Systematic Review with Meta-Analysis: Efficacy and Safety of Lusutrombopag for Severe Thrombocytopenia in Patients with Chronic Liver Disease Undergoing Invasive Procedures

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ABSTRACT

Introduction: Lusutrombopag is an oral thrombopoietin receptor agonist (TPO-RA). Clinical trials have shown lusutrombopag's efficacy in reducing need for preoperative platelet transfusion in patients with chronic liver disease (CLD) and severe thrombocytopenia. This analysis assessed efficacy and safety of lusutrombopag in patients with severe thrombocytopenia and CLD undergoing planned invasive procedures.

Methods: An electronic database search (through 1 December 2020) identified three randomised, placebo-controlled, double-blind clinical trials comparing lusutrombopag with placebo in patients with CLD and platelet count below 50×10^9/L scheduled to undergo a procedure with a perioperative bleeding risk. A random-effects meta-analysis examined treatment effect, with Cochrane Collaboration's tool assessing risk of bias.

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Results: The meta-analysis included 343 (lusutrombopag 3 mg, $n = 173$; placebo, $n = 170$) patients. More patients met the criteria for treatment response (platelet count at least 50×10^9/L and increase of at least 20×10^9/L from baseline anytime during the study) with lusutrombopag versus placebo (risk ratio [RR] 6.39; 95% confidence interval [CI] 3.69, 11.07; $p < 0.0001$). The primary efficacy outcome, proportion of patients requiring no platelet transfusion and no rescue therapy for bleeding for at least 7 days post procedure, was achieved by more patients treated with lusutrombopag versus placebo (RR 3.42; 95% CI 1.86, 6.26; $p = 0.0001$). The risk of any bleeding event was significantly lower with lusutrombopag compared to placebo (RR 0.55; 95% CI 0.32, 0.95; $p = 0.03$); conversely, thrombosis event rates were similar between lusutrombopag and placebo (RR 0.79; 95% CI 0.19, 3.24; $p = 0.74$).

Conclusion: This meta-analysis showed that treatment of severe thrombocytopenia with lusutrombopag in patients with CLD prior to a planned invasive procedure was efficacious and safe in increasing platelet counts, avoiding the need for platelet transfusions, and reducing risk of bleeding, thereby enhancing the certainty of evidence supporting the efficacy and safety of lusutrombopag.

Keywords: Chronic liver disease; Invasive procedure; Lusutrombopag; Meta-analysis; Severe thrombocytopenia; Thrombopoietin receptor agonist

Key Summary Points

Why carry out this study?

Although treatment guidelines recommend prophylactic use of platelet transfusions to raise platelet counts prior to invasive procedures, they carry significant well-known risks and limitations that could be avoided if pre-procedural treatment with an oral thrombopoietin receptor antagonist (TPO-RA) such as lusutrombopag is considered.

This random-effects meta-analysis reviews the previously published findings from randomised clinical trials of lusutrombopag in this patient population, with an aim to increase the certainty of evidence that pre-procedural lusutrombopag treatment durably increases platelet counts and reduces the risk of bleeding events, thus avoiding platelet transfusion, while offering a safety profile similar to that of placebo.

What was learned from the study?

The primary efficacy outcome, proportion of patients requiring no platelet transfusion and no rescue therapy for bleeding for at least 7 days post procedure, was achieved by more patients treated with lusutrombopag versus placebo (risk ratio [RR] 3.42; 95% CI 1.86, 6.26; $p = 0.0001$).

Furthermore, the risk of any bleeding event was significantly lower with lusutrombopag compared to placebo (RR 0.55; 95% CI 0.32, 0.95; $p = 0.03$), and thrombosis event rates were similar between lusutrombopag and placebo (RR 0.79; 95% CI 0.19, 3.24; $p = 0.74$).

This meta-analysis showed that treatment of severe thrombocytopenia with lusutrombopag in patients with chronic liver disease (CLD) prior to a planned invasive procedure was efficacious and safe in increasing platelet counts, avoiding the need for platelet transfusions, and reducing risk of bleeding, thereby enhancing the certainty of evidence supporting the efficacy and safety of lusutrombopag.

INTRODUCTION

Thrombocytopenia is a common complication in patients with severe chronic liver disease (CLD), irrespective of the aetiology [1, 2]. Thrombocytopenia is generally defined as a

platelet count below the lower limit of normal ($< 150 \times 10^9$/L), and can be further classified as mild ($\geq 100 \times 10^9$/L to $< 150 \times 10^9$/L), moderate (50×10^9/L to $< 100 \times 10^9$/L), or severe ($< 50 \times 10^9$/L) [1, 3]. Six percent of patients with chronic hepatitis and as many as 84% of patients with cirrhosis report thrombocytopenia, though the prevalence of moderate or severe instances has been estimated to range from 1% to 13% [1, 4–6]. Thrombocytopenia has also been used as an indicator of portal hypertension in patients with chronic liver disease [1, 7].

Management of patients with CLD often requires invasive diagnostic and therapeutic procedures, such as percutaneous paracentesis, transcatheter arterial chemoembolization (TACE), liver biopsies, and endoscopic polypectomy. A low platelet count is considered a major risk factor for bleeding during and after such procedures [2, 8–10]. In a study of patients with cirrhosis and thrombocytopenia, 31% of patients with CLD and a preoperative platelet count below 75×10^9/L had a procedure-related bleeding complication [8].

Nationally and internationally recognised treatment guidelines recommend prophylactic use of platelet transfusions to raise platelet count levels above 50×10^9/L in patients undergoing invasive procedures [11–16]. Although transfusions continue to be an acknowledged option for raising platelet counts prior to invasive procedures, the challenge of balancing their benefits and risks has been noted in the published literature. As a result of the lack of robust evidence on how platelet transfusions reduce the risk of bleeding [12, 13, 17, 18], treatment guidelines for patients with CLD recommend an evidence-based approach to administering transfusions pre-emptively or as rescue therapy [19, 20]. The potential limitations of platelet transfusions are well known. For example, platelet transfusions are associated with potentially serious adverse events such as allergic reactions, febrile non-haemolytic reactions, haemolysis, transfusion-related lung injury (TRALI), transfusion-associated circulatory overload (TACO), and transmission of infections (e.g. cytomegalovirus, bacterial infections) [11, 21–23]. Furthermore, 30–70% of multi-transfused patients may

become refractory and may require human leucocyte antigen (HLA)-selected platelets, increasing the cost of treatment [2, 24].

Despite these limitations, platelet transfusions have historically been the only pre-procedural treatment option for severe thrombocytopenia in patients with CLD undergoing invasive procedures. However, thrombopoietin receptor agonists (TPO-RAs) have recently emerged as alternatives to platelet transfusions for this indication, and have been recognised in updated guidelines, including the American Gastroenterological Association 2019 Clinical Practice Update and the 2020 American Association for the Study of Liver Diseases Practice Guidance [19, 25]. TPO is a hemopoietic growth factor synthesised mainly by the liver [2, 4]. It binds to and activates the TPO receptor on megakaryocytes, megakaryocyte precursors, platelets, and stem cells to induce intracellular signalling pathways that prime platelet production [26]. Lusutrombopag is an oral, second-generation small molecule TPO-RA that binds the transmembrane domain of the human TPO receptor to activate the signal transduction pathway stimulated by endogenous TPO, thereby leading to increased platelet production [27, 28]. Lusutrombopag has been approved in Japan and the USA (2015 and 2018, respectively) for treatment of thrombocytopenia, and in the European Union (2019), including the UK, for treatment of severe thrombocytopenia, associated with CLD in patients undergoing planned invasive procedures, with a recommended dosage of 3 mg daily for 7 days [27, 29, 30]. Three randomised clinical trials (RCTs) have assessed lusutrombopag in patients with CLD and severe thrombocytopenia (platelet count $< 50 \times 10^9$/L) who were scheduled to undergo planned invasive procedures. In all three studies, treatment with lusutrombopag significantly reduced the need for preoperative platelet transfusion in a higher proportion of patients compared to placebo [31–33].

This analysis reviews the previously published findings from the lusutrombopag RCTs in patients with CLD and severe thrombocytopenia scheduled to undergo a planned invasive procedure. A random-effects meta-analysis

model was conducted with the objective of providing a precise estimate of the relative treatment effect of lusutrombopag versus placebo. This study investigates the efficacy and safety of lusutrombopag to treat thrombocytopenia in patients with CLD prior to invasive procedures by assessing the proportion of patients treated with lusutrombopag versus placebo requiring no platelet transfusion prior to the invasive procedure and no rescue therapy for bleeding from randomisation through 7 days after the invasive procedure; proportion achieving a platelet count of at least 50×10^9/L and an increase of at least 20×10^9/L from baseline; proportion achieving a platelet count of at least 50×10^9/L on the day of procedure; proportion experiencing an increase in platelet count of at least 20×10^9/L from baseline; proportion requiring no platelet transfusion during the study period; and proportion of patients requiring no platelet transfusion prior to the procedure.

METHODS

A systematic literature review and meta-analysis was originally prepared as a submission to the National Institute for Health and Care Excellence (NICE) as a single technology appraisal and conducted in accordance with the Cochrane Collaboration and the NICE Decision Support Unit recommendations.

Search Strategy and Study Selection

MEDLINE, EMBASE, PubMed (e-publications/ahead-of-print/in process), CENTRAL (Cochrane Central Register of Controlled Trials), Cochrane Database of Systematic Reviews (CDSR), and UK National Institute for Health Research Health Technology Assessment (NIHR-HTA) were searched using a structured literature search from database inception to 1 December 2020 [34]. Conference proceedings (American Society of Haematology, European Haematology Association, European Association for the Study of the Liver, International Liver Congress, American Association for the Study of Liver Diseases; 2016–2018) were searched, and a hand search of

the clinicaltrials.gov clinical trial registry was also performed. Details regarding the search strategy are provided in Tables S4 and S5 of the supplementary material.

Scope of the Meta-Analysis

The data for the meta-analysis were from prospective, parallel-design, randomised, placebo-controlled, double-blind clinical trials that enrolled adults (18 years of age or older) with CLD and severe thrombocytopenia (platelet count < 50×10^9/L) at study baseline [31–33]. All patients were scheduled to undergo a planned invasive procedure. Patients included in the three studies were classified according to the status of their cirrhosis, namely Child–Pugh A or B (Child–Pugh C patients excluded) [31–33], and had a score less than 2 on the WHO bleeding scale at randomisation (data on file, Shionogi & Co., Ltd) [31]. Patients were randomised to receive lusutrombopag 3 mg once daily (other studied doses not included in this analysis) or placebo, administered for 4–7 days (treatment period included days 1–7). The need for a preoperative platelet transfusion was determined on or after day 8, with a platelet transfusion indicated if the platelet count remained below 50×10^9/L. The planned invasive procedure was to be performed during the post-treatment period (days 9–14), and patients were followed for at least 28 days after receiving treatment.

Study Outcomes

The primary efficacy outcome reported for L-PLUS 1 and the phase 2b study was the proportion of patients not requiring platelet transfusion immediately prior to invasive procedure [32, 33], which differed from the primary efficacy outcome reported for L-PLUS 2 (proportion of patients not requiring platelet transfusion before the invasive procedure and not requiring rescue therapy for bleeding from randomisation through 7 days post procedure) [31]. For the purposes of this meta-analysis, the efficacy data were matched across the three trials to ensure consistency. The main efficacy outcome used

for this meta-analysis was the proportion of patients with thrombocytopenia treated with lusutrombopag versus placebo who required no platelet transfusion prior to the invasive procedure, and no rescue therapy for bleeding from randomisation through 7 days after the invasive procedure. Additional efficacy outcomes included in the meta-analysis were the proportion of patients achieving platelet count of at least 50×10^9/L and an increase of at least 20×10^9/L from baseline, the proportion of patients achieving a platelet count of at least 50×10^9/L on the day of procedure, the proportion of patients experiencing an increase in platelet count of at least 20×10^9/L from baseline, the proportion of patients requiring no platelet transfusion during the study period, and lastly the proportion of patients requiring no platelet transfusion prior to the procedure. A post hoc subgroup analysis was used to assess efficacy and safety outcomes in the subset of patients scheduled to undergo gastrointestinal (GI)-related or liver-related procedures. GI-related procedures included (but were not limited to) endoscopic variceal ligation (EVL); endoscopic injection sclerotherapy (EIS); and GI endoscopy regardless of polypectomy or biopsy. Liver-related procedures included (but were not limited to) percutaneous radiofrequency ablation/microwave coagulation therapy (RFA/MCT), TACE, and liver biopsy. Additional post hoc subgroup analysis assessed the change in platelet count in patients receiving lusutrombopag 3 mg without platelet transfusion versus patients receiving placebo with platelet transfusion. Safety outcomes included the proportion of patients with bleeding events during the study, patients not undergoing their planned procedures, patients requiring rescue treatment for bleeding during the study, and treatment-emergent thrombosis events. Portal vein thrombosis (PVT) was prospectively assessed by computed tomography or magnetic resonance imaging, and by ultrasonography. PVTs, cardiac ventricular thromboses, and mesenteric vein thromboses were counted in aggregate rather than by type because of the low rate of thrombotic events in the RCT populations.

Meta-Analysis Methods

A random-effects meta-analysis was conducted in Stata MP v16.12 using the *meta* command [35–37]. Empirical Bayes method was used for the between-study variance parameter [38, 39]. Statistical heterogeneity was assessed using the I^2 statistic [40–42]. Alternative random-effects meta-analyses are presented in Supplementary Material 2.

For binomial outcomes where a study contained a zero observation (e.g. no patients had an event), 0.5 was added [43, 44]. A p value of less than 0.05 was considered statistically significant; p values were not adjusted to account for multiple comparisons.

The efficacy outcomes analysis was conducted on an intent-to-treat (ITT) basis, using the full analysis set, defined as all randomised patients who had received a least one dose of their allocated treatment and had a platelet count measurement at baseline and at least one platelet count measurement during follow-up. The safety analysis set included all randomised patients who had received at least one dose of their allocated treatment. Only study arms using licensed doses of lusutrombopag were included in the analysis.

A sensitivity analysis was conducted for the primary efficacy outcome using data from the per protocol (PP) study population (all randomised patients with no major deviations from the clinical trial protocol). Reasons for exclusion from the PP population included noncompliance with pre-procedural platelet transfusion instructions, out-of-window for pre-procedure platelet transfusion assessment, noncompliance with study drug, not meeting eligibility criteria, and use of prohibited concomitant medication.

Binomial outcome data have been expressed as risk ratio (RR) to help interpretation [45]. For completeness, treatment effects expressed as odds ratios (OR) are provided for key outcomes in the supplement. Continuous outcomes are expressed as mean difference. A 95% confidence interval (CI) was the measure of uncertainty around the treatment effect estimates.

Risk of Bias Assessment

A risk of bias assessment of the included RCTs was conducted using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials [46, 47], and the certainty of the evidence was rated on the basis of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria [48]. Assessment criteria and scheme for downgrading evidence are shown in Table S1 and S2, respectively, in the supplementary material. The overall assessment scheme is provided in Table S3 in the supplementary material.

In relation to statistical heterogeneity, the I^2 statistic was used, with $I^2 > 50\%$ considered to be substantial heterogeneity [40–42].

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

A total of 1612 articles were screened for eligibility. After exclusion of 428 duplicate records, an additional 1133 records were excluded after title and abstract screening. Of the 51 full-text citations identified, 26 were excluded because they were not primary publications on the study outcomes, leaving 25 citations. Of these, three citations describing randomised, placebo-controlled trials investigating treatment with lusutrombopag in adults with CLD presenting with platelet count below 50×10^9/L and scheduled for planned invasive procedures were included: one phase 2b study, and two phase 3 studies, L-PLUS 1 and L-PLUS 2, were selected for inclusion in the meta-analysis (Fig. S1 in the supplementary material) [31–33].

Study and Patient Baseline Characteristics

A total of 343 (lusutrombopag 3 mg, $n = 173$; placebo, $n = 170$) patients were included in the meta-analysis, all of whom were adults with CLD and platelet count below 50×10^9/L who were scheduled to undergo a planned invasive procedure. In all studies, patients were randomised to receive lusutrombopag 3 mg or placebo once daily on day 1 of the treatment period. Treatment continued for up to 7 days. The planned invasive procedure was performed between days 9 and 14, and post-treatment follow-up lasted through day 35. The phase 2b study was conducted in patients who were scheduled to undergo percutaneous liver ablation for primary hepatic cancer [33]. In L-PLUS 1 and L-PLUS 2, the planned invasive procedures included liver biopsy, endoscopic injection sclerotherapy, endoscopic variceal ligation, microwave coagulation therapy, radiofrequency ablation, transcatheter arterial chemoembolization, and dental extraction [31, 32].

Although the study design was consistent across the RCTs evaluated, there was some variability in patient characteristics that could be expected because phase 2b and L-PLUS 1 studies were conducted only in Japan, and L-PLUS 2 was conducted globally, with 85% of patients of non-Asian descent (data on file, Shionogi & Co., Ltd) (Table 1) [31–33]. Overall mean age across the three RCTs was 64.1 years, the mean weight was 66.9 kg, and 59% of patients were male (data on file, Shionogi & Co., Ltd). Patients in the phase 2b and L-PLUS 1 studies were older (68.4 years), weighed less (61.3 kg), and were less frequently male (54%) compared to L-PLUS 2 (55.7 years, 78 kg, 62% male) (data on file, Shionogi & Co., Ltd). Patients had a mixed CLD aetiology, with viral hepatitis being the most common (75% overall; 84%, 87%, and 69% in phase 2b, L-PLUS1, and L-PLUS 2, respectively). Autoimmune hepatitis was rare (0% L-PLUS 1 and phase 2b, 4.7% in L-PLUS 2). The mean baseline platelet count across all study arms was 39.9×10^9/L, with a mean baseline platelet count of 41.8×10^9/L in the phase 2b study, 40.4×10^9/L in L-PLUS 1, and 36.9×10^9/L in L-PLUS 2. The percentage of patients in each of the studies with a baseline platelet count below 35×10^9/L was 27% in the phase 2b study, 18% in L-PLUS 1, and 35% in L-PLUS 2.

Table 1 Summary of lusutrombopag study patient demographics and baseline characteristics

	L-PLUS 2[a] [31] Phase 3, global (N = 215)		L-PLUS 1[a] [32] Phase 3, Japan (N = 96)		Phase 2b Study[a] [33] Phase 2b[b], Japan (N = 31)	
	LUSU	PBO	LUSU	PBO	LUSU	PBO
Randomised patients (ITT), n	108	107	49	48	16	15
Full analysis set, n	108	107	48	48	16	15
Patients receiving allocated treatment, n	107	107	48	48	16	15
Age, mean (SD)	55.2 (11.6)	56.1 (11.0)	68.9 (6.6)	66.8 (10.2)	66.8 (8.1)	70.9 (8.6)
Male, %	60	65	44	63	56	53
White, %	79	80	0	0	0	0
Asian, %	15	17	100	100	100	100
PC $< 35 \times 10^9$/L, %	33	36	15	21	19	27
Hepatic cancer, %	19	17	79	67	100	100
Viral liver disease, %	69	67	90	83	88	87
Alcoholic hepatitis, %	22	24	4	13	13	7
Non-alcoholic hepatitis, %	11	14	6	8	0	7
Child–Pugh class, %						
A	66.7	58.9	54	46	56	60
B	30.6	40.2	46	54	44	40
C	2.8	0	0	0	0	0
Unknown	0	0.9	0	0	0	0
Previous PLT, %	44	58	58	54	57	47
Liver ablation scheduled, %	7	5	42	44	100	100

LUSU lusutrombopag, *PBO* placebo, *PC* platelet count, *PLT* platelet transfusion, *SD* standard deviation

[a]Data on file, Shionogi & Co., Ltd

[b]Study arms using unlicensed doses of lusutrombopag were not included in the analysis

Risk of Bias Assessment

On the basis of the Cochrane Collaboration's tool for assessing risk of bias in randomised trials, all three studies were judged to have low risk of bias in all domains (randomisation procedures and allocation concealment were adequate; studies were double-blinded; all randomised patients accounted for/ITT analysis; all primary and secondary outcomes reported; no other biases noted) [46, 47]. The study designs, populations, treatment arms, and outcomes were judged to be sufficiently similar for the data from all three trials to be combined in the meta-analysis. For the response to treatment efficacy outcome (increasing the platelet count to $\geq 50 \times 10^9$/L with an increase of $\geq 20 \times 10^9$/L from baseline at some point during the study) the meta-analysis was judged to be of low risk of bias. For the remaining outcomes, the risk of bias of the evidence was moderate. In general, the reason for a downgrade from high to moderate was due to substantial heterogeneity, unless otherwise stated

(other reasons were imprecision due to a low event rate or subgroup analysis where groups were not randomly allocated at study baseline). Additional details of GRADE assessment scoring and downgrades are given in Supplementary Material 1.

Meta-Analysis Results

Lusutrombopag Versus Placebo

On the basis of the results of the meta-analysis, treatment with lusutrombopag 3 mg prior to planned invasive procedures increased platelet counts to at least 50×10^9/L in patients in the ITT population, with an increase of at least 20×10^9/L from baseline at any time during the study, significantly more often than placebo treatment (RR 6.39; 95% CI 3.69, 11.07; I^2 13.23%; $p < 0.0001$; low risk of bias) (Fig. 1A, Table S3). Lusutrombopag 3 mg treatment also resulted in platelet counts of at least 50×10^9/L on the day of the procedure more frequently than placebo treatment (RR 3.51; 95% CI 1.90, 6.48; I^2 60.42%; $p < 0.0001$; moderate risk of bias) (Fig. 1A).

With respect to the primary composite outcome, significantly more patients randomised to lusutrombopag 3 mg, compared to placebo, in the ITT population required no platelet transfusion prior to the invasive procedure and did not require rescue therapy for bleeding for up to 7 days after the procedure (RR 3.42; 95% CI 1.86, 6.26; I^2 58.43%; $p = 0.0001$; moderate risk of bias) (Table 2, Fig. 2A). Figure S2A

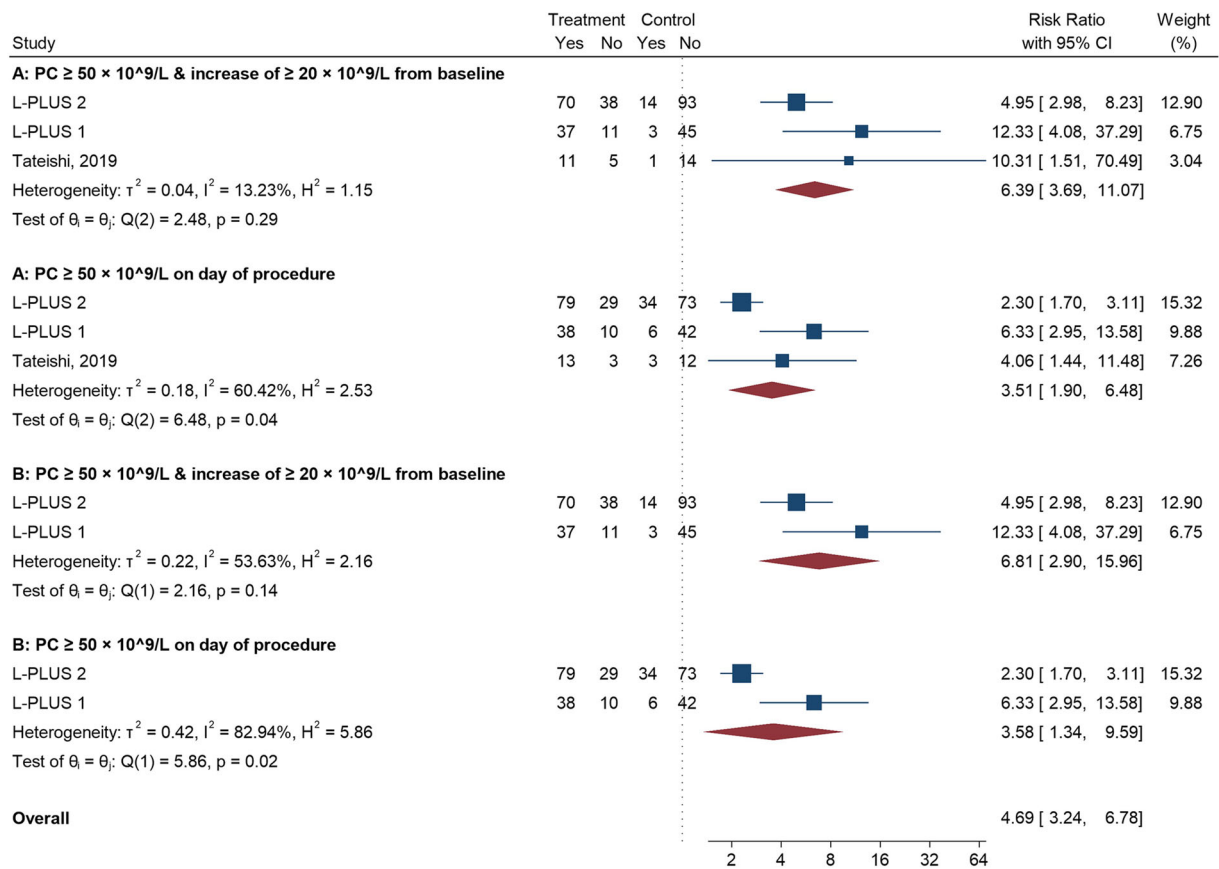

Fig. 1 Forest plot of outcomes for platelet count response: **A** Estimate including three RCTs (ITT); **B** Estimate including phase 3 studies only (ITT). Results of a random-effects empirical Bayes model. Dotted line represents 'no-effect,' where risk ratio = 1. Risk ratio > 1 favours lusutrombopag compared to placebo. *CI* confidence interval, *ITT* intent-to-treat, *PC* platelet count

Table 2 Percentage of patients requiring, receiving, and failing to receive pre-procedure transfusion

	L-PLUS 2 [31] (N = 215)		L-PLUS 1 [32] (N = 96)		Phase 2b Study [33] (N = 31)	
	LUSU	PBO	LUSU	PBO	LUSU	PBO
Required PLT pre-procedure, %	27	68	21	88	19	80
Did not receive pre-procedure platelet transfusion when indicated	3	10	0	0	0	0
Received pre-procedure platelet transfusion when not indicated	5	0	0	0	0	0

LUSU lusutrombopag, *PBO* placebo

in the supplementary material shows additional forest plots of the primary composite outcome with data split by L-PLUS 2, L-PLUS 1, and phase 2b studies (estimates presented as OR).

When these endpoints were considered individually, more patients randomised to lusutrombopag 3 mg in the ITT population avoided platelet transfusion both prior to the procedure (RR 3.51; 95% CI 1.90, 6.48; I^2 60.42%; $p = 0.0001$; moderate risk of bias), and at any point during the 5-week study period (RR 3.47; 95% CI 1.82, 6.65; I^2 63.37%; $p = 0.0002$; moderate risk of bias) compared to placebo (Table 2, Fig. 2A). The risk of a bleeding event of any type or severity throughout the study period was significantly lower for lusutrombopag 3 mg compared to placebo in the ITT population (RR 0.55; 95% CI 0.32, 0.95; I^2 0.00%; $p = 0.03$; moderate risk of bias, downgraded from low risk of bias because of imprecision [small study effects]) (Fig. 3A). No significant differences were observed between lusutrombopag 3 mg and placebo treatments in the risk of cancellation of the planned procedure (RR 0.71; 95% CI 0.28, 1.76; $p = 0.45$; moderate risk of bias) (Fig. 3A). Similarly, no significant differences in the risk of receiving rescue treatment for bleeding at any time during the study were observed between patients treated with lusutrombopag 3 mg and those treated with placebo (RR 0.56; 95% CI 0.09, 3.37; $p = 0.53$; moderate risk of bias) (Fig. 3A).

Treatment-emergent thrombosis was investigated as an adverse event of special interest. No significant differences in the rates of treatment-emergent thrombosis were observed between patients treated with lusutrombopag 3 mg and placebo (RR 0.79; 95% CI 0.19, 3.24; $p = 0.74$; moderate risk of bias) (Fig. 3A). Among the 171 patients receiving lusutrombopag 3 mg, three treatment-emergent thrombosis events were reported, two of which (1.2%) were PVTs. Four treatment-emergent thrombosis events were reported in the 170 patients receiving placebo, and two (1.2%) were PVTs, indicating no observed difference in rate of PVTs between lusutrombopag- and placebo-treated patients, although a meta-analysis could not be conducted because of the low frequency of events.

A sensitivity analysis excluding the phase 2b study produced similar results for efficacy and safety outcomes (Figs. 1B, 2B, 3B), except for risk of bleeding events throughout the study, which was not significantly different between lusutrombopag 3 mg- and placebo-treated patients when only phase 3 study data were considered (RR 0.53; 95% CI 0.26, 1.07; $p = 0.076$; moderate risk of bias) (Fig. 3B). A sensitivity analysis using alternative random-effects analyses also produced similar results for efficacy and safety outcomes (Table S6 in the supplementary material).

The PP analysis of the primary composite outcome, shown in Fig. 2C, indicates that patients treated with lusutrombopag 3 mg were significantly more likely to require no pre-procedural platelet transfusion and no rescue therapy for bleeding for up to 7 days after the procedure (RR 3.98; 95% CI 2.78, 5.70; $p < 0.0001$; moderate risk of bias, groups not randomly allocated at study baseline). No statistical heterogeneity ($I^2 = 0$) was observed in
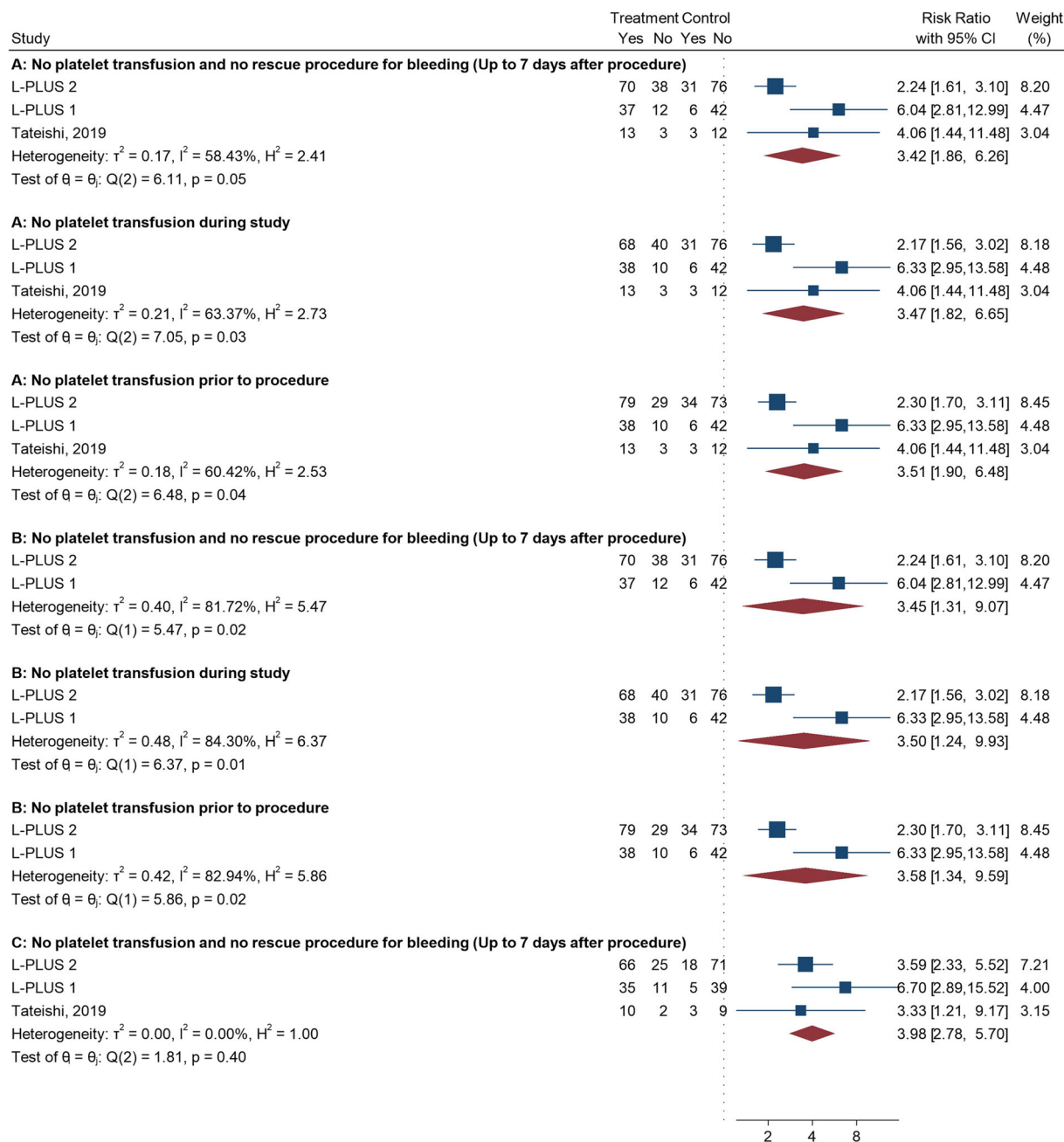
Fig. 2 Forest plot of outcomes for platelet transfusion requirements: A Estimate including three RCTs (ITT); B Estimate including phase 3 studies only (ITT); C Estimate including three RCTs (PP). Results of a random-effects empirical Bayes model. Dotted line represents 'no-effect,' where risk ratio = 1. Risk ratio > 1 favours lusutrombopag compared to placebo. CI confidence interval, ITT intent-to-treat, PC platelet count

this analysis. In the L-PLUS 2 study, some protocol violations included cases in which a pre-procedure platelet transfusion was indicated but not received (13 out of 35 violations) or a pre-procedure transfusion was received but not indicated (5 out of 35 violations) (Table 2). No transfusion-related protocol violations were reported for the L-PLUS 1 or phase 2b studies.

Study	Treatment Yes	No	Control Yes	No		Risk ratio with 95% CI	Weight (%)
A: Any bleeding							
L-PLUS 2	3	104	6	101		0.50 [0.13, 1.95]	5.97
L-PLUS 1	7	41	13	35		0.54 [0.24, 1.23]	16.13
Tateishi, 2019	5	11	8	7		0.59 [0.25, 1.39]	14.67
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$						0.55 [0.32, 0.95]	
Test of $\theta_i = \theta_j$: Q(2) = 0.04, p = 0.98							
Test of $\theta = 0$: z = -2.14, p = 0.03							
A: Patient did NOT undergo scheduled procedure							
L-PLUS 2	6	102	9	98		0.66 [0.24, 1.79]	11.08
L-PLUS 1	0	48	1	47		0.33 [0.01, 7.98]	1.09
Tateishi, 2019	1	15	0	15		2.82 [0.12, 64.39]	1.13
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$						0.71 [0.28, 1.76]	
Test of $\theta_i = \theta_j$: Q(2) = 0.99, p = 0.61							
Test of $\theta = 0$: z = -0.75, p = 0.45							
A: Required rescue for bleeding during the study							
L-PLUS 2	0	108	2	105		0.20 [0.01, 4.08]	1.21
L-PLUS 1	0	48	1	47		0.33 [0.01, 7.98]	1.09
Tateishi, 2019	1	15	0	15		2.82 [0.12, 64.39]	1.13
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$						0.56 [0.09, 3.37]	
Test of $\theta_i = \theta_j$: Q(2) = 1.58, p = 0.45							
Test of $\theta = 0$: z = -0.63, p = 0.53							
A: TEAE thrombosis							
L-PLUS 2	2	105	2	105		1.00 [0.14, 6.97]	2.93
L-PLUS 1	1	47	1	47		1.00 [0.06, 15.53]	1.47
Tateishi, 2019	0	16	1	14		0.31 [0.01, 7.15]	1.13
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$						0.79 [0.19, 3.24]	
Test of $\theta_i = \theta_j$: Q(2) = 0.42, p = 0.81							
Test of $\theta = 0$: z = -0.33, p = 0.74							
B: Any bleeding							
L-PLUS 2	3	104	6	101		0.50 [0.13, 1.95]	5.97
L-PLUS 1	7	41	13	35		0.54 [0.24, 1.23]	16.13
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$						0.53 [0.26, 1.07]	
Test of $\theta_i = \theta_j$: Q(1) = 0.01, p = 0.93							
Test of $\theta = 0$: z = -1.77, p = 0.08							
B: Patient did NOT undergo scheduled procedure							
L-PLUS 2	6	102	9	98		0.66 [0.24, 1.79]	11.08
L-PLUS 1	0	48	1	47		0.33 [0.01, 7.98]	1.09
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$						0.62 [0.24, 1.61]	
Test of $\theta_i = \theta_j$: Q(1) = 0.16, p = 0.69							
Test of $\theta = 0$: z = -0.98, p = 0.33							
B: Required rescue for bleeding during the study							
L-PLUS 2	0	108	2	105		0.20 [0.01, 4.08]	1.21
L-PLUS 1	0	48	1	47		0.33 [0.01, 7.98]	1.09
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$						0.25 [0.03, 2.27]	
Test of $\theta_i = \theta_j$: Q(1) = 0.05, p = 0.82							
Test of $\theta = 0$: z = -1.23, p = 0.22							
B: TEAE thrombosis							
L-PLUS 2	2	105	2	105		1.00 [0.14, 6.97]	2.93
L-PLUS 1	1	47	1	47		1.00 [0.06, 15.53]	1.47
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$						1.00 [0.21, 4.88]	
Test of $\theta_i = \theta_j$: Q(1) = 0.00, p = 1.00							
Test of $\theta = 0$: z = 0.00, p = 1.00							

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◄ **Fig. 3** Forest plot of bleeding outcomes, cancelled procedures, and thrombosis events: **A** Estimate including three RCTs (ITT); **B** Estimate including phase 3 studies only (ITT). Results of a random-effects empirical Bayes model. Dotted line represents 'no-effect,' where risk ratio = 1. Risk ratio < 1 favours lusutrombopag compared to placebo. L-PLUS 2 endpoints used ITT population (lusutrombopag $n = 108$, placebo $n = 107$) or safety population (lusutrombopag $n = 107$, placebo $n = 107$). The TEAE thrombosis outcome includes 4 PVTs (LUSU 3 mg: 2; PBO: 2), 1 cardiac ventricular thrombosis (LUSU 3 mg), and 2 mesenteric vein thromboses (PBO: 2). *CI* confidence interval, *ITT* intent-to-treat, *PVT* portal vein thrombosis, *TEAE* treatment-emergent adverse event

Subgroup Analysis: Lusutrombopag Versus Placebo in GI- vs Liver-Related Procedures

Treatment with lusutrombopag 3 mg prior to planned GI- or liver-related invasive procedures increased platelet counts to at least 50×10^9/L, with an increase of at least 20×10^9/L from baseline at any time during the study, significantly more frequently than placebo treatment (GI-related procedures RR 9.05; 95% CI 4.00, 20.50; $p < 0.0001$; moderate risk of bias, groups not randomly allocated at study baseline; liver-related procedures RR 9.64; 95% CI 4.11, 22.62; $p < 0.0001$; moderate risk of bias, groups not randomly allocated at study baseline] (Fig. 4A). Assessment of between-group heterogeneity indicated no significant difference in response to treatment among patients undergoing GI-related procedures versus those undergoing liver-related procedures ($p = 0.92$) (Fig. 4A).

With respect to the primary composite outcome, significantly more patients receiving lusutrombopag 3 mg avoided platelet transfusions prior to GI- or liver-related invasive procedures, and did not require rescue therapy for bleeding for up to 7 days after the procedure compared to placebo-treated patients in these subgroups (GI-related procedures RR 2.81; 95% CI 1.84, 4.31; $p < 0.0001$; moderate risk of bias, groups not randomly allocated at study baseline; liver-related procedures RR 3.85; 95% CI 2.03, 7.31; $p < 0.0001$; moderate risk of bias, groups not randomly allocated at study baseline) (Fig. 4B). Assessment of between-group heterogeneity indicated no significant
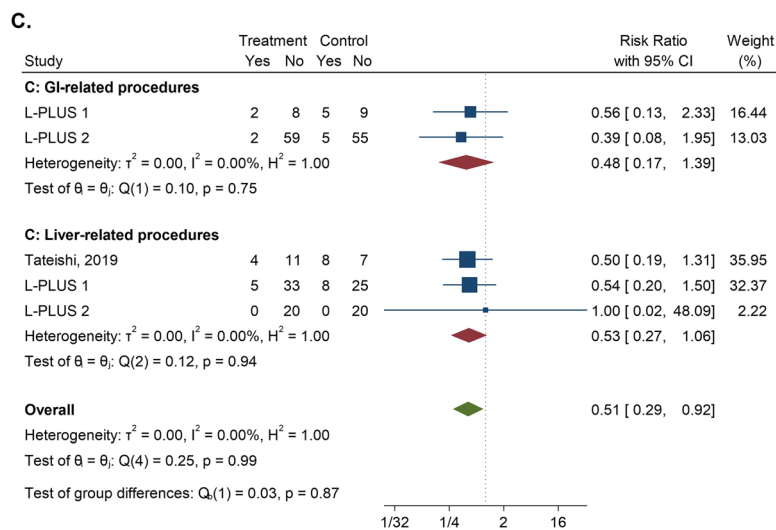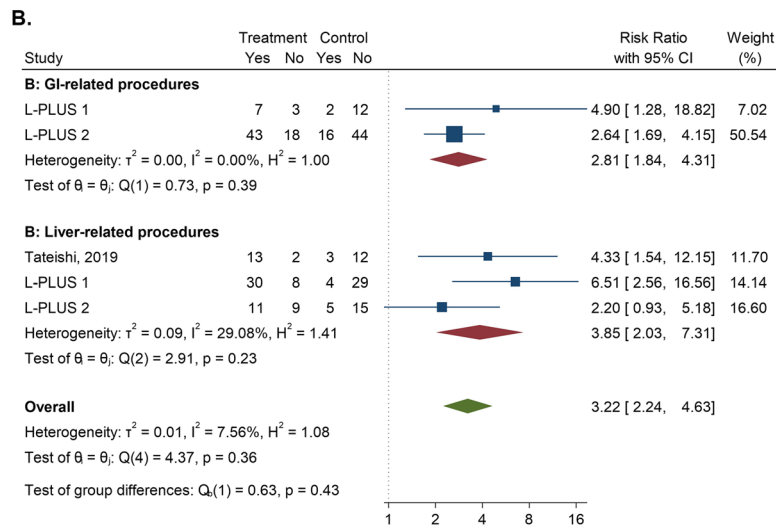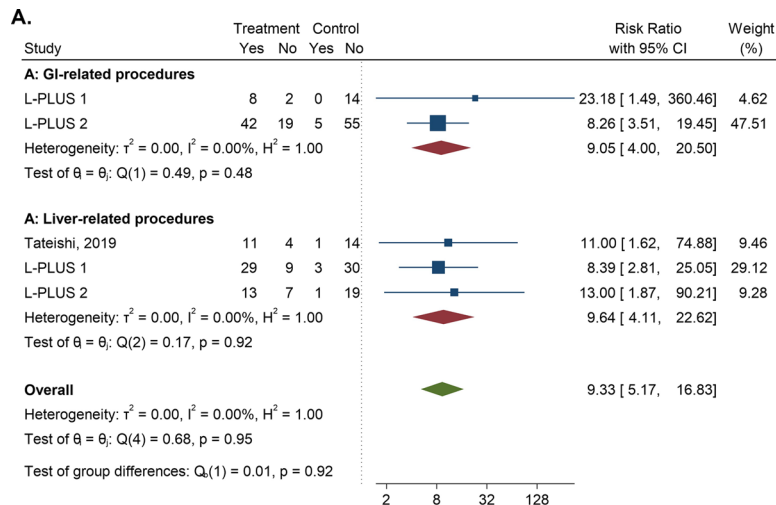
difference in platelet transfusion requirements between patients undergoing GI-related procedures and those undergoing liver-related procedures ($p = 0.43$) (Fig. 4B).

Bleeding risk with lusutrombopag 3 mg treatment did not reach statistical significance compared to placebo treatment in either subgroup (GI-related procedures, $p > 0.1$; liver-related procedures, $p = 0.071$), although a trend toward lower risk after lusutrombopag treatment was observed (Fig. 4C). No significant difference in bleeding risk was observed between the subgroups of patients undergoing GI-related procedures and patients undergoing liver-related procedures ($p = 0.87$) (Fig. 4C).

DISCUSSION

Randomised clinical trials of lusutrombopag, an orally bioavailable small molecule TPO-RA, have demonstrated its efficacy in treating severe thrombocytopenia in patients with CLD prior to a planned invasive procedure, providing a promising treatment alternative in patients who otherwise would have been indicated to receive platelet transfusions. This meta-analysis found that lusutrombopag was superior to placebo in reducing the need for both platelet transfusion prior to an invasive procedure, and post-procedural rescue therapy in adults with CLD and platelet counts below 50×10^9/L. The findings of this analysis complement and extend the results presented in the recently published meta-analysis by Armstrong et al. [49], which assessed TPO-RAs (lusutrombopag and avatrombopag) compared to placebo. Our analysis covers a comprehensive set of outcomes and analysis using data for lusutrombopag, including an extended sensitivity analysis of the primary composite outcome, response outcomes in terms of platelet count, as well as safety outcomes. In addition, we conducted comparisons of platelet response, the primary composite outcome, and bleeding rate for the subgroup of patients undergoing high-risk procedures (gastrointestinal or liver-related procedures).

On the basis of the data available from three RCTs, patients treated with lusutrombopag

A.

Study	Treatment Yes No	Control Yes No	Risk Ratio with 95% CI	Weight (%)
A: GI-related procedures				
L-PLUS 1	8 2	0 14	23.18 [1.49, 360.46]	4.62
L-PLUS 2	42 19	5 55	8.26 [3.51, 19.45]	47.51
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$			9.05 [4.00, 20.50]	
Test of $\theta = \theta_i$: Q(1) = 0.49, p = 0.48				
A: Liver-related procedures				
Tateishi, 2019	11 4	1 14	11.00 [1.62, 74.88]	9.46
L-PLUS 1	29 9	3 30	8.39 [2.81, 25.05]	29.12
L-PLUS 2	13 7	1 19	13.00 [1.87, 90.21]	9.28
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$			9.64 [4.11, 22.62]	
Test of $\theta = \theta_i$: Q(2) = 0.17, p = 0.92				
Overall			9.33 [5.17, 16.83]	
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$				
Test of $\theta = \theta_i$: Q(4) = 0.68, p = 0.95				
Test of group differences: $Q_b(1) = 0.01$, p = 0.92				

2   8   32   128

B.

Study	Treatment Yes No	Control Yes No	Risk Ratio with 95% CI	Weight (%)
B: GI-related procedures				
L-PLUS 1	7 3	2 12	4.90 [1.28, 18.82]	7.02
L-PLUS 2	43 18	16 44	2.64 [1.69, 4.15]	50.54
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$			2.81 [1.84, 4.31]	
Test of $\theta = \theta_i$: Q(1) = 0.73, p = 0.39				
B: Liver-related procedures				
Tateishi, 2019	13 2	3 12	4.33 [1.54, 12.15]	11.70
L-PLUS 1	30 8	4 29	6.51 [2.56, 16.56]	14.14
L-PLUS 2	11 9	5 15	2.20 [0.93, 5.18]	16.60
Heterogeneity: $\tau^2 = 0.09$, $I^2 = 29.08\%$, $H^2 = 1.41$			3.85 [2.03, 7.31]	
Test of $\theta = \theta_i$: Q(2) = 2.91, p = 0.23				
Overall			3.22 [2.24, 4.63]	
Heterogeneity: $\tau^2 = 0.01$, $I^2 = 7.56\%$, $H^2 = 1.08$				
Test of $\theta = \theta_i$: Q(4) = 4.37, p = 0.36				
Test of group differences: $Q_b(1) = 0.63$, p = 0.43				

1   2   4   8   16

C.

Study	Treatment Yes No	Control Yes No	Risk Ratio with 95% CI	Weight (%)
C: GI-related procedures				
L-PLUS 1	2 8	5 9	0.56 [0.13, 2.33]	16.44
L-PLUS 2	2 59	5 55	0.39 [0.08, 1.95]	13.03
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$			0.48 [0.17, 1.39]	
Test of $\theta = \theta_i$: Q(1) = 0.10, p = 0.75				
C: Liver-related procedures				
Tateishi, 2019	4 11	8 7	0.50 [0.19, 1.31]	35.95
L-PLUS 1	5 33	8 25	0.54 [0.20, 1.50]	32.37
L-PLUS 2	0 20	0 20	1.00 [0.02, 48.09]	2.22
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$			0.53 [0.27, 1.06]	
Test of $\theta = \theta_i$: Q(2) = 0.12, p = 0.94				
Overall			0.51 [0.29, 0.92]	
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$				
Test of $\theta = \theta_i$: Q(4) = 0.25, p = 0.99				
Test of group differences: $Q_b(1) = 0.03$, p = 0.87				

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◀ **Fig. 4** Forest plot showing outcomes for patients with planned GI- or liver-related procedures: **A** Platelet response; **B** Primary composite outcome; **C** Bleeding outcomes. Results of a random-effects empirical Bayes model. Dotted line represents 'no-effect,' where risk ratio = 1. Risk ratio > 1 favours lusutrombopag compared to placebo. *CI* confidence interval, *ITT* intent-to-treat, *GI* gastrointestinal

3 mg prior to a planned invasive procedure were more likely than placebo-treated patients to have preoperative platelet counts of at least 50×10^9/L, with an increase of at least 20×10^9/L from baseline at any time during the study ($p < 0.001$). Lusutrombopag-treated patients also had platelet counts of at least 50×10^9/L on the day of the planned procedure ($p < 0.0001$) more frequently than placebo-treated patients. These results are consistent with a recent systematic review and meta-analysis of TPO-RAs, which found a significant increase in platelet count, decreased rates of platelet transfusion, and overall decreased rate of periprocedural bleeding after pre-procedural treatment with eltrombopag, avatrombopag, or lusutrombopag [50]. The platelet count elevation observed in lusutrombopag-treated patients versus placebo-treated patients persisted for 3 weeks after treatment, through study day 28 ($p = 0.0001$), thus raising and maintaining platelet levels well into the postoperative healing period. A subgroup analysis of patients treated with lusutrombopag 3 mg without receiving any pre-procedure platelet transfusion before the planned procedure and after the procedure window, demonstrated a significantly greater increase in platelet count over the perioperative period compared to patients who received placebo and a pre-procedure platelet transfusion ($p < 0.0001$, Supplementary Material 3).

Studies have shown that platelet counts below 50 to 75×10^9/L can be associated with a higher risk of bleeding in patients undergoing a range of invasive procedures, requiring platelet transfusions or other rescue therapies for bleeding, posing a substantial healthcare burden in these patients [8, 10, 51–54]. Recently, a pooled post hoc analysis of the lusutrombopag phase 2b, L-PLUS 1, and L-PLUS 2 studies found that patients treated with lusutrombopag without platelet transfusion demonstrated a trend toward fewer procedural and post-procedural bleeding events compared to patients receiving platelet transfusions plus placebo treatment [55]. Consistent with these findings, the present analysis found that patients treated with lusutrombopag 3 mg experienced a significantly reduced risk of a bleeding event of any type compared with placebo-treated patients ($p = 0.03$). In addition, lusutrombopag-treated patients were more likely to avoid both pre-procedural platelet transfusions and rescue therapy for bleeding for up to 7 days after their procedures ($p < 0.0001$).

Reducing the need for pre-procedural platelet transfusions and rescue treatment for up to 7 days post procedure in patients with severe thrombocytopenia may have a significant positive impact on their healthcare resource utilization. As an oral treatment, given once a day for 7 days, lusutrombopag is simple to administer, and can be easily scheduled in advance of a planned procedure, a significant contrast to the resources an inpatient pre-procedural platelet transfusion would require, especially in a post-pandemic environment [51].

Platelet transfusions are widely used despite their known risk of serious adverse events, such as serious allergic reactions, TACO, TRALI, febrile non-haemolytic reactions, haemolysis, and risk of infection. In the ADAPT-1 and ADAPT-2 studies of avatrombopag, for example, four transfusion reactions and one anaphylactic transfusion reaction were reported in the placebo arms ($n = 91$) [56, 57]. These types of serious reactions can be eliminated entirely when pre-procedural platelet transfusions are avoided [11, 21–23].

Previously published phase 3 data have shown that use of eltrombopag to treat thrombocytopenia in patients with CLD undergoing a planned procedure was associated with an increased risk of PVTs (OR 6.3; 95% CI 0.8–53.0; $p = 0.09$, calculated in a later meta-analysis [58]), leading to the termination of that trial [59]. Currently, only avatrombopag and lusutrombopag are approved for use in this indication, given their demonstrated efficacy

and low incidence of PVTs in treated versus placebo patients [31, 32, 56, 58]. The data presented in this meta-analysis are consistent with these findings, namely, no significant difference in the rate of any type of treatment-emergent thrombosis was observed between patients treated with lusutrombopag 3 mg and placebo. PVTs also occurred at a similar rate in patients treated with lusutrombopag 3 mg versus placebo. Similarly, in a recent meta-analysis carried out for avatrombopag and lusutrombopag, no significant differences were observed for avatrombopag vs placebo or lusutrombopag for any of the safety outcomes [60]. Of note, prospective imaging was used to detect the occurrence of asymptomatic PVTs in the lusutrombopag phase 3 trials, increasing confidence in its safety profile; this was not performed in the avatrombopag studies [31, 32, 56].

This current lusutrombopag meta-analysis used outcome data from a population consisting almost entirely of patients with Child–Pugh class A (59%) and B (40%) CLD with mixed aetiology undergoing a variety of invasive procedures, representative of a range of procedural risks. The study arms were balanced with respect to procedural risk. Fifteen bleeding events (of any type) occurred in 171 patients treated with lusutrombopag 3 mg and 27 bleeding events occurred in the 170 patients receiving placebo. These low event rates resulted in a downgrade in risk of bias (GRADE) assessment for the bleeding event meta-analysis due to imprecision.

Bleeding risk is dependent on patient characteristics as well as procedure type. For example, procedures such as liver biopsy, RFA, TACE, transarterial radioembolization (TARE), or GI-related procedures, including variceal ligation, are associated with an increased bleeding risk [61, 62]. To address the efficacy and safety of lusutrombopag specifically in patients undergoing high-risk procedures, an analysis of the subgroup of patients scheduled for GI-related or liver-related invasive procedures was conducted. Among patients treated with lusutrombopag 3 mg prior to planned GI-related or liver-related invasive procedures, response to treatment (increased platelet count) was observed significantly more frequently than in placebo-treated patients ($p < 0.0001$), and significantly fewer pre-procedural platelet transfusions and post-procedural rescue therapy for bleeding were observed compared to those treated with placebo ($p < 0.0001$). These results suggest that lusutrombopag 3 mg is efficacious in patients who are undergoing higher-risk invasive procedures.

There are three potential limitations associated with this analysis: heterogeneity, bias, and characterization of bleeding events. Each is addressed in turn.

Heterogeneity: One potential limitation when conducting meta-analyses is how to estimate between-study heterogeneity when there are few studies. To address this limitation, a random-effects meta-analysis was conducted using an empirical Bayes estimator for the between-study variance, as this method is less likely to underestimate between-study heterogeneity compared to other methods. To test the robustness of the results, two alternative random-effect modelling approaches were used, and results were similar across all the random-effect analyses (results in Supplementary Material 2). Variance in the study-level treatment effect estimates may be due to differences in study design and clinical trial protocols. The clinical study protocol for the three lusutrombopag studies pre-specified that patients were to receive a platelet transfusion if platelet counts remained below 50×10^9/L prior to the invasive procedure. In the multi-country trial L-PLUS 2, the study criteria for a pre-procedure platelet transfusion may have been superseded by local guidelines: five patients with a pre-procedure platelet count above 50×10^9/L but below 70×10^9/L received platelet transfusions, and 13 patients with platelet counts below 50×10^9/L did not receive a platelet transfusion prior to their planned invasive procedures (data on file, Shionogi & Co., Ltd) [31]. No protocol variations were reported for the L-PLUS 1 and phase 2b studies (Japan only). A PP analysis was conducted to assess the impact of excluding patients with protocol violations from the meta-analysis, as these could lead to an over- or underestimation of the efficacy of lusutrombopag. When patients with protocol violations were excluded from the meta-analysis of the

main efficacy outcome, statistical heterogeneity was reduced to zero and lusutrombopag was statistically significantly superior to placebo ($p < 0.0001$), consistent with the findings for the ITT population. This PP population best reflects the impact of treatment when the platelet transfusion decision strictly adheres to current international guidelines, whereas the ITT population is more representative of the observed treatment effect in clinical practice where the decision to schedule a platelet transfusion may incorporate a wider range of clinical observations.

Bias: Bias is an additional potential limitation with the analysis; however the studies included in this meta-analysis were assessed to have a low risk of bias (adequate allocation concealment, adequate blinding, no incomplete accounting of patients, no incomplete reporting of outcomes, no other forms of bias noted), and the meta-analysis results were judged to be of moderate to low risk of bias (based on the GRADE assessment). To ensure consistency, the outcome definitions were matched across studies before conducting the analysis and alternative definitions of the primary composite outcome and response outcomes were explored. By combining data from the three studies, the meta-analysis estimates have more statistical power than individual study results and the results concur with previously published findings [31–33].

Characterization of bleeding events: A final limitation relates to the estimated treatment effect on the risk of bleeding. It should be noted that this analysis included any type of bleeding event and bleeding at any time during the study period. A more informative analysis would distinguish between bleeding that occurred during or after the procedure and differentiate between minor bleeding and bleeding events that require rescue therapy and resource-intensive medical care. As the number of bleeding events observed across the three lusutrombopag RCTs was low, further studies with a large sample of patients may be required to establish the impact of lusutrombopag on procedural-related bleeding risk and the effects of lusutrombopag treatment in different settings.

CONCLUSION

This meta-analysis synthesised data from randomised, placebo-controlled trials to provide an overall estimate of the efficacy and safety of lusutrombopag and the uncertainty around these estimates. The meta-analysis results were consistent across the extended sensitivity analysis and confirm that treatment with lusutrombopag 3 mg was superior to placebo in producing a durable increase in platelet count in patients with CLD and baseline platelet count below 50×10^9/L who were undergoing planned invasive procedures. Pre-procedural lusutrombopag treatment allowed patients to avoid platelet transfusions, significantly lowering their risk of bleeding events compared to placebo, while demonstrating a safety profile similar to placebo, with no increase in the rate of thrombosis, including PVT.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. Most of the data that support these findings were derived from three open access publications, available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6849531/, https://www.cghjournal.org/article/S1542-3565(18)31324-7/fulltext, and https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6349796/. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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