National Institute for Health and Care Excellence

Multiple Technology Appraisal (MTA)

ID1520 Avatrombopag and lusutrombopag for treating thrombocytopenia in people with chronic liver disease needing elective surgery

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness			
Avatrombopag	Dova Pharmaceuticals	Yes. This topic is appropriate to be referred to NICE for appraisal. There is a significant unmet medical need that is summarised in the Innovation section of the form.	Thank you for your comment. No changes to the scope are needed.
	British Society for Haematology and the Royal College of Pathologists	Yes, I am in favour of NICE undertaking this TA	Thank you for your comment. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments [sic]	Action
Lusutrombopag	Shionogi	NICE guideline NG24 recommends consideration of prophylactic platelet transfusions as the option to increase platelet count above $50x10^9$ per blood litre for patients who are having invasive procedures. Lusutrombopag's clinical evidence (three phase III studies of which two are pivotal registration studies) is specific to patients with chronic liver disease (CLD) who have severe thrombocytopenia (TCP) and are undergoing invasive elective procedures, which is a subset of the NICE guideline NG24 patient population. Severe TCP is defined as patients having a platelet count less than $50x10^9$ per blood litre. The reported 27,927 admissions with liver disease in England which is referenced by NICE in the draft scope will significantly overestimate the patient population for lusutrombopag which is specific only to patients with CLD and severe thrombocytopenia (TCP) who will undergo elective invasive procedures. Market research conducted by Shionogi indicates that approximately 11% of this cohort (27,927 admissions with liver disease in England) would be eligible for platelet transfusions. Therefore, using the estimate provided in the draft scope, Shionogi would consider 3,071 patients to be eligible for lusutrombopag or platelet transfusions and hence anticipate a small budget impact given lusutrombopag dose and administration will be oral once-daily for seven days. It is also anticipated that lusutrombopag is likely to be a specialist prescription from the approximately 40 hepatology specialist centres across England and Wales. The approval of lusutrombopag is expected to decrease the use of platelet transfusions in the CLD severe TCP patient population leading to a shift in medical practice from using blood products (platelet transfusions) to that of a TPO receptor agonist with an approved indication for this patient sub-population. This is then expected to preserve a scarce donor provided blood product (platelet transfusions) and thus the technology is expected to benefit the NHS and the NHS Blood and Transplant service (NHSBT).	Comment noted. NICE uses the topic selection process for deciding which topics NICE will produce technology appraisal guidance on. NICE aims to consider all new significant drugs and indications. The paragraph describing the prevalence of thrombocytopenia and liver disease is intended as a general overview only and does not estimate the number of patients likely to be eligible for treatment with lusutrombopag.

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		Considering these points (low budget impact and potential preservation of platelet resourcing) it is not clear to Shionogi whether a Single Technology Appraisal (STA) is the ideal method of evaluation or whether an update of NICE guideline NG24 would be more appropriate.	
	Royal College of Pathologists/British Society for Haematology	Yes	Comment noted.
Wording			
Avatrombopag	Dova Pharmaceuticals	No. The actual indication in the EU MAA is [redacted] Therefore, the remit wording should be amended to reflect the MAA indication. *"To appraise the clinical and cost effectiveness of avatrombopag within its marketing authorisation for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure"*	Thank you for your comment. The technology will be appraised within its marketing authorisation. The remit of the scope has been amended to 'To appraise the clinical and cost effectiveness of avatrombopag within its marketing authorisation for treating thrombocytopenia in people with chronic liver disease needing an elective procedure'

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	British Society for Haematology and the Royal College of Pathologists	'Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider? If not, please suggest alternative wording.' - **Yes**	Thank you for your comment. The technology will be appraised within its marketing authorisation. The remit of the scope has been amended to 'To appraise the clinical and cost effectiveness of avatrombopag within its marketing authorisation for treating thrombocytopenia in people with chronic liver disease needing an elective procedure'
Lusutrombopag	Shionogi	Shionogi expects the most predominant patient population that will be prescribed lusutrombopag to be CLD patients with severe TCP (vast majority of these patients will have cirrhosis) who are having elective invasive procedures. Shionogi conducted a number of RCTs in CLD patients with severe TCP that were designed in line with current clinical practice including that of NICE guideline NG24, (i.e. to consider prophylactic platelet transfusions to raise the platelet count above 50×10^9 per litre in patients who are having invasive elective procedures). Hence Shionogi recommends the wording of the scoping document to be amended to focus on CLD patients with severe TCP	Comment noted. The wording of the scope is kept broad and reflects the anticipated marketing authorisation. However, the description of the trial has been amended to specify 'a platelet count of <50 x 10^9 per blood litre associated with chronic liver disease

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		who are having invasive elective procedures. This is a sub-population of the broader patient population who is diagnosed with CLD.	requiring elective invasive surgery'
	Royal College of Pathologists/British Society for Haematology	The scope is accurate, but does not completely reflect the morbidity and mortality in patients with liver disease and thrombocytopenia and the lack of an acceptable treatment. I.e. there is no existing treatment, apart from supportive care with platelet transfusions. And this is often not adequate, with poor responses and many short and long term adverse effects.	Comment noted. The scope background section includes the risks associated with surgery in people with thrombocytopenia and that currently there are no treatments available.
Timing Issues			
Avatrombopag	Dova Pharmaceuticals	Avatrombopag is under review with the EMA and an EC approval and UK launch can be expected in [redacted]. Please refer to Comment 4 section in the form for commercial in confidence details on the timings.	Thank you for your comment. No changes to the scope are needed.
	British Society for Haematology and the Royal College of Pathologists	Platelet transfusion is a relative scarce resource with its own complication rate and should be avoided if possible with alternatives to transfusions	Thank you for your comment. No changes to the scope are needed.
Lusutrombopag	Shionogi	There is little evidence that use of platelet transfusions in CLD patients with severe TCP in this prophylactic setting raises platelet levels effectively. The evidence from Shionogi RCTs reinforces a comparatively small platelet rise with a very short term (<1 day) maintenance of that effect.	Comment noted.

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		In addition, for CLD patients with severe thrombocytopenia who are unable to receive platelet transfusions either for clinical reasons or personal patient preference, there is no current alternative treatment option. Hence Shionogi does view this new treatment option as having urgency to be funded for patients given the unmet medical need.	
	Royal College of Pathologists/British Society for Haematology	Urgent.	Comment noted.
Additional comments on the draft remit			
Avatrombopag	Dova Pharmaceuticals	*Dova Pharmaceuticals (Dova) wish to highlight that the potential side effects associated with platelet transfusions importantly complicate the clinical management of patients with chronic liver disease and can have significant health consequences for these patients as well as increase overall health care costs. These risks include transfusion reactions and infections that occur in up to 30% of patients receiving platelet transfusions and can be fatal, the potential development of anti-platelet antibodies that can lead to platelet refractoriness, and the competing priorities for access to the limited platelet supply that can result in delays in necessary diagnostic and therapeutic procedures.* *As people with chronic liver disease need to undergo multiple procedures to manage their overall health, progressive liver disease and potential candidacy for liver transplant, e.g., clinically necessary liver biopsies, thoracenteses, endoscopies/colonoscopies/bronchoscopies with and without biopsies, chemoablation and radiofrequency ablation, intrahepatic shunt placement, vascular catheterizations, and even dental procedures, they are likely to require repeated platelet transfusions (1-3 per year) each of which carries a*	Thank you for your comment. No changes to the scope are needed.

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		bleeding risk and increases the risks of complications. Importantly, the need for patients with thrombocytopenia and chronic liver disease to receive multiple transfusions each year puts them at increased risk for the development of platelet refractoriness, thus rendering future platelet transfusions ineffective, and importantly can also negatively impact their subsequent eligibility for liver transplantation. *In fact, published studies have demonstrated that patients who require repeated platelet transfusions, like those with chronic liver disease, have a decrease in the magnitude of the platelet increase and the duration of that increase post-platelet transfusion that progressively decrease with the increasing number of transfusions. The development of refractoriness to platelet transfusions is particularly detrimental in this patient population with liver disease and seriously complicates their effective management, because of the high prevalence of oesophageal and gastric varices (60-80%), their high risk of spontaneous gastrointestinal bleeding (25-35%) and mortality (20%), and the associated coagulopathies that are additional comorbidities of chronic liver disease.* *Finally in addition to the risks outlined above, platelet transfusions do not consistently increase platelet counts because of their rapid loss of activity after collection, short shelf life (5-days) and short effective lifespan post-transfusion (hours), which further complicate clinical management logistics by requiring the coordination of administration on the same day as the planned procedure, and the need to re-administer platelets if prophylaxis for delayed post-procedure bleeding is desired.* *References can be provided by Dova upon request.*	

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information			
Avatrombopag	Dova Pharmaceuticals	Dova recommends the wording in the Draft Scope Background can be enhanced, with the revised wording as follows: *Thrombocytopenia is a reduction in the number of circulating platelets within the blood. Platelets are produced by megakaryocytes in the bone marrow. They play a critical role in haemostasis, a normal process which causes bleeding to stop. Thrombocytopenia is classified on the basis of the platelet count in the blood. It is defined as a platelet count of less than 150 x 10^9 per litre of blood and can be mild, moderate or severe depending on the magnitude of the platelet count decrease.* *Thrombocytopenia is a common complication in people with chronic liver disease either as a direct result of the liver pathology or a consequence of interferon-based antiviral therapy. Mild to moderate thrombocytopenia may cause bleeding during invasive procedures including liver biopsy or variceal banding, and severe thrombocytopenia increases the risk of excessive bleeding during and after procedures and can have a significant impact on the clinical management of chronic liver disease.* *It can delay or prevent the start of appropriate diagnostic or therapeutic procedures leading to increased morbidity and mortality and a reduced quality of care. Patients with chronic liver disease undergo on average 1 to 3 schedules procedures every year, each of which carries a bleeding risk.*	Thank you for your comments. The background section is intended to provide a brief overview of the disease and its associated management. No changes to the scope are needed.

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		The prevalence of thrombocytopenia in people with chronic liver disease varies from 15% to 70% depending on the stage of liver disease and worsens as the disease progresses. Between 2016 and 2017, Hospital Episode Statistics showed 27,927 admissions[1] with liver disease in England *There are currently no licensed treatment options in the UK for treating thrombocytopenia in people with chronic liver disease undergoing scheduled procedures, and platelet transfusions remain as the current standard of care. The clinical decision making regarding the use of platelet transfusions to manage individual patients includes considerations of the degree of thrombocytopenia, the risk of the planned procedure, and the side effect profile of platelet transfusions. Because of the current lack of other treatment alternatives and the risks associated with platelet transfusions, healthcare providers are in some cases assessing a negative benefit-risk for the use of transfusions and are either not performing necessary procedures or are taking some risk in proceeding with the procedure in the presence of thrombocytopenia.* *The availability of a new treatment option for increasing platelet counts in patients with thrombocytopenia and chronic liver disease would improve the clinical management of these patients and by safely increasing platelet counts and minimizing bleeding risks. Since avatrombopag is an oral thrombopoietin receptor agonist (TPO) that stimulates the body's own megakaryocytes to produce platelets, it eliminates the risk of transfusion reactions or infections, and prevents the development of antiplatelet antibodies and platelet refractoriness.* *The safety and efficacy data support a favourable benefit-risk profile for avatrombopag as an alternative treatment option to platelet transfusions for patients with thrombocytopenia and chronic liver disease scheduled for a*	

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		procedure. In addition, it has the potential to change clinical decision making by allowing physicians to consider safely increasing platelet counts in those patients for whom they are currently not using platelet transfusions that puts patients at risk of experiencing a bleeding complication. The results of two randomized, placebo-controlled Phase 3 studies demonstrate that avatrombopag reproducibly improves clinical management, reduces safety risks and addresses an important unmet medical need for this patient population.	
	British Society for Haematology and the Royal College of Pathologists	Adequate for a draft proposal	Thank you for your comment. No changes to the scope are needed.
Lusutrombopag	Shionogi	NICE guideline NG24 recommends consideration of prophylactic platelet transfusions as the option to increase platelet count above $50x10^9$ per blood litre for patients who are having invasive procedures. Lusutrombopag's clinical evidence (three phase III studies of which two are pivotal registration studies) is specific to patients with chronic liver disease (CLD) who have severe thrombocytopenia (TCP) and are undergoing invasive elective procedures, which is a subset of the NICE guideline NG24 patient population. For CLD patients who require prophylactic platelet transfusions for procedures due to their TCP, currently there is no licensed alternative to platelet transfusions. There is very little to no off-label use of other TPO agonists for this patient population. With regard to eltrombopag, the ELEVATE study (phase III RCT) investigated the use of eltrombopag in CLD patients with severe TCP undergoing invasive elective procedures and was terminated early due to an increase of portal-	Comment noted.

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		vein thrombosis (PVT) vs. placebo. The ELEVATE Study Group concluded a non-recommendation for use of eltrombopag in this patient population. With regard to romiplostim, for patients with TCP undergoing elective procedures there is some evidence of efficacy related to the use of romiplostim (namely, one RCT of 65 CLD patients with TCP, one open-label study of 35 CLD patients with TCP and a retrospective review of 47 TCP patients). If lusutrombopag gains approval for the proposed indication, it will be the first TPO receptor agonist to be licensed in this setting.	
	Royal College of Pathologists/British Society for Haematology	Could better reflect the severity of bleeding in patients, increased morbidity, mortality and increased hospital admissions and the lack of any other intervention apart from platelet transfusions. Hence, there is often a delay in surgical procedures and sometimes surgery will be avoided altogether, resulting in increased morbidity and mortality.	Comment noted. This section of the scope aims to provide a brief overview of the background for the appraisal; additional details may be considered by the committee, if appropriate, at the time of the appraisal.
The technology/ intervention			
Avatrombopag	Dova Pharmaceuticals	No. The wording needs correcting to the following to better describe the technology:	Comment noted. This section of the scope aims to provide a brief overview of the technology; additional details may be

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		Avatrombopag (brand name unknown, Dova Pharmaceuticals) is a small molecule thrombopoietin receptor agonist which targets the c-Mpl thrombopoietin cell surface receptor on megakaryocytes to stimulate platelet production. Avatrombopag is administered orally. *An MAA for avatrombopag is currently under review by EMA and does not currently have a marketing authorisation in the UK. Avatrombopag has been studied in clinical trials compared with placebo in people with thrombocytopenia associated with chronic liver disease undergoing a procedure and in other indications, including two global, randomized Phase 3 trials.*	considered by the committee, if appropriate, at the time of the appraisal. A minor change has been performed in line with the request.
	British Society for Haematology and the Royal College of Pathologists	'Is the description of the technology or technologies accurate?' - **Yes**	Thank you for your comment. No changes to the scope are needed.
Lusutrombopag	Shionogi	The main description of the technology is accurate with lusutrombopag being an oral once-a-day, 7-day treatment to temporarily raise platelet count (on average 21 days) for patients who are having an invasive elective procedure.	Comment noted.
	Royal College of Pathologists/British Society for Haematology	Yes	Comment noted.
Population			
Avatrombopag	Dova Pharmaceuticals	No.	Thank you for your comment. The

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		The corrected wording for the population section should reflect the indication in the MAA. *"People (adults) with thrombocytopenia associated with chronic liver disease who are scheduled to undergo a procedure."*	population section of the scope has been amended to 'People with thrombocytopenia associated with chronic liver disease needing an elective procedure'.
	British Society for Haematology and the Royal College of Pathologists	Yes, chronic liver disease with a low platelet count <50	Thank you for your comment. The population section of the scope has been amended to 'People with thrombocytopenia associated with chronic liver disease needing an elective procedure'.
	British Association for the Study of the Liver (BASL)	Could be used prior to any surgery. Two options would be 1. High risk liver operations eg liver resection for HCC or transplant. 2. General surgery procedures in those with chronic liver disease. Optimal group would depend on treatment effect size and aim for market. Presume emergency operations not included due to delay between administration and surgery.	Thank you for your comment. The population section of the scope has been amended to 'People with thrombocytopenia associated with chronic liver disease needing an elective procedure'.

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Lusutrombopag	Shionogi	The studied patient population was specific to CLD patients with severe TCP (platelet count below 50,000x10^6 per blood litre) undergoing elective invasive procedures.	The description of the trial has been amended to specify 'a platelet count of <50 x 10^9 per blood litre associated with chronic liver disease requiring elective invasive surgery'.
	Royal College of Pathologists/British Society for Haematology	Yes	Comment noted.
Comparators			
Avatrombopag	Dova Pharmaceuticals	Yes. The standard of care in the NHS is platelet transfusions.	Thank you for your comment. No changes to the scope are needed.
	British Society for Haematology and the Royal College of Pathologists	Platelet transfusion to cover surgical intervention is the standard treatment at present	Thank you for your comment. No changes to the scope are needed.
	British Association for	'Is platelet transfusion the only relevant comparators for avatrombopag as included in the scope?' – **No, also Lusutrombopag**	Thank you for your comment.

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	the Study of the Liver (BASL)	'Are all relevant comparator included?' - **No. Tranexamic also used if issue of functionality**. https://www.ncbi.nlm.nih.gov/pubmed/20962655	avatrombopag and lusutrombopag have been referred to a Multiple Technology Appraisal. The Appraisal Committee will consider avatrombopag and lusutrombopag together in the same technology appraisal. The comparator part in the scope should remain broad and inclusive. No changes to the scope are needed.
Lusutrombopag	Shionogi	As per NICE guideline NG24, patients with a platelet count below 50,000x106 should be considered for platelet transfusion. Platelet transfusions are the current mainstay of treatment to raise platelet counts for patients with severe TCP undergoing elective invasive procedures; there are no approved pharmaceuticals for this patient population to raise platelet counts in advance of elective invasive procedures. Splenic embolisation and splenectomy are not recognised medical practice to address low platelet counts prior to an elective invasive procedure.	Comment noted.

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	British Association for the Study of the Liver (BASL)	There are no routinely used comparators. Absence of comments on clotting profiles and control in background which needs to be considered in patients with chronic liver disease. Need comments that number as well as function of platelets needs to be considered.	Comment noted. This section includes established clinical management.
	Royal College of Pathologists/British Society for Haematology	Yes	Comment noted.
Outcomes			
Avatrombopag	Dova Pharmaceuticals	In principle yes. However, some outcomes such as number of blood transfusions, use of concurrent treatments, bleeding score, mortality, health related quality of life are either not relevant to consider as outcomes and/or data will be unavailable, therefore these outcomes should be considered for exclusion.	Thank you for your comment. The list of outcomes in the scope is not intended to be exhaustive, the appraisal committee can consider other outcomes if appropriate. NICE would encourage the company to review its Guide to the methods of technology appraisal, especially section 5 which covers the reference case, also

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			the Process guide, especially relevant sections for health related quality of life.
	British Society for Haematology and the Royal College of Pathologists	Yes outcome measures are stringent, specific and appropriate	Thank you for your comment. No changes to the scope are needed.
Lusutrombopag	Shionogi	All reasonable outcome measures have been included in the draft scope, however, it is important to note that there is no validated patient reported outcomes (PRO) instrument to measure health-related quality of life specific to this patient population (patients with CLD and severe TCP undergoing elective invasive procedures). With regards to platelet count it is also important to consider magnitude of change and sustainability of platelet counts post procedure.	Comment noted. The list of outcomes in the scope is not intended to be exhaustive, the appraisal committee can consider other outcomes if appropriate.
	British Association for the Study of the Liver (BASL)	No Should grade surgical complications eg Clavien Dindo classification. Patient centred end points would include hospital stay, ITU stay, AKI and duration of dialysis/ ventilation.	Comment noted. The list of outcomes in the scope is not intended to be exhaustive, the appraisal committee can consider other outcomes if appropriate.
	Royal College of Pathologists/Brit	No. I would include: Reduction in cancelation of surgery (i.e. intervention should result in fewer cancelations) May also result in shorter hospital admissions	Comment noted. The list of outcomes in the scope is not intended to

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	ish Society for Haematology	May result in a quicker surgical intervention (quicker platelet increment).	be exhaustive, the appraisal committee can consider other outcomes if appropriate.
Economic Analysis			
Avatrombopag	Dova Pharmaceuticals	Current standard of care is platelet transfusion immediately prior to the procedure. Avatombopag will be taken orally for 5 consecutive days beginning 10 to 13 days prior to the planned procedure. The patient should undergo their procedure 5 to 8 days after the last dose of avatrombopag.	Thank you for your comment. No changes to the scope are needed.
	British Society for Haematology and the Royal College of Pathologists	As soon as possible but the guidance will affect a large number of people	Thank you for your comment. No changes to the scope are needed.
Lusutrombopag	Shionogi	The economic analysis will focus on CLD patients with severe TCP who are having an elective invasive procedure. There is a significant lack of data in the literature characterising the efficacy and safety of platelet transfusions in CLD patients with severe TCP; there is also no precedent with regard to a modelling approach within this subpopulation. There is no other pharmaceutical approved licensed indication of increasing platelet counts in CLD patients with severe TCP prior to invasive procedures. Shionogi is still evaluating the appropriate time horizon for purposes of modelling.	Comment noted.
	British Association for	Likely will be used in those undergoing major surgery with background sever chronic liver disease.	Comment noted.

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	the Study of the Liver (BASL)	May bias use to larger hospitals and HPB/Tx units.	
	Royal College of Pathologists/British Society for Haematology	Difficult to assess this. It should include reduced morbidity and mortality from surgical intervention and may result in a quicker diagnosis or correction of defect (what has indicated the surgery) which will impact on HRQOL	Comment noted.
Equality and Diversity			
Avatrombopag	Dova Pharmaceuticals	Dova does not see any issues of equality under the proposed remit and scope.	Thank you for your comment. No changes to the scope are needed.
	British Society for Haematology and the Royal College of Pathologists	This TA does not affect any of these issues and does not need to change any wording on the account of equality	Thank you for your comment. No changes to the scope are needed.
Lusutrombopag	Shionogi	There is a group of patients that for religious reasons will not receive blood products (platelet transfusions); hence availability of lusutrombopag will be an important treatment option for these patients with CLD and severe TCP having elective invasive procedures.	Comment noted.
	British Association for	None	Comment noted.

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	the Study of the Liver (BASL)		
Other considerations			
Avatrombopag	Dova Pharmaceuticals	None	Thank you for your comment. No changes to the scope are needed.
	British Society for Haematology and the Royal College of Pathologists	None	Thank you for your comment. No changes to the scope are needed.
Lusutrombopag	Shionogi	No other considerations.	Comment noted.
Innovation			
Avatrombopag	Dova Pharmaceuticals	Yes. This topic is appropriate to be referred to NICE for appraisal. *There is a significant unmet medical need that Dova summarises below, and the use of an agent that directly stimulates the patient's own megakaryocytes*	Thank you for your comment. The innovative nature of the technology will be considered by the appraisal committee based on evidence

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		to produce platelets would be an innovative new treatment option that eliminates the risk of transfusion reactions or infections and prevents the development of antiplatelet antibodies and platelet refractoriness. *Thrombocytopenia is a common, serious comorbidity in patients with chronic liver disease that is estimated to affect up to 70% of patients who develop liver fibrosis or cirrhosis.* *Thrombocytopenia is a chronic condition that presents a significant challenge in the day-to-day clinical management of patients with chronic liver disease, with the extent of thrombocytopenia worsening over time with the severity of the liver disease. Severe thrombocytopenia is associated with a poor clinical outcome, because it increases the risk of bleeding from invasive procedures, complicates therapy, and increases the risk of mortality in these patients.* *Patients with chronic liver disease require multiple diagnostic and therapeutic procedures, routinely 1 to 3 invasive procedures annually, including clinically necessary liver biopsies, thoracenteses, endoscopies, colonoscopies, or bronchoscopies with and without biopsies, chemoablation and radiofrequency ablation, intrahepatic shunt placement, vascular catheterizations, and dental procedures. Many of these procedures are required to support patients with chronic liver disease, and their candidacy for lifesaving liver transplantation. Each of these procedures carries a risk of bleeding, ranging from high to low, which is dependent on the invasive nature of the procedure, and is further complicated by coexisting coagulopathies that are common comorbidities of chronic liver disease.* *If not effectively treated, thrombocytopenia can lead to serious uncontrolled bleeding in these patients during and/or following these procedures, negatively impacting their clinical care and resulting in prolonged*	presented to it, when the topic is referred for appraisal.

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		hospitalizations, serious post procedure complications, and poor clinical outcomes. *With no approved pharmaceutical options, the standard of care for treatment of thrombocytopenia in patients with chronic liver disease is platelet transfusions. Treatment decisions for managing thrombocytopenia are guided by platelet count measurements and clinical guidelines, as well as by healthcare providers' clinical judgment regarding the risk of bleeding for each category of procedure. Because of the risk of severe bleeding in patients with platelet counts under 50 x 10^9/L, invasive procedures necessary for routine care may be avoided or delayed in the patients with platelet counts below this threshold. Patients with thrombocytopenia associated with chronic liver disease are commonly administered platelet transfusions immediately prior to diagnostic or therapeutic procedures in order to proactively mitigate the risk of bleeding. The extent of the bleeding risk relates to the degree of thrombocytopenia, the extent of other coexisting coagulopathy(ies), and the type of scheduled procedure. As noted above, clinical decision making regarding the use of platelet transfusions to manage individual patients includes considerations of the degree of thrombocytopenia, the risk of the planned procedure, and the side effect profile of platelet transfusions.* *Because of the current lack of treatment alternatives and the risks associated with platelet transfusions, healthcare providers are in some cases assessing a negative benefit-risk for the use of transfusions and are either not performing necessary procedures or are taking some risk in proceeding with the procedure in the presence of thrombocytopenia.*	

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		In conclusion, the presence of thrombocytopenia (a platelet count <50 x 10^9/L) in patients with chronic liver disease is associated with significant morbidity and may lead to increased mortality in this population. There is, therefore, an unmet medical need for a safe and effective alternative treatment option to the standard of care, platelet transfusion, for patients with chronic liver disease and thrombocytopenia, undergoing scheduled procedures as part of their routine clinical care, to reduce the need for platelet transfusions and their potential associated side effects and risks.	
	British Society for Haematology and the Royal College of Pathologists	'Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?' - **Yes**	Thank you for your comment. No changes to the scope are needed.
	British Association for the Study of the Liver (BASL)	Potentially. Yes. Would be better to widen the QoL measurement with EQ5D	Thank you for your comment. EQ-5D is the preferred measure of health-related quality of life in adults in NICE technology appraisals. Please see details in our methods guide.
Lusutrombopag	Shionogi	Lusutrombopag will be the first oral thrombopoietin receptor agonist approved for use in CLD patients with TCP who are having invasive procedures. Lusutrombopag will be a once-daily 7-day treatment option.	Comment noted.

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		Lusutrombopag provides the opportunity to be treated at home rather than at hospital (for those patients who otherwise would need a platelet transfusion); it also reduces potential unwanted effects due to platelet transfusions. In addition, it can lead to a reduction in length of stay in hospital and therefore improve patient and carers' health-related quality of life. Lusutrombopag may also reduce inequalities for certain social and religious groups by allowing access to an alternative to platelet transfusions.	
	British Association for the Study of the Liver (BASL)	Need patient centred improved end points to its use. Use in liver transplant could result in major saving in use of blood products and reduce transfusion associated reactions which may not be reflected in QALYs. NHSBT holds data on all UK blood product use during liver transplant.	Comment noted.
	Royal College of Pathologists/British Society for Haematology	Yes. This is the first intervention available to liver disease patients, apart from platelet transfusions, which is not very effective. It is likely to have other impacts which might not be collected in the analysis.	Comment noted.
Questions for consultation			
Avatrombopag	Dova Pharmaceuticals	In the documentation provided by NICE the technology assessment mentioned is both an STA and an MTA. Dova recommends that Avatrombopag is assessed by NICE under an STA and not under an MTA given the likely EC approval and UK launch timing for Avatrombopag.	Thank you for your comment. In this section, NICE would welcome comments on the questions proposed in the scope under the

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			'Questions for consultation' section. This topic has been referred as a Multiple Technology Appraisal.
	British Society for Haematology and the Royal College of Pathologists	Which Liver conditions will be covered specifically by this TA?	Thank you for your question. In this section, NICE would welcome comments on the questions proposed in the scope under the 'Questions for consultation' section.
	British Association for the Study of the Liver (BASL)	No. Assessment of complications inadequate. Need validated system for surgical complications. Would suggest using Clavien Dindo. 'Are there any subgroups of people in whom avatrombopag is expected to be more clinically effective and cost effective or other groups that should be examined separately?' - **See above. Platelet deficiency and dysfunction common with chronic liver disease. Could be used for minor or major surgery, GI bleeds, nose bleeds, dental extractions**'. 'Where do you consider avatrombopag will fit into the existing Liver conditions or Blood conditions NICE pathway?' - **Probably only for those with severe thrombocytopaenia requiring major surgery but that is what trial needs**	Thank you for your comments. No changes to the scope are needed. Thank you for your question. In this section,

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		to identify. With minimally reduced platelets and minor ops probably will not be cost effective. 'To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.' - **Major problem with thrombocytopaenia in chronic liver disease is acute bleeding episodes. Drug may not work quickly enough to help this group**. 'NICE intends to appraise this technology through its Multiple Technology Appraisal (MTA) Process with ID1149 Lusutrombopag for treating thrombocytopenia in people with chronic liver disease needing elective surgery. We welcome comments on the appropriateness of appraising this topic through this process'. Do you mean a head to head study with Lusutrombobag?	NICE would welcome comments on the questions proposed in the scope under the 'Questions for consultation' section.
Lusutrombopag	Shionogi	**Have all relevant comparators for lusutrombopag been included in the scope?** As per NICE guideline NG24, patients with a platelet count below 50,000x106 should be considered for platelet transfusion prior to having an invasive procedure. Platelet transfusions are the current mainstay of treatment; there are currently no approved pharmaceuticals for this patient population to raise platelet counts in advance of elective invasive procedures; splenic	Comment noted.

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		embolisation and splenectomy are not recognised medical practice to address low platelet counts prior to an invasive procedure. **Are the outcomes listed appropriate?** All reasonable outcome measures have been included in the draft scope, however, it is important to note that there is no validated patient reported outcomes (PRO) instrument to measure health-related quality of life specific to this patient population (patients with CLD and severe TCP undergoing elective invasive procedures). With regard to platelet count, it is also important to consider magnitude of change and sustainability of platelet counts post procedure. **Are there any subgroups of people in whom lusutrombopag is expected to be more clinically effective and cost effective or other groups that should be examined separately?** Shionogi will explore the clinical trial evidence in line with current clinical practice to determine whether there are any clinically relevant subpopulations and cost-effective subgroups of patients that could benefit most from lusutrombopag use. **Where do you consider lusutrombopag will fit into the existing Liver conditions or Blood conditions NICE pathway?** Based on the review of the NICE guideline NG24, the liver conditions pathway is most relevant and should be updated to include use of TPO receptor agonists that are EMA approved with an indication specific for use in CLD patients with TCP undergoing invasive procedures. There is a group of patients that for religious reasons will not utilise blood products (platelet transfusions); hence availability of lusutrombopag will be an	Comment noted. Comment noted. Comment noted.

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		important treatment option for these patients specific to CLD and severe TCP having elective invasive procedures. **Do you consider lusutrombopag to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** Lusutrombopag will be the first oral approved thrombopoeitin receptor agonist for CLD patients with TCP who are having invasive procedures. Lusutrombopag provides the opportunity to be treated at home rather than at hospital (for those patients who otherwise would require a platelet transfusion); it also reduces potential unwanted effects of platelet transfusions. In addition, use of lusutrombopag could lead to a reduction in hospital length of stay and therefore improve patient and carers' health-related quality of life. Lusutrombopag may also reduce inequalities for certain social and religious groups by providing an alternative treatment option to platelet transfusions. **Do you consider that the use of lusutrombopag can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** Focusing on the QALY specifically may lose sight that platelet concentrate is a donor-provided scarce resource, and physicians therefore should seek alternative pharmacotherapy options that are platelet transfusion sparing.	Comment noted. Comment noted. If the topic is referred to Technology Appraisals, the committee will consider any benefits

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		Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. A comprehensive clinical development program, which includes multiple randomised controlled trials as part of the phase II and phase III studies, that demonstrate the clinical benefit of lusutrombopag in CLD patients with severe TCP undergoing elective invasive procedures. It should be noted that the clinical trials that demonstrate the treatment effect of platelet transfusions in this patient setting are those TPO receptor agonists that have conducted studies in this patient population. The data published that documents the efficacy and safety of the current available TPO receptor agonists, eltrombopag and romiplostim, in this patient population (CLD patients with TCP undergoing invasive procedures) includes for eltrombopag the ELEVATE phase III RCT, and for romiplostim, one RCT of 65 CLD patients with TCP, one open-label study of 35 CLD patients with TCP and a retrospective review of 47 TCP patients. Neither eltrombopag nor romiplostim have an approved indication in this patient sub-population. **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** The company concurs with NICE that a key NHS priority is the implementation of platelet thresholds, transfusion dosing and platelet targets for patients who are having invasive procedures. It is anticipated that lusutrombopag will facilitate a more reliable attainment of platelet thresholds	not captured by the QALY. Comment noted.

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		prior to an elective invasive procedure, and as such, is likely to be adopted in this small patient population when the timing of the elective procedure fits with the pharmacological activity of lusutrombopag.	Comment noted.
Lusutrombopag	British Association for the Study of the Liver (BASL)	**Have all relevant comparators for lusutrombopag been included in the scope? Which treatments are considered to be established clinical practice in the NHS for thrombocytopenia associated with chronic liver disease requiring surgery?** There are no routinely used comparators. Absence of comments on clotting profiles and control in background which needs to be considered in patients with chronic liver disease. Need comments that number as well as function of platelets needs to be considered. **Are the outcomes listed appropriate?** No Should grade surgical complications eg Clavien Dindo classification. Patient centred end points would include hospital stay, ITU stay, AKI and duration of dialysis/ ventilation. **Are there any subgroups of people in whom lusutrombopag is expected to be more clinically effective and cost effective or other groups that should be examined separately? Where do you consider lusutrombopag will fit into the existing Liver conditions or Blood conditions NICE pathway?**	Comment noted. The comparator section includes established clinical management. Comment noted. The list of outcomes in the scope is not intended to be exhaustive, the appraisal committee can consider other outcomes if appropriate. Comment noted.

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		Likely will be used in those undergoing major surgery with background sever chronic liver disease. May bias use to larger hospitals and HPB/Tx units. **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 the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:** **· could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which lusutrombopag 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;** **· could 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.** **Do you consider lusutrombopag to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?**	Comments noted. Comment noted. If the topic is referred to Technology Appraisals, the committee will consider any benefits not captured by the QALY.

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		The agent is novel and if successful may provide a step change Need patient centred improved end points to its use. **Do you consider that the use of lusutrombopag can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** Use in liver transplant could result in major saving in use of blood products and reduce transfusion associated reactions which may not be reflected in QALYs **Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** NHSBT holds data on all UK blood product use during liver transplant. **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** It is an oral medication. Most patients that develop bleeding problems during surgery are not able to take oral medication. If an oral medication is to be used an algorithm would need to be produced to predict patients in advance of elective surgery.	Comment noted.
Additional comments on the draft scope			
Avatrombopag	Dova Pharmaceuticals	None	Thank you for your comment. No changes to the scope are needed.

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Lusutrombopag	British Association for the Study of the Liver (BASL)	It is an oral medication. Most patients that develop bleeding problems during surgery are not able to take oral medication. If an oral medication is to be used an algorithm would need to be produced to predict patients in advance of elective surgery.	Comment noted.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Royal College of Physicians (endorse the response submitted by Royal College of Pathologists and British Society for Haematology)
Department of Health and Social Care