the licensed indication and clinical evidence for lusutrombopag (Table 2) and is based on the expected use of lusutrombopag in clinical practice.

The primary efficacy endpoint for L-PLUS 1 was the proportion of patients who required no platelet transfusion prior to the primary invasive procedure. The primary endpoint for L-PLUS 2 was the proportion of subjects who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomisation through 7 days after the primary invasive procedure.

Table 3. Clinical effectiveness evidence

Study	L-PLUS 1	L-PLUS 2 (NCT02389621)	Phase 2b (Izumi 2014)
Study design	Japanese, multicentre, randomised, double blind, parallel-group, placebo-controlled, Phase 3.	International, multicentre, randomised, double blind, parallel-group, placebo-controlled, Phase 3.	Japanese, multicentre, randomised, double blind, parallel group, placebo-controlled, Phase 2b.
Population	• Thrombocytopenia due to CLD (Child-Pugh class A and B) • Platelet count of <50,000/μL at screening • Undergoing an invasive procedure (9–14 days after treatment initiation) other than laparotomy, thoracotomy, craniotomy, open-heart surgery, organ resection, or partial organ resection (except for	• Thrombocytopenia due to CLD (Child-Pugh class A and B) • Platelet count of <50,000/μL at screening • Undergoing an invasive procedure (9–14 days after treatment initiation) other than laparotomy, thoracotomy, craniotomy, open-heart surgery, organ resection, or partial organ resection (except for	• Thrombocytopenia due to CLD (Child-Pugh class A and B) • Platelet count of <50,000/μL at screening • Undergoing RFA for primary hepatic carcinoma

	procedures comparable to tissue resection)	procedures comparable to tissue resection)	
Intervention(s)	Orally administered lusutrombopag 3 mg once daily up to 7 days	Orally administered lusutrombopag 3 mg once daily for up to 7 days	Orally administered lusutrombopag once daily up to 7 days 3 doses: 2 mg, 3 mg, 4 mg
Comparator(s)	Orally administered placebo once daily for up to 7 days	Orally administered placebo once daily for up to 7 days	Orally administered placebo once daily for up to 7 days
Reported outcomes specified in the decision problem	• Proportion of patients who required no platelet transfusion prior to the scheduled invasive procedure • Proportion of patients who required no platelet transfusion during the study, the frequency of platelets transfusion, and the dose (unit) transfused during the study • Proportion of responders (defined as patients who achieved a platelet count ≥50,000/μL with an increase ≥20,000/μL from baseline) • Duration of the increase in platelet count, defined as the number of days during which the platelet count was maintained as ≥50,000/μL • Time course of platelet count • Adverse events	• Proportion of patients who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomisation through 7 days after the primary invasive procedure • Proportion of patients who required no platelet transfusion during the study • Proportion of responders (defined as patients who achieved a platelet count ≥50,000/μL with an increase ≥20,000/μL from baseline) • Duration of sustained platelet count increase (defined as the number of days during which the platelet count was maintained at ≥50,000/μL, 70,000/μL, and 50,000/μL with an increase of 20,000/μL from baseline • Proportion of patients who required rescue therapy for bleeding at any time during the study • Frequency of platelet transfusions and dose (unit) transfused during the study • Time course of platelet count	• Proportion of patients who did not require platelet transfusion during the study • Proportion of patients who required no platelet transfusion prior to percutaneous liver ablation • The proportion of responders (defined as patients who achieved a platelet count ≥50,000/μL with an increase ≥20,000/μL from baseline) • Duration of the increase in platelet count, defined as the number of days during which the platelet count was maintained as ≥50,000/μL • The frequency of platelet transfusion, and the dose (unit) transfused during the study • Time course of platelet count • Adverse events

		• Adverse events	

Abbreviations: CLD, chronic liver disease; RFA, radiofrequency ablation.
Source: Tateishi et al, 2018;[22] Study M0626 CSR;[51] Izumi et al., 2015;[50] Hidaka et al., 2019;[24] L-PLUS 1 CSR;[19] Peck-Radosavljevic et al., 2019;[21] ClinicalTrials.gov;[23] L-PLUS 2 CSR.[20]

3.2 Summary of methodology of the relevant clinical effectiveness evidence

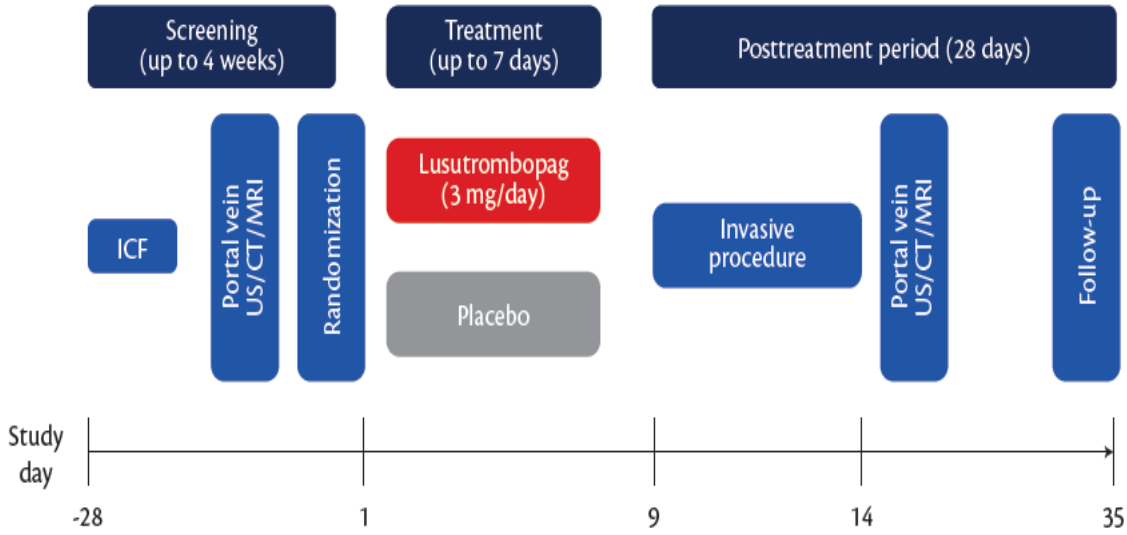
L-PLUS 1 and L-PLUS 2 methodology

L-PLUS 1 and L-PLUS 2 comprised the following three study periods: a screening period (up to 28 days prior to randomisation), a treatment period of up to 7 days, and a post-treatment period (through 28 days post-treatment) (Figure 2). Thus, the study duration for any subject was up to 63 days. Eligible patients were assigned 1:1 to receive oral lusutrombopag 3 mg or oral placebo. For L-PLUS 1, the primary endpoint was the proportion of patients who required no platelet transfusion prior to the primary invasive procedure. The secondary efficacy endpoints were the responder rate (defined as the proportion of patients for whom the platelet count reached ≥50,000/μL with an increase of ≥20,000/μL from baseline), the duration of sustained platelet count increase, and the time course of changes in platelet count.

The primary endpoint in L-PLUS2 was the proportion of subjects who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomisation through seven days after the primary invasive procedure. Key secondary endpoints included the proportion of patients who required no platelet transfusion during the study. the proportion of responders, and the number of days during which the platelet count was maintained at ≥50,000/μL (Table 4).

The methodology detailing how the data for L-PLUS 1 and L-PLUS 2 were pooled, is summarised in Appendix C.4.

Figure 2. Lusutrombopag clinical trial design (L-PLUS 1, L-PLUS 2, Phase 2b)



*To prevent an excessive increase in platelet count, administration of the study drug was for 4 to 7 days, based on whether a patient met the treatment completion criteria (platelet count had reached ≥50,000/μL and with an increase of ≥20,000/μL from baseline).
During the screening period, patients underwent scanning with portal vein US, CT and MRI.

Abbreviations: CT, computed tomography; ICF, informed consent form; MRI, magnetic resonance imaging; US, ultrasonography.
Source: Adapted from L-PLUS 1 and L-PLUS 2 CSRs.[19, 20, 24]

Table 4. Summary of methodologies for L-PLUS 1 and L-PLUS 2

Study	L-PLUS 1	NCT02389621 (L-PLUS 2)
Location	This study was conducted at 81 centres across Japan.	This study was conducted at 138 sites in 22 countries
Duration of study	The study duration for any subject was up to 63 days.	
Method of randomisation	Study drug assignment was performed by block randomisation for 4 patients in each block.	An IVRS/IWRS was used for central subject randomisation and study drug assignment.
Method of blinding	• Double blind: All subjects, the investigator, and study site and Shionogi personnel were blinded to the treatment assigned at randomisation until database lock • Unblinding at the investigator's request occurred only in the event of an emergency or an AE where details of the treatment assigned were required to determine an appropriate course of therapy.	
Trial drugs and method of administration	• Lusutrombopag 3 mg orally once daily for up to 7 days • Placebo orally once daily for up to 7 days	
Permitted and disallowed concomitant medication	With the exception of the medications listed in the protocol, investigators may have prescribed any concomitant medications or treatments necessary to provide adequate supportive care[a]	
Primary outcomes	• Proportion of patients who required no platelet transfusion prior to the primary invasive procedure.	• Proportion of subjects who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomisation through 7 days after the primary invasive procedure.
Secondary outcomes	• Proportion of patients who required no platelet transfusion during the study, the frequency of platelets transfusion, and the dose (unit) transfused during the study • Responder rate (defined as the proportion of patients for whom the platelet count reached ≥ 50,000/μL with an increase of ≥ 20,000/μL from baseline) • Duration of the maintenance of the increase in platelet count, which is defined as follows: ○ The number of days during which platelet count was maintained as ≥ 50,000/μL ○ The number of days during which platelet count was maintained as ≥ 70,000/μL ○ The number of days during which platelet count was maintained as ≥ 50,000/μL with	• Proportion of subjects who required no platelet transfusion during the study • Proportion of responders (defined as subjects who achieved a platelet count of ≥ 50,000/μL with an increase of ≥ 20,000/μL from baseline at any time during the study) • Duration of the increase in platelet count, defined as the number of days during which the platelet count was maintained as ≥ 50,000/μL • Proportion of subjects who required rescue therapy for bleeding at any time during the study • Frequency of platelet transfusions and dose (unit) transfused during the study • Time course of platelet count • Safety outcomes ○ Incidence of AEs

	an increase of ≥ 20,000/μL from baseline • Time course of platelet count • Safety outcomes ○ Incidence of AEs and ADRs ○ Incidence of bleeding-related AEs ○ Incidence of thrombus-related AEs	○ Severity of bleeding

[a]Permitted and disallowed concomitant medication are presented in Appendix C.3.
Abbreviations: ADR, adverse drug reaction; AE, adverse event; CLD, chronic liver disease; IVRS, interactive voice response system; IWRS, interactive web response system.
Source: Hidaka et al., 2019;[24] L-PLUS 1 CSR;[19] Peck-Radosavljevic et al., 2019;[21] L-PLUS 2 CSR.[20]

Phase 2b methodology

The methodology used in the Phase 2b trial was broadly similar to that of L-PLUS 1 and L-PLUS 2. A summary of the methodology of this trial can be found in Appendix C1.

Quality assessments

All three RCTs were determined to be of high quality; full details of the quality assessments performed are presented in Appendix B.6.3.

3.3 Baseline characteristics for patients in the lusutrombopag clinical trial programme

Baseline characteristics for patients in L-PLUS 1 and L-PLUS 2

Comparison of L-PLUS 1 and L-PLUS 2 shows a greater percentage of subjects had Child-Pugh class B liver disease in L-PLUS 1 (lusutrombopag, 45.8%; placebo, 54.2%) than in L-PLUS 2 (lusutrombopag, 30.6%; placebo, 40.2%), indicating that the severity of liver disease could be considered as worse in the L-PLUS 1 population. The mean baseline platelet count was higher in subjects in L-PLUS 1 (40,900 and 39,900/μL in the lusutrombopag and placebo groups, respectively) than in L-PLUS 2 (37,700 and 37,400/μL in the lusutrombopag and placebo groups, respectively). The baseline characteristics were balanced within each trial; between trial differences merely reflect the different geographical regions from which the studies recruited, and there is no evidence that the geographical differences observed involve any effect modifiers (the only plausible confounding factor resulting from geographical differences could be disease aetiology, as alcoholic-related and viral disease prevalence may differ between Japan and the West).[52] Despite these differences, these were small enough to permit comparison between studies and pooling of the data to inform inputs for the cost-effectiveness model (Appendix B.5) Within each study, baseline characteristics were comparable between treatment groups. Key baseline demographics and clinical characteristics for the patients included in the ITT population are presented in Table 5.

Table 5. Baseline characteristics of the ITT population in L-PLUS 1 and L-PLUS 2

Characteristic	L-PLUS 1		L-PLUS 2	
	LUSU 3 mg (n=48)	Placebo (n=48)	LUSU 3 mg (n=108)	Placebo (n=107)
Mean age, years (SD)	68.9 (6.6)	66.8 (10.2)	55.2 (11.6)	56.1 (11.0)

Male, n (%)	21 (43.8)	30 (62.5)	65 (60.2)	69 (64.5)
Mean height, cm (SD)	–	–	168.32 (9.80)	168.29 (10.47)
Mean weight, kg (SD)	59.73 (10.50)	63.87 (14.92)	77.86 (17.77)	78.53 (19.22)
Mean BMI, kg/m2 (SD)	–	–	[redacted]	[redacted]
Ethnicity, n (%)				
Hispanic/Latino	0	0	14 (13.0)	12 (11.2)
Not Hispanic/Latino	48 (100.00)	48 (100.00)	93 (86.1)	95 (88.8)
Unknown	–	–	1 (0.9)	0
Cause of CLD, n (%)				
Hepatitis C	39 (81.3)	32 (66.7)	51 (47.2)	51 (47.7)
Hepatitis B	4 (8.3)	8 (16.7)	24 (22.2)	21 (19.6)
Alcoholic hepatitis	2 (4.2)	6 (12.5)	24 (22.2)	26 (24.3)
Non-alcoholic hepatitis	3 (6.3)	4 (8.3)	12 (11.1)	15 (14.0)
Autoimmune hepatitis	0	0	5 (4.6)	5 (4.7)
History of any transfusion, n (%)	28 (58.3)	26 (54.2)	48 (44.4)	62 (57.9)
Child-Pugh class				
A	26 (54.2)	22 (45.8)	72 (66.7)	63 (58.9)
B	22 (45.8)	26 (54.2)	33 (30.6)	43 (40.2)
C[a]	–	--	3 (2.8)	0
Missing	0	0	0	1 (0.9)
Planned invasive procedure, n (%)				
Liver ablation/coagulation[b]	20 (41.7)	21 (43.8)	7 (6.5)	5 (4.7)
Other	28 (58.3)	27 (56.3)	101 (93.5)	102 (95.3)
Platelet count at randomisation, n (%)[c]	–	–		
<35,000/µL			[redacted]	[redacted]
≥35,000/µL				
Platelet count at screening, n (%)				
<35,000/µL	9 (18.8)	9 (18.8)	–	–
≥35,000/µL to <45,000µL	22 (45.8)	24 (50.0)		
≥45,000/µL	17 (35.4)	15 (31.3)		
Mean baseline platelet count, x10^3/µL (SD)[d]	40.9 (6.3)	39.9 (6.9)	37.7 (9.0)	37.4 (7.8)
Baseline platelet count, n (%)				
<35,000/µL	7 (14.6)	10 (20.8)	36 (33.3)	38 (35.5)
≥35,000/µL to <45,000µL	26 (54.2)	25 (52.1)	–	–
≥35,000/µL	–	–	71 (65.7)	68 (63.6)
≥45,000/µL	15 (31.3)	13 (27.1)	–	–
Performance status, n (%)				
Grade 0	43 (89.6)	45 (93.8)	83 (76.9)	95 (88.8)
Grade 1	5 (10.4)	3 (6.3)	25 (23.1)	12 (11.2)

Gastroesophageal varix, n (%)				
Yes	42 (87.5)	41 (85.4)	92 (85.2)	90 (84.1)
No	6 (12.5)	7 (14.6)	15 (13.9)	14 (13.1)
Missing	–	–	1 (0.9)	3 (2.8)
Splenomegaly, n (%)				
Yes	45 (93.8)	46 (95.8)	95 (88.0)	95 (88.8)
No	3 (6.3)	2 (4.2)	13 (12.0)	12 (11.2)
Ascites, n (%)				
Yes	11 (22.9)	14 (29.2)	22 (20.4)	25 (23.4)
No	37 (77.1)	34 (70.8)	86 (79.6)	82 (76.6)
WHO bleeding scale, n (%)				
Grade 0	42 (87.5)	42 (87.5)	101 (93.5)	97 (90.7)
Grade 1	6 (12.5)	6 (12.5)	6 (5.6)	10 (9.3)
Missing	–	–	1 (0.9)	0

[a]Child-Pugh Class C patients were excluded in L-PLUS 1 and LPLUS 2, although 3 patients with disease of this nature were erroneously included in L-PLUS 2.
[b]Reported as RFA/MCT in L-PLUS 1
[b]Platelet count used for the randomisation
[c]Platelet count observed on Day 1 before administration of the initial dose of study drug. If this value was missing, the most recent value obtained prior to Day 1 within the 7 preceding days was used as baseline
Abbreviations: BMI, body mass index; CLD, chronic liver disease; LUSU, lusutrombopag; SD, standard deviation; WHO, World Health Organisation.
Source: Hidaka et al., 2019;[24] Izumi et al., 2015;[50] L-PLUS 1 CSR;[19] Peck-Radosavljevic et al., 2019;[21] ClinicalTrials.gov;[23] L-PLUS 2 CSR;[20] Lusutrombopag EPAR.[26]

Baseline characteristics for patients in Phase 2b

The baseline characteristics of patients included in the Phase 2b trial are summarised in Appendix C.1.2. These were largely comparable to that of the phase 3 trials, L-PLUS 1 and L-PLUS 2.

3.4 Statistical analysis and definition of study groups

The analysis populations used for the analysis of outcomes in L-PLUS 1 and L-PLUS 2 are detailed in Table 6, while a summary of statistical analyses is presented in Table 76.

In L-PLUS 1, a total of 97 patients were randomised (lusutrombopag, 49; placebo, 48).[19] Of these, 48 (98%) and 47 (97.9%) of patients completed the study in the lusutrombopag and placebo groups, respectively. In L-PLUS 2, a total of 215 patients were randomised (lusutrombopag, 108; placebo, 107).[20, 23] Of these, 98 (90.7%) and 102 (95.3%) completed the study in the lusutrombopag and placebo arms, respectively. The CONSORT diagrams of the population flow in L-PLUS 1 and L-PLUS 2 can be found in Appendix C.2.

Table 6. Analysis populations for L-PLUS 1 and L-PLUS 2

Analysis	L-PLUS 1 and L-PLUS 2
Full analysis set (FAS)	• Includes all subjects who received at least 1 dose of the study drug and had a platelet count measured at baseline and at least once after initiation of study drug administration. • The FAS was the primary efficacy analysis population for the analysis of L-PLUS 1
Intention-to-treat (ITT) population	• Includes all randomised subjects. Subjects were analysed according to the treatment to which they were randomised. • This population was the primary population for the analysis of efficacy for L-PLUS 2
Per-protocol (PP) population	• Includes all randomised subjects who had no major protocol deviations pertaining to the efficacy evaluation. Deviations were determined prior to unblinding of the study data. • This population was used in a sensitivity analysis of the primary endpoint in L-PLUS 2.
Safety population	• Includes all randomised subjects who received at least 1 dose of the study drug. This population was analysed according to the treatment that subjects received, rather than the treatment to which they were randomised. • This population was the primary population for the analysis of safety.

Abbreviations: FAS, full analysis set; ITT, intention-to-treat; PP, per protocol.
Source: L-PLUS 1 CSR;[19] L-PLUS 2 CSR.[20]

Table 7. Summary of statistical analyses for L-PLUS 1 and L-PLUS 2

Trial acronym	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
L-PLUS 1	• NR	• Summary statistics, including the number of subjects, arithmetic mean, standard deviation, median, and minimum and maximum values were calculated for continuous variables. • The number and proportion of subjects in each category were calculated for categorical variables. • Unless otherwise noted, all statistical tests were performed at a two-sided significance level of 0.05.	• Based on the results of the Phase 2b study (Izumi 2014), it was assumed that similar proportions of patients reaching the primary endpoint in the lusutrombopag (81.3%) and placebo (20.0%) would be obtained in this study, although the required proportion is 70% in clinical practice. Based on this assumption, a minimum of 24 patients per group was required to detect the difference in proportion between the two groups with 90% or higher power at a significance level of 0.05. • To minimise the risk of overlooking thrombosis related adverse events (reported at 6.5% in Phase 2b), at least 45 patients per group was required to reduce the probability that the study could not detect AEs with an incidence of 6.5% to less than 5%.	• Missing values were not imputed. All analyses were performed using actual observations.
L-PLUS 2	• The null hypothesis for the primary efficacy endpoint was that there was no difference for up to 7 days between the lusutrombopag	• Summary statistics, including the number of subjects, arithmetic mean, standard deviation, median, and minimum and maximum	• Based on the results of L-PLUS 1, it was assumed that the difference in the primary endpoint to be obtained in this study was	• Unless otherwise noted, missing values were not imputed. All analyses were performed using actual observations.

	and placebo groups regarding the proportion of patients who require no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomisation until 7 days after the primary elective procedure. • Testing of the major secondary endpoints was performed hierarchically if the superiority of lusutrombopag versus placebo was demonstrated at a two-sided significance level of 0.05.	values were calculated for continuous variables. • The number and proportion of subjects in each category were calculated for categorical variables. • Unless otherwise noted, all statistical tests were performed at a two-sided significance level of 0.05.	50% between lusutrombopag and placebo. Assuming that the proportion of patients who met the primary endpoint was 20% in the placebo group and 70% in the lusutrombopag group, 100 patients per arm would provide 99% power to detect a difference of 50% between lusutrombopag and placebo at a two-sided significance level of 0.05. • With 100 patients per arm, from the safety point of view, the sample size ensured at least 95% probability to detect an AE with an incidence of 3% or more.	• If a patient received platelet transfusion on the same day as an invasive procedure but the time of either platelet transfusion or invasive procedure was missing, the patient was considered as if he/she underwent the invasive procedure after receiving platelet transfusion. • If a patient had a platelet transfusion and platelet count on the same day but the time of either platelet transfusion or collection of blood sample for platelet count was missing, the patient was considered as if they received the platelet transfusion after collection of the blood sample for platelet count.

Abbreviations: AE, adverse event; NR, not reported.
Source: L-PLUS 2 Clinical Study Protocol;[53] L-PLUS 2 Statistical Analysis Plan.[54]

Statistical analyses in Phase 2b

The statistical analyses and analysis populations used in the Phase 2b trial are broadly similar to those used in L-PLUS 1 and L-PLUS 2. These are summarised in Appendix C.1.3.

3.5 Clinical effectiveness results of the relevant trials

The following sections detail the relevant outcomes from L-PLUS 1 and L-PLUS 2 to the current decision problem. A summary of the key outcomes from the Phase 2b trial is shown in Section 3.5.7, with full results presented in Appendix C.1.4. The data reported for L-PLUS 1 in this section of the submission is derived from the pre-specified analysis of the clinical trial data (including both the intention-to-treat analysis and a sensitivity analysis conducted with the per-protocol data); the data presented in the lusutrombopag summary of product characteristics is derived from a post hoc re-analysis of the data to align with the primary endpoint of L-PLUS 2, conducted during the EMA regulatory process. This re-analysis is incorporated in Appendix C.4.

A number of outcomes specified in the draft scope were not assessed in either the L-PLUS 1 or L-PLUS 2 CSRs, covering:

- Number of whole blood transfusions
- Return to operating theatre

3.5.1 Summary of clinical effectiveness results from the lusutrombopag clinical trials

Lusutrombopag consistently demonstrated statistically significant improvements in comparison with placebo in both Phase 3 studies. Both trials achieved their primary endpoints, with significantly more patients who received lusutrombopag in L-PLUS 1 requiring no preoperative platelet transfusion (lusutrombopag, 79.2%; placebo, 12.5%).[19, 24] Furthermore, in L-PLUS 2 significantly more patients treated with lusutrombopag (64.8%) required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomisation through 7 days after the procedure, in comparison to placebo (29.0%).[20, 21, 23] In addition, treatment with lusutrombopag reduced the number of platelet transfusions and dose transfused in subjects who required a platelet transfusion,[20, 23] demonstrating that lusutrombopag provides benefits both in terms of reducing the need for platelet transfusion and, where platelet transfusion are still needed, the number of required transfusions. Results from the Phase 2b trial were consistent; 81.3% of patients in the lusutrombopag group and 20.0% of patients in the placebo group did not require pre-operative platelet transfusion, and higher proportions of patients in the lusutrombopag arm (68.8%) than the placebo arm (6.7%) met the responder criteria.

3.5.2 Platelet transfusions in L-PLUS 1 and L-PLUS 2

L-PLUS 1 primary endpoint: proportion of subjects who required no platelet transfusion prior to procedure

The primary endpoint of L-PLUS 1 was the proportion of patients who did not require platelet transfusion prior to the procedure; significantly more patients in the lusutrombopag group (79.2% [38/48 patients]) achieved this outcome than the placebo group (12.5% [6/48 patients]; $p<0.0001$) (Table 8).[19] To explore the impact of protocol violations on the primary endpoint, a sensitivity analysis was performed using the per-protocol population; the number of patients

reaching the primary endpoint was significantly greater in the lusutrombopag group ([redacted] than placebo group ([redacted]).[19]

Table 8. Proportion of patients who required no platelet transfusion prior to the primary invasive procedure in L-PLUS 1

	ITT		PP	
	LUSU 3 mg (n=48)	Placebo (n=48)	LUSU 3 mg (n=46)	Placebo (n=44)
Proportion of subjects who met endpoint, % (n)[a]	79.2 (38)	12.5 (6)	[redacted]	[redacted]
95% CI	65.0, 89.5	4.7, 25.2	[redacted]	[redacted]
Relative risk (95% CI)	6.16 (2.92, 13.00)		[redacted]	
p-value from CMH test[a]	<0.0001		[redacted]	

[a]Planned surgery and platelet count at screening as stratification factors.
Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; ITT, intention-to-treat; LUSU, lusutrombopag; PP, per-protocol.
Source: Hidaka et al., 2019;[24] L-PLUS 1 CSR;[19] Lusutrombopag EPAR.[26]

L-PLUS 2 primary endpoint: proportion of subjects who required no platelet transfusion prior to primary invasive procedure and no rescue therapy for bleeding from randomisation through 7 days after the procedure

The primary endpoint of L-PLUS 2 was the proportion of subjects who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomisation through 7 days after the procedure; significantly more patients in the lusutrombopag group achieved this outcome (64.8% [70/108 subjects]) than in the placebo group (29.0% [31/107 subjects]; p<0.0001) (Table 9).[20, 21, 23] To explore the impact of protocol violations on the primary endpoint, a sensitivity analysis was performed using the per-protocol population; the number of patients reaching the primary endpoint was significantly greater in the lusutrombopag group (72.5%) than placebo group (20.2%, p<0.0001).[20, 21]

Table 9. Proportion of subjects who required no platelet transfusion prior to primary invasive procedure and no rescue therapy for bleeding from randomisation through 7 days after the procedure in L-PLUS 2

	ITT population		PP population	
	LUSU 3 mg (n=108)	Placebo (n=107)	LUSU 3 mg (n=91)	Placebo (n=89)
Proportion of subjects who met endpoint, % (n)[a]	64.8 (70/108)	29.0 (31/107)	72.5 (66/91)	20.2 (18/89)
95% CI	55.0, 73.8	20.6, 38.5	62.2, 81.4	12.4, 30.1
Difference in proportion (95% CI)	36.7 (24.9, 48.5)		53.3 (42.1, 64.5)	
p-value from CMH test	<0.0001		<0.0001	

[a]Proportion of subjects who required no platelet transfusion prior to the primary invasive procedure and

no rescue therapy for bleeding from randomization through 7 days after the primary invasive procedure. In addition to subjects who received platelet transfusion, subjects who did not undergo an invasive procedure regardless of the reason were considered as receiving platelet transfusion.
Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; ITT, intention-to-treat; LUSU, lusutrombopag; PP, per protocol.
Source: ClinicalTrials.gov;[23] Peck-Radosavljevic et al., 2019;[21] L-PLUS 2 CSR.[20]

Proportion of subjects who required no platelet transfusion prior to the primary invasive procedure and during the study

In L-PLUS 1, the proportion of patients who required no platelet transfusion was significantly greater in the lusutrombopag 3 mg group (79.2%) than in the placebo group (12.5%, p<0.0001) (Table 10). Similarly, the proportion of patients who required no platelet transfusion during L-PLUS 2 was significantly greater in the lusutrombopag 3 mg group (63.0%) than in the placebo group (29.0%, p<0.0001) (Table 11).

Table 10. Proportion of patients who required no platelet transfusion during L-PLUS 1

	L-PLUS 1	
	LUSU 3 mg (n=48)	**Placebo (n=48)**
Proportion of subjects who met endpoint, % (n)	79.2 (38)	12.5 (6)
95% CI	65.0, 89.5	4.7, 25.2
Relative risk (95% CI)	6.16 (2.92, 13.00)	
p-value from CMH test[a]	<0.0001	

[a]Planned surgery and platelet count at screening as stratification factors
Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; LUSU, lusutrombopag.
Source: Izumi et al., 2015;[50] L-PLUS 1 CSR;[19] Lusutrombopag EPAR.[26]

Table 11. Proportion of patients who required no platelet transfusion during L-PLUS 2

	L-PLUS 2	
	LUSU 3 mg (n=108)	**Placebo (n=107)**
Proportion of subjects who met endpoint, % (n)	63.0 (68)	29.0 (31)
95% CI	53.1, 72.1	20.6, 38.5
Difference in proportion (95% CI)	34.8 (22.8, 46.8)	
p-value from CMH test[a]	<0.0001	

[a]Planned surgery and platelet count at screening as stratification factors
Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; LUSU, lusutrombopag.
Source: Peck-Radosavljevic et al., 2019;[21] ClinicalTrials.gov;[23] L-PLUS 2 CSR.[20]

Frequency of platelet transfusion and dose transfused in L-PLUS 1 and L-PLUS 2

The frequency of platelet transfusion and the dose transfused during the study was reported in both L-PLUS 1 and L-PLUS 2 (Table 12 and Table 13).

In L-PLUS 1, fewer subjects in the lusutrombopag group than in the placebo group received platelet transfusion during the study ([redacted] versus [redacted]).[19] [redacted] of the subjects receiving platelet transfusion received only a single platelet transfusion in the lusutrombopag group, whereas [redacted] subjects required multiple platelet transfusions in the placebo group. The mean

(standard deviation) units per platelet transfusion was [redacted] in the lusutrombopag group [redacted] and [redacted] in the placebo group [redacted].[19]

In L-PLUS 2, fewer subjects in the lusutrombopag group than in the placebo group received platelet transfusion during the study (31.5% vs. 68.2%).[20, 23] All of the subjects receiving platelet transfusion (n=34) received only a single platelet transfusion in the lusutrombopag group, whereas [redacted]/73 subjects required multiple platelet transfusions in the placebo group.[20, 21, 23] The main reason for platelet transfusion during the study was given as platelet count <50,000/μL before the invasive procedure ([redacted] subjects [redacted] in the lusutrombopag group compared with [redacted] subjects [redacted] in the placebo group).[20, 23] Where data were available (99/107 patients who received platelet transfusion), the mean (range) dose per platelet transfusion was [redacted] platelets in the lusutrombopag group [redacted] and [redacted] platelets in the placebo group [redacted].[20]

Table 12. Summary of patients with platelet transfusion and dose transfused in L-PLUS 1

	LUSU 3 mg (n=48)	Placebo (n=48)
Patients with platelet transfusion, n (%)	[redacted]	[redacted]
Reason for use, n (%) Before invasive surgery and platelet count <50,000/μL Adverse events related to bleeding Other	[redacted]	[redacted]
Frequency of platelet transfusion, n (%) 1 2	[redacted]	[redacted]
Platelet content transfused n (data available) Mean platelet content transfused, unit (SD)	[redacted]	[redacted]

Abbreviations: LUSU, lusutrombopag; SD, standard deviation.
Source: L-PLUS 1 CSR.[19]

Table 13. Summary of patients with platelet transfusion and dose transfused in L-PLUS 2

	LUSU 3 mg (n=108)	Placebo (n=107)
Patients with platelet transfusion, n (%)	34 (31.5)	73 (68.2)
Reason for use, n (%) Before invasive surgery and platelet count <50,000/μL Adverse events related to bleeding Other	[redacted]	[redacted]
Frequency of platelet transfusion, n (%) 0 1 2 3 4 5	[redacted]	[redacted]
Platelet content transfused n (data available) Mean platelet content transfused, x10^{11} (SD)	[redacted]	[redacted]

[a]The data not able to estimate were removed from the analysis (n=8). If patient received platelet transfusion more than once during the study, average amount per
once for the patient was used.

Abbreviations: LUSU, lusutrombopag; SD, standard deviation.
Source: Peck-Radosavljevic et al., 2019;[21] ClinicalTrials.gov;[23] L-PLUS 2 CSR.[20]

3.5.3 Responder rate in L-PLUS 1 and L-PLUS 2

A responder was defined as a patient who achieved platelet count of ≥ 50,000/μL with an increase of ≥ 20,000/μL from baseline. In L-PLUS 1, significantly more patients in the lusutrombopag group (77.1%) met the responder criterion at least once throughout the study than in the placebo group (6.3%, p<0.0001).[19, 50] Similarly, in L-PLUS 2, a significantly greater proportion of patients in the lusutrombopag group (64.8%) met the responder criterion at least once throughout the study than in the placebo group (13.1%, p<0.0001).[20, 23]

Summaries of the proportion of responders during L-PLUS 1 and L-PLUS 2 are shown in Table 14 and Table 15, respectively.

Table 14. Proportion of patients who met responder criteria at least once during L-PLUS 1

	L-PLUS 1	
	LUSU 3 mg (n=48)	**Placebo (n=48)**
Proportion of responders, % (n)	77.1 (37)	6.3 (3)
95% CI	62.7, 88.0	1.3, 17.2
Relative risk (95% CI)	11.91 (4.00, 35.44)	
p-value from CMH test[a]	<0.0001	

[a]Planned surgery and platelet count at screening as stratification factors
Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; LUSU, lusutrombopag.
Source: Hidaka et al., 2019;[24] Izumi et al., 2015;[50] L-PLUS 1 CSR;[19] Lusutrombopag EPAR.[26]

Table 15. Proportion of patients who met responder criteria at least once during L-PLUS 2

	L-PLUS 2	
	LUSU 3 mg (n=108)	**Placebo (n=107)**
Proportion of responders, % (n)	64.8 (70)	13.1 (14)
95% CI	55.0, 73.8	7.3, 21.0
Difference in proportion (95% CI)	52.5 (42.0, 62.9)	
p-value from CMH test[a]	<0.0001	

[a]Planned surgery and platelet count at screening as stratification factors
Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; LUSU, lusutrombopag.
Source: Peck-Radosavljevic et al., 2019;[21] ClinicalTrials.gov;[23] L-PLUS 2 CSR.[20]

3.5.4 Platelet count measurements in L-PLUS 1 and L-PLUS 2

Duration of increase in platelet count

The duration of the increase in platelet count was defined as the number of days during which the platelet count was maintained as ≥50,000/μL. Data from the re-analysis of L-PLUS 1 reported in the SmPC and presented in Appendix C.4.1, demonstrates that for all patients (with and without platelet transfusion), the duration of platelet count increase was significantly greater in the lusutrombopag arm (21.1 days) than placebo arm (3.4 days, p=0.0197).[25] Similarly, for L-

PLUS 2, the duration of maintenance of platelet count increase was significantly longer in the lusutrombopag arm (15.1 days) than in the placebo arm (1.0 days, p=0.0002) (Table 17).[20, 21, 23]

Although breaking the trial randomisation, analysing the results based on the receipt of platelet transfusion further reinforces the clinical value of lusutrombopag. In L-PLUS 1, this was significantly greater in the lusutrombopag group compared with the placebo group both in patients who received platelet transfusion (p<0.0001) and patients who did not receive a platelet transfusion (p=0.0420) (Table 16).[19, 26] Similarly, in L-PLUS 2, the number of days during which the platelet count was ≥50,000/μL this was significantly greater in the lusutrombopag group without platelet transfusion than in the placebo group with platelet transfusion (p<0.0001).[20, 23] The median duration of platelet count ≥50,000/μL in L-PLUS 1 was 22.1 days in the lusutrombopag group without platelet transfusion and 3.3 days in the placebo group with platelet transfusion.[19, 26] The median duration of platelet count ≥50,000/μL in L-PLUS 2 was 19.21 days in the lusutrombopag group without platelet transfusion and 0 days in the placebo group with platelet transfusion.[20, 23] Whilst not the main question that these studies were designed to formally address, these data suggest that treatment with platelet transfusion results in a limited increase in platelets, with a short-term maintenance of the effect, compared with lusutrombopag.

Table 16. Duration of increase in platelet count ≥50,000/μL in L-PLUS 1

	LUSU 3 mg (n=48)			Placebo (n=47)		
	With PT (n=10)	Without PT (n=38)	Total (n=48)	With PT (n=40)	Without PT (n=7)	Total (n=47)
Median, days	10.3	22.1	NR[b]	3.3	18.5	NR[b]
Minimum–Maximum, days	0.0, 23.0	5.7, 33.5	NR[b]	0.0, 22.3	4.2, 34.8	NR[b]
p-value[a]	<0.0001	0.0420	NR[b]	–	–	–

[a]Wilcoxon rank sum test.
[b]Values overall population, regardless of receipt of platelet transfusion, were not available in the CSR. However, these are available from the re-analysis of L-PLUS 1 which is reported in the SmPC, and are presented in Appendix C.4.1.
Abbreviations: LUSU, lusutrombopag; PT, platelet transfusion.
Source: Izumi et al., 2015;[50] L-PLUS 1 CSR;[19] Lusutrombopag EPAR.[26]

Table 17. Duration of increase in platelet count ≥50,000/μL in L-PLUS 2

	LUSU 3 mg (n=108)			Placebo (n=107)		
	With PT (n=34)	Without PT (n=74)	Total (n=108)	With PT (n=73)	Without PT (n=34)	Total (n=107)
Median	1.73	19.21	15.11	0.00	8.86	0.98
25–75 percentile	0.00, 14.00	12.64, 28.00	6.59, 23.88	0.00, 5.04	0.00, 18.73	0.00, 9.22
p-value	–	<0.0001[a]	0.0002[b]	–	–	–

[a]Comparison between lusutrombopag without platelet transfusion and placebo with platelet transfusion by Wilcoxon rank sum test.
[b]Comparison between lusutrombopag and placebo by van Elteren test stratified with platelet transfusion during the study
Abbreviations: LUSU, lusutrombopag; PT, platelet transfusion.
Source: Peck-Radosavljevic et al., 2019;[21] ClinicalTrials.gov;[23] L-PLUS 2 CSR.[20]

Time course of platelet count in L-PLUS 1 and L-PLUS 2

The time courses of platelet count were analysed for patients with and without platelet transfusion separately; whilst this breaks the randomisation of the studies, receipt of platelet transfusion is inherently confounding factor in this analysis given that the primary endpoints centre on avoidance of platelet transfusion. The time courses of mean platelet count for patients with and without platelet transfusion in L-PLUS 1 and L-PLUS 2 are shown in Figure 3. A summary of the maximum platelet count and maximum increases from baseline is given in Table 18 and Table 19. L-PLUS 1 additionally reported the change in platelet count after the first platelet transfusion (Table 20); this was not reported for L-PLUS 2.

In L-PLUS 1, the mean maximum platelet count was greater in the lusutrombopag group without platelet transfusion (90,200/μL) than in the placebo group with platelet transfusion (52,800/μL).[19, 25, 26] In patients who did not receive a platelet transfusion, the mean time to reach the maximum platelet count was shorter in the lusutrombopag group than the placebo group (13.4 days and 17.0 days, respectively). Similar results were observed in L-PLUS 2; the mean maximum platelet count was greater in the lusutrombopag group without platelet transfusion (86,900/μL) than in the placebo group with platelet transfusion ([redacted]).[20, 25] In patients who did not receive a platelet transfusion, the mean time to reach the maximum platelet count was shorter in the lusutrombopag group than the placebo group (12.4 days and 18.2 days, respectively).[20]

Table 18. Summary of maximum platelet count and maximum increase from baseline in platelet count in L-PLUS 1.

	LUSU 3 mg (n=48)		Placebo (n=47)	
	With PT (n=10)	Without PT (n=38)	With PT (n=7)	Without PT (n=41)
Mean maximum platelet count, platelets/μL (SD)	68,500 (16,100)	90,200 (22,100)	52,800 (10,800)	66,700 (16,800)
Mean maximum increase from baseline in platelet count, platelets/μL (SD)	30,200 (14,900)	48,600 (21,200)	13,700 (9,100)	22,000 (16,300)
Time to reach the maximum platelet count, days (SD)	–	13.4 (3.8)	–	17.0 (12.8)

Abbreviations: LUSU, lusutrombopag; PT, platelet transfusion.
Source: L-PLUS 1 CSR;[19] Lusutrombopag EPAR.[26]

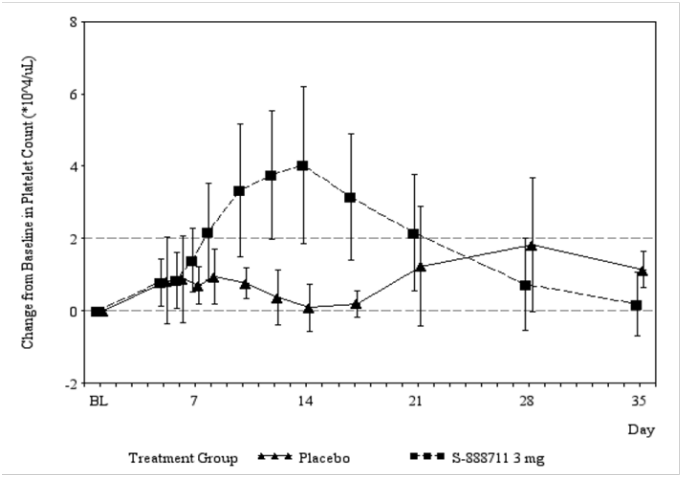
Table 19. Summary of maximum platelet count and maximum increase from baseline in platelet count in L-PLUS 2.

	LUSU 3 mg (n=108)		Placebo (n=107)	
	With PT (n=34)	Without PT (n=74)	With PT (n=73)	Without PT (n=34)
Mean maximum platelet count, platelets/μL (SD)	[redacted]	86,900 [redacted]	[redacted]	[redacted]
Mean maximum increase from baseline in platelet count, platelets/μL (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Time to reach the maximum platelet count, days (SD)	–	12.4 (4.7)	–	18.2 (10.4)

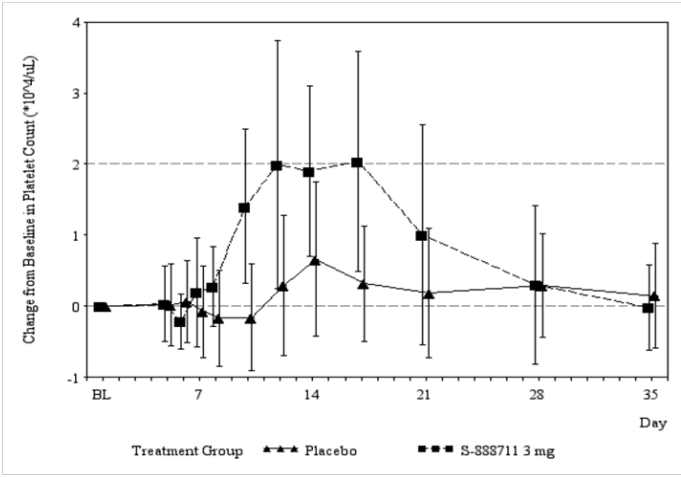
Abbreviations: LUSU, lusutrombopag; PT, platelet transfusion.
Source: Peck-Radosavljevic et al., 2019;[21] L-PLUS 2 CSR.[20]

Figure 3. Mean platelet count in patients with and without platelet transfusion in L-PLUS 1 and L-PLUS 2

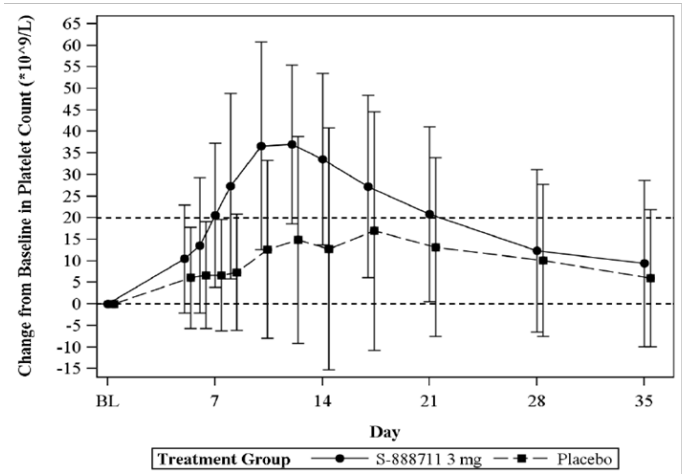
a) Mean (SD) change from baseline in platelet count in patients without platelet transfusion in LPLUS-1



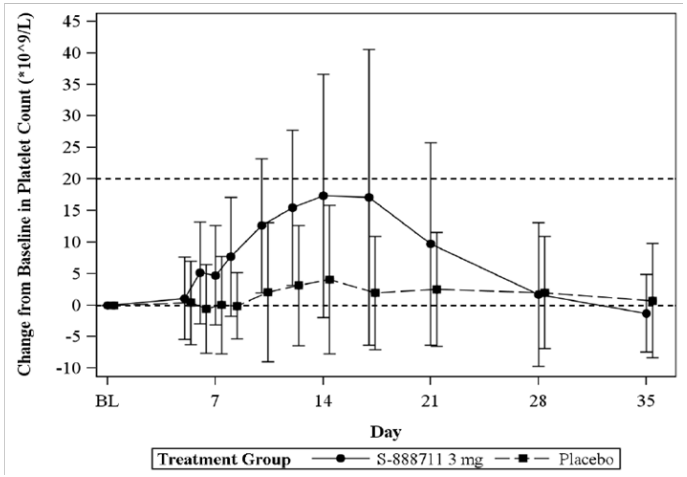
b) Mean (SD) change from baseline in platelet count in patients with platelet transfusion in LPLUS-1



c) Mean (SD) change from baseline in platelet count in patients without platelet transfusion in LPLUS-2



d) Mean (SD) change from baseline in platelet count in patients with platelet transfusion in LPLUS-2



Abbreviations: SD, standard deviation; S-888711, lusutrombopag.
Source: Hidaka et al., 2019;[24] L-PLUS 1 CSR;[19] L-PLUS 2 CSR;[20] Lusutrombopag SmPC.[25]

Table 20. Change in platelet count from prior to first platelet transfusion in patients with platelet transfusion in L-PLUS 1

Timepoint	Lusutrombopag (n=48)	Placebo (n=48)
Platelet count prior first platelet transfusion ($x10^9$), mean (SD; n)	[redacted]	[redacted]
Change from platelet count prior to first platelet transfusion ($x10^9$):		
Shortly after platelet transfusion, mean (SD; n)	[redacted]	[redacted]
Next day after platelet transfusion, mean (SD; n)	[redacted]	[redacted]
Two days after platelet transfusion, mean (SD; n)	[redacted]	[redacted]

3.5.5 Rescue therapy in L-PLUS 1 and L-PLUS 2

Rescue therapy was defined as platelet transfusion or use of an anti-thrombotic drug in the instance of bleeding events. The proportion of subjects who required rescue therapy for bleeding events are summarised in Table 21 and Table 22, for L-PLUS 1 and L-PLUS 2, respectively. No subject in the lusutrombopag group of either trial received rescue therapy for bleeding events, compared with 1/48 (2.1%) and 2/107 (1.9%) in the placebo group of L-PLUS 1 and L-PLUS 2, respectively.[20, 23, 24]

Table 21. Summary of patients with rescue therapy in L-PLUS 1

	LUSU 3 mg (n=48)	Placebo (n=48)
Patients who received rescue therapy for bleeding-related events, n (%)	0	1 (2.1)

Abbreviations: LUSU, lusutrombopag.
Source: Hidaka et al., 2018.[24]

Table 22. Summary of patients with rescue therapy in L-PLUS 2

	LUSU 3 mg (n=108)	Placebo (n=107)
Patients who received rescue therapy for bleeding events, n (%) [a]	0	2 (1.9)
Patients who received rescue therapy other than platelet transfusion for bleeding events	[redacted]	[redacted]
Patients who received platelet transfusion due to adverse events related to bleeding	[redacted]	[redacted]

[a]Patients who received concomitant medication for bleeding events and/or who received platelet transfusion due to adverse events related to bleeding. One patient treated with lusutrombopag experienced two events.
Abbreviations: LUSU, lusutrombopag.
Source: Peck-Radosavljevic et al., 2019;[21] ClinicalTrials.gov;[23] L-PLUS 2 CSR.[20]

3.5.6 Subgroup analyses of L-PLUS 1 and L-PLUS 2

In both L-PLUS 1 and L-PLUS 2, subgroup analyses were performed for their respective primary endpoints. These are summarised in Table 23 and Table 24, respectively. Subgroups demonstrated a similar trend as in the intention-to-treat and per-protocol population analyses, with lusutrombopag consistently resulting in avoidance of platelet transfusion.

Table 23. Subgroup analysis of the proportion of subjects who met the primary endpoint in L-PLUS 1

Characteristic	LUSU 3 mg (n=48) [n/N (%)]	Placebo (n=48) [n/N (%)]	Relative risk (95% CI)	P value for homogeneity[a]
Baseline platelet count				
<35,000/μL				
≥35,000/μL to <45,000μL				
≥45,000/μL				
Performed primary invasive procedure				
Percutaneous				
RFA/MCT				
EVL				
EIS				
TACE				
Other				
Child-Pugh class				
A				
B				

[a]Breslow-Day test for the relevant subgroup-by-treatment interaction.
Note: The patients who discontinued in the study before surgery are defined as treatment failure. Therefore, they are treated as patients who required platelet transfusion.
Abbreviations: EIS, endoscopic injection sclerotherapy; EVL, endoscopic variceal ligation; LUSU, lusutrombopag; MCT, microwave coagulation therapy; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization.
Source: L-PLUS 1 CSR.[19]

Table 24. Subgroup analysis of the proportion of subjects who met the primary endpoint in L-PLUS 2

Characteristic	LUSU 3 mg (n=108) [n/N (%)]	Placebo (n=107) [n/N (%)]	Comparison with placebo[a]	Test of homogeneity[b]
Baseline platelet count				
<35,000/μL	15/36 (41.7)	7/38 (18.4)		
≥35,000/μL	55/71 (77.5)	23/68 (33.8)		
Performed primary invasive procedure				
Percutaneous				
RFA/MCT				
EVL				
EIS				
TACE				
Other				
Not performed				

Sex				
Male	37/65 (56.9)	16/69 (23.2)	[redacted]	[redacted]
Female	33/43 (76.7)	15/38 (39.5)		
Age				
<65 years	55/84 (65.5)	25/88 (28.4)	[redacted]	[redacted]
≥65 years	15/24 (62.5)	6/19 (31.6)		
Baseline body weight				
<75 kg	37/53 (69.8)	17/50 (34.0)	[redacted]	[redacted]
≥75 kg	33/55 (60.0)	13/56 (23.2)		
Race				
White	59/85 (69.4)	25/86 (29.1)	[redacted]	[redacted]
Non-white	11/23 (47.8)	6/21 (28.6)		
Child-Pugh class				
A	45/72 (62.5)	19/63 (30.2)	[redacted]	[redacted]
B	24/33 (72.7)	12/43 (27.9)		
C	[redacted]	[redacted]	[redacted]	

[a]Fisher's exact test.
[b]Breslow-Day test for the relevant subgroup-by-treatment interaction. Regarding Child-Pugh class, subjects with class C are not included.
Note: The primary endpoint was the proportion of subjects who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomization through 7 days after the primary invasive procedure. In addition to subjects who received platelet transfusion, subjects who did not undergo an invasive procedure regardless of the reason were considered as receiving platelet transfusion.
Abbreviations: EIS, endoscopic injection sclerotherapy; EVL, endoscopic variceal ligation; LUSU, lusutrombopag; MCT, microwave coagulation therapy; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization.
Source: Peck-Radosavljevic et al., 2019;[21] L-PLUS 2 CSR.[20]

3.5.7 Phase 2b lusutrombopag trial

A Phase 2b study reports results that are consistent with those of L-PLUS 1 and L-PLUS 2. A summary of these are presented in Table 25. Full results are presented in Appendix C.1.4.

Table 25. Summary of key outcomes from Phase 2b trial

Endpoint	LUSU 3mg (n=16)	PBO (n=15)
Proportion of patients who required no preoperative platelet transfusion, n (%)	13 (81.3)	3 (20.0)
Proportion of patients who met responder criteria at least once, n (%)	11 (68.8)	1 (6.7)
Median duration of platelet count ≥50,000/μL, days		
With platelet transfusion (n=3 [LUSU]; n=12 [PBO])	3.3	0.0
Without platelet transfusion (n=13 [LUSU]; n=3 [PBO])	11.9	0.0

Abbreviations: LUSU, lusutrombopag; PBO, placebo.
Source: Study M0626 CSR.[51]

3.5.8 Meta-analysis of lusutrombopag trials

A meta-analysis of the lusutrombopag trials was conducted to facilitate incorporation of pooled data in the economic model. A summary of the results for the pooled lusutrombopag trials from the random-effects meta-analysis is presented in Table 26; for full details of the methodology and results refer to Appendix B.5.

Table 26. Summary of the random-effects meta-analysis for the pooled lusutrombopag trials

Endpoint	OR LUSU 3 mg vs. PBO (95% CI)	p-value
Primary composite outcome: no platelet transfusion and rescue for bleeding up to 7 days after procedure	[redacted]	[redacted]
Baseline platelet count <35,000/μL	[redacted]	[redacted]
Baseline platelet count ≥35,000/μL	[redacted]	[redacted]
Response: platelet count ≥ 50,000/μL and increase of ≥ 20,000/μL from baseline during study	[redacted]	[redacted]
Response: platelet count ≥ 50,000/μL prior to procedure	[redacted]	[redacted]
Transfusion requirements: Platelet transfusion required prior to procedure	[redacted]	[redacted]
Transfusion requirements: No platelet transfusion required during the study	[redacted]	[redacted]
Patient did not undergo scheduled procedure	[redacted]	[redacted]
Bleeding: Any bleeding during the study	[redacted]	[redacted]
Bleeding: Rescue for bleeding during the study	[redacted]	[redacted]
Treatment emergent AEs: Thrombosis	[redacted]	[redacted]

Abbreviations: AE, adverse event; CI, confidence interval; LUSU, lusutrombopag; OR, odds ratio; PBO, placebo.

3.5.9 Post marketing surveillance

A Japanese post-marketing study has additionally provided real-world data for lusutrombopag.[55] Results are consistent with those of L-PLUS 1 and L-PLUS 2; of patients treated with lusutrombopag, 16% (4/25) required a platelet transfusion before an invasive procedure, compared with 54% (69/128) cirrhotic controls. Further details are presented in Appendix C.6.1.

A second real-world evidence study further demonstrates consistency with the clinical trial results, although this study includes patients with a baseline platelet count >50,000/μL.[56] In this study, of 300 patients (effectiveness analysis set N= 315) who were not refractory to platelet transfusion and underwent an invasive procedure, 282 patients (94.0%) did not receive a platelet transfusion.[56] For further details, please refer to Appendix C.6.2.

3.6 Indirect and mixed treatment comparisons

No indirect treatment comparison (ITC) was conducted for lusutrombopag. Whilst data are available for avatrombopag in this indication (ADAPT-1 and ADAPT-2 trials),[15] the trials were not sufficiently similar to permit a robust comparison. There were important and potentially clinically meaningful differences in the design of the avatrombopag trials; critically, patients were included in the study with a baseline platelet count of <59,000/μL, above the 50,000/μL threshold for response. Patient stratification and imaging also differ. Furthermore, avatrombopag is not licensed or standard of care and there is no price associated with this compound with which to perform a cost-effectiveness analysis. Additional key differences between the avatrombopag and lusutrombopag clinical trials, rendering an ITC inappropriate are:

- Variation in endpoints: L-PLUS 1 had a single endpoint of platelet avoidance, L-PLUS 2 had a composite endpoint, and ADAPT 1 & 2 had a composite primary endpoint.
- Platelet transfusions were not mandatory in the avatrombopag trials, and were administered at the investigators' discretion, whereas these were mandated with a platelet count of <50,000/μL in the lusutrombopag trials. This would result in a lower chance of utilisation in the avatrombopag trials.
- In the avatrombopag trials, platelet count was the mean of two values, with no one value >60,000/μL, compared with a platelet count of <50,000/μL in the lusutrombopag trials.
- In the avatrombopag trials, only symptomatic portal vein transfusions were categorised, due to a lack of imaging; in the lusutrombopag trials, imaging was undertaken pre- and post-treatment.
- The ratio for randomisation differed between the avatrombopag (2:1) and lusutrombopag (1:1) trials.
- The number of days on which platelet count was checked was less in the avatrombopag trials (6 visits) than the lusutrombopag trials (12 visits).
- In the avatrombopag trials, there were no stopping criteria; all patients received avatrombopag for 5 days, compared with between 5–7 days dependent on whether patients met the responder criterion and for potential safety reasons in the lusutrombopag trials.

3.7 Safety

The clinical safety of lusutrombopag in the proposed indication is based on a pooled analysis of 20 of the 22 clinical studies of lusutrombopag, including:

- 12 Phase 1 studies in healthy subjects and healthy subjects with mild or moderate hepatic impairment
- 8 studies in thrombocytopenic subjects with CLD:
    - 1 Phase 1 study (M061B)
    - 1 Phase 1/Phase 2 study
    - 2 uncontrolled Phase 2 studies
    - 1 controlled Phase 2b study (Izumi 2014)
    - 2 controlled Phase 3 studies (L-PLUS 1 and L-PLUS 2)
    - 1 uncontrolled Phase 3b study

A total of 653 adult subjects were exposed to lusutrombopag in the 20 studies, including 362 thrombocytopenic subjects with CLD. The size of the safety database is justified as the intended patient population is small: only 1% to 2.6% of the total CLD population in the EU (approximately 29 million) have severe thrombocytopenia (< 50,000/μL),[2, 4, 5] and only a fraction of these patients undergoes invasive procedures. A summary of the safety data from the key studies reported in this submission (L-PLUS 1, L-PLUS 2, and Phase 2b) is provided in Appendix C.5.

An overview of adverse events is provided in Table 27 for the controlled studies and Table 28 for the uncontrolled studies in thrombocytopenic subjects with CLD.

Table 27. Overview of adverse events (controlled studies)

	Phase 2b				L-PLUS 1 and L-PLUS 2		Overall	
Subjects with:	**LUSU 2 mg (n=15)**	**LUSU 3 mg (n=16)**	**LUSU 4 mg (n=15)**	**Placebo (n=15)**	**LUSU 3 mg (n=155)**	**Placebo (n=155)**	**LUSU 3 mg (n=171)**	**Placebo (n=170)**
At least 1 AE, n (%)	15 (100.0)	16 (100.0)	14 (93.3)	15 (100.0)	96 (61.9)	100 (64.5)	112 (65.5)	115 (67.6)
At least 1 AE with an outcome of death, n (%)	1 (6.7)	0	0	0	3 (1.9)	0	3 (1.8)	0
At least 1 serious AE[a], n (%)	3 (20.0)	1 (6.3)	0	1 (6.7)	8 (5.2)	11 (7.1)	9 (5.3)	12 (7.1)
At least 1 AE leading to withdrawal of study drug, n (%)	0	0	0	0	0	1 (0.6)	0	1 (0.6)
At least 1 treatment-related AE, n (%)	5 (33.3)	3 (18.8)	3 (20.0)	0	10 (6.5)	14 (9.0)	13 (7.6)	14 (8.2)
At least 1 treatment-related serious AE, n (%)	0	0	0	0	2 (1.3)	1 (0.6)	2 (1.2)	1 (0.6)

[a]Includes fatal and nonfatal serious adverse events.
Abbreviations: AE, adverse event; LUSU, lusutrombopag.
Source: Lusutrombopag EPAR.[26]

Table 28. Overview of adverse events (uncontrolled studies)

Subjects with:	**LUSU 0.25–1 mg (n=16)**	**LUSU 1.5–2.5 mg (n=24)**	**LUSU 3 mg (n=108)**	**LUSU 4 mg (n=8)**
At least 1 AE, n (%)	16 (100.0)	23 (95.8)	98 (90.7)	8 (100.0)
At least 1 AE with an outcome of death, n (%)	1 (6.3)	0	0	0
At least 1 serious AE[a], n (%)	1 (6.3)	2 (8.3)	5 (4.6)	1 (12.5)
At least 1 AE leading to withdrawal of study drug, n (%)	0	0	0	0
At least 1 treatment-related AE, n (%)	3 (18.8)	2 (8.3)	6 (5.6)	0
At least 1 treatment-related serious AE, n (%)	0	0	1 (0.9)	0

[a]Includes fatal and nonfatal serious adverse events.
Abbreviations: AE, adverse event; LUSU, lusutrombopag.
Source: Lusutrombopag EPAR.[26]

Across the clinical development program for lusutrombopag, five deaths occurred; all were in thrombocytopenic subjects with CLD who were treated with once-daily doses of lusutrombopag ranging from 0.5–3 mg for up to seven days.[26] None of the deaths were considered by the investigator to be study drug-related.[26]

In the pooled controlled studies (Phase 2b, L-PLUS 1 and L-PLUS 2), 7 (4.1%) subjects treated with lusutrombopag 3 mg and 12 (7.1%) subjects treated with placebo had one or more serious nonfatal adverse events.[26] Additionally, in the uncontrolled studies, 5 (4.6%) patients treated with lusutrombopag 3 mg had one or more serious nonfatal AEs.[26]

In the pooled controlled studies, the incidences of adverse events were similar in the lusutrombopag and placebo groups.[26] Common adverse events (incidence ≥5%) in the lusutrombopag group were procedural pain, postoperative fever, procedural hypertension, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), decreased oxygen saturation, and increased blood bilirubin.[26] The incidence of most common adverse events was similar in the lusutrombopag and placebo groups or lower in the lusutrombopag group than in the placebo group.[26]

In the pooled controlled studies, 3.0% of lusutrombopag-treated subjects and 7.5% of placebo-treated subjects had bleeding events before the procedure, and 6.7% and 10.6%, respectively, had bleeding-related events after the procedure.[26] The most frequent bleeding-related events were procedural haemorrhage, subcutaneous haemorrhage, purpura, and postprocedural hemorrhage.[26] Regardless of severity, lower rates of procedural and post-procedural bleeding events were observed in patients treated with lusutrombopag and not receiving platelet transfusion (6/124, 6.5%) than those treated with placebo who received a platelet transfusion (n=15/126, 11.9%).[57]

There were two adverse events of special interest considered in the lusutrombopag clinical development program; thrombotic adverse events and worsening liver function. In the pooled controlled studies, 3 (1.8%) subjects treated with lusutrombopag 3 mg and 4 (2.4%) treated with placebo had a thrombotic event.[25, 26] In the pooled controlled studies, 4 (2.3%) subjects in the lusutrombopag group and 8 (4.7%) subjects in the placebo group had worsening liver function.[26] Worsening liver function was defined AST or ALT ≥ 3 times the upper limit of normal plus bilirubin ≥ 2 times the upper limit of normal on the same day.[26] The worsening liver function was reversible and temporary; at the last observation, 1 (0.6%) subject in the lusutrombopag group and 3 (1.8%) subjects in the placebo group met the criterion for worsening liver function.[26]

3.8 Interpretation of clinical effectiveness and safety evidence

3.8.1 Principal findings from the clinical evidence base

Lusutrombopag is the first pharmacological therapy to be approved for the treatment of severe thrombocytopenia associated with CLD in patients undergoing planned invasive procedures.[25] The principal evidence for the efficacy and safety of lusutrombopag is derived from two multicentre, randomised, double blind, parallel-group, placebo-controlled, Phase 3 trials (one Japanese, one global). Further evidence is derived from a third, Phase 2b, study.

Consistent data from these two Phase 3 studies and a Phase 2b study have confirmed that lusutrombopag 3 mg orally once daily for up to 7 days provides a statistically significant platelet response avoiding the requirement for pre-procedural platelet transfusion in patients undergoing

a range of elective invasive procedures. In L-PLUS 1, 79% of patients in the lusutrombopag group required no preoperative platelet transfusion, mandated at 50,000/μL, which was a statistically significantly greater proportion than the placebo group (13%).[19, 26] This was consistent with the per-protocol analysis which demonstrated that significantly more patients met the primary endpoint in the lusutrombopag group ([redacted]) than placebo group ([redacted]).[19] In L-PLUS 2, statistically significantly more patients required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomisation through 7 days after the procedure in the lusutrombopag group (65%) than in the placebo group (29.0%).[20, 23] Similarly, a sensitivity analysis using the per-protocol population of L-PLUS 2 demonstrated that the number of patients reaching the primary endpoint was significantly greater in the lusutrombopag group (72.5%) than placebo group (20.2%).[20, 21] Results from the Phase 2b trial further support this; 81.3% of patients in the lusutrombopag group and 20.0% of patients in the placebo group did not require pre-operative platelet transfusion. A reduced requirement for pre- and post-operative platelet transfusion with lusutrombopag treatment alleviates the risks associated with invasive platelet transfusions, potentially resulting in a positive impact on HRQoL as well as on overall system outcomes.

In addition to this, treatment with lusutrombopag reduces the number of platelet transfusions and dose transfused in subjects who required a platelet transfusion.[19, 20, 23] These data demonstrate that lusutrombopag has benefits in terms of both reducing the need for platelet transfusion and, where platelet transfusions are required, reducing the number of required transfusions. A significantly greater proportion of patients met the responder criterion in the lusutrombopag group in both L-PLUS 1 (lusutrombopag, 77.1%; placebo, 6.3%) and L-PLUS 2 (lusutrombopag, 64.8%; placebo, 13.1%).[19, 20, 23, 50] Similarly, higher proportions of patients in the lusutrombopag arm (68.8%) than the placebo arm (6.7%) met the responder criteria in the phase 2b trial. Data from the re-analysis of L-PLUS 1, demonstrates that for all patients (with and without platelet transfusion), the duration of platelet count increase was significantly greater in the lusutrombopag arm (21.1 days) than placebo arm (3.4 days, p=0.0197).[25] Similarly, for L-PLUS 2, the duration of maintenance of platelet count increase was significantly longer in the lusutrombopag arm (15.1 days) than in the placebo arm (1.0 days, p=0.0002) (Table 17).[20, 21, 23] These results demonstrate the efficacy of lusutrombopag in increasing the platelet count of patients, permitting a broader window in which to undertake planned invasive procedures, in comparison to treatment with placebo. These clinical efficacy results are also supported by a Phase 2b trial.[22, 51]

In addition to consistently demonstrating improved clinical efficacy, in a pooled analysis of 20 studies, lusutrombopag has been shown to be well-tolerated by thrombocytopenic subjects with CLD who are undergoing a planned invasive procedure. Whilst overall AEs were comparable between lusutrombopag and placebo in the pooled controlled studies (Phase 2b, L-PLUS 1 and L-PLUS 2), serious nonfatal AEs occurred at a lower rate in patients treated with lusutrombopag (4%) than in patients treated with placebo (7%).[26]

A clear unmet medical need exists for thrombocytopenic CLD patients, and notably those with severe thrombocytopenia, who are at risk of bleeding when undergoing planned invasive procedures. These patients commonly receive platelet transfusions to reduce the risk of procedural bleeding, to treat secondary bleeding complications and to allow repeat procedures, and can thus be exposed repeatedly to the risks associated with these transfusions, with unwanted clinical variation.[16] A seven day course of lusutrombopag 3 mg can reduce the need for platelet transfusion; by raising platelet counts above 50,000/μL for approximately 3 weeks on average, the use of platelet transfusions can be avoided not only for the initial planned procedure

but for any additional procedures, required by over 20% of patients, that might be needed during the time platelet counts remain above 50,000/μL.[26] Thus lusutrombopag provides a clear advantage over the existing standard of care.

3.8.2 Strengths and limitations of the clinical evidence base

Aside from lusutrombopag, there are no approved pharmaceutical therapies in this indication, therefore the trials included in the clinical evidence base for lusutrombopag are limited by not including active pharmacological comparators. Additionally, limited evidence for the efficacy of lusutrombopag in patients with Child-Pugh Class C liver disease was available; these patients were excluded in L-PLUS 1 and LPLUS 2, although 3 patients with disease of this nature were erroneously included in L-PLUS 2. However, a descriptive review of patient data from three studies (n=21 Child-Pugh Class C patient), including a Phase 1/2 study of lusutrombopag in 5 Child-Pugh Class C patients, has found that lusutrombopag provides a favourable treatment effect in these patients; in lusutrombopag treated patients, the mean maximum platelet count was 84,000/μL, 80,000/μL and 89,500/μL in a Phase 1/2 study (n=4), a Phase 3 study (n=1) and in post-marketing surveillance (n=13), respectively.[58]

Nonetheless, the clinical evidence base for lusutrombopag is sourced from two well-designed clinical trials with low risk of bias that are highly relevant to the decision problem, L-PLUS 1 and L-PLUS 2, with additional evidence from a controlled Phase 2b study. Treatment with lusutrombopag was consistently observed to result in clinical benefits in both trials, and across subgroups in both trials. Additionally, the pooled safety analysis of 20 studies demonstrates the highly tolerable safety profile of lusutrombopag. Lusutrombopag therefore offers a highly efficacious, effective and well-tolerated addition to the clinical armamentarium for patients whose only treatment option at present is invasive and potentially risky platelet transfusion.

4 Cost-effectiveness

Summary of Cost Effectiveness

- A *de novo* model was developed to assess lusutrombopag for CLD patients with severe thrombocytopenia undergoing planned invasive procedures. A short-term (decision tree) model presents an ICER based on the QALY benefit demonstrated during the 35-day clinical trial period; a long-term (Markov) model presents an ICER based on QALY benefit and mortality over a lifetime time horizon.
- The analysis compared lusutrombopag to platelet transfusion, with efficacy data based on the pooled lusutrombopag trials (L-PLUS 1, L-PLUS 2 and the Phase 2b trial).
- Additional inputs, including mortality estimates, utility values and costs were derived from the literature.
- The model was constructed from a UK NHS and Personal Social Services (PSS) perspective, and where appropriate, costs and outcomes were annually discounted at 3.5%.
- The cost-effectiveness model found that lusutrombopag was more efficacious and less costly than platelet transfusion with incremental cost savings of £172 and QALY benefits of 0.0147:
    - The base case results and most scenario analyses found that lusutrombopag was the dominant treatment strategy.
    - Where results from the one-way deterministic sensitivity analysis or scenario analyses did not show dominance, lusutrombopag was cost-effective at willingness-to-pay thresholds of £20,000/QALY and £30,000/QALY in all cases, including scenarios that tested much lower costs for platelet transfusion than were used in previous relevant appraisals.
- Reflecting these robust deterministic findings, the probabilistic sensitivity analysis (PSA) found an 81% probability of lusutrombopag being cost-effective at a willingness-to-pay threshold of

£20,000/QALY. At a willingness-to-pay threshold of £30,000/QALY, the PSA found an 87% probability of lusutrombopag being cost-effective.
    - The probability of lusutrombopag being cost-effective was greater than 50% at all willingness-to-pay thresholds, including zero.
- Notably, had lusutrombopag been assessed under the Single Technology Appraisal process it would have qualified for the Fast Track Appraisal process.
- Lusutrombopag represents a valuable new treatment option for the NHS, benefiting patient and payer alike. Given the clear unmet need, demonstrable efficacy and safety, added convenience and cost-savings to the NHS,

4.1 Economic analysis

An economic model was developed to evaluate the cost-effectiveness of lusutrombopag versus the current standard of care (platelet transfusion) for the treatment of severe thrombocytopenia in patients with CLD requiring planned invasive procedure. An SLR did not identify any relevant previous economic evaluations relevant to the decision problem (Appendix D), therefore a *de novo* model was developed. The submission does not include avatrombopag in the cost-effectiveness analysis; avatrombopag has an unknown license and unknown price, and there were critical differences in trial design (Section 3.6) preventing an ITC with this treatment.

4.1.1 Patient population

The model considered patients with CLD with severe thrombocytopenia (platelet count <50,000/μL), who required a planned invasive procedure. Patient characteristics were based on the lusutrombopag trials.[19, 20, 51] The base case of the model considers pooled data from the three lusutrombopag trials. However, data from the L-PLUS 2 trial was included as a scenario analysis, as this was the sole international trial which included patients from the UK.

4.1.2 Model structure

The model was constructed in Microsoft Excel. Given the short treatment duration of lusutrombopag and length of follow-up of the pivotal trials (35 days), a decision tree was considered the most appropriate structure, as presented in Figure 4.

The model was constructed from a UK NHS and Personal Social Services (PSS) perspective. The model structure was determined to be appropriate by three clinical and economic experts at validation meetings conducted on 28 September 2018 and 30 November 2018 (see Section 4.8.1). The structure of the model is shown in Figure 4, this structure was used to assess both treatments in the model. The initial decision tree model has a 35-day time horizon, in line with the trial data, and includes chance nodes for the following:

- Receiving/not receiving platelet transfusion
- Death/no death following platelet transfusion
- Receiving/not receiving planned invasive procedure within the 35-day study period
- Death/no death before rescheduled procedure
- Bleeding/no bleeding following planned or rescheduled invasive procedure
- Recue therapy/no rescue therapy following bleeding
- Death/no death from bleeding for those not receiving rescue therapy
- Death/no death from bleeding for those receiving rescue therapy

The model structure was selected based on the endpoints of L-PLUS 1 and L-PLUS 2, and the key clinical value of lusutrombopag relative to the comparator. Lusutrombopag reduces the need for patients to undergo platelet transfusion prior to a planned invasive procedure; platelet transfusions are costly and can be associated with complications which further increase costs and reduce patient quality of life. Platelet transfusion may additionally lead to increased mortality,[59] and it is expected that patients receiving lusutrombopag would have a lower risk of bleeding. In the pooled controlled studies, 3.0% of lusutrombopag-treated subjects and 7.5% of placebo-treated subjects had bleeding events before the procedure, and 6.7% and 10.6%, respectively, had bleeding-related events after the procedure.[26]

Data from the key clinical trials for lusutrombopag were used, where available, to determine the proportion of patients receiving platelet transfusion prior to their planned invasive procedure, the proportion receiving their planned invasive procedure, the proportion with bleeding following their planned invasive procedure and the proportion receiving rescue therapy following a bleed for each treatment. The model assumes that the probabilities at each node are conditional on the outcomes of previous nodes.

Each branch of the decision tree was designed to capture key clinically meaningful outcomes. Costs were attributed to any platelet transfusions given, any procedure received and for any rescue therapy that was required, in addition to treatment acquisition, administration, AE, monitoring and societal costs where appropriate. One-off quality-adjusted life year (QALY) decrements for platelet transfusions, bleeding and AEs were also applied to each branch, where appropriate.

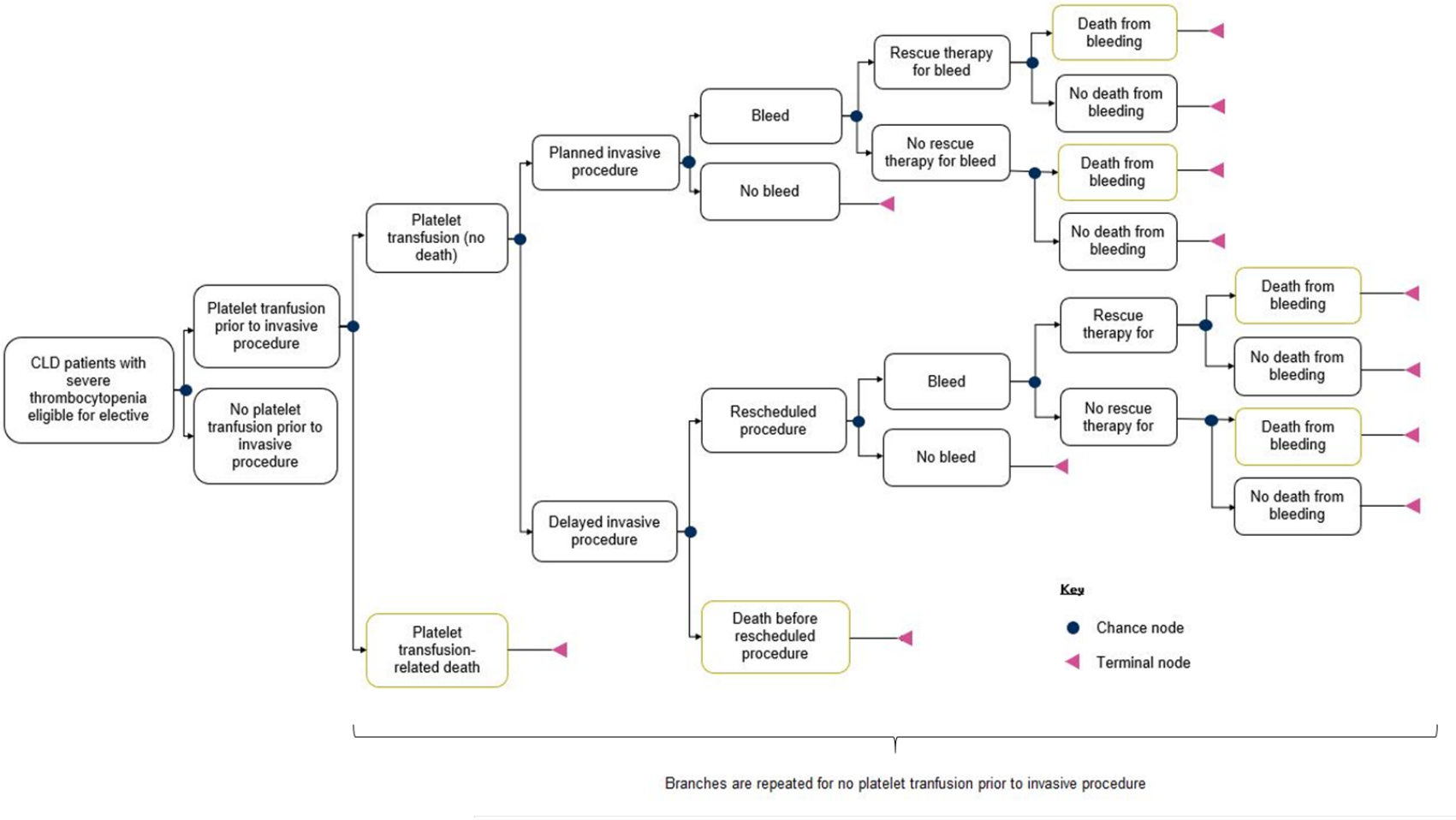
CLD-related mortality and utility values are used to estimate the number of QALYs that would be accrued over the patient's expected remaining lifetime using a yearly cycle length.[60, 61] The model considers a lifetime time horizon, which incorporates the short-term decision tree model and long-term Markov model.

The base case of the model considers the mortality benefit associated with lusutrombopag (long-term model). Scenario analyses were conducted with the exclusion of mortality in the long-term model.

The standard 3.5% discount rate was applied in the long-term model only, as this was the only scenario the discount rate is relevant to.

The *de novo* model structure is aligned with the primary objective of treatment with lusutrombopag, to prevent the need for platelet transfusion prior to a planned invasive procedure and avoid use of rescue therapy. The model captures the benefits of lusutrombopag treatment including the reduced probability of requiring a platelet transfusion or having a bleed, in addition to reduced treatment costs due to the cost of platelet transfusions themselves and complications associated with these. The model also captures the costs associated with the procedure received, and impact on patient quality of life and mortality through avoiding platelet transfusions and bleeds.

Figure 4. Decision tree model structure



Nodes in yellow can be switched off by setting probability to 0.
Abbreviations: CLD, chronic liver disease

4.1.3 Intervention technology and comparators

Intervention

The intervention considered in the model is lusutrombopag (Section 2.3.4). Consistent with the SmPC, lusutrombopag is administered orally once daily at a dose of 3 mg for 7 days, and a minimum of 9 days prior to the procedure. Lusutrombopag has received approval in Japan (September 2015) and FDA approval (31st July 2018) for the treatment of thrombocytopenia in CLD patients undergoing planned procedures, and EU marketing authorisation (18th February 2019) for the treatment of severe thrombocytopenia in adult patients with CLD undergoing invasive procedures.[17, 46, 62]

Comparator

Platelet transfusion

For patients undergoing an invasive procedure with severe thrombocytopenia (platelet count <50,000/μL) in the UK, NICE recommends the use of platelet transfusion to increase platelet levels (Blood transfusions NG24).[9]

4.2 Clinical parameters and variables

4.2.1 Efficacy

Efficacy data was based on the results from the three controlled studies from the lusutrombopag clinical trial program (L-PLUS 1, L-PLUS 2 and Phase 2b).[19, 20, 51] The base case for this submission utilises data from the meta-analysis of lusutrombopag clinical trials, as this has increased power and was therefore considered more relevant to decision-making. The L-PLUS 2 data were included as a scenario analysis. An additional scenario analysis was conducted using the efficacy data from the per-protocol analysis set.

Efficacy inputs included the following for each treatment arm:

1. Proportion of patients receiving a platelet transfusion prior to the planned invasive procedure
2. Proportion of patients with bleeding
3. Proportion of patients not receiving their planned invasive procedure during the trial period (conditional based on receipt of prior platelet transfusion)
4. Proportion of patients receiving rescue therapy following bleeding (conditional based on receipt of prior platelet transfusion and receipt of planned invasive procedure)

Efficacy inputs 1 and 2 were calculated as follows: For the platelet transfusion arm of the model, the proportion of patients achieving each outcome was taken directly from the placebo arm of the lusutrombopag clinical trials. To determine the equivalent proportions for the lusutrombopag arm of the model, the ORs estimated from either the L-PLUS 2 trial alone or the pooled lusutrombopag trials were applied to the 'platelet transfusion' arm. Pooled ORs were based on a meta-analysis of outcomes across L-PLUS 1, L-PLUS 2 and Phase 2b (Appendix B.5).

In the base case, efficacy inputs 3 and 4 were calculated as conditional probabilities using individual patient data from the lusutrombopag trials. Unconditional efficacy inputs, as calculated for inputs 1 and 2, were utilised in a scenario analysis.

The modelling approach and inputs were considered to be appropriate and clinically plausible by clinical and economic experts during model validation.

4.2.1.1 Proportion of patients receiving a platelet transfusion prior to the planned invasive procedure

Three experts engaged by Shionogi suggested that 100% of the placebo arm patients would receive platelet transfusion in clinical practice due to less intensive monitoring of platelet count prior to the procedure. This is assumed in the base case analysis, however a scenario analysis was conducted which did not assume that 100% of the placebo arm patients would receive platelet transfusion, and instead used the proportion from trial data presented in Table 30.

The ORs for receiving a platelet transfusion for lusutrombopag versus placebo and the resulting proportions of patients receiving a platelet transfusion prior to planned invasive procedure used in the model are presented in Table 29 and Table 30.

Table 29. OR for receiving a platelet transfusion for lusutrombopag versus placebo

	OR vs. PT	95% CI Lower	95% CI Upper
LUSU (L-PLUS 2)	[redacted]	[redacted]	[redacted]
LUSU (Pooled)	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; LUSU, lusutrombopag; OR, odds ratio; PT, platelet transfusion.

Table 30. Proportions of patients receiving a platelet transfusion prior to planned invasive procedure used in the model

Treatment	L-PLUS 2	Pooled
Platelet transfusion	[redacted]	[redacted]
Lusutrombopag	[redacted]	[redacted]

The OR for active treatment was applied to the platelet arm of either L-PLUS 2 or the pooled lusutrombopag trial data. Both scenarios are presented.

4.2.1.2 Proportion of patients with bleeding

The ORs for patients with bleeding for lusutrombopag versus placebo and the resulting proportions of patients with bleeding used in the model are presented in Table 31 and Table 32.

Table 31. OR for bleeding for lusutrombopag versus placebo

	OR vs. PT	95% CI Lower	95% CI Upper
LUSU (L-PLUS 2)	[redacted]	[redacted]	[redacted]
LUSU (Pooled)	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; LUSU, lusutrombopag; OR, odds ratio; PT, platelet transfusion.

Table 32. Proportions with bleeding used in the model

Treatment	L-PLUS 2	Pooled
Platelet transfusion	[redacted]	[redacted]
Lusutrombopag	[redacted]	[redacted]

The OR for active treatment was applied to the platelet arm of either L-PLUS 2 or the pooled lusutrombopag trial data. Both scenarios are presented.

4.2.1.3 *Proportion of patients not receiving their planned invasive procedure during the trial period*

The conditional probabilities for patients not receiving the planned invasive procedure for the lusutrombopag and placebo arms of the model are presented in Table 33.

Table 33. Conditional probabilities for not receiving planned invasive procedure (i.e. procedure delayed beyond trial period)

	Placebo, % (n/N)[a]	Lusutrombopag, % (n/N)
Pooled		
Proportion not receiving planned invasive procedure as planned, having received a prior platelet transfusion	[redacted]	[redacted]
Proportion not receiving planned invasive procedure as planned with no prior platelet transfusion	[redacted]	[redacted]
L-PLUS 2		
Proportion not receiving planned invasive procedure as planned, having received a prior platelet transfusion	[redacted]	[redacted]
Proportion not receiving planned invasive procedure as planned with no prior platelet transfusion	[redacted]	[redacted]

[a]This data informs the platelet transfusion arm of the model, however it is not certain that patients will receive platelet transfusion in this arm.

The ORs for patients not receiving the planned invasive procedure for lusutrombopag versus placebo and the resulting proportions of patients not receiving the planned invasive procedure used in a scenario analysis are presented in Table 33 and Table 35. These are not based on conditional probabilities, rather derived from the meta-analysis conducted for the lusutrombopag trials.

Table 34. OR for not receiving planned elective invasive procedure for lusutrombopag versus placebo (i.e. procedure delayed beyond trial period)

	OR vs. PT	95% CI Lower	95% CI Upper
LUSU (L-PLUS 2)	[redacted]	[redacted]	[redacted]
LUSU (Pooled)	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; LUSU, lusutrombopag; OR, odds ratio; PT, platelet transfusion.

Table 35. Proportions of patients not receiving planned invasive procedure used in the model

Treatment	L-PLUS 2	Pooled
Platelet transfusion	[redacted]	[redacted]
Lusutrombopag	[redacted]	[redacted]

The proportions of patients not receiving their planned elective invasive procedure on each treatment arm was calculated by applying the odds ratio for each treatment to the proportion of patients not receiving their planned elective procedure on the platelet transfusion arm (either L-PLUS 2 or pooled). Both scenarios are presented.

4.2.1.4 Proportion of patients receiving rescue therapy following bleeding

The conditional probabilities for patients receiving rescue therapy for lusutrombopag and placebo used in the model are presented in Table 36.

Table 36. Conditional probabilities for receiving rescue therapy for lusutrombopag and placebo

	Placebo, % (n/N)[a]	Lusutrombopag, % (n/N)
Pooled		
Received rescue therapy having received a prior platelet transfusion AND planned invasive procedure	[redacted]	[redacted]
Received rescue therapy having received a prior platelet transfusion AND delayed planned invasive procedure	[redacted]	[redacted]
Received rescue therapy with no prior platelet transfusion AND planned invasive procedure	[redacted]	[redacted]
Received rescue therapy with no prior platelet transfusion AND delayed planned invasive procedure	[redacted]	[redacted]
L-PLUS 2		
Received rescue therapy having received a prior platelet transfusion AND planned invasive procedure	[redacted]	[redacted]
Received rescue therapy having received a prior platelet transfusion AND delayed planned invasive procedure	[redacted]	[redacted]
Received rescue therapy with no prior platelet transfusion AND planned invasive procedure	[redacted]	[redacted]
Received rescue therapy with no prior platelet transfusion AND delayed planned invasive procedure	[redacted]	[redacted]

[a]This data informs the platelet transfusion arm of the model, however it is not certain that patients will receive platelet transfusion in this arm.

The ORs for patients with bleeding for lusutrombopag versus placebo and the resulting proportions of patients with bleeding used in a scenario analysis are presented in Table 37 and Table 38.

Table 37. OR for requiring rescue therapy for lusutrombopag versus placebo

	OR vs. PT	95% CI Lower	95% CI Upper
LUSU (L-PLUS 2)	[redacted]	[redacted]	[redacted]
LUSU (Pooled)	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; LUSU, lusutrombopag; OR, odds ratio; PT, platelet transfusion.

Table 38. Proportion of patients requiring rescue therapy following bleeding used in the model

Treatment	L-PLUS 2	Pooled	L-PLUS 2	Pooled
			Patients who had a bleed	
Platelet transfusion	[redacted]	[redacted]	[redacted]	[redacted]
Lusutrombopag	[redacted]	[redacted]	[redacted]	[redacted]

The OR for active treatment was applied to the platelet arm of either L-PLUS 2 or the pooled lusutrombopag trial data. Both scenarios are presented.

4.2.2 Mortality

The base case of the model considers the mortality benefit associated with lusutrombopag. Mortality in the short-term model can be due to platelet transfusion, bleeding or delayed invasive procedures. An alternative scenario analysis was conducted which does not consider the mortality benefit associated with lusutrombopag.

4.2.2.1 Platelet transfusion related mortality

The base case for mortality associated with platelet transfusion in the model was sourced from van Eerd et al. (2010), which reports the incidence of complications due to transfusions of fresh frozen plasma (FFP) and the mortality associated with these.[37] These mortality estimates from van Eerd et al. were considered appropriate for use in the model during clinical validation. However, the model assumes that the incidence of infectious complications is 0%, as clinicians highlighted that screening of blood products has improved since the study was published. The final estimates for mortality are presented in Table 39. Based on this data, the mortality risk per transfusion of FFP is estimated to be 0.3315%. For simplicity, this excludes the annual mortality associated with prion disease.

A scenario analysis was conducted utilising an alternative source of mortality data identified in the literature, based on a publication by Vamvakas et al. (2009). The authors estimated the number of deaths due to allogenic blood transfusions to be 3.5 per million components (transfusions) using UK Serious Hazards of Transfusion (SHOT) data between 1996-2004. There were 167 transfusion-related deaths during this period which resulted in an incidence of 0.0004%.[59] However, these data were considered to be less relevant during clinical validation.

The probability of platelet transfusion-related death from no platelet transfusion prior to procedure is assumed to be zero. All patients who do not receive a platelet transfusion are assumed to progress to either a planned or delayed procedure.

Table 39. Complications of transfusion and associated mortality

Complication	Incidence per transfusion (FFP)*	Mortality	Incidence per event/annual?	Weighted by proportion	Source
Transfusion-related acute lung injury	3.30%	10.00%	Event	0.33%	van Eerd et al. (2010)[37]
Hepatitis A Virus	0%	0.50%	Event	0.00%	
Hepatitis B Virus	0%	NR	NR	NR	
Hepatitis C Virus	0%	NR	NR	NR	
Human Immunodeficiency Virus	0%	NR	NR	NR	
Parvovirus B19	0%	2.70%	Event	0.00%	
Prion disease	0.00039%	60.00%	Annually	0.00%	
Severe allergic reaction	0.015%	10.00%	Event	0.0015%	
Mortality risk applied in model per transfusion				**0.3315%**	
Mortality risk applied in model per transfusion				0.0004%	Vamvakas et al. (2009)[59]

*As a proxy for platelets
Abbreviations: FFP, fresh frozen plasma; NR, not reported.

4.2.2.2 Bleeding related mortality

For bleeding-related mortality, the base case of the model utilises data from Takaki et al. (2012) (Table 40).[63] These data were considered appropriate as the procedure considered in the publication (RFA) matched most closely with the procedures performed during the lusutrombopag trials.

Table 40. Bleeding related mortality

Study	Mortality	Details
Takaki (2012)[63]	**0.83%**	**Death due to bleeding following RFA – major and minor**

Abbreviations: RFA, radiofrequency ablation.

4.2.2.3 Mortality due to delayed procedures

The model assumes that the probability of death as a result of a delayed invasive procedure is 0%, as clinical experts stated that probability of death resulting from a delayed procedure is not relevant and therefore does not need to be included within the model.

4.2.2.4 CLD-related mortality

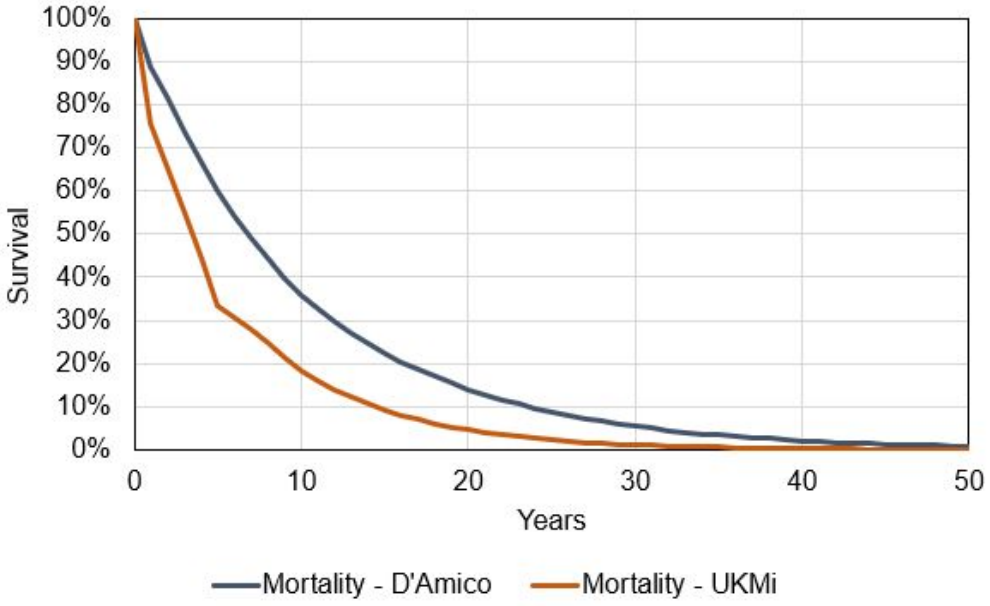
To estimate long-term QALYs for the proportion of patients surviving the initial 35-day trial period, estimates of mortality for patients with CLD were required.

The base case of the model considers CLD-related mortality sourced from a systematic review by D'Amico et al. (2006).[60] In this study, survival at 1 and 2 years for each Child-Pugh grade were used to estimate the survival rate which was then extrapolated over the model time horizon and weighted based on the proportions of patients with each Child-Pugh score to generate a weighted survival curve for patients with CLD.

An alternative scenario, using data from UK Medicines Information (UKMi), is explored in the model.[64] For these data, linear interpolation was used to estimate survival per year based on reported survival at 1, 5 and 10 years for each Child-Pugh category, then annual probability of death was weighted based on the proportions of patients with each Child-Pugh score to generate a weighted survival curve for patients with CLD.

D'Amico et al. (2006) was chosen as the base case for this submission as clinicians considered the estimates from UKMi to be too low, with one-year survival estimated as 84% in the UKMi data. CLD-related mortality for both sources is presented in Figure 5.

Figure 5. CLD-related mortality



Abbreviations: UKMi, UK Medicines Information

4.2.3 Safety

Severe adverse events can have an impact on costs and health-related quality of life (HRQoL), and have therefore been included in the model. The severity of the disease itself results in a high proportion of treatment-emergent AEs, therefore AEs were only included in the model if they were possibly or probably related to the study drug. Thrombus-related AEs are particularly relevant to TPO agonists, therefore all severe possibly/probably related thrombus-related events were included in the model based on all three lusutrombopag trials.[19, 20, 51] For the Phase 2b trial, only patients on the 3 mg dose arm were included as this reflects the licensed dose.

Across the three lusutrombopag RCTs, 3 (1.8%) subjects treated with lusutrombopag 3 mg and 4 (2.4%) treated with placebo had a thrombotic event.[25, 26] There was one severe, possibly or probably related, thrombus-related treatment-emergent AE (portal vein thrombosis) in a patient on lusutrombopag 3 mg (equating to an incidence of 0.58%), and zero for patients in the placebo arm. Comprehensive data for all platelet transfusion-specific AEs were not available; therefore, platelet transfusion-specific AEs were sourced from an external literature source reporting AEs for patients per unit of FFP transfused (as a proxy for platelets).[37] Clinicians agreed with the estimates from the literature but, as discussed in Section 4.2.2.1, stated that, as blood products are now screened, the risk of contracting infections is conservatively assumed to be 0%.

The incidence of AEs is presented in Table 41. The incidence per unit was multiplied by the average number of units transfused based on clinical expert opinion (i.e. 3 units) to determine incidence per transfusion.

Table 41. Incidence of platelet transfusion complications used in the model

AE/complication	Incidence per unit FFP*	Incidence per transfusion of platelets**	Source
Transfusion-related acute lung injury	1.1%	3.30%	van Eerd (2010)[37]

Hepatitis A Virus	0.000%	0.000%	Clinical validation 30 November 2018
Hepatitis B Virus	0.000%	0.000%	Clinical validation 30 November 2018
Hepatitis C Virus	0.000%	0.000%	Clinical validation 30 November 2018
Human Immunodeficiency Virus	0.000%	0.000%	Clinical validation 30 November 2018
Parvovirus B19	0.000%	0.000%	Clinical validation 30 November 2018
Prion disease	0.00013%	0.0004%	van Eerd (2010)[37]
Severe allergic reaction	0.00508%	0.0152%	van Eerd (2010)[37]

*As a proxy for platelets; **Based on average of 3 units per transfusion (clinical validation)
Abbreviations: AE, adverse event; FFP, fresh frozen plasma.

An additional scenario analysis was conducted, with an increased TRALI incidence (29%),[65] compared to 1.1% in the base case.

Over the lusutrombopag trials, there were three fatalities in patients treated with the approved dose of lusutrombopag, and none in patients treated with placebo (Table 42). However none were considered by investigators to be treatment related and so are not modelled.

Table 42. Death events in lusutrombopag studies

Dose received	Relevant history	Fatal event
Lusutrombopag 3 mg	Cirrhosis with decomposition	Hepatic cirrhosis
Lusutrombopag 3 mg	Hepatocellular carcinoma	Vessel perforation
Lusutrombopag 3 mg	Alcoholic liver disease	Multiple organ failure Cardiac arrest

4.3 Measurement and valuation of health effects

HRQoL data were not collected in the lusutrombopag clinical trials, and were therefore sourced from a systematic literature review.[19, 20, 51] Utility values were used in both the short-term and the long-term model to calculate QALYs.

4.3.1 Utilities used in the short-term model

As HRQoL data were not collected during the lusutrombopag clinical trials, the model base case assumes the same baseline utility across both treatments, with one-off QALY decrements associated with platelet transfusions, bleeds, rescue therapy, delayed procedures and AEs.

4.3.1.1 Baseline utility

The base case of the model includes a baseline utility estimate for patients with chronic liver disease/cirrhosis of 0.54, sourced from Sullivan et al. (2011).[61] This was considered to be more appropriate as this value is UK-specific, and has been used and accepted in previous health technology assessments.

4.3.1.2 Disutilities

Platelet transfusion

The base case of the model considers disutilities associated with platelet transfusion sourced from NICE TA293, which was considered to be the most appropriate source in clinical validation of the model. Accordingly, a disutility of 0.1 for serious platelet transfusion related AEs was applied for one model cycle (i.e. 4 weeks).[66] This was converted to a QALY decrement and multiplied by the proportion of patients experiencing a serious transfusion reaction based on a publication by Hendrickson et al. (2016), identified through literature searches.[67]

The disutility, duration and QALY decrements applied in the model for platelet transfusion are presented in Table 43. Importantly, due to the short time horizon over which the disutilities apply, the resulting QALY decrements are extremely small.

Table 43. QALY decrements for platelet transfusion

Complication	Disutility (mean)*	Duration (weeks)	QALY decrement	Incidence	QALY decrement weighted by incidence	Reference
Platelet transfusion – serious AE	**0.1**	**4**	**0.00766**	**1.09%**	**0.0000837**	**Disutility based on NICE TA293;[66] incidence based on Hendrickson (2016)[67]**

*Uncertainty information not reported in source, SE assumed 10% of mean; **Disutility due to prion disease not included in model for simplicity due to extremely low incidence
Abbreviations: AE, adverse event; QALY, quality-adjusted life year; SE, standard error.

Bleeds

Disutility values for bleeding were taken from publications identified in the literature review. The literature identified classed bleeds as either major or minor, and bleeding-related disutility was dependent on bleed severity. No studies were identified which were able to identify the proportion of major and minor bleeds following planned invasive procedures in this patient population. Therefore, it was assumed in the base case that all bleeds in the model are major bleeds, as minor bleeds would be expected to have a minor impact on cost and quality of life. It is also assumed that the disutility per major bleed is applied for a duration of one week. Table 44 presents the bleeding-related disutility and QALY decrement included in the model. Importantly, due to the short time horizon, the resulting QALY decrements are extremely small.

Table 44. QALY decrements for bleeding

Bleed severity	Disutility (mean)*	Duration (weeks)	QALY decrement	Reference
Major bleed	**0.397**	**1**	**0.008**	**Jugrin (2015)[68]**

*Uncertainty information not reported in source, SE assumed 10% of mean
Abbreviations: QALY, quality-adjusted life year

Rescue therapy

During the validation meeting conducted on 28 September 2018, clinicians stated that rescue therapy was usually defined as further platelet transfusion(s). Whilst some patients in the lusutrombopag clinical trials additionally received pharmacotherapy as part of their rescue therapy, this was not included in the model to align better with UK clinical practice and to avoid unnecessary complexity. Therefore, disutilities and durations for the small proportion of patients receiving rescue therapy were assumed to be the same as those for platelet transfusions.

AEs

The SLR did not identify any thrombus-related AE disutilities, therefore the model used a disutility of −0.029 based on Jugrin et al. (2015).[68] This is based on a disutility for related thrombotic events: index deep vein thrombosis and index pulmonary embolism. Clinical experts confirmed that this source was appropriate, however highlighted that these inputs have a small impact on the results. The experts agreed with the assumption of a duration of 1 week over which the disutility was applied, resulting in a final QALY decrement of 0.001 per portal vein thrombosis event.

Planned invasive procedures

No studies reporting the disutility for delays to planned invasive procedures were identified in the literature. Therefore, no disutility was applied in the model as this input could not be quantified. This could be a conservative assumption as lusutrombopag may improve HRQoL based on fewer patients experiencing a delay to receiving required therapeutic or diagnostic procedures.

4.3.2 Utilities used in the long-term model

Lifetime QALYs were estimated for survivors at the end of the short-term model, requiring estimates of mortality and utility. Estimates of mortality are detailed in Section 4.2.2. For utility, the baseline utility as used in the short-term model for patients with cirrhosis/CLD was used.[61] The proportion of patients alive each year based on Child-Pugh scores was used to determine the proportion of patients in “alive” and “dead” health states each year. These estimates were half-cycle corrected to account for death occurring at any time throughout the model cycle, rather than at the start, for increased accuracy. Life-years were calculated by multiplying the proportion of patients alive each year by the cycle length (1-year). Life-years were then summed over the model time horizon to calculate total life-years accrued. To estimate QALYs, estimates of life-years were weighted according to patient utility and total QALYs were calculated by summing over the model time horizon. Life-years and QALYs were discounted at annual rates of 0% and 3.5% per annum, respectively, as recommended in the NICE Methods Guide.[69] Total discounted QALYs were added to the total QALYs from the short-term model for each treatment, before determining ICERs.

4.3.3 Age adjustment

As recommended in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 12, utility values were adjusted for the natural decline in utility observed with increasing age. The published regression equation by Ara and Brazier (2010) was used to generate utility multipliers by age and sex.[70] The regression coefficients are presented in Table 45.

Table 45. Regression coefficients for age adjusted utility

Variable	Regression coefficient
Sex	0.0212126

Age	-0.0002587
age^2	-0.0000332
_cons	0.9508566

Source: Ara and Brazier, 2011.[70]

4.3.4 Health-related quality-of-life data used in the cost-effectiveness analysis

A summary of HRQoL data in this submission is presented in Table 46. These values were derived from SLRs and validated by clinical experts.

Table 46. Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)
Baseline utilities			
Utility, chronic liver disease, Sullivan	0.54 (0.05)	(0.4,0.6)	Section 4.3.4.1, p.56
Disutilities			
Transfusion-related reaction, NICE	0.10 (0.01)	(0.1,0.1)	Section 4.3.4.2, p.56
Portal vein thrombosis, Jugrin	0.03 (0.00)	(0.0,0.0)	Section 4.3.4.2, p.57
Major bleed, Jugrin	0.40 (0.04)	(0.3,0.5)	Section 4.3.4.2, p.56

Abbreviations: NICE, National Institute for Health and Care Excellence

4.4 Cost and healthcare resource use identification, measurement and valuation

The model considers a comprehensive range of cost categories: drug acquisition costs, platelet transfusion costs, invasive procedure costs, rescue therapy costs and complications of platelet transfusion are the standard cost categories included. Cost categories were confirmed by experts in the initial validation meeting. Costs were sourced through an SLR and standard UK cost sources. Costs for procedures and personnel were taken from NHS reference costs and the Unit Costs of Health and Social Care, respectively.[71, 72] The cost year in the model is 2018.

4.4.1 Intervention and comparators' costs and resource use

4.4.1.1 Drug acquisition costs

The cost for lusutrombopag in the model was £800. Lusutrombopag is administered at a dose of 3 mg orally, daily for 7 days. In the lusutrombopag trials, treatment was administered for up to 7 days, with a stopping rule after day 4. However, the majority of patients in the lusutrombopag trials received the full treatment course (L-PLUS 1, 86/96 (89.6%); L-PLUS 2, 170/215 (79.1%),[21, 24] and the SmPC states that lusutrombopag should be administered for 7 days.[25] Furthermore, during model validation experts agreed that in clinical practice, patients would take 7 days of treatment home (and therefore any unused tablets will be wasted). Therefore, in the model, patients incur the entire 7-day pack cost for lusutrombopag. Drug acquisition costs are summarised in Table 47.

Table 47. Drug posology, pack size and costs used in the model

	Lusutrombopag
Dose	3 mg
Daily Frequency	1
Route	Oral
Duration	7 days
Pack size	7
Pack cost	£800

Source: L-PLUS 2 CSR;[20] Clinical expert opinion; Lusutrombopag PI.[73]

4.4.1.2 Platelet transfusion costs

The base case of the model includes the cost of platelet transfusion as reported in the NICE submission for eltrombopag for treating chronic immune (idiopathic) thrombocytopenic purpura (TA293).[66] The submission used a cost of £57.72 for the baseline cost of transfusion, and a cost of £230.39 per unit of platelets used. Clinicians at the validation meeting agreed that patients would receive either 2 or 4 units of platelets per transfusion, therefore, costs were calculated assuming an average of 3 units. The total 2012 cost was inflated to 2018 prices using the "New Health Services Index using Consumer Price Index (CPI) Health", published in the Unit Costs for Health and Social Care 2018,[71] resulting in a final total 2018 cost of £812.61. The cost of transfusion based on NICE TA293 was considered most appropriate as it is most aligned with the cost of £1,000 expected by clinical experts.

In NICE TA293, an additional follow-up cost of £262.00 was investigated as a scenario analysis. Transfusion costs based on TA293 are summarised in Table 48.

Table 48. Platelet transfusion costs, NICE TA293

	NICE TA293 (base case)	NICE TA293 (sensitivity analysis)
Transfusion cost	£57.72	£57.72
Cost per unit platelets	£230.39	£230.39
Follow-up cost	£0.00	£262.00
Total cost 2012*	£748.90	£1,010.90
Total cost inflated to 2018	£812.61	£1,096.90

*Based on an average of 3 units of platelets per transfusion
Abbreviations: NICE, National Institute for Health and Care Excellence; TA, Technology Appraisal

Two additional cost scenarios were explored, based on NHS reference costs (2017–2018), the standard UK cost source, and a publication by Varney et al (2003).[8, 74] The Healthcare Resource Group (HRG) code for Single Plasma Exchange or Other Intravenous Blood Transfusion was selected as the most representative HRG for platelet transfusion. Costs per setting (either day case or elective inpatient) were weighted according to activity. The final weighted cost is presented in Table 49. A limitation of using NHS reference costs is the lack of accuracy as the HRG code is not specific to platelet transfusions, and encompasses other transfusion types which may be costlier or less costly than platelet transfusion.

Table 49. NHS reference costs, platelet transfusion

HRG Code	Description	Setting	Cost	Activity	Proportion activity	Cost weighted by activity
SA44A	Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over	Day case	£499.20	121,878	96%	£517.28
SA44A	Single Plasma Exchange or Other Intravenous Blood Transfusion, 19 years and over	Elective inpatient	£971.06	4,856	4%	

Abbreviations: HRG, Healthcare Resource Group.

The final scenario was to base platelet transfusion costs on a poster by Varney et al. (2003). [74] The cost per unit adult platelet concentrate of £347 was multiplied by the average units of platelets per transfusion and inflated to 2018 prices resulting in a final cost per transfusion of £1493.21.

The cost of treating each complication/transfusion-related reaction associated with platelet transfusion was based on costs reported by van Eerd et al. (2010). These were inflated to 2018 using the "New Health Services (HS) index using CPI (Health)" based on the Unit Costs of Health and Social Care 2018.[71] Costs were weighted by the proportion of experiencing each complication.[71] Costs for the complications of platelet transfusions used in the model are presented in Table 50.

Table 50. Cost of treating the complications of platelet transfusion

Complication	Unit cost	Incidence per transfusion*	Weighted cost	Reference
Transfusion-related lung injury	£3,538	3.30%	£116.75	van Eerd (2010)[37] inflated to 2018
Prion disease	£52,719	0.0004%	£0.01	van Eerd (2010)[37] inflated to 2018
Severe allergic reactions	£478	0.0152%	£0.54	van Eerd (2010)[37] inflated to 2018
Total weighted cost	£117.30			Calculation

*Based on average of 3 units per transfusion

The average per patient cost of platelet transfusions was calculated using the sourced costs, and the efficacy data reported in Section 4.2.1.1. The resulting average number of platelet transfusions and average cost of platelet transfusions is presented in Table 51.

Table 51. Average number and cost of platelet transfusions applied in the model

Treatment	Number of platelet transfusions prior to surgery* (L-PLUS 2)	Number of platelet transfusions prior to surgery* (Pooled)	Platelet transfusion cost per treatment (L-PLUS 2)	Platelet transfusion cost per treatment (Pooled)
Lusutrombopag	[redacted]	[redacted]	£928.29	£989.26
Platelet transfusion	[redacted]	[redacted]	£1,182.61	£1,143.93

*For those receiving a platelet transfusion at all

4.4.1.3 Cost associated with second line treatment

Patients who are refractory to platelet transfusions may require second-line therapy, and the NICE draft scope for lusutrombopag states that treatment for severe thrombocytopenia can include platelet transfusion, splenic artery embolisation and surgical splenectomy.[10] This was not included in the model based on clinical expert opinion that the percentage of patients receiving these is very low.

4.4.1.4 Administration costs

For platelet transfusion, the cost of the transfusion covers both administration and platelets, therefore, no additional administration cost was assumed. Lusutrombopag is taken orally by the patient at home, therefore no cost for administration applies.

4.4.1.5 Rescue therapy costs

In the lusutrombopag clinical trials, the use of the following therapies was permitted as rescue therapy for bleeding events:

- Platelet preparations
- Other blood preparations including red blood cells and plasma
- Volume expanders

During the initial validation meeting, clinicians stated that rescue therapy is usually defined as further platelet transfusions. Therefore, the same cost as for platelet transfusion is assumed to apply for those patients requiring rescue therapy. Due to lack of patient level data to state otherwise, it was conservatively assumed that patients requiring rescue therapy required only one platelet transfusion for rescue therapy across both treatments.

4.4.1.6 Invasive procedure costs

The model includes the cost for planned invasive procedures. Clinical validation highlighted that all patients would receive their planned invasive procedure eventually, although it may be rescheduled for a later date. Therefore all patients, in both arms, are expected to incur the cost of planned invasive procedure.

The base case of the model considers the proportions of each planned invasive procedure based on the meta-analysis of the three lusutrombopag clinical trials. It was agreed by experts that the list of invasive procedures from the trial was reflective of clinical practice in the UK. Clinicians also stated that the type of invasive procedure and the proportion receiving each type of invasive procedure would not differ by treatment received and so the same costs are applied to all treatment arms. Procedures were costed using NHS reference costs (2017–2018), in the elective inpatient setting (as per the treatment indication).[8] Although this cost is not expected to differ between treatment arms, the cost has been included for completeness and for the clinical credibility of the model. Proportions of patients receiving each procedure, unit costs and final costs weighted by proportions are presented in Appendix E1.

4.4.2 Adverse reaction unit costs and resource use

For patients in the platelet transfusion arm, the cost for managing transfusion-related reactions is discussed in Section 4.4.1.2. For lusutrombopag, the only relevant AE was portal vein thrombosis. The cost for managing portal vein thrombosis applied in the model was assumed to

be £958.95 based on the NHS reference code YR23B: Percutaneous Transluminal, Embolectomy or Thrombolysis, of Blood Vessel, with CC Score 0-4. The day case setting was used. The incidence of portal vein thrombosis was multiplied by the cost to determine the total AE cost for lusutrombopag. An additional scenario analysis that excluded the cost of managing portal vein thrombosis was conducted.

4.4.3 Miscellaneous unit costs and resource use

4.4.3.1 Sunk costs from cancelled/delayed elective invasive procedures

At a validation meeting held on the 28 September 2018, clinicians stated that all patients will eventually receive their invasive procedure (unless they die) as procedures are rescheduled for a later date if the planned procedure was cancelled. Patients who have a cancelled/delayed planned invasive procedure incur an additional sunk cost (in addition to the procedure cost itself). This is because a cancelled appointment is anticipated to impact clinician time or hospital beds/resources which have been pre-assigned for the procedure (i.e. there may not be enough time to reallocate a pre-assigned clinician/hospital bed to other procedures, so the clinician's time is wasted). The inclusion of this sunk cost was supported by clinical experts at the initial validation meeting and is supported by the literature.[75, 76] In the instance of a cancelled/delayed procedure, for example due to technical reasons, scheduling conflicts, platelet availability, a second platelet transfusion would likely be required due to the short "procedure window" afforded by a prophylactic platelet transfusion; with lusutrombopag, the window is broader, and a patient may not require re-dosing.

The sunk cost for a cancelled/delayed procedure was taken from a publication by Cookson et al. (2017) based NHS reference costs 2009/2010, code WA14Z for a planned procedure not carried out.[75] This reference cost code was removed from subsequent years' NHS reference costs, however has been assumed to apply in the model due to lack of more appropriate estimates. The cost was inflated to 2018 prices resulting in a final sunk cost for a delayed procedure of £566.05.

4.4.3.2 Multiple procedures with one course of treatment

Of the 220 patients treated with lusutrombopag from all studies in thrombocytopenic patients with chronic liver disease, [redacted] patients ([redacted]%) underwent invasive procedures more than once, [redacted] of whom ([redacted]%) had a second or subsequent invasive procedure on a different day during the study period.[13] The model therefore includes a scenario analysis that considers multiple procedures undertaken following a single course of treatment with lusutrombopag.

4.5 Summary of base case analysis inputs and assumptions

4.5.1 Summary of base case analysis inputs

A summary of the base case analysis inputs is included in Appendix E2.

4.5.2 Assumptions

The assumptions required for development of the economic model are listed below:

Clinical data

- The model assumed that the incidence of infectious complications following platelet transfusion was 0%, as screening of blood products has improved since the study from which these data were obtained was published, which is conservative.
- The model assumes that the probability of death as a result of a delayed invasive procedure is 0%, as clinical experts stated that probability of death resulting from a delayed procedure is not relevant and therefore does not need to be included within the model.
- The probability of platelet transfusion-related death from no platelet transfusion procedure is assumed to be zero.
- All patients who do not receive a platelet transfusion are assumed to progress to either a planned or delayed procedure.
- There were no conditional probability data available for rescue therapy for patients undergoing delayed planned invasive procedures, so these probabilities were assumed equal to those for patients who received the initial planned invasive procedure.
- It was conservatively assumed that patients requiring rescue therapy require only one platelet transfusion for rescue therapy across both treatments. For major bleeds in particular this would be considered low given that clinicians confirmed that 2–4 platelet transfusions would be given prior to the invasive procedure, if necessary.

Utilities

- In the absence of HRQoL data collected in the lusutrombopag clinical trials, the model assumes the same baseline utility across both treatments, with one-off QALY decrements associated with platelet transfusions, bleeds, rescue therapy, delayed procedures and AEs.
- It is assumed that the disutility of platelet transfusion complications should be applied for four weeks; this was clinically validated.
- It is assumed that all bleeds in the model are major bleeds, as minor bleeds would be expected to be immaterial to cost and quality of life. The disutility was assumed to apply for one week.
- It is assumed that the disutility per major bleed is applied for a duration of one week.
- Disutilities and duration for the small proportions of patients receiving rescue therapy were assumed to be the same as those for platelet transfusions, as clinical validation highlighted that rescue therapy is usually defined as further platelet transfusion(s).
- No disutility for delays to planned invasive procedures were applied in the model, due to a lack of relevant data in the literature. This may be a conservative assumption as lusutrombopag may improve HRQoL based on fewer patients experiencing a delay to receiving surgery.
- It is assumed that a disutility for DVT is applicable to PVT

Costs

- Costs for platelet transfusion were calculated assuming an average of 3 units per transfusion; clinical validation determined that patients could receive either 2 or 4 units of platelets per transfusion.

- The cost for managing portal vein thrombosis applied in the model was assumed to be £958.95 based on the NHS reference code YR23B: Percutaneous Transluminal, Embolectomy or Thrombolysis, of Blood Vessel, with CC Score 0-4. The day case setting was used.
- The same cost as for platelet transfusion is assumed to apply for those patients requiring rescue therapy, as clinical validation indicated that rescue therapy is usually defined as further platelet transfusions.
- No cost is assumed for administration of the oral therapy (administered at home)
- No medical resource use or monitoring costs are included (clinician confirmed)

4.6 Base case results

Base case results are presented in the following sub-sections.

4.6.1 Base case incremental cost-effectiveness analysis results

Base case results for the cost-effectiveness of lusutrombopag versus platelet transfusion in severely thrombocytopenic CLD patients undergoing planned invasive procedures are reported in Table 52. Total costs were estimated to be £172 lower with lusutrombopag than with platelet transfusion, and lusutrombopag was projected to yield 0.0147 more QALYs than platelet transfusion. The ICER for lusutrombopag versus platelet transfusion was therefore estimated to be dominant. Given a willingness-to-pay threshold of £20,000/QALY, the NMB was £465.44; at a willingness-to-pay threshold of £30,000/QALY, the net monetary benefit (NMB) was £612.23.

Table 52. Base case results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	Life years*	ICER (£/QALY)
Platelet transfusion	£3,743.64	4.0208	-	-	10.0656	-
Lusutrombopag	£3,571.78	4.0354	-£172	0.0147	10.0309	Dominant

* undiscounted. **Abbreviations:** ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years.

4.7 Sensitivity analyses

4.7.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analyses (PSAs) were generated based on 1,000 simulations with sampling from relevant probability distributions associated with each parameter to assess the combined uncertainty of the model results. Where possible, standard deviations for each probability distribution were based on reported standard errors in the literature. In all other cases, standard deviations were assumed to be 20% of the mean value. Results for the comparison of lusutrombopag versus platelet transfusion are presented in Figure 6 and summarised in Table 53. The mean ICER from the PSA was dominant. At a willingness-to-pay threshold of £20,000/QALY, the mean NMB was £347.37. Given a willingness-to-pay threshold of £30,000/QALY, the mean NMB was £481.94, which is lower than the deterministic base case. The cost-effectiveness acceptability curve is shown in Figure 7 and demonstrates that lusutrombopag was likely to be cost-effective at any willingness-to-pay threshold.

Figure 6. PSA scatter plot

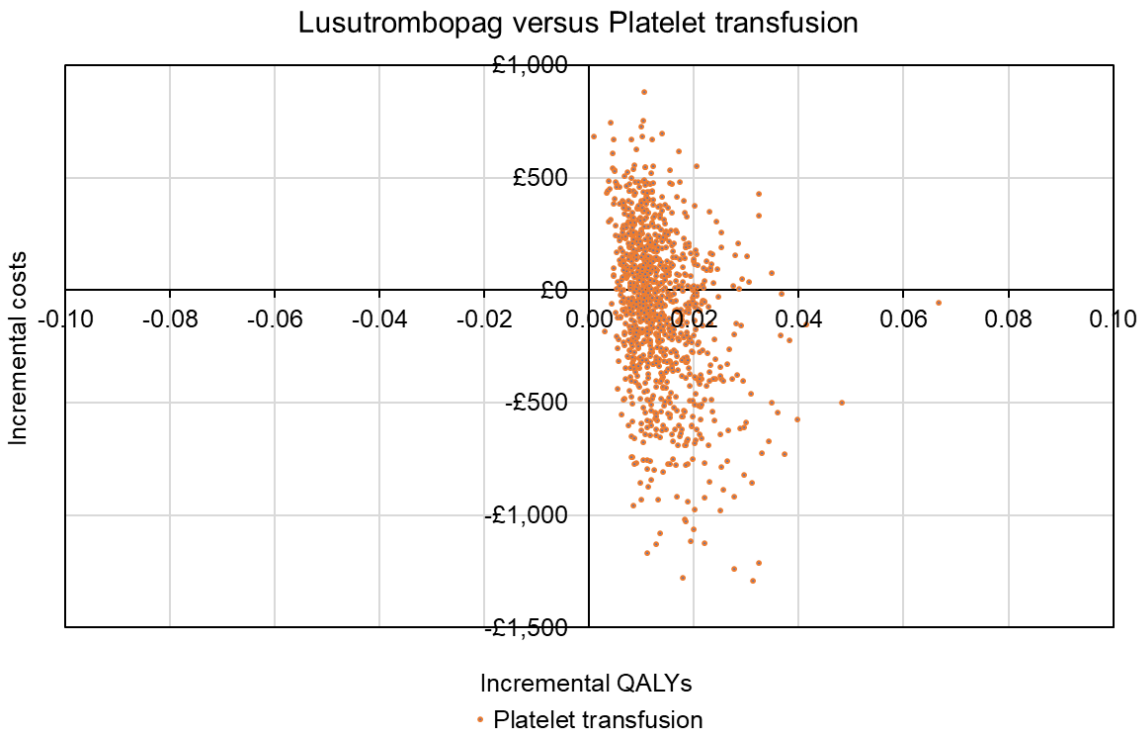
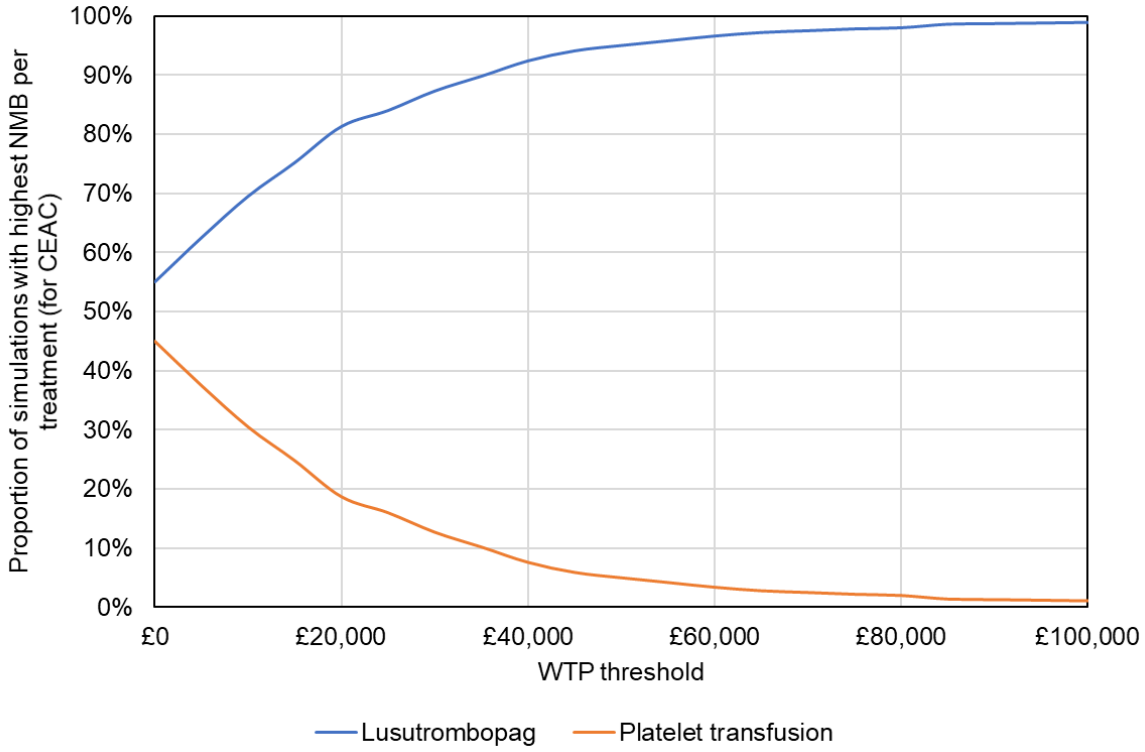


Table 53. Results of PSA of lusutrombopag versus platelet transfusion

	Value
Percent of simulations in quadrant of CE plane	
Northeast (more costly and more effective)	45%
Southeast (dominant)	55%
Southwest (less costly and less effective)	0%
Northwest (dominated)	0%
NMB	
Mean (WTP = £30,000 per QALY) (£)	£481.94
Mean (WTP = £20,000 per QALY) (£)	£347.37
Probability that therapy is preferred (WTP = £30,000)	
Lusutrombopag	87.3%
Platelet transfusion	12.7%
PSA mean ICER (ratio of mean incremental cost to mean incremental QALYs) (£)	Dominant
Probability that therapy is preferred (WTP = £20,000)	
Lusutrombopag	81.3%
Platelet transfusion	18.7%
PSA mean ICER (ratio of mean incremental cost to mean incremental QALYs) (£)	Dominant

Abbreviations: CE, cost-effectiveness; ICER: incremental cost-effectiveness ratio; NMB, net monetary benefit; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; WTP, willingness-to-pay.

Figure 7. Cost-effectiveness acceptability curve

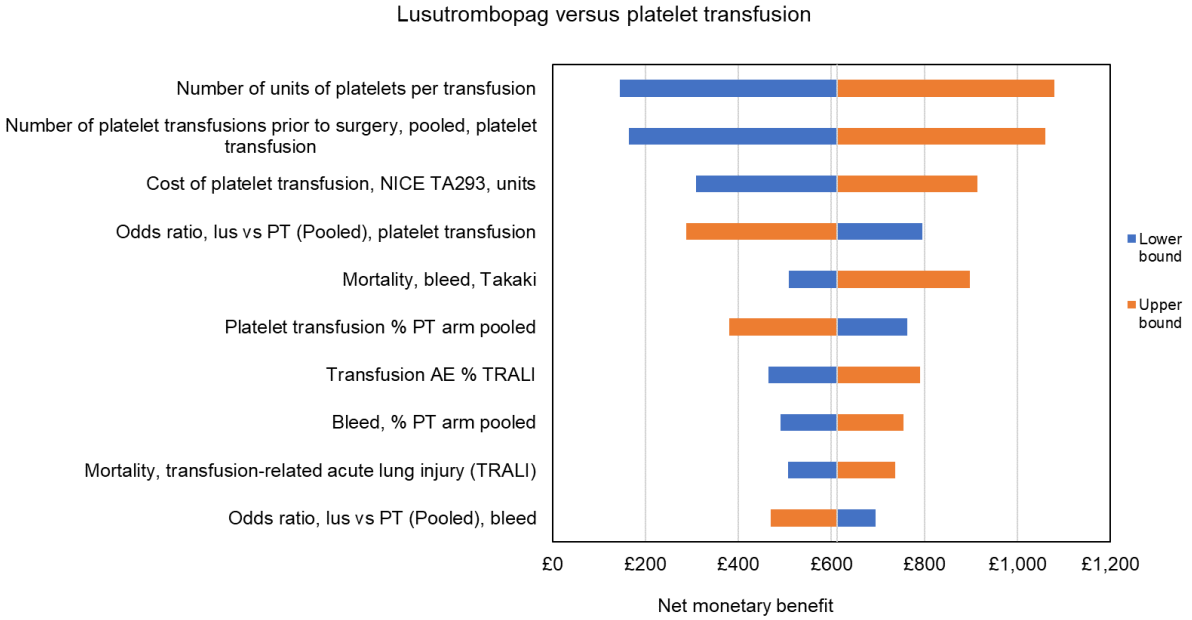


Abbreviations: NMB, net monetary benefit; WTP, willingness-to-pay.

4.7.2 Deterministic sensitivity analysis

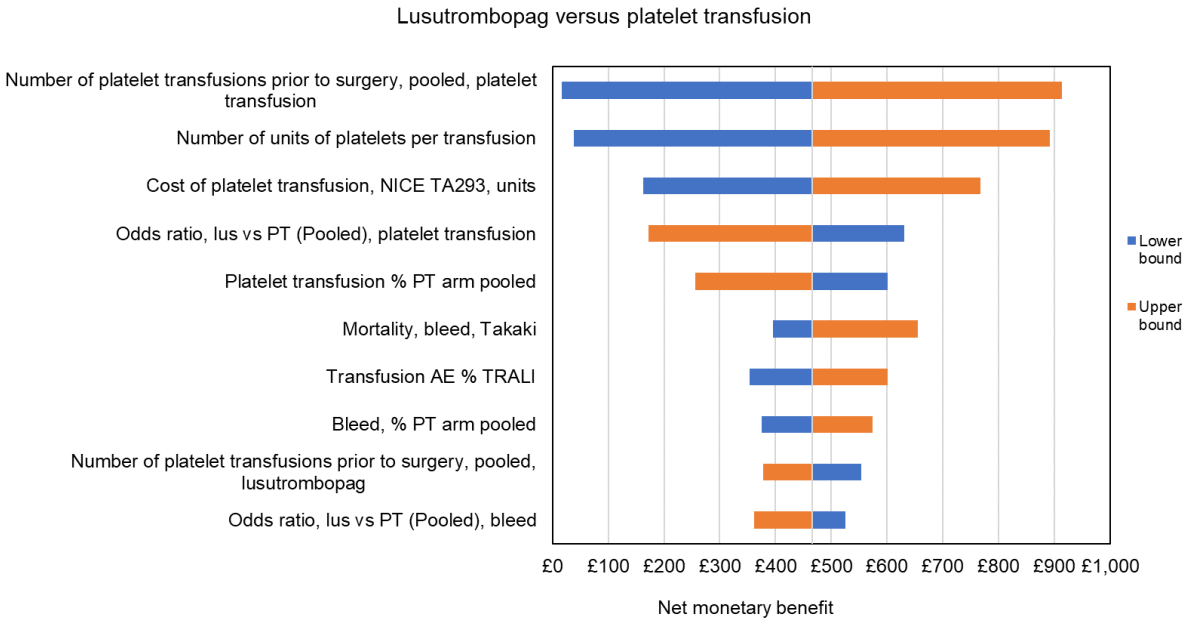
A one-way deterministic sensitivity analysis was undertaken and reported in Figure 8. Where possible, upper and lower bounds were based on confidence intervals reported in the literature. In all other cases, bounds were assumed to be ±20% of the parameter value. The sensitivity analysis found that lusutrombopag remained cost-effective at both the £30,000/QALY and £20,000/QALY WTP thresholds when all parameters were individually varied to their upper and lower bounds (Figure 8 and Figure 9, respectively). This demonstrates the stability of the results to parameter uncertainty, as shown in the probabilistic sensitivity analysis.

Figure 8. Deterministic sensitivity analysis results (WTP threshold of £30,000/QALY)*



* Net monetary benefit calculated at a willingness-to-pay threshold of £30,000/QALY
Abbreviations: AE, adverse event; PT, platelet transfusion; TRALI, transfusion-related acute lung injury.

Figure 9. Deterministic sensitivity analysis results (WTP threshold of £20,000/QALY)*



* Net monetary benefit calculated at a willingness-to-pay threshold of £20,000/QALY
Abbreviations: AE, adverse event; PT, platelet transfusion; TRALI, transfusion-related acute lung injury.

4.7.3 Scenario analysis

A number of scenario analyses were undertaken; these results are reported in Table 54. Most scenarios continued to find lusutrombopag to be the dominant option and all scenarios found lusutrombopag to be the cost-effective option at the lower NICE threshold of £20,000/QALY.

Table 54. Results of scenario analyses

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case					
Platelet transfusion	£3,743.64	4.0208	-		
Lusutrombopag	£3,571.78	4.0354	-£171.86	0.0147	Dominant
Scenario: Unconditional probabilities used					
Platelet transfusion	£3,672.83	4.0208	-		
Lusutrombopag	£3,547.48	4.0354	-£125.35	0.0147	Dominant
Scenario: L-PLUS 2 study used as the efficacy source					
Platelet transfusion	£3,719.36	4.2477	-		
Lusutrombopag	£3,508.00	4.2592	-£211.36	0.0115	Dominant
Scenario: Multiple procedures with one course of treatment (2 procedures, cost-adjusted only)					
Platelet transfusion	£7,363.18	4.0208	-		
Lusutrombopag	£6,054.09	4.0354	-£1,309.09	0.0147	Dominant
Scenario: Multiple procedures with one course of treatment (3 procedures, costs adjusted only)					
Platelet transfusion	£10,982.72	4.0208	-		
Lusutrombopag	£8,536.39	4.0354	-£2,446.32	0.0147	Dominant
Scenario: Multiple procedures with one course of treatment (4 procedures, cost-adjusted only)					
Platelet transfusion	£14,602.26	4.0208	-		
Lusutrombopag	£11,018.70	4.0354	-£3,583.35	0.0147	Dominant
Scenario: All patients in the platelet transfusion arm not assumed to receive a platelet transfusion					
Platelet transfusion	£3,504.84	4.0236	-		
Lusutrombopag	£3,571.78	4.0354	£66.94	0.0118	£5,666.92
Scenario: Mortality due to platelet transfusion source – Vamvakas *et al*. (2009)					
Platelet transfusion	£3,752.28	4.0339	-		
Lusutrombopag	£3,573.67	4.0384	-£178.61	0.0045	Dominant
Scenario: Platelet transfusion cost source – NHS reference costs					
Platelet transfusion	£3,358.39	4.0208	-		
Lusutrombopag	£3,490.50	4.0354	£132.10	0.0147	£8,999.27
Scenario: Platelet transfusion cost source – assumed equal to the NHS reference cost elective inpatient value					
Platelet	£3,950.33	4.0208	-		

transfusion					
Lusutrombopag	£3,615.39	4.0354	-£334.94	0.0147	Dominant
Scenario: Increased risk of TRALI incidence (29%)					
Platelet transfusion	£7,369.44	3.6875	-		
Lusutrombopag	£4,339.00	3.9595	-£3,030.45	0.2721	Dominant
Scenario: No cost of managing PVT					
Platelet transfusion	£3,743.64	4.0354	-		
Lusutrombopag	£3,566.17	4.0354	-£177.47	0.0147	Dominant
Scenario: No mortality benefit					
Platelet transfusion	£3,752.29	0.0503	-		
Lusutrombopag	£3,573.67	0.0512	-£178.62	0.0009	Dominant
Scenario: Per protocol analysis					
Platelet transfusion	£3,743.64	4.0208	-		
Lusutrombopag	£3,591.28	4.0352	-£152.36	0.0144	Dominant
Scenario: Assumed 2 units per platelet transfusion					
Platelet transfusion	£3,369.51	4.0252	-		
Lusutrombopag	£3,492.87	4.0364	£123.36	0.0113	£10,935.13

Abbreviations: ICER, incremental cost-effectiveness ratio; PVT, portal vein thrombosis; QALYs: quality-adjusted life years; TRALI, transfusion-related acute lung injury.

4.8 Model validation

4.8.1 Expert validation

Validation of the model structure, methods and inputs was conducted with one external health economics expert, and two clinical experts. Validation was conducted during two meetings held on 28 September 2018 and 30 November 2018.

The experts were presented with an overview of the project and model including the following:

- Disease background
- Decision problem
- Model structure
- Model inputs
    - Clinical efficacy
    - Safety and adverse events
    - Health-related quality of life and utilities
    - Costs and resource use

For each topic, the experts were asked to provide their opinion on whether the approaches taken within the model were appropriate and plausible. The experts confirmed during the validation that the methods and inputs used were appropriate and plausible.

Key outcomes based on the initial validation meeting included a scenario testing L-PLUS 2 as an alternative source of efficacy data for lusutrombopag, as opposed to the pooled analysis base case. Another recommendation from the economic expert was to simplify the decision tree so that the first step was based on whether or not patients received a transfusion (rather than being based on responder status), as this is the primary outcome of the lusutrombopag trials. Furthermore, it was recommended to add mortality to the initial structure (which did not include mortality due to lack of trial data on this outcome). The economic expert stated that mortality could feasibly be explored using estimates from external literature, to fully capture the benefit and costs associated with lusutrombopag. The economic expert also recommended the inclusion of the sunk cost for patients experiencing delays to planned procedures. A further suggestion was to further explore CLD-related mortality – the model was updated based on a more clinically plausible mortality source as initial estimates were deemed too pessimistic by clinicians. Clinicians discussed and agreed with the proposed external literature informing mortality. Finally, clinical experts recommended that the cost of lusutrombopag should be for the full 7-day pack; as lusutrombopag is administered at home, even if they discontinue treatment early, the full cost of the treatment course will have been incurred when the pack is dispensed.

Key outcomes based on the second validation meeting included further amendments to the model structure to allow for patients experiencing delays to a procedure to be at the same risk of bleeding and receiving rescue therapy as those receiving their procedure as planned. Furthermore, clinicians were presented with the complications of transfusion sourced in the SLR and agreed that these seemed reasonable but suggested the removal of infectious complications. Finally, clinicians stated that the cost of platelet transfusion based on NHS reference costs was too low, and the true cost is expected to be in the region of £1,000.

4.8.2 Technical validation

Upon finalisation of the model base case, a full technical validation was conducted whereby input data and coding were verified through quality control checklists and model stress tests to check for potential programming errors, and to verify the model's predictions against the data used. This ensured that the results produced by the model were accurate and robust to extreme input values. These thorough quality control checks were conducted by an independent health economist.

4.9 Interpretation and conclusions of economic evidence

4.9.1 Strengths and limitations of the economic analysis

Strengths

Strengths of the analysis are that the cost-effectiveness model is based on robust data from double-blind randomised controlled trials. In addition, SLRs were conducted to inform model inputs not available from the trial data such as utilities, mortality and costs.

The model has the advantage that its structure accurately reflects the decision problem and includes the outcome of the lusutrombopag trials as the initial step. The model has also undergone extensive validation, both at the conceptualisation stage and after model construction

was complete. The model design has undergone many iterations based on the valuable input received from clinical and economic experts. It is felt that the model is simple to understand and adapt however has the necessary complexity to reflect the decision problem and trial data accurately.

A full range of sensitivity analyses were used to assess the robustness of the cost-effectiveness results and identify key drivers of cost-effectiveness.

Limitations

Limitations of the analysis include the lack of utility data collected in the lusutrombopag trials, in addition to the lack of data on platelet-transfusion related reactions and mortality. As a consequence, many model parameters were sourced through systematic reviews of the literature and subsequently validated by clinical experts. More robust data demonstrating the mortality and quality of life benefit of lusutrombopag would be beneficial, particularly since these are key drivers of the cost-effectiveness results.

Further information could be included in the model on the impact of quality of life, morbidity and mortality based on delays to invasive procedures, in addition to increased resource use costs whilst patients are waiting for treatment, however data could not be identified to inform this. Therefore, the model conservatively assumes no benefit of lusutrombopag on these important parameters. Additionally, the cost for increased length of stay in hospital for patients receiving platelet transfusions and experiencing bleeding is not included due to lack of data.

A current limitation of the model was that patient-level data were not available for determining the distribution of patients per frequency of platelet transfusions both before and after the invasive procedure, with data only available for the entire study period.

Another limitation is the use of data for FFP as a proxy for platelets, for the incidence, costs and disutilities of transfusion-related complications. However, clinicians considered this a reasonable proxy.

A final limitation is the assumption of standard errors of 20% of the mean for some parameters due to lack of uncertainty information in the sources identified.

4.9.2 Conclusion

The cost-effectiveness model shows a small QALY benefit in favour of lusutrombopag in comparison to platelet transfusion; when combined with the cost-savings from lusutrombopag, the base case results and most scenario analyses found that lusutrombopag was the dominant treatment strategy. Where results from the one-way deterministic sensitivity analysis or scenario analyses did not find lusutrombopag to be the dominant strategy they found that it was cost-effective at the lower NICE WTP threshold of £20,000/QALY, including scenarios that tested much lower costs for platelet transfusion than were used in previous relevant appraisals. Reflecting these robust deterministic findings, the probabilistic sensitivity analysis found an 81% probability of lusutrombopag being cost-effective at a WTP threshold of £20,000/QALY, an 87% probability of lusutrombopag being cost-effective at a WTP threshold of £30,000/QALY, and indeed found that the probability of lusutrombopag being cost-effective was greater than 50% even at a willingness-to-pay threshold of zero.

Notably, had lusutrombopag been assessed under the Single Technology Appraisal process it would have qualified for the Fast Track Appraisal process. Given the clear unmet need,

demonstrable efficacy and safety, added convenience and cost-savings to the NHS, lusutrombopag represents a valuable new treatment option benefiting patient and payer alike and it is to be hoped that a positive recommendation will be made as rapidly as possible.

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Multiple Technology Appraisal (MTA)

Avatrombopag and lusutrombopag for treating thrombocytopenia in people with chronic liver disease needing an elective procedure

Section A: Clarification on effectiveness data (Lusutrombopag, Shionogi Inc)

The data presented in response to the following questions are derived from analyses of the ITT populations from the relevant clinical trials; Shionogi would like to note that, given the protocol deviations reported in response to question A4, a per protocol analysis might be more informative. For the primary endpoints of L-PLUS 1 and L-PLUS 2, this has been presented in the company submission.

A1. Please provide effectiveness outcomes separately for each of the L-PLUS-1, L-PLUS-2 and Phase 2b (Izumi 2014, JapicCTI-121944) trials for the subgroups <40,000/µL and 40,000 to <50,000/µL for the following outcomes:

a. the number/proportion of patients who received neither a platelet transfusion nor rescue therapy

The number of patients who received neither a platelet transfusion nor rescue therapy for bleeding from randomization through 7 days after the primary invasive procedure is shown in Table 1 and Table 2 for the subgroups <40,000/µL and 40,000 to <50,000/µL, respectively. Across all three studies and both subgroups, the proportion of patients not receiving a platelet transfusion or rescue therapy was higher in the lusutrombopag group; this was statistically significantly greater for both L-PLUS 1 and L-PLUS 2.

Table 1. Proportion of subjects who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomization: subgroup with baseline platelet count <40,000/µl

Study	Arm	n/N[a]	% with event	OR LUSU 3mg vs. PBO (95% CI)	P value
M0626	LUSU 3 mg	[redacted]	[redacted]	[redacted]	[redacted]
	PBO	[redacted]	[redacted]		
L-PLUS 1	LUSU 3 mg	[redacted]	[redacted]	[redacted]	[redacted]
	PBO	[redacted]	[redacted]		
L-PLUS 2	LUSU 3 mg	[redacted]	[redacted]	[redacted]	[redacted]
	PBO	[redacted]	[redacted]		

[a]Number of patients measured at follow-up.

Abbreviations: CI, confidence interval; LUSU, lusutrombopag; OR, odds ratio; PBO, placebo.

Table 2. Proportion of subjects who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomization: subgroup with baseline platelet count 40,000/µl to <50,000/µl

Study	Arm	n/N[a]	% with event	OR LUSU 3mg vs. PBO (95% CI)	P value
M0626	LUSU 3 mg	[redacted]	[redacted]	[redacted]	[redacted]
	PBO	[redacted]	[redacted]		
L-PLUS 1	LUSU 3 mg	[redacted]	[redacted]	[redacted]	[redacted]
	PBO	[redacted]	[redacted]		
L-PLUS 2	LUSU 3 mg	[redacted]	[redacted]	[redacted]	[redacted]
	PBO	[redacted]	[redacted]		

[a]Number of patients measured at follow-up.
†Includes continuity correction - 0.5 added to each cell of a trial where a zero is encountered to enable finite variance estimators to be derived.
Abbreviations: CI, confidence interval; LUSU, lusutrombopag; OR, odds ratio; PBO, placebo.

b. the number/proportion of patients who required a platelet transfusion prior to the elective procedure (as opposed to as a rescue procedure)

The proportion of patients who required a no platelet transfusion prior to the elective procedure is shown in Table 3 and Table 4 for the subgroups <40,000/µL and 40,000 to <50,000/µL, respectively. Across all three studies and both subgroups, the proportion of patients not receiving a platelet transfusion prior to the elective procedure was higher in the lusutrombopag group; this was statistically significantly greater for both L-PLUS 1 and L-PLUS 2.

Table 3. Proportion of subjects who required no platelet transfusion prior to the primary invasive procedure: subgroup with baseline platelet count <40,000/µl

Study	Arm	n/N[a]	% with event	OR LUSU 3mg vs. PBO (95% CI)	P value
M0626	LUSU 3 mg	[redacted]	[redacted]	[redacted]	[redacted]
	PBO	[redacted]	[redacted]		
L-PLUS 1	LUSU 3 mg	[redacted]	[redacted]	[redacted]	[redacted]
	PBO	[redacted]	[redacted]		

L-PLUS 2	LUSU 3 mg	[redacted]	[redacted]	[redacted]	[redacted]
	PBO	[redacted]	[redacted]		

[a]Number of patients measured at follow-up
Abbreviations: CI, confidence interval; LUSU, lusutrombopag; OR, odds ratio; PBO, placebo.

Table 4. Proportion of subjects who required no platelet transfusion prior to the primary invasive procedure: subgroup with baseline platelet count 40,000/µl to <50,000/µl

Study	Arm	n/N[a]	% with event	OR LUSU 3mg vs. PBO (95% CI)	P value
M0626	LUSU 3 mg	[redacted]	[redacted]	[redacted]	[redacted]
	PBO	[redacted]	[redacted]		
L-PLUS 1	LUSU 3 mg	[redacted]	[redacted]	[redacted]	[redacted]
	PBO	[redacted]	[redacted]		
L-PLUS 2	LUSU 3 mg	[redacted]	[redacted]	[redacted]	[redacted]
	PBO	[redacted]	[redacted]		

[a]Number of patients measured at follow-up.
†Includes continuity correction - 0.5 added to each cell of a trial where a zero is encountered to enable finite variance estimators to be derived.
Abbreviations: CI, confidence interval; LUSU, lusutrombopag; OR, odds ratio; PBO, placebo.

c. the number/proportion of patients who received a specified number of platelet transfusions (0, 1, 2, 3, 4, 5), separately for before the elective procedure and as rescue therapy

The frequency of platelet transfusions by baseline platelet count sub-group is shown in Table 5.

Table 5. Frequency of platelet transfusions by baseline platelet count sub-group

Study	Number of PT	Baseline Platelet Count of <40,000/µL				Baseline Platelet Count of ≥40,000/µL to <50,000/µL			
		Prior to Primary IP		PT as Rescue		Prior to Primary IP		PT as Rescue	
		LUSU 3mg	PBO	LUSU 3mg	PBO	LUSU 3mg	PBO	LUSU 3mg	PBO
M0626	1	[redacted]							
	2								
	3								
	4								
	5								

	Total								
L-PLUS 1	1								
	2								
	3								
	4								
	5								
	Total								
L-PLUS 2	1								
	2								
	3								
	4								
	5								
	Total								

Abbreviations: IP, invasive procedure; LUSU, lusutrombopag; OR, odds ratio; PBO, placebo; PT, platelet transfusion.

d. mean (SD) number/proportion of units of platelets transfused, separately for before the elective procedure and as rescue therapy

The dose per platelet transfusion by baseline platelet count sub-group is shown in Table 6.

Table 6. Dose per platelet transfusion by baseline platelet count sub-group

Study		Baseline Platelet Count of <40,000/µL				Baseline Platelet Count of >= 40,000/µL to <50,000/µL			
		Prior to Primary IP		PT as Rescue		Prior to Primary IP		PT as Rescue	
		LUSU 3mg	PBO	LUSU 3mg	PBO	LUSU 3mg	PBO	LUSU 3mg	PBO
M0626	n								
	Mean								
	SD								
L-PLUS 1	n								
	Mean								
	SD								
L-PLUS 2	n								
	Mean								
	SD								

This table summarizes the amount of platelet content (*10^11 platelets) per platelet transfusion. With regard to the amount of transfused platelets observed in the studies M0626 and L-PLUS 1, 1 JP unit was considered as 2*10^10 platelets. For the study L-PLUS 2, the sponsor estimated it as minimum platelet content according to a guideline for platelet transfusion in each country. The data not able to estimate were removed from the analysis. If patient received platelet transfusion more than once during the study, average amount per once for the patient was used.

Abbreviations: IP, invasive procedure; LUSU, lusutrombopag; PBO, placebo; PT; platelet transfusion, SD; standard deviation

e. the number/proportion of patients receiving each type of rescue therapy

Table 5 above summarises the number/proportion of patients receiving PT as rescue therapy. Otherwise see Table 7. Other types of rescue were used infrequently.

[redacted].

Table 7. Summary of patients with rescue therapy for bleeding events in L-PLUS 2

	Lusutrombopag 3 mg (N=108)	Placebo (N=107)
Patients who received rescue therapy for bleeding events, n (%)	0	2 (1.9)
Patients who received rescue therapy other than platelet transfusion for bleeding events, n (%)	[redacted]	[redacted]
Patients who received platelet transfusion due to adverse events related to bleeding, n (%)	[redacted]	[redacted]

Source: L-PLUS 2 CSR.[6]

f. the number/proportion of patients who experienced a bleeding related adverse event (by severity)

The proportion of patients who experienced bleeding-related adverse events by severity and baseline platelet count subgroup is shown in Table 8. The number of patients experiencing severe bleeding-related adverse events was generally comparable between the placebo and lusutrombopag groups, across all three trials and both subgroups.

Table 8. Incidence of adverse events related to bleeding by baseline platelet count sub-group

	Baseline Platelet Count	M0626		L-PLUS 1		L-PLUS 2	
		LUSU 3 mg	Placebo	LUSU 3 mg	Placebo	LUSU 3 mg	Placebo
Subjects with at least 1 AE related to bleeding	<40,000/µL	[redacted]					
	≥40,000/µL to <50,000/µL	[redacted]					
Subjects with at least 1 severe AE related to bleeding	<40,000/µL	[redacted]					
	≥40,000/µL to <50,000/µL	[redacted]					
Subjects with at least 1 moderate AE related to bleeding	<40,000/µL	[redacted]					
	≥40,000/µL to <50,000/µL	[redacted]					
Subjects with at	<40,000/µL	[redacted]					

	Baseline Platelet Count	M0626		L-PLUS 1		L-PLUS 2	
		LUSU 3 mg	Placebo	LUSU 3 mg	Placebo	LUSU 3 mg	Placebo
least 1 mild AE related to bleeding	≥40,000/µL to <50,000/µL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Included only treatment-emergent adverse events. Bleeding-related event was defined as an adverse event that belong to the standard MedDRA queries 'Haemorrhage terms (except laboratory terms).'
Abbreviations: AE, adverse event; LUSU, lusutrombopag.

g. the number/proportion of patients who a required a rescue procedure

The lusutrombopag clinical trials did not include a rescue procedure. A summary of additional procedures by study arm can be found in the response to question A2.

h. the number/proportion of patients who experienced a thrombotic adverse event

The number/proportion of patients the number/proportion of patients who experienced a thrombotic adverse event is presented in Table 9. The number of patients experiencing such events was comparable between baseline platelet count subgroups, and between treatment arms.

Table 9. Incidence of adverse events related to thrombotic and thromboembolic by baseline platelet count sub-group

Baseline Platelet Count	M0626		L-PLUS 1		L-PLUS 2	
	LUSU 3 mg	Placebo	LUSU 3 mg	Placebo	LUSU 3 mg	Placebo
<40,000/µL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥40,000/µL to <50,000/µL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Included only treatment-emergent adverse events. Thrombotic and thromboembolic event was defined as an adverse event that belong to the following the standard MedDRA queries: 'Embolic and thrombotic events, arterial,' 'Embolic and thrombotic events, venous' and 'Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous.'
Abbreviations: LUSU, lusutrombopag.

i. the number/proportion of patients who experienced a portal vein thrombosis

The number/proportion of patients who experienced a portal vein thrombosis throughout the period of the study is reported in Table 10. The number of patients experiencing such events was comparable between baseline platelet count subgroups, and between treatment arms.

Table 10. Incidence of adverse events of portal vein thrombosis by baseline platelet count sub-group

Baseline Platelet Count	M0626		L-PLUS 1		L-PLUS 2	
	LUSU 3 mg	Placebo	LUSU 3 mg	Placebo	LUSU 3 mg	Placebo
<40,000/µL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥40,000/µL to <50,000/µL	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Included only treatment-emergent adverse events. Thrombotic and thromboembolic event was defined as an adverse event that belong to the following the standard MedDRA queries: 'Embolic and thrombotic events, arterial,' 'Embolic and thrombotic events, venous' and 'Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous.'
Abbreviations: LUSU, lusutrombopag.

A2. In the cost effectiveness model, there is an option to account for more than 1 procedure occurring in the short term. Did any patient receive more than 1 planned elective procedure in the trial period?

The clinical trials design did not plan for multiple procedures (more than 1 procedure) during the study periods, nor was it intended for physicians to carry out multiple procedures. During the trials, however, it appears that due to clinical or healthcare circumstances a non-negligible number of patients did undergo multiple procedures following one course of treatment during the study period. [redacted]

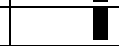
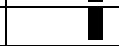
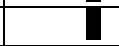
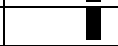
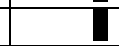
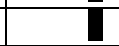
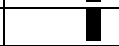
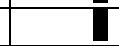
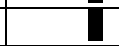
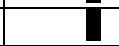
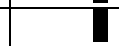
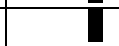
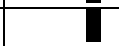
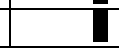
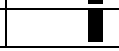
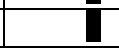
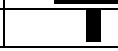
To reflect the potential economic value associated with being able to perform multiple procedures following just one course of lusutrombopag, the cost-effectiveness model allows a scenario to estimate the cost-effectiveness of lusutrombopag in patients undergoing multiple procedures.

A3. Please provide adverse event data, including mortality, bleeding (by severity) and thrombotic events (including portal vein thrombosis) for all studies of 3 mg lusutrombopag including, but not necessarily restricted to, the following trials: 1525M0627, 1514M061E, 1301M061B, 1112M0625 and 1338M0633.

As requested, please find the adverse event data, including mortality, bleeding and thrombotic events in Table 11 below. Shionogi is unaware of study 11514M061E. These data indicate that lusutrombopag is generally well-tolerated, with a reasonable safety profile.

Table 11. Summary of adverse events for non-RCT lusutrombopag studies

	M061B 3 mg N = 8	M0625 3 mg N = 7	M0625 All N = 21	M0627 3 mg N = 5	M0633 A/B-1 N = 47	M0633 A/B-2 N = 47	M0633 Non-naïve N = 8
Total TEAE, n (%)							
Gastrointestinal, n (%)							
Deaths, n (%)							
Serious TEAE, n (%)							
TEAE leading to withdrawal of study drug, n (%)							
TEAE related to bleeding, n [events] (%)							
Contusion, n (%)							
Epistaxis, n (%)							
Gingival bleeding, n (%)							
Haematochezia, n (%)							
Haemobilia, n (%)							
Haemorrhoidal haemorrhage, n (%)							
Haemothorax, n (%)							
Post procedural haematoma, n (%)							
Post procedural haemorrhage, n (%)							
Procedural haemorrhage, n (%)							
Puncture site haemorrhage, n (%)							
Purpura, n (%)							
Subcutaneous haemorrhage, n (%)							

Traumatic haematoma, n (%)							
Vascular disorder- haematoma, n (%)							
Treatment-emergent thrombosis, n (%)							
Portal vein thrombosis, n (%)							
Mesenteric vein thrombosis, n (%)							
Tumour thrombosis							

Abbreviations: TEAE, treatment-emergent adverse event.

A4. Please provide the number/proportion and nature of major protocol deviations per arm for each of the trials including receipt of any antithrombotic medication or fresh frozen plasma.

Summaries of the protocol deviations for each L-PLUS 2, L-PLUS 1 and M0626 are shown in Table 12, Table 13 and Table 14.

Table 12. Summary of protocol deviations in L-PLUS 2

	Placebo, n (%)	Lusutrombopag 3 mg, n (%)
Number randomised	107	**108**
Noncompliance with pre-procedure platelet transfusion instructions	[redacted]	[redacted]
Did **not** receive a platelet transfusion but should have (pre-procedural platelet counts <50 × 10^9/L)	[redacted]	[redacted]
Received a platelet transfusion but should **not** have (pre-procedural platelet counts ≥50 × 10^9/L)	[redacted]	[redacted]
Out of window of pre-procedure platelet transfusion assessment	[redacted]	[redacted]
Poor study drug administration: subject received less than 5 days of study drug but did not fulfil the stopping criterion for study drug	[redacted]	[redacted]
No study drug administration	[redacted]	[redacted]
Child-Pugh class C	[redacted]	[redacted]
Received other TPO receptor agonist	[redacted]	[redacted]
Platelet count >50 × 10^9/L at baseline on Day 1 prior to randomization	[redacted]	[redacted]
Use of prohibited concomitant medications and therapies	[redacted]	[redacted]
Patient self-medicated with eltrombopag during screening and post-procedure period	[redacted]	[redacted]
Received an antithrombotic drug for thrombotic events [a]	[redacted]	[redacted]

[a] not a protocol deviation

Table 13. Summary of protocol deviations in L-PLUS 1

	Placebo, n (%)	Lusutrombopag 3 mg, n (%)
Number randomised	48	49
Non-compliance with study drug	[redacted]	[redacted]
No study drug administration	[redacted]	[redacted]
Out of window of pre-procedure platelet transfusion assessment	[redacted]	[redacted]
Prohibited concomitant drugs	[redacted]	[redacted]
Filgrastim	[redacted]	[redacted]
Anti-thrombotic drug: human antithrombin III	[redacted]	[redacted]

Prohibited concomitant therapy/procedure	[redacted]	[redacted]

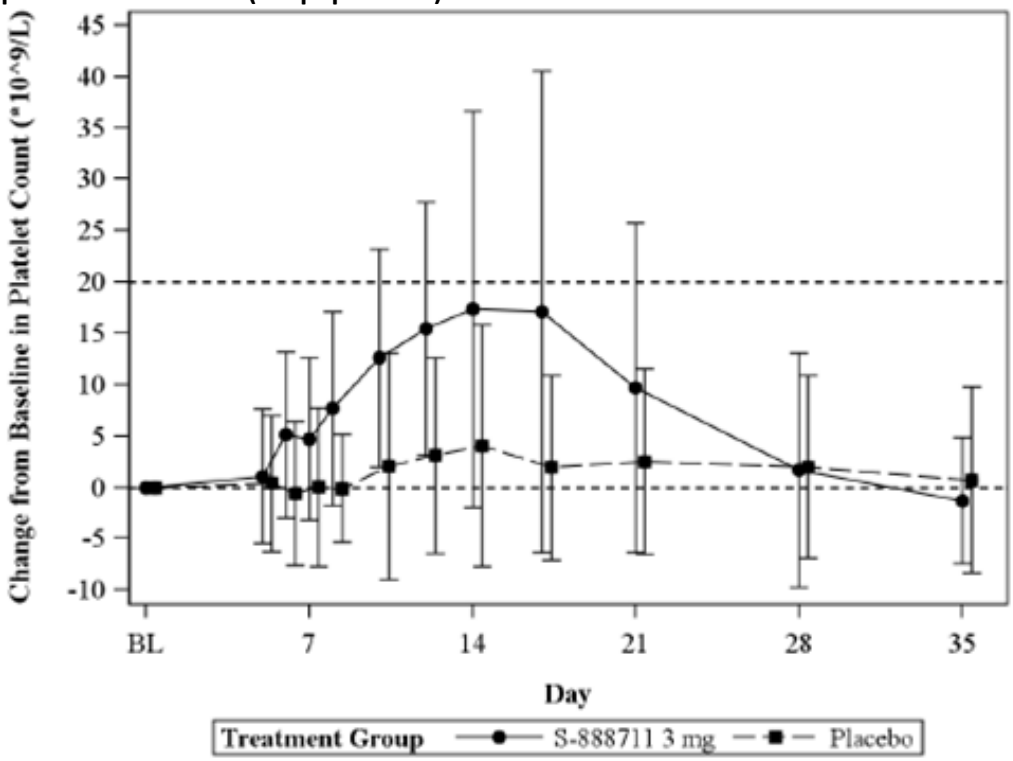
Table 14. Summary of protocol deviations in M0626

	Placebo, n (%)	LUSU 2 mg, n (%)	LUSU 3 mg, n (%)	LUSU 4 mg, n (%)
Number randomised	15	15	16	15
Non-compliance with study drug	[redacted]	[redacted]	[redacted]	[redacted]
No study drug administration	[redacted]	[redacted]	[redacted]	[redacted]
Out of window of pre-procedure platelet transfusion assessment	[redacted]	[redacted]	[redacted]	[redacted]
Prohibited concomitant drug	[redacted]	[redacted]	[redacted]	[redacted]
Hemostatic drugs: arbazochrome sodium sulfonate and/or tranexamic acid	[redacted]	[redacted]	[redacted]	[redacted]
Lenograstim	[redacted]	[redacted]	[redacted]	[redacted]
Platelet preparations	[redacted]	[redacted]	[redacted]	[redacted]
Anti-thrombotic drug	[redacted]	[redacted]	[redacted]	[redacted]
Prohibited concomitant therapy/procedure	[redacted]	[redacted]	[redacted]	[redacted]

A5. Please provide one-week follow up results from L-PLUS-1 and L-PLUS-2 for number/proportion of participants who achieved platelet count of ≥50,000/μL with an increase of ≥20,000/μL from baseline?

For information, the median duration of platelet count ≥50,000/μL in L-PLUS 1 was 22.1 days in the lusutrombopag group without platelet transfusion, and 3.3 days in the placebo group with platelet transfusion. The median duration of platelet count ≥50,000/μL in L-PLUS 2 was 19.21 days in the lusutrombopag group without platelet transfusion and 0 days in the placebo group with platelet transfusion. The time course of mean platelet counts in L-PLUS 2 is presented in Figure 1. It would be appreciated if NICE could provide further clarification as to the timeframe in this question (at Day 7, 7 days after procedure or other timepoint) and the outcome measure.

Figure 1. Mean (± standard deviation) change from baseline in platelet count in subjects with platelet transfusion (ITT population)



A6. Please provide the number/proportion of patients in the RCTs who had received a procedure that required platelet transfusion prior to entry into the studies

The clinical protocols of the RCTs in the lusutrombopag clinical trial program excluded patients that had invasive procedures 90 days prior to randomisation, or blood transfusion within fourteen days prior to randomisation. The specific exclusion criteria are listed below:

- Any of the following invasive procedures within 90 days prior to randomisation:
  − laparotomy, thoracotomy, craniotomy, or open-heart surgery
  − procedures involving any organ resection or any partial organ resection (tissue resection associated with an endoscopic examination is permitted)
  − partial splenic embolization
- Any invasive procedure (except for the treatment of gastro-oesophageal varices) within 14 days prior to randomisation
- Blood transfusion (except for red blood cell products and albumin preparations) within 14 days prior to randomisation

There is limited information regarding history of procedures requiring a transfusion prior to study enrolment, however the information in Table 15 below is provided as an alternative.

Table 15. Baseline characteristics and entry criteria: number/proportion of patients that had previously received a transfusion and inclusion criteria regarding platelet transfusions during enrolment period

Study	Study arm	Baseline, N	Previous transfusions, n (%)	Study inclusion/ exclusion criteria

L-PLUS 2	Lusutrombopag 3 mg orally once daily	108	[redacted]	No invasive procedure or blood transfusion within 14 days prior to randomization
	Placebo orally once daily	107	[redacted]	
L-PLUS 1	Lusutrombopag 3 mg orally once daily	48	[redacted]	No invasive procedure or blood transfusion within 14 days prior to randomization
	Placebo orally once daily	48	[redacted]	
M0626	Lusutrombopag 3 mg orally once daily	16	[redacted]	No invasive procedure or blood transfusion within 14 days prior to randomization
	Placebo orally once daily	15	[redacted]	

Section B: Clarification on cost-effectiveness data (Shionogi Inc)

Utilities

B1. Is it possible to clarify how the disutility for platelet transfusion was measured (value taken from TA293, which in turn refers to TA221), given that the Evidence Review Group Report for TA293 notes "There is no obvious explanation within section 7.2.8.3 of the TA221 manufacturer submission of how these values were arrived at." (p. 78).

Section 7.2.7.4 of the TA221 submission states that "A utility decrement is estimated for the adverse events. The same technique is used for less severe AEs using a smaller estimated utility decrement. There is a paucity of data on the utility decrement associated with the AEs and therefore these have had to be estimated to reflect the unpleasant treatments available as alternatives. The effect of varying the AE rates and related utility decrements is examined in sensitivity analysis and show that the cost effectiveness is not particularly sensitive to these assumptions."[1] As in TA221, exploration of alternative disutilities indicated that the impact upon model parameters through use of different utilities was minimal, as they are applied for a short time period in the model; therefore, the uncertainty surrounding the source for the disutility applied in the base case will likely have little impact on the cost-effectiveness of lusutrombopag.

During model development, disutilities taken from the van Eerd 2010 study were considered as alternative values and are included as an alternative option in the model.[2] However, in the company submission, the 0.1 disutility from TA221 was utilised as it had previously been accepted by NICE and represented a conservative estimate, given that it was considerably smaller than the van Eerd estimates (Table 16). Use of the alternative van Eerd estimates results in a minor increase in incremental QALYs, rising from 0.0147 in the base case to 0.0154 (Table 17). The ICER for lusutrombopag versus platelet transfusion remained dominant, indicating that the choice of utility value had little impact on the model parameters.

Table 16. Disutilities associated with platelet transfusion

Source	Complication	Disutility (mean)	Duration (weeks)	QALY decrement	Incidence	QALY decrement weighted by incidence
van Eerd (2010)[2]	TRALI	0.4	4	0.030663929	3.30%	0.00102
	HAV	0.03	4	0.002299795	0.00%	
	HBV	0.16	4	0.012265572	0.00%	
	HCV	0.46	4	0.035263518	0.00%	
	HIV	0.5	4	0.038329911	0.00%	
	P-B19	0.03	4	0.002299795	0.00%	
	Prion disease (CJD)**	0.7	-	-	0.0004%	
	Severe allergic reactions	0.4	4	0.030663929	0.0152%	
Disutility based on	Platelet transfusion –	0.1	4	0.00766	1.09%	0.0000837

NICE TA293;[3] incidence based on Hendrickson (2016)[4]	serious AE					

*Disutility due to prion disease not included in model for simplicity due to extremely low incidence.
Abbreviations: HAV, Hepatitis A Virus; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus; P-B19, Parvovirus B-19; AE, adverse event; CJD, Creutzfeldt-Jakob disease; QALY, quality-adjusted life year; SE, standard error; TRALI, transfusion-related lung injury.

Table 17. Scenario analysis with alternate source of disutilities

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case					
Platelet transfusion	£3,743.64	4.0208	-		
Lusutrombopag	£3,571.78	4.0354	-£171.86	0.0147	Dominant
Scenario: Use of platelet transfusion-associated disutilities from van Eerd 2010					
Platelet transfusion	£3,743.64	4.0198	-		
Lusutrombopag	£3,571.78	4.0352	-£171.86	0.0154	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

Costs

B2. Table 48 of the company submission quotes platelet transfusion costs from TA293. Please clarify where these costs can be found in TA293 (document name, table number, reference number, page number etc)

These platelet transfusion costs can be found on page 207 of the manufacturers submission (first full paragraph). This is supported by reference 16, and additionally refers to TA221. Please see below for the relevant text:

"In the model, platelet transfusions were assumed to comprise a cost of blood transfusion (weighted average cost of £57.72, code 821 blood transfusion) and the cost of two units of platelets (2 x £230.393).[16] A sensitivity analysis which incorporates all data from TA221 (where possible) assumes a follow up cost of £262 per 4 week cycle."

B3. In Table 49 of the company submission, HRG codes are listed and a weighted value provided. What assumptions have been made about the number of units of plasma that can be delivered during a single plasma exchange?

In the model, the Healthcare Resource Group (HRG) code for Single Plasma Exchange or Other Intravenous Blood Transfusion was selected as the most representative HRG for platelet transfusion. The accuracy of this cost source is therefore limited as the HRG code is not specific to platelet transfusion, encompassing other transfusion types which may be more or less costly than platelet transfusion. No assumptions have been made regarding the number of units of *plasma* delivered during a single plasma exchange, rather the model assumes that one 'Single Plasma Exchange or *Other Intravenous Blood Transfusion*' is sufficient to transfuse the number of units required for each patient receiving a platelet transfusion.

Clinical validation highlighted that a patient would typically receive 2–4 units, with an assumed average of 3 units used in the model; therefore it is assumed that at least 3 units can be delivered in a single transfusion episode.

B4. What was the average number of units of platelets used per platelet transfusion in the trial data (pooled and L-PLUS-2 separately)?

Across the lusutrombopag clinical trial program, there was a large variation in how the volume of platelets transfused was recorded and this was not standardised. In L-PLUS 1, the Japanese study, the dose of platelets was consistently recorded as either 10, 15 or 20 "units", however it is not clear what volume of platelets this equates to or how this relates to definitions of units in UK clinical practice. In L-PLUS 2, the dose of platelets transfused was entered in a free text field; as such, various units were recorded including "units", "international units", "bags", millilitres, number of platelets and "dose". It is possible that inter-country, and to a lesser extent inter-centre, differences in clinical practice may have contributed to the variation in reporting observed in L-PLUS 2. Shionogi are therefore unable to provide an estimation of the average number of units used in the lusutrombopag clinical trial program, as this was not a focus of the clinical trial design. Additionally, given the small numbers of subjects receiving platelet transfusion, and the even smaller number of transfusions with dose reported in specific units, any estimate would be highly uncertain and not necessarily representative of UK clinical practice.

In the absence of interpretable data from the lusutrombopag clinical trial program, the median number of platelets transfused per platelet transfusion is available from the international trial of eltrombopag in subjects with chronic liver disease and thrombocytopenia undergoing elective invasive procedures (ELEVATE, NCT00678587).[5] In ELEVATE, the median number of transfused platelet units was 3.0 (2.5 units from a single donor and 3.0 units from multiple donors) in the eltrombopag group, as compared with a median of 4.0 platelet units (2.0 units from a single donor and 5.0 units from multiple donors) in the placebo group.[5] This is supportive of the assumption that an average of 3 units were required per platelet transfusion in the model for lusutrombopag.

B5. The company submission states that other blood preparations and volume expanders were also allowed as rescue therapies in the trials. How often were each of these used (pooled and L-PLUS 2 separately)?

In L-PLUS 2, use of the following therapies was permitted as rescue therapy for bleeding events:[6]

- Platelet preparations
- Other blood preparations and plasma
- Volume expanders

However, in L-PLUS 1 and the Phase 2b trial, platelet preparations were the only permitted rescue therapy for bleeding events.[7, 8] Despite this, in L-PLUS 1, [redacted] received rescue therapy; [redacted].

The summary of patients who received rescue therapy for bleeding events in L-PLUS 2 is reported in Table 18. [redacted] received rescue therapy other than platelet transfusion for a bleeding event. Rescue therapy for [redacted].[6]

Table 18. Summary of patients with rescue therapy for bleeding events in L-PLUS 2.

	Lusutrombopag 3 mg (N=108)	Placebo (N=107)
Patients who received rescue therapy for bleeding events, n (%)	0	2 (1.9)
Patients who received rescue therapy other than platelet transfusion for bleeding events, n (%)	[redacted]	[redacted]
Patients who received platelet transfusion due to adverse events related to bleeding, n (%)	[redacted]	[redacted]

Source: L-PLUS 2 CSR.[6]

B6. What evidence exists that other blood preparations and volume expanders are not used as standard care rescue therapies in UK?

A targeted search of the literature has not identified any evidence that other blood preparations are used as standard of care rescue therapies in the UK. Clinical validation highlighted that rescue therapy is usually defined as further platelet transfusion.

The British Society for Haematology guidelines for platelet transfusion, which recommend platelet transfusion following trauma-associated bleeding to maintain the platelet count ≥50,000/μL, provided recommendations for other alternatives or additions to platelet transfusion.[9] This states that in severe perioperative bleeding or bleeding associated with major trauma, fibrinogen should be considered in certain circumstances; however, this is not specific to patients with (severe) thrombocytopenia and is dependent on fibrinogen levels in the blood. No other blood products or volume expanders are recommended as alternatives to platelet transfusion.

It is important to note that the function of platelet transfusion as a rescue therapy is different to that of volume expanders and other blood products. Platelet transfusion serves to supplement the patients platelet count, reducing the severity of thrombocytopenia and facilitating clotting and cessation of bleeding. Contrastingly, volume expanders and other blood products are used to achieve target blood pressure until bleeding can be controlled, in order to maintain tissue oxygenation.[10] This approach does not treat the bleeding, rather occasionally being detrimental to wound repair through dislodgement of blood clots and dilution of coagulation factors.

The company submission considers lusutrombopag for the treatment of severely thrombocytopenic CLD patients undergoing planned invasive procedures; therefore it is anticipated that the use of platelet transfusion will be critical to the management of such patient requiring rescue therapy for bleeding events.

B7. Can rescue therapy be implemented which is less costly than platelet transfusion? If yes, what is it, how often is it used and how much does it cost?

Apart from platelet transfusion, Shionogi have not identified any rescue therapies that would be appropriate for use in *severely thrombocytopenic* patients. Clinical validation highlighted that rescue therapy is usually defined as further platelet transfusion.

Alternative agents which have been proposed as potential replacements of platelet transfusions include artificial platelet substitutes, platelet-poor plasma, recombinant factor VIIa (rFVIIa), fibrinogen, recombinant factor XIII (rFXIII), and antifibrinolytic drugs (e.g. tranexamic acid, TXA).[11] However, there is no randomised controlled trial evidence for these agents in the setting of managing TCP in CLD. Given the lack of evidence demonstrating efficacy, the considerable financial cost, and the concern for negative side effect profiles, these agents should not be considered as alternatives to platelet transfusion. Other treatment options, such as splenic artery embolization and splenectomy, are invasive, and their utility is limited by significant complications.

B8. Are complications of platelet transfusion assumed to occur in the same cycle as the transfusion?

Platelet transfusions are modelled within the branches of the decision tree (short-term) phase of the model only. Complications arising from platelet transfusions are assumed to have a duration of 4 weeks in the model following transfusion (based on clinical validation) and are thus assumed to be incurred within the 35-day time horizon of the short-term phase of the model.

This is a conservative assumption; in reality, if viral infection was obtained through transfusion, the incubation is typically longer than 4 weeks and the full effect of the disutility will not occur until substantially later, and may be sustained for longer. Given the low incidence of infection in clinical practice, this assumption was considered reasonable. Contrastingly, the 4-week interval is realistic for TRALIs, which occur at a higher incidence.

B9. What evidence is there that sunk costs will be experienced? Specifically, what proportion of times will theatre/clinical time be unused as opposed to being re-allocated to other patients/procedures?

Patients who have a cancelled or delayed planned invasive procedure incur an additional sunk cost (in addition to the procedure cost itself). This is because a cancelled appointment is anticipated to impact clinician time or hospital beds/resources which have been pre-assigned for the procedure (i.e. there may not be enough time to reallocate a pre-assigned clinician/hospital bed to other procedures, so the clinician's time is wasted). The inclusion of this sunk cost was supported by clinical experts at the initial validation meeting, and have been used in the literature, including in a recent cost estimate of platelet transfusion in the United States for patients with CLD and associated thrombocytopenia undergoing elective procedures.[12, 13] In the instance of a cancelled/delayed procedure, for example due to technical reasons, scheduling conflicts, platelet availability, a second platelet transfusion would likely be required due to the short "procedure window" afforded by a prophylactic platelet transfusion; with lusutrombopag, the window is broader, and a patient may not require re-dosing.

In current medical practice, the specific reasons for cancellations and delays are not typically reported, and there is a lack of specific and quantitative evidence for the experiencing of sunk costs. Unfortunately, Shionogi are therefore unable to provide estimates of the resources which are unused as opposed to being reallocated to other patients/procedures.

It is anticipated that the number of delays or cancellations are minor, likely due to increased surveillance of these patients and cancellation before the date of admission.[14] In a study which utilised the Hospital Episode Statistics (HES) inpatient dataset between 1st April 2012 and 31st March 2017 to investigate the costs associated with thrombocytopenia in CLD, only 6 patients over the study period underwent a cancellation of scheduled surgery.[14] When compared to total patient numbers (not specifically those with severe thrombocytopenia undergoing elective procedures) over the study period, which rose from 21,268 to 28,098, this is a small proportion of patients.

A scenario analysis which considers exclusion of sunk costs from the model demonstrates that these make a small contribution to the overall cost-effectiveness of lusutrombopag; removal of the sunk costs results in a minor decrease in the incremental costs, with the ICER remaining dominant (Table 19). The absence of sufficient data should therefore not be a critical factor when evaluating the current decision problem.

Table 19. Scenario analysis with exclusion of sunk costs from the model

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Base case					
Platelet transfusion	£3,743.64	4.0208	-		
Lusutrombopag	£3,571.78	4.0354	-£171.86	0.0147	Dominant
Scenario: Exclusion of sunk costs					
Platelet transfusion	£3,688.60	4.0208	-		
Lusutrombopag	£3,543.77	4.0354	-£144.83	0.0147	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year.

B10. In the "Costs" sheet of the cost effectiveness model (cells C85-C87) there are values for the percentage of patients receiving a second line treatment as they were refractory to initial platelet transfusion. Please clarify the source of this data.

This data is derived from Thrombocytopenia in Chronic Liver Disease report produced by Method Analytics (2018).[14] This was previously provided in the reference pack which accompanied the budget impact analysis document as reference number 34. The data presented in the report is from an analysis of HES inpatient data between 1st April 2012 and 31st March 2017. The relevant information, which can be found on page 9 of the report, is presented in Table 20.

Table 20. Percentage of patients receiving a second line treatment due to platelet refractoriness

Procedure	Patients (n=[redacted])*
Splenic artery embolisation, n (%)	[redacted]
Splenectomy, n (%)	[redacted]
TIPPS, n (%)	[redacted]

*For splenic artery embolisation, the report states [redacted] patients received this equating to [redacted]%. Assuming [redacted] patients gives a percentage closest to [redacted]%. For TIPPs, the report states [redacted]% of patients received this treatment, however when calculated using the number of patients this is [redacted]%.
Abbreviations: TIPPS, transluminal intrahepatic portosystemic shunt.
Source: Method Analytics, 2018.[14]

Section C: Textual clarifications and additional points (Shionogi Inc)

B11. Please provide full transcripts of validation meetings with clinicians, including where possible, details of the experience/expertise of the clinical experts.

Reports of validation meetings with clinicians have been provided as accompanying documents.

References

1. National Institute for Health and Care Excellence. TA221: Romiplostim for the treatment of chronic immune (idiopathic) thrombocytopenic purpura. 2011.
2. van Eerd MC, Mario Ouwens JN, de Peuter MA. Cost-effectiveness study comparing pharmaceutically licensed plasma for transfusion (OctaplasLG(R)) versus fresh frozen plasma (FFP) in critically Ill patients in the UK. Transfus Apher Sci 2010;43:251-9.
3. National Institute for Health and Care Excellence (NICE). TA293: Eltrombopag for adult patients with chronic immune thrombocytopenic purpura (cITP), 2012.
4. Hendrickson JE, Roubinian NH, Chowdhury D, et al. Incidence of transfusion reactions: a multicenter study utilizing systematic active surveillance and expert adjudication. Transfusion 2016;56:2587-2596.
5. Afdhal NH, Giannini EG, Tayyab G, et al. Eltrombopag before procedures in patients with cirrhosis and thrombocytopenia. New England Journal of Medicine 2012;367:716-724.
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9. Estcourt L, Birchall J, Allard S, et al. Guidelines for the use of platelet transfusions. British journal of haematology 2016;176.
10. Rossaint R, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. Crit Care 2016;20:100.
11. Desborough M, Estcourt LJ, Chaimani A, et al. Alternative agents versus prophylactic platelet transfusion for preventing bleeding in patients with thrombocytopenia due to chronic bone marrow failure: a network meta-analysis and systematic review. The Cochrane database of systematic reviews 2016;2016.
12. Cookson G, Jones S, Laliotis I. Cancelled Procedures in the English NHS: Evidence from the 2010 Tariff Reform. Health Econ 2017;26:e126-e139.
13. Barnett CL, Mladsi D, Vredenburg M, et al. Cost estimate of platelet transfusion in the United States for patients with chronic liver disease and associated thrombocytopenia undergoing elective procedures. J Med Econ 2018;21:827-834.
14. Method Analytics. Thrombocytopaenia in Chronic Liver Disease. 2018.

Multiple Technology Appraisal (MTA)

Avatrombopag and lusutrombopag for treating thrombocytopenia in people with chronic liver disease needing an elective procedure

Section A: Clarification on effectiveness data (Avatrombopag, Dova Pharmaceuticals)

A1. Please provide clinical study reports for ADAPT-1, ADAPT-2 and trial NCT00914927 {Terrault, 2014 #198}

A2. What is the expected licensed dose and indication for avatrombpag? Will it reflect the ADAPT trials i.e. (60 mg if baseline platelet count <40,000/μL or 40 mg if 40,000 to <50,000/μL)?

A3. Please provide the following outcomes separately for ADAPT-1, ADAPT-2 and trial NCT00914927 and, within each trial, separately for each dose i.e. 40 mg and 60 mg:

a. the number/proportion of patients who required a platelet transfusion prior to the elective procedure (as opposed to as a rescue procedure)
b. the number/proportion of patients who received a specified number of platelet transfusions (0, 1, 2, 3, 4, 5), separately for before the elective procedure and as rescue therapy
c. mean (SD) number/proportion of units of platelets transfused, separately for before the elective procedure and as rescue therapy
d. the number/proportion of patients receiving each type of rescue therapy
e. the number/proportion of patients who experienced a bleeding related adverse event (by severity)
f. the number/proportion of patients who a required a rescue procedure
g. the number/proportion of patients who experienced a thrombotic adverse event
h. the number/proportion of patients who experienced a portal vein thrombosis

A4. Why was trial NCT03326843 {Dova Pharmaceuticals, #4600} terminated early? What is meant by ‘enrolment problems’?

A5. It is reported that eligibility for the avatrombopag RCTs was determined by mean platelet count during the screening period and at baseline. {Terrault, 2018 #68} What proportion of patients in ADAPT-1 and ADAPT-2 had a platelet count above 50,000/μL at baseline?

A6. In the ADAPT studies how were platelet transfusions determined prior to the elective procedure? i.e. what was the decision rule and was it solely according to platelet count or that and other factors?

A7. In the RCTs avatrombopag was administered for 5 days for all patients. {Terrault, 2018 #68} What stopping rule is expected in clinical practice? If this differs from the trials, what are the likely implications for efficacy and safety?

A8. Please provide the number/proportion and nature of major protocol deviations per arm for each of the trials including receipt of any antithrombotic medication or fresh frozen plasma.

A9. Please provide the number/proportion of patients in the RCTs who received a procedure that required platelet transfusion prior to entry into the studies.

Multiple Technology Appraisal (MTA)

Avatrombopag and lusutrombopag for treating thrombocytopenia in people with chronic liver disease needing an elective procedure

Section A: Clarification on effectiveness data (Avatrombopag, Dova Pharmaceuticals)

A1. Please provide clinical study reports for ADAPT-1, ADAPT-2 and trial NCT00914927 {Terrault, 2014 #198}

A2. What is the expected licensed dose and indication for avatrombpag? Will it reflect the ADAPT trials i.e. (60 mg if baseline platelet count <40,000/μL or 40 mg if 40,000 to <50,000/μL)?

Licensed dose will be dependent on baseline platelet count:

- 60 mg if baseline platelet count <40,000/μL
- 40 mg if 40,000 to <50,000/μL

A3. Please provide the following outcomes separately for ADAPT-1, ADAPT-2 and trial NCT00914927 and, within each trial, separately for each dose i.e. 40 mg and 60 mg:

a. the number/proportion of patients who required a platelet transfusion prior to the elective procedure (as opposed to as a rescue procedure)

Summary of Patients Receiving Platelet Transfusion Prior to Elective Procedure - FAS

ADAPT-1	***AVA 60 mg N=90 n (%)***	***PBO 60 mg N=48 n (%)***	***AVA 40 mg N=59 n (%)***	***PBO 40 mg N=34 n (%)***
	19 (21.1)	*22 (45.8)*	*4 (6.8)*	*17 (50.0)*
ADAPT-2	***AVA 60 mg N=70 n (%)***	***PBO 60 mg N=43 n (%)***	***AVA 40 mg N=58 n (%)***	***PBO 40 mg N=33 n (%)***
	12 (17.1)	*21 (48.8)*	*3 (5.2)*	*15 (45.5)*

Note: "Prior to Elective Procedure" was determined based on the procedure start date/time and the platelet transfusion start date/time when sufficient information was available. Time data was only used if available for both the elective procedure and platelet transfusion event.

Source: Ad hoc analysis

b. the number/proportion of patients who received a specified number of platelet transfusions (0, 1, 2, 3, 4, 5), separately for before the elective procedure and as rescue therapy

Summary of Number of Platelet Transfusions Received Prior to Elective Procedure - FAS

ADAPT-1	AVA 60 mg N=90 n (%)	PBO 60 mg N=48 n (%)	AVA 40 mg N=59 n (%)	PBO 40 mg N=34 n (%)
1 Transfusion	19 (21.1)	19 (39.6)	4 (6.8)	5 (14.7)
2 Transfusions	0	3 (6.3)	0	2 (5.9)
3 Transfusions	0	0	0	0
4 Transfusions	0	0	0	0
5 Transfusions	0	0	0	0
ADAPT-2	**AVA 60 mg N=70 n (%)**	**PBO 60 mg N=43 n (%)**	**AVA 40 mg N=58 n (%)**	**PBO 40 mg N=33 n (%)**
1 Transfusion	11 (15.7)	19 (44.2)	3 (5.2)	15 (45.5)
2 Transfusions	0	2 (4.7)	0	0
3 Transfusions	0	0	0	0
4 Transfusions	0	0	0	0
5 Transfusions	0	0	0	0

Source: Ad hoc analysis

c. mean (SD) number/proportion of units of platelets transfused, separately for before the elective procedure and as rescue therapy

Descriptive Statistics – Number of Units of Platelet Transfusion Prior to Elective Procedure - FAS

ADAPT-1	AVA 60 mg	PBO 60 mg	AVA 40 mg	PBO 40 mg
N*	19	25	4	19
Mean (SD)	3.9 (3.34)	5.3 (3.22)	7.5 (3.79)	5.6 (3.11)
Median	2	6	9	6
Min, Max	1, 12	1, 12	2,10	1, 12
ADAPT-1	**AVA 60 mg**	**PBO 60 mg**	**AVA 40 mg**	**PBO 40 mg**
N*	12	23	3	15

Mean (SD)	*6.9 (3.63)*	*7.4 (5.88)*	*2.7 (2.89)*	*5.6 (4.21)*
Median	*8*	*6*	*1*	*6*
Min, Max	*1, 10*	*1, 20*	*1, 6*	*1, 15*

**N represents number of platelet transfusions. A patient may have received more than one platelet transfusion.*

Source: Ad hoc analysis

Platelet Transfusion as Rescue Therapy:

ADAPT-1:

- *Patient 4802-1001 (PBO 40 mg) received 6 units of platelet transfusion as a rescue therapy on Day 11.*
- *Patient 4201-1005 (PBO 60 mg) received 8 units of platelet transfusion as a rescue therapy on Day 16.*

ADAPT-2:

- *Patient 5912-1003 (PBO 40 mg) received 15 units of platelet transfusion as a rescue therapy on Day 14.*
- *Patient 3905-1003 (PBO 40 mg) received 1 unit of platelet transfusion as a rescue therapy on Day 11.*

Source: Listings 16.2.6.5, 16.2.6.4

d. the number/proportion of patients receiving each type of rescue therapy

Summary of Rescue Therapy - FAS

ADAPT-1	***AVA 60 mg N=90 n (%)***	***PBO 60 mg N=48 n (%)***	***AVA 40 mg N=59 n (%)***	***PBO 40 mg N=34 n (%)***
Platelet transfusion		*1 (2.1)*		*1 (2.9)*
Fresh Frozen Plasma (FFP)		*1 (2.1)*		
Adrenalin injected at bleeding site		*1 (2.1)*		
Tranexamic acid	*1 (1.1)*	*1 (2.1)*		
ADAPT-2	***AVA 60 mg N=70 n (%)***	***PBO 60 mg N=43 n (%)***	***AVA 40 mg N=58 n (%)***	***PBO 40 mg N=33 n (%)***
Platelet transfusion				*2 (6.1)*
Fresh Frozen Plasma (FFP)				*1 (3.0)*

Acidum aminomethylbenzoicum				*1 (3.0)*
Aminocaproic acid			*1 (1.7)*	
Carbazochrome Sodium Sulfonate Hydrate				*1 (3.0)*
Dicynone				*1 (3.0)*
Glypressin	*1 (1.4)*			
Tranexamic acid				*1 (3.0)*

Source: Listing 16.2.6.5

e. the number/proportion of patients who experienced a bleeding related adverse event (by severity)

Summary of Adverse Events of Special interest of Bleeding Events by CTCAE Grade - SAF

ADAPT-1	***AVA 60 mg N=89 n (%)***	***PBO 60 mg N=48 n (%)***	***AVA 40 mg N=58 n (%)***	***PBO 40 mg N=32 n (%)***
Grade 1	*3 (3.4)*	*1 (2.1)*	*0*	*0*
Grade 2	*2 (2.2)*	*2 (4.2)*	*0*	*1 (3.1)*
Grade 3	*0*	*0*	*2 (3.4)*	*0*
ADAPT-2	***AVA 60 mg N=70 n (%)***	***PBO 60 mg N=43 n (%)***	***AVA 40 mg N=57 n (%)***	***PBO 40 mg N=33 n (%)***
Grade 1	*0*	*0*	*1 (1.8)*	*0*
Grade 2	*0*	*0*	*0*	*2 (6.1)*
Grade 3	*1 (1.4)*	*0*	*0*	*0*

Source: Ad hoc analysis

f. the number/proportion of patients who a required a rescue procedure

Summary of Patients Who Required Rescue Therapy – FAS

ADAPT-1	***AVA 60 mg N=90 n (%)***	***PBO 60 mg N=48 n (%)***	***AVA 40 mg N=59 n (%)***	***PBO 40 mg N=34 n (%)***

	1 (1.1)	*2 (4.2)*	*0*	*1 (2.9)*
ADAPT-2	***AVA 60 mg N=70 n (%)***	***PBO 60 mg N=43 n (%)***	***AVA 40 mg N=58 n (%)***	***PBO 40 mg N=33 n (%)***
	1 (1.4)	*0*	*1 (1.7)*	*3 (9.1)*

Source: Listing 16.2.6.5

g. the number/proportion of patients who experienced a thrombotic adverse event

Summary of Patients Experienced Thromboembolic Event - SAF

ADAPT-1	***AVA 60 mg N=89 n (%)***	***PBO 60 mg N=48 n (%)***	***AVA 40 mg N=58 n (%)***	***PBO 40 mg N=32 n (%)***
	0	*0*	*0*	*0*
ADAPT-2	***AVA 60 mg N=70 n (%)***	***PBO 60 mg N=43 n (%)***	***AVA 40 mg N=57 n (%)***	***PBO 40 mg N=33 n (%)***
	0	*0*	*1 (1.8)*	*2 (6.1)*

Source: Table 14.3.2.6.1

h. the number/proportion of patients who experienced a portal vein thrombosis

Summary of Patients Experienced Portal Vein Thrombosis Event - SAF

ADAPT-1	***AVA 60 mg N=89 n (%)***	***PBO 60 mg N=48 n (%)***	***AVA 40 mg N=58 n (%)***	***PBO 40 mg N=32 n (%)***
	0	*0*	*0*	*0*
ADAPT-2	***AVA 60 mg N=70 n (%)***	***PBO 60 mg N=43 n (%)***	***AVA 40 mg N=57 n (%)***	***PBO 40 mg N=33 n (%)***
	0	*0*	*1 (1.8)*	*0*

Source: Table 14.3.2.6.1

A4. Why was trial NCT03326843 {Dova Pharmaceuticals, #4600} terminated early? What is meant by ‘enrolment problems’?

The study was enrolling patients slower than expected. A decision was required to determine which clinical program to continue funding with Avatrombopag, and

the decision was made to stop this trial but continue the chemo-therapy induced trial.

A5. It is reported that eligibility for the avatrombopag RCTs was determined by mean platelet count during the screening period and at baseline. {Terrault, 2018 #68} What proportion of patients in ADAPT-1 and ADAPT-2 had a platelet count above 50,000/μL at baseline?

The inclusion criteria was as follows:
Subjects who have a mean baseline platelet count of <50 × 109/L. Platelet counts must be measured on 2 separate occasions, during the Screening Period and at Baseline, and must be performed at least 1 day apart with neither platelet count >60 × 109/L. The mean of these 2 platelet counts (mean baseline platelet count) will be used for entry criteria and for assignment to the low or high baseline platelet count cohort.

Overall, only 2 patients included in the study had a platelet count > 50 X109/L.

A6. In the ADAPT studies how were platelet transfusions determined prior to the elective procedure? i.e. what was the decision rule and was it solely according to platelet count or that and other factors?

The administration of platelet transfusion was at the sole discretion of the investigator. There was not a stipulation to require a platelet transfusion regardless of the count on procedure day.

A7. In the RCTs avatrombopag was administered for 5 days for all patients. {Terrault, 2018 #68} What stopping rule is expected in clinical practice? If this differs from the trials, what are the likely implications for efficacy and safety?

It is expected that all patients who are treated will receive 5 days of dosing. Patients who have been treated in the US have all received 5 days of drug.

A8. Please provide the number/proportion and nature of major protocol deviations per arm for each of the trials including receipt of any antithrombotic medication or fresh frozen plasma.

Summary of Major Protocol Deviations - FAS

ADAPT-1	***AVA 60 mg N=90 n (%)***	***PBO 60 mg N=48 n (%)***	***AVA 40 mg N=59 n (%)***	***PBO 40 mg N=34 n (%)***
Subjects with any major protocol deviations	*20 (22.2)*	*19 (39.6)*	*8 (13.6)*	*9 (26.5)*
Concomitant Medication Criteria	*0*	*1 (2.1)*	*2 (3.4)*	*0*
Eligibility and Entry	*2 (2.2)*	*5 (10.4)*	*1 (1.7)*	*1 (2.9)*
IP Compliance	*2 (2.2)*	*1 (2.1)*	*0*	*0*

Randomization	*1 (1.1)*	*0*	*0*	*0*
Serious Adverse Event	*3 (3.3)*	*5 (10.4)*	*1 (1.7)*	*1 (2.9)*
Study Procedures	*12 (13.3)*	*10 (20.8)*	*4 (6.8)*	*8 (23.5)*
ADAPT-2	***AVA 60 mg N=70 n (%)***	***PBO 60 mg N=43 n (%)***	***AVA 40 mg N=58 n (%)***	***PBO 40 mg N=33 n (%)***
Subjects with any major protocol deviations	*10 (14.3)*	*12 (27.9)*	*9 (15.5)*	*6 (18.2)*
Eligibility and Entry	*0*	*3 (7.0)*	*0*	*1 (3.0)*
IP Compliance	*2 (2.9)*	*1 (2.3)*	*3 (5.2)*	*0*
Informed Consent	*1 (1.4)*	*0*	*0*	*0*
Laboratory Assessment	*0*	*1 (2.3)*	*0*	*0*
Randomization	*0*	*0*	*1 (1.7)*	*0*
Serious Adverse Event	*0*	*0*	*0*	*1 (3.0)*
Study Procedures	*6 (8.6)*	*7 (16.3)*	*4 (6.9)*	*4 (12.1)*
Visit Schedule	*1 (1.4)*	*0*	*1 (1.7)*	*1 (3.0)*

Source: Table 14.1.2

Receipt of any antithrombotic medication or fresh frozen plasma was not prohibited during the study and, therefore was not considered a protocol deviation.

A9. Please provide the number/proportion of patients in the RCTs who received a procedure that required platelet transfusion prior to entry into the studies.
This information was not collected in the CLD studies.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Avatrombopag and lusutrombopag for treating thrombocytopenia in people with chronic liver disease needing an elective procedure [ID1520]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: British Association for the Study of the Liver (BASL)
Are you (tick all that apply):

- √ a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- √ an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Avatrombopag and lusutrombopag for treating thrombocytopenia in people with chronic liver disease needing an elective procedure [ID1520]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS?

Platelet transfusion at time of the procedure.

Is there significant geographical variation in current practice?

No

Are there differences of opinion between professionals as to what current practice should be?

Controversy would be whether platelet transfusion reduces the risk for medium or small procedures.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

No alternative drug therapies

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?

No

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

Benefit obtained is likely to be related to the extent of procedure. More major surgery/ procedure eg liver surgery or transplant most likely to benefit.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?

Could be relevant to all cirrhotic patients with thrombocytopaenia requiring an intervention.

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

No

If the technology is already available, is there variation in how it is being used in the NHS?
In clinical trials at present.

Is it always used within its licensed indications?

Don't know.

If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Not in guidelines as yet.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

It is a new technology and not replacing a current treatment.
Experience in use and monitoring of dose/ duration will be required.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

These will be identified in the clinical trials

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

I have not seen the clinical trial data

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

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We do not have experience of use in clinical practise as yet.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

No

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition?

Would have major impact for a small number of UK patients

Would NHS staff need extra education and training?

Yes. On indications for use, SEs, dose and duration plus monitoring.

Would any additional resources be required (for example, facilities or equipment)?

Will need method of monitoring which is not likely to be available in routine haematology/haemophilia lab.

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Multiple Technology Appraisal (MTA)

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Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;

No

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

No

- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

No

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

None

Additional comments on scope of appraisal.
Outcomes

- Should include number and type of interventional procedures. Patients may not return to surgery with complication which will be managed by interventional radiology/endoscopy.
- Include hospital stay/ ITU stay
- Return to normal activities (work/family care). Partly covered by QoL and Health Economic assessment.

……

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Avatrombopag and lusutrombopag for treating thrombocytopenia in people with chronic liver disease needing an elective procedure [ID1520]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

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To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: British Society of Gastroenterology (BSG)
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

None

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Avatrombopag and lusutrombopag for treating thrombocytopenia in people with chronic liver disease needing an elective procedure [ID1520]

What is the expected place of the technology in current practice?

There is currently considerable variability in the way that thrombocytopenia in the setting of chronic liver disease is managed across the NHS. The management of thrombocytopenia and hence perceived bleeding risk associated with elective procedures is often based on historical practice and dogma and reflects a lack of clear evidence base and poor understanding of platelet function in liver disease.

Thrombocytopenia in advanced liver disease is usually encountered in the context of cirrhosis with portal hypertension and tends to be a permanent and progressive abnormality once it occurs. Elective procedures performed in patients with chronic liver disease can be divided into procedures directly related to consequences of liver disease and those coincidental to liver pathology. Most elective procedures will fall into the first category and include abdominal paracentesis, liver biopsy, endoscopic treatment of varices and locoregional therapy for hepatocellular cancer (HCC), including radiofrequency ablation (RFA) and chemoembolization.

Though there is little guidance around how thrombocytopenia should be managed prior to elective procedures in chronic liver disease, a range of guidelines do address the platelet cut-off values below which platelet transfusion should be given to reduce the perceived excess risk of procedure related bleeding. The majority of this guidance is based on expert opinion rather than an evidence-base. The subject matter itself falls within the remit of a number of different specialities so guidance if provided by liver disease societies (AASLD, EASL, BSG), societies of interventional radiology and of haematology. In the absence of a robust evidence base, it is unsurprising that there is no universal consensus between these guidelines on how platelet function and associated bleeding risk should be measured, or even on an absolute platelet count threshold below which prophylaxis should be considered. The balance of evidence as it exists suggests that a platelet count of >50^10^9 is sufficient to perform invasive elective procedures in patients with liver disease. Furthermore, some common invasive procedures, such as abdominal paracentesis, carry such low absolute risk of bleeding, that platelet prophylaxis does not need to be considered at all. If avatrombopag and lusutrombopag are to be recommended for this indication, it will be important to provide clear guidance as the platelet count thresholds below which their use is advocated. Further research to better understanding platelet function and bleeding risks if patients with thrombocytopenia due to chronic liver disease is also needed.

The advantages and disadvantages of the technology

The use of avatrombopag and lusutrombopag to treat thrombocytopenia in patients with chronic liver disease who are due to undergo elective procedures would act as a substitute to prophylactic platelet transfusion. The phase 3 trial data available for both products clearly shows that platelet transfusion can be significantly reduced in this context with equivalent very low procedure related bleeding events.

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Avatrombopag and lusutrombopag for treating thrombocytopenia in people with chronic liver disease needing an elective procedure [ID1520]

The practice of prophylactic platelet transfusion is variable across the UK, with significant differences in platelet cut-off at which prophylaxis is given, the number of platelets pools administered and whether platelet count is checked after transfusion prior to the procedure. Platelets transfused in the context of portal hypertension and splenomegaly (usually always present in patients with chronic liver disease and thrombocytopenia) will only last in the circulation for a matter of hours and the incremental increase for a given pool of platelets is very inconsistent between individual patients. Smaller hospitals will often have to order in platelets from elsewhere for routine use, as they will not be stored on site.

The advantages of using a thrombopoietin agonist over prophylactic platelet transfusion are as follows

1. A more gradual and predictable increase in platelet count can be achieved in a controlled and measurable manner over several days in an outpatient setting. Elective procedures could then be scheduled more easily and accurately to coincide with peak platelet count.
2. A more sustained elevation in platelet count, which would mean that the therapeutic window during which an elective procedure could be performed is much longer. If a procedure has be cancelled on the day (as often the case for operational reasons in the NHS), there may still be opportunity to perform the procedure in the following days without needing to provide additional drug.
3. The administration of platelets requires a clinical setting in which this can be delivered as well as nursing time to administer the transfusion and monitor the patient thereafter. How this occurs will vary between hospitals in the NHS but includes elective admission to a daycare ward, a bed on an inpatient ward, or to a specific facility within the department performing the elective procedure. Avatrombopag and lusutrombopag are administered orally and are likely to be prescribed in the outpatient clinic and taken by the patient at home. This will likely lead to NHS cost saving, improved efficiency and free up NHS bed resource by saving on nursing time and ward bed space for other patients.
4. Use of avatrombopag and lusutrombopag would reduce the number of platelet transfusions and thereby avoid the use of a blood product. The phase 3 clinical trial data clearly shows this. There are inherent advantages to reducing blood product usage such as mitigation against the risk of cross-infection and the preservation of a limited national resource for other indications. Platelet transfusions are also rarely associated with serious and rarely life threatening side effects such as transfusion associated lung injury.
5. TPOs such as avatrombopag and lusutrombopag have the additional theoretical advantage of maintaining elevated platelet counts over several days, whereas platelet transfusions will only sustain platelets count over a matter of hours. Occasionally, patients will experience delayed bleeding after an elective procedure, such as a liver biopsy. The clinical trials of avatrombopag and lusutrombopag were not designed to look at delayed bleeding, but there is a hypothetical additional safety advantage over platelet transfusion to mitigate the small risk of a delayed bleed.

I do not foresee that any specific additional monitoring that would be required for patients receiving thrombopoietin (TPO) agonist therapy. I would envisage that patients would prefer to receive an oral drug taken once daily in the lead up to their planned elective procedure rather than an infusion of platelets, a blood-related transfusion product.

Earlier studies in patients with cirrhosis receiving TPO agonists (such as eltrombopag) had reported higher rates of portal vein thrombosis (PVT), a complication in liver disease with significant consequences. The phase 3 clinical trials of avatrombopag and lusutrombopag have addressed this concern and show that these two products have favourable side effect profiles compared to placebo, without increased risk of PVT.

An important consideration will be the relative cost of avatrombopag and lusutrombopag compared to platelet transfusion. It will be important to consider the overall cost to the NHS of providing and delivering platelet transfusion, not just the cost of the blood product itself. It is common experience in NHS practice that elective procedures in patients with liver disease are cancelled or delayed due to logistical difficulties in obtaining timely platelet transfusion prior to the procedure, to natural fluctuations in a patient's platelet count in the days leading up to a procedure, or due to the requirement by some operators to have a repeat platelet count checked after platelet transfusion before the procedure itself. These difficulties are likely to be averted if TPO agonist therapy is used to achieve gradual and sustained elevation in platelet count observable in the days leading up to the elective procedure. This will allow more predictable planning of a procedure, and elective re-scheduling if necessary. It is anticipated this strategy would lead to fewer procedure delays or unexpected procedure cancellations leading to NHS cost savings and efficiencies. It is important to factor this in when considering the relative costs of avatrombopag and lusutrombopag use vs. platelet transfusion.

The phase 3 clinical trials of avatrombopag and lusutrombopag have focussed on minimisation of platelet transfusion as primary endpoints of their studies. This is a useful outcome measure and indicates a key area where the NHS can make more efficient use of a valuable resource. Secondary endpoints of platelet count incrementation and procedure related bleeding rates show that these two products can work effectively as prophylaxis against procedure related bleeding. Drug safety has been well demonstrated. Avatrombopag and Lusutrombopag have not been used yet in clinical practice in advanced liver disease so no comment can be made on how this data compares to real world clinical practice.

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Multiple Technology Appraisal (MTA)

Avatrombopag and lusutrombopag for treating thrombocytopenia in people with chronic liver disease needing an elective procedure [ID1520]

Any additional sources of evidence
Implementation issues
I do not foresee any implementation issues or specific additional training requirement or NHS facilities if these two products were to be made available.
Equality I do not foresee any issues with equality or inequity of access to these two products.

……..

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Avatrombopag and lusutrombopag for treating thrombocytopenia in people with chronic liver disease needing an elective procedure [ID1520]

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 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 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
- 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	**Vickie McDonald**
2. Name of organisation	**Royal London Hospital**

3. Job title or position	**Consultant Haematologist and Honorary Senior Lecturer, Queen Mary University of London**
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 this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☒ Other (please specify): specialist in management of low platelets including ITP.
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.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To increase the platelet count in patients with chronic liver disease to a level that is safe for invasive procedures and surgery.
8. 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.)	Increase in platelet count to a level that minimises the bleed risk and avoids the use of blood products where possible. The target platelet count will depend on several factors, including the type of procedure and patient co-morbidities.
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes: e.g. • British Committee for Standards in Haematology : Guidelines for the use of platelet transfusions, Escourt L et al, British Journal of Haematology, 2017, 176, 365–394 • NICE CG 24
• 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.)	I can't comment on the specific pathway of care because my role would be to advise other physicians on the requirement for platelets, rather than be directly responsible for their care. If a patient with chronic liver disease is found to have low platelets, below a recommended threshold for procedures and where the bleed risk was thought to be significant, then a platelet transfusion would be required. If platelets are required the process would be: • Requested by the clinical team from the laboratory • Platelets administered a few hours before the procedure with a check blood count depending on the procedure. Patients may require further pools of platelets if the rise in count is insufficient. • Sometime we simply advise the platelets to be given during procedure, and not check repeat count, if the bleed risk is not too high • Monitor patient for bleeding after the procedure – this may necessitate overnight hospital stay Broad guidance has been developed for platelet targets for procedures, however there is some variability in practice across the country
• What impact would the technology have on the	Reduction in the use of platelet transfusions, reduced time in hospital receiving the transfusion

current pathway of care?	
11. 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?	Current care would be to administer platelets before +/- during the procedure with rescue therapy afterwards if there is any bleeding. Rescue therapies include platelets, red cells and tranexamic acid. Use of the technology, would be as an outpatient, commenced before the procedure.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care and specialist clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	I am not sure what specific investment would be needed.
12. Do you expect the technology to provide clinically meaningful benefits compared	

with current care?	
• Do you expect the technology to increase length of life more than current care?	No
• Do you expect the technology to increase health-related quality of life more than current care?	Don't know
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not applicable
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current	The technology will be much easier to use than current care. The technology is well tolerated, and these agents, unlike earlier versions of the thrombopoietin receptor agonists (TPO-RA) such as eltrombopag, have no dietary restrictions. Use of these agents to reduce blood product transfusion would reduce the time required to prepare patients

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.)	for procedures, avoid the potential complications of transfusions, and reduce the risk of alloimmunisation that may influence the success of transplantation later down the line.
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients would be required to have proven thrombocytopenia After starting the drug, platelet count should be checked to ensure response, and measure peak count.
16. 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	I am not an expert on QALY calculations; however potential additional benefits would be a reduction in alloimmunisation (from avoiding platelet transfusions). Alloimmunisation means that a patient develops antibodies that may make future platelet transfusions less effective and more expensive if HLA matched platelets are required. In addition alloimmunisation impacts on the success of transplantation.

(QALY) calculation?	
17. 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?	Yes, this is an innovative approach for this patient group, and will minimise exposure to blood products, although this class of drug is used to manage thrombocytopenia in other clinical areas such as ITP and aplastic anaemia.
• Is the technology a 'step-change' in the management of the condition?	Yes, avoidance of blood products and associated time / costs is a step change improvement.
• Does the use of the technology address any particular unmet need of the patient population?	No
18. How do any side effects or adverse effects of the technology affect the management of the condition	Most adverse events for these agents are mild and self-limiting. The most significant is the potential for thrombosis, although the trial data doesn't reveal a substantial thrombosis rate above current standard of care. We are aware that the use of TPO-RA can contribute to the development of thrombosis but evidence from other disease areas such as ITP and aplastic anaemia suggest that this is due to inherent risk factors

and the patient's quality of life?	for thrombosis in the patients themselves. Development of a thrombus would mean the patient would require anticoagulation which can be challenging in a patient with liver disease and thrombocytopenia
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	Technology is not used for chronic liver disease yet. However, the data from the trials could be extrapolated to the UK population.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Reduction in platelet transfusion before procedures Reduction in rescue medication
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light	No

subsequently?	
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	No
22. How do data on real-world experience compare with the trial data?	I am not aware of any real world data for the technology.
Equality	
23a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

23b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
1. Is there an independent association in chronic liver disease between platelet level and bleeding during/following procedures? 2. Is there a platelet level below which bleeding occurs, and above which it does not?	There are limited large studies on this, however lower platelet counts (broadly <30 x10^9/L) are generally accepted to be associated with an increased risk of bleeding. In liver disease, the haemostatic picture is complex, and in addition to low platelets there is reduction in synthesis of clotting factors balanced out by a reduction in natural anticoagulants. The type of procedure is also important when considering bleed risk. The clinical picture is not clear cut because bleed risk depends not only on platelet count but also procedure type, other medical conditions (kidney failure, infection, bleeding disorder, hypertension), therapies (antiplatelet drugs, anticoagulants, antidepressants) and age. Procedures where very low platelet counts (down to 20 x10^9/L) are considered acceptable are central venous access insertion, paracentesis, routine endoscopy in some centres. Although practice does vary across Trusts. The guidelines (e.g. BCSH) recommend a platelet count of 50 x10^9/ L for major surgery, 100 x10^9/L for neurosurgery and 80 x10^9/L for epidural. However, as we've stressed before there is limited data to back

	this up.
3. Related to this, does NHS practice treat people with platelet counts under 50,000/μL, or is the value lower?	This depends on what is meant by 'treat'. We would aim for targets as above to cover procedures. However outside of this, in the absence of bleeding then simple monitoring for patients with low platelets is satisfactory in the setting of chronic liver disease (unless there is another cause such as hepatitis C).
4. Is there an independent association between platelet levels and fatal bleeds?	I am not aware of a specific study showing this in liver disease. We do see that there is an association with low platelets and bleeding in ITP, marrow failure etc.
5. Is there evidence (proof) that treating (prophylaxis) with platelets lowers the frequency of bleeds? Fatal bleeds?	I am not aware of specific studies in this area. It is 'accepted practice' to manage patients according to certain platelet thresholds but the evidence base is limited. The BCSH guidance gives a summary of evidence where it exists.
6. Do platelet transfusions become less effective over time? What proportion of people (if any) become refractory	There is a risk of alloimmunisation with repeated platelet transfusions. This is where patients develop antibodies to proteins on the surface of platelets that are 'foreign' to them. These antibodies mean that subsequent platelet transfusions are less effective. I can't give specific figures on the proportion affected.

to platelet transfusions?	
7. The drugs for this appraisal are given prior to an invasive procedure. How many procedures would people with chronic liver disease expect to have in their lifetime? One-off or multiple	I can't answer this – would need hepatology input.
8. If people have a delayed procedure could the resource e.g. surgeon time be used elsewhere, or another patient take the slot?	Again, I can't answer this – would need hepatology input.
9. Does the post platelet transfusion platelet level have to be higher for certain types of procedures e.g. open surgery to the thorax, abdomen etc compared with less invasive	Yes, as per question 2 responses.

diagnostic procedures?	

Key messages

25. In up to 5 bullet points, please summarise the key messages of your statement.

- This is novel model for increasing platelet count before surgery or procedures in thrombocytopenia due to chronic liver disease
- The evidence suggests a reduction in platelet transfusions for both agents avatrombopag and lusutrombopag
- Reduction in the use of platelet transfusion has benefits for the patient, NHS resources and the overall supply of platelets
- The agents appear to be well tolerated
- Defined timelines, markers and monitoring would be needed to ensure safe use

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Avatrombopag and lusutrombopag for treating thrombocytopenia in people with chronic liver disease needing an elective procedure [ID1520]

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 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.

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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	**Professor Debbie L Shawcross**
2. Name of organisation	**King's College Hospital NHS Foundation Trust and King's College London**

3. Job title or position	**Professor of Hepatology and Chronic Liver Failure**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **X** a specialist in the treatment of people with this condition? **X** a specialist in the clinical evidence base for this condition 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 ☐ no, I disagree with it **X** 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.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Patients with cirrhosis of the liver invariably develop thrombocytopenia which worsens with increasing severity of liver disease. Up to 75% patients may develop some degree of thrombocytopenia with 13% being documented in one study as having platelet counts between 50,000 and 75,000 (normal platelet count considered to be >150,000). There are no good data on the incidence of severe thrombocytopenia (<50,000 platelets) in patients with cirrhosis but we see it frequently in clinical practice. Physicians presume that the bleeding risk is increased in those with platelet counts <50,000 but there are no good data on this and there is no strong evidence base to support an increased bleeding risk in those with platelets <50,000. Bleeding risk overall is low in this population with for example a risk of <0.3% being quoted for percutneous liver biopsy and rates of 5% being quoted for radiofrequency ablation of liver tumours. There is concern among physicians and radiologists that the procedural bleeding risk is moderately high in patients with cirrhosis and platelets <50,000 and therefore it is widespread practice to transfuse platelets to patients with cirrhosis and platelets <50,000 undergoing routine invasive procedures such as liver biopsy, endoscopy and variceal band ligation, radiofrequency ablation and TIPS for example to reduce bleeding risk. Whether this does actually reduce bleeding risk remains to be seen.
8. 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.)	Platelet transfusion administered to those with platelet counts <50,000 rarely leads to significant increments in the platelet count but may raise the count by 10,000-30,000. There is no good evidence that incrementing the platelet count reduces bleeding risk. Some interventional radiologists and surgeons insist on the platelet count being increased to >60,000 or even 90,000 prior to performing surgery for fear of being penalised should the patient bleed as a result of the procedure. Frequently this results in patients having their procedures delayed or cancelled. Incrementing the platelet count with an infusion may result in a statistically significant rise in platelets but this may not be clinically meaningful.

9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Patients with advanced chronic liver disease often are subjected to multiple transfusions of blood products (platelets, fresh frozen plasma and packed red cells) in the course of their disease. A patient for example that I recently managed on the ward had received 114 units of blood productsf or treatment of chronic insidious blood loss and during a number of gastrointestinal investigations including gastroscopy and colonoscopy over 3 months. This is an enormous resource burden to the NHS as well as impacting significantly on their quality of life. Transfusion of blood products unnecessarily is a waste of a precious resource and is costly. Shortages are not unknown and patients requiring frequent transfusion often develop antibodies that necessitate apheresed platelet transfuions. Patients frequently are also brought in one day early before their procedure/surgery so that platelets or clotting products can be given adding a night's hospital stay to their NHS care bill. There are some groups of patients who decline to have blood products such as Jehovah's Witnesses (137,000 patients in the UK) and these groups then have investigations declined and can not be considered for liver transplantation if they have thrombocytopenia. Lastly, transfusing patients is not without risk. Transfusion reactions are common (mild transfusion reactions can be as frequent as 1 in 10) and may result in transfusion-related lung injury. This is associated with significant morbidity and mortality. I have also undertaken research which has shown giving a platelet transfusion induces the release of reactive oxygen species from white blood cells which can cause endothelial activation and inflammation.
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	It is current practice in most units for clinicians to prescribe 1 pool of platelets (1 pool contains donations from 5 patients) within 30-60 minutes of a procedure being undertaken in a patient with cirrhosis and

	platelets <50,000. Many physicians have a lower threshold and may transfuse when the platelet count is <75,000.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	In short no. The British Society of Gastroenetrology published guideance in 2004 suggesting that a threshold of 60,000 platelets warrants a platelet transfusion prior to undertaking a liver biopsy. No guidance exists for radiofrequency ablation or chemoembolization.
• 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.)	The pathway of care is not well defined and there are no published guidelines or protocols. Hepatologists are likely to use less platelet transfusions as their understanding of the real risks of bleeding are probably less than feared and those performing the procedures such as interventional radiologists probably insist on using more to reach non-evidence based thresholds which are poorly defined. There is global variation in the number of units of platelets transfused but generally in the UK, only 1 pool tends to be given before a procedure.
• What impact would the technology have on the current pathway of care?	Being able to prescribe an oral thrombopoietin agonist for me would have significant impact on my practice for the following reasons: 1. Avoidance of transfusion of blood product when there is a safe oral alternative is a 'no brainer' as unnecessary transfusion should be avoided at all costs. 2. Patients do not like being admitted the night before a procedure with all the hassle that entails as well as being cannulated and enduring transfusion and any resultant side effects. This would improve their quality of life. 3. We would save many NHS bed days if procedures could be done as day cases. 4. There would be less procedure cancellations/delays. 5. Patients with liver disease have low thrombopoeitin levels (it is made in the liver). Increasing thrombopoietin production would increase their platelet count for longer and reduce the bleeding risk

	for up to 30 days rather than just working for a few hours only. This may bridge them for several treatments/procedures. 6. We would be able to treat patients who are Jehovah's Witnesses.
11. 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?	We do not currently have access to use TPO agonists therefore if available, whilst it might not negate the use for platelet transfusion completely, it would allow elective invasive investigations and procedures to be undertaken without the need to give platelets beforehand. Many of these could then be done as daycases on necessitate only 1 night hospital admission instead of 2.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary and tertiary care settings.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Very little if any investment required other than to develop clear pathways with primary care so that the TPOs can be prescribed to patients 10 days prior to the procedure being undertaken.
12. Do you expect the technology to provide clinically	Yes, it will reduce the need for blood transfusion and the risks that this entails for the patient.

meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	No
• Do you expect the technology to increase health-related quality of life more than current care?	Yes, as being admitted repeatedly for cannulation and transfusion is a burden to patients and a disruption to their family and working life.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Jehovah's Witness patients would benefit as they are currently deprived of being able to undergo these procedures including liver transplantation. It will also allow more dental precedures and extractions to be undertaken in the community rather than bringing these patients into hospital where the procedures are undertaking by max fax surgeons after platelet transfusion.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare	It will simplify the pathway in my opinion. The only potential stumbling block is that it will require closer working with GPs so that they can prescribe these drugs for their patients 10 days prior to their procedure being due.

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.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Not specifically no. I would however say that these patients will in all likelihood receive 7 days treatment as standard of care as to check the platelet count mid way through the 7 days in the community would be inpracticable and unfeasible.
16. 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	The reduction in inpatient bed usage is not factored into the QALY in the submission/ERG report as currently this cost is included in the procedure tariff. Furthermore, it would increase the availability of blood products across the UK and make shortages less likely.

quality-adjusted life year (QALY) calculation?	
17. 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?	Yes, as outlined above.
• Does the use of the technology address any particular unmet need of the patient population?	Yes, as outlined above.
18. How do any side effects or adverse effects of the technology affect the	There are no significant side effects that have been identified in the phase 3 clinical trials to date.

management of the condition and the patient's quality of life?	
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	
• If not, how could the results be extrapolated to the UK setting?	The published trials were undertaken in Japan and the USA in the main where more platelets tend to transfused. The trial participants may differ from the UK cirrhotic population but overall I would expect that the results can be extrapolated.
• What, in your view, are the most important outcomes, and were they measured in the trials?	Quality of life was not evaluated in these trials.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not	No

apparent in clinical trials but have come to light subsequently?	
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	There are no published systematic reviews.
21. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	No
22. How do data on real-world experience compare with the trial data?	They are fairly equitable.
Equality	
23a. Are there any potential equality issues that should be	Jehovah's Witnesses could access treatment which they are currently deprived of when they have platelets <50,000.

taken into account when considering this treatment?	
23b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
1. Is there an independent association in chronic liver disease between platelet level and bleeding during/following procedures?	Yes. Bleeding risk cannot be directly attributed to platelet number. Platelet function is also important.
2. Is there a platelet level below which bleeding occurs, and above which it does not?	No but generally a platelet threshold of <50,000 is considered to increase the platelet risk. This is not backed up by hard clinical endpoints and trial data are scarce.
3. Related to this, does NHS practice treat people with platelet	The NHS generally treats patients with platelets <50,000 and sometimes <90,000.

counts under 50,000/μL, or is the value lower?	
4. Is there an independent association between platelet levels and fatal bleeds?	Yes
5. Is there evidence (proof) that treating (prophylaxis) with platelets lowers the frequency of bleeds? Fatal bleeds?	None whatsoever.
6. Do platelet transfusions become less effective over time? What proportion of people (if any) become refractory to platelet transfusions?	Yes, patients may develop alloimmunisation.
7. The drugs for this appraisal are given prior to an invasive procedure. How many procedures would people with chronic liver	Multiple from n=5 - 20 on average. Higher in those with hepatocellular carcinoma.

disease expect to have in their lifetime? One-off or multiple	
8. If people have a delayed procedure could the resource e.g. surgeon time be used elsewhere, or another patient take the slot?	Often not.
9. Does the post platelet transfusion platelet level have to be higher for certain types of procedures e.g. open surgery to the thorax, abdomen etc compared with less invasive diagnostic procedures?	Yes, for surgical procedures and TIPSS particularly.
Key messages	

25. In up to 5 bullet points, please summarise the key messages of your statement.

- If a safe and effective oral tablet is available to replace/reduce the transfusion of a blood product, it is a no brainer to change practice.
- This would in practice result in a reduction in health resource utilisation as on average one bed day would be saved per patient for elective procedures which could be done as day cases.
- The risk of transfusion-related complications would be negated.
- Increasing thrombopoietin levels for up to 30 days means that patients may be able to undergo multiple procedures and their overall bleeding risk be reduced post procedure.
- Jehovahs Witness patients could access investigations and therapies that they are currently deprived of including liver transplantation.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Patient expert statement

Avatrombopag and lusutrombopag for treating thrombocytopenia in people with chronic liver disease needing an elective procedure

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.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	**Vanessa Hebditch**
2. Are you (please tick all that apply):	☐ a patient with the condition? ☐ a carer of a patient with the condition?

	x☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	British Liver Trust
4. Did your nominating organisation submit a submission?	☐ yes, they did ☐**x** 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 ☐ **x** 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.)	☐ yes
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: ☐ **x** I am drawing on others' experiences. Please specify how this information was gathered: Feedback from our Helpline calls and enquiries and patients on our online forum (18,000 members). Review of literature and discussions with hepatologists.
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?	Liver disease is complex, varied and fluctuates, meaning that no one person's experience of liver disease is the same as another. Patients experience of liver problems may vary from day to day. This is partly because the liver has a huge number of functions and so liver failure can affect almost every part of their body and the way they feel. Patients who have chronic liver disease and thrombocytopenia (low platelet count) tend to have end stage liver disease and many will be on the list for transplant. It's estimated that around 25% of those patients with end stage chronic liver disease will have low platelet count (<50). These people are extremely unwell, suffer from severe tiredness, feel vulnerable, anxious and often express sadness. Many have debilitating and dangerous complications including hepatic encephalopathy, ascites and variceal bleeding. They will often require invasive procedures that require platelet transfusion so that they can be performed

	safely. Patients report feelings of helplessness and sometimes liver transplant is their only hope for survival. Having to go into hospital for multiple appointments and procedures can put an incredible additional strain on individuals and their family members.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Patients with chronic liver disease who have significant thrombocytopenia often require multiple platelet infusions every time they have invasive procedures (for example endoscopy, liver biopsy, treatment for cancers etc) as they are at increased risk of bleeding. Platelet transfusions are often seen as “one more thing” to endure. They are a frequent topic of ‘concern’ on the British Liver Trust online forum (approximately 18,000 active users) with patients reporting having to wait for long times and being called in the night before a procedure (rather than for example having an endoscopy as an out-patient on a single day). It is particularly difficult for those patients who may have to travel for long distances to receive a transfusion. Some patients are concerned with the perceived risks associated with the transfusion of blood and blood products such as platelets.
10. Is there an unmet need for patients with this condition?	Blood platelet transfusions meet the same need. However, the improved quality of life and convenience issues mean that this offers an improved option for patients who are already very sick.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	The main advantage is that it can be taken orally and at home. Thus, decreasing the need for platelet infusions and hospital admissions. Patients have also mentioned altruistically that it will preserve scarce blood products for other patients in the NHS.

Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Patients have not expressed any disadvantages. We are not aware of the costs of this new treatment
Patient population	
13. 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.	We think this treatment will improve the quality of life for all people who require a transfusion. The prospect having a simple oral tablet rather than having additional time in hospital is seen as extremely beneficial. However, it will be of particular benefit to patients who are Jehovah's Witnesses, whose beliefs do not allow them to accept blood products. It will also be of particular benefit to those who are frequently required to be in hospitals for recurrent procedures and those who have a long way to travel to hospital.
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Jehovah's Witnesses – see above.

Other issues	
15. Are there any other issues that you would like the committee to consider?	No

Key messages

16. In up to 5 bullet points, please summarise the key messages of your statement:

- Patients dislike having to go into hospital for blood platelet transfusions
- Blood platelet transfusions can take up considerable time and sometimes involve an overnight stay
- An oral tablet that can be taken at home is seen as a major advantage and will improve quality of life
- It will be of particular benefit to Jehovah's Witnesses, those who have to have long distances to travel to hospital and those who have recurrent needs for procedures

Thank you for your time.

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