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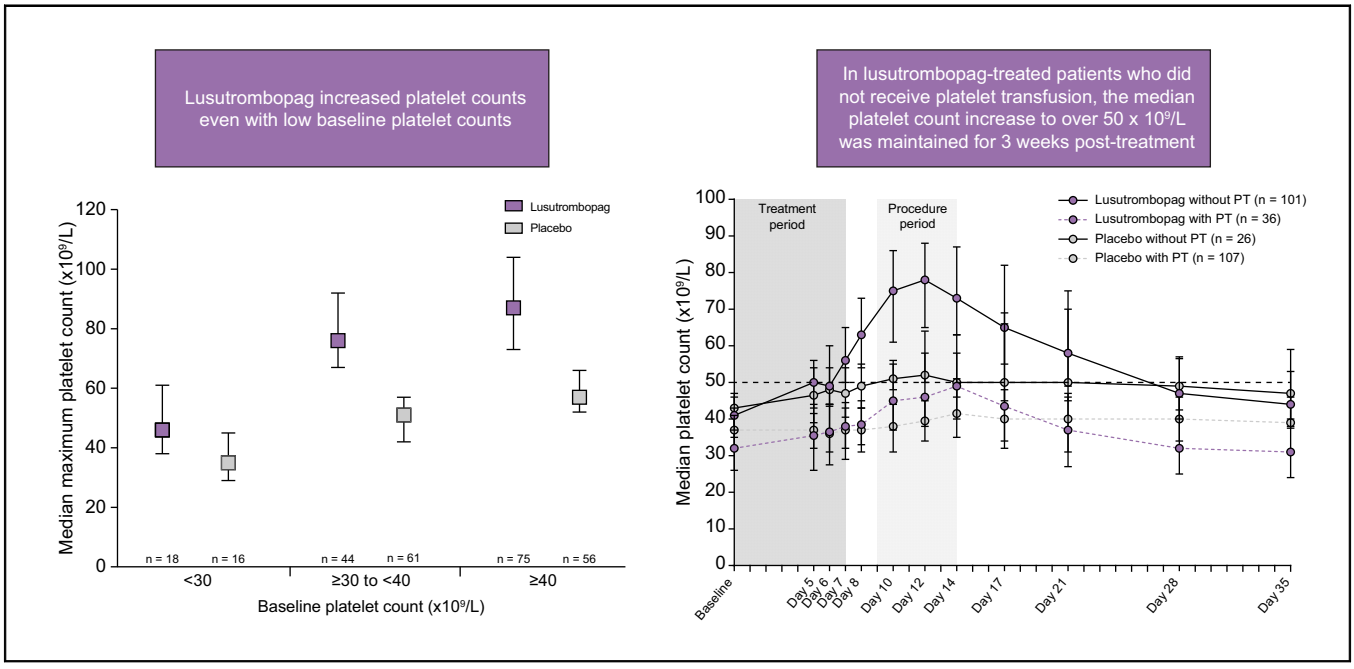
Graphical abstract



Highlights

- Thrombocytopaenia is common in patients with chronic liver disease.
- Lusutrombopag increased platelet count ≥1.5-fold in most patients with chronic liver disease-induced thrombocytopaenia.
- Lusutrombopag doubled platelet count in half of patients treated.
- Lusutrombopag-induced platelet count increases (without platelet transfusion) lasted for 3 weeks.

Lay summary

Patients with low platelet counts caused by chronic liver disease may not receive planned invasive procedures or surgeries because of an increased risk of bleeding. Lusutrombopag has previously demonstrated efficacy in raising platelet counts and is approved to treat chronic liver disease patients with low platelet counts in advance of a planned surgery. Physicians need to understand more clearly what to expect in terms of platelet count change when using lusutrombopag; this integrated analysis provides data to help guide its clinical application.

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Research article

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Assessing the periprocedural magnitude of platelet count change in response to lusutrombopag

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Background & Aims: Despite limitations, platelet transfusion has been used to minimise bleeding risk in patients with thrombocytopaenia. Lusutrombopag is an oral, thrombopoietin receptor agonist approved for treatment of thrombocytopaenia associated with chronic liver disease in patients undergoing planned invasive procedures. This *post-hoc* analysis assessed the magnitude of platelet count change based on the integrated per-protocol population from 2 similar phase III multicentre, randomised, double-blind, placebo-controlled trials.

Methods: Adults with chronic liver disease-induced thrombocytopaenia and platelet count <50 (× 10^9/L) received lusutrombopag 3 mg or placebo ≤7 days before invasive procedure scheduled 9–14 days after randomisation. Platelet transfusion was required per protocol if the platelet count remained <50 no more than 2 days before the planned invasive procedure. *Post-hoc* analysis included: proportion of patients with platelet count ≥50, ≥1.5-fold increase, and a doubling of platelet count; maximum and maximum change in platelet count; and platelet count time course.

Results: Platelet count ≥50, a platelet count increase ≥1.5-fold, and at least a doubling in platelet count were achieved in 88.3%, 86.9%, and 52.6% of patients in the lusutrombopag group (n = 137) *vs.* 58.6%, 32.3%, and 6.0% of patients in the placebo group (n = 133), respectively. In the lusutrombopag group, median maximum platelet count across baseline platelet counts of <30, ≥30 to <40, and ≥40 was 46, 76, and 87, respectively. Median maximum change in platelet count by baseline platelet count was +24, +42, and +40, respectively. Patients who received lusutrombopag without platelet transfusion achieved a median platelet count ≥50 for 3 weeks.

Conclusions: Patients treated with lusutrombopag experienced a clinically relevant response in platelet count for a substantial duration of time.

Lay summary: Patients with low platelet counts caused by chronic liver disease may not receive planned invasive procedures or surgeries because of an increased risk of bleeding. Lusutrombopag has previously demonstrated efficacy in raising platelet counts and is approved to treat chronic liver disease patients with low platelet counts in advance of a planned surgery. Physicians need to understand more clearly what to expect in terms of platelet count change when using lusutrombopag; this integrated analysis provides data to help guide its clinical application.

Introduction

Patients with thrombocytopaenia associated with chronic liver disease (TCP-CLD) are at risk for both thrombotic and haemorrhagic complications given the complex, altered balance between thrombosis and bleeding in this patient population.[1–3] TCP is a reflection of the severity of CLD and contributes to the potential increased risk of bleeding in CLD patients in conjunction with the interplay between multiple elements in the haemostatic system such as platelet dysfunction, anti-platelet antibodies, platelet sequestration and destruction related to hypersplenism, myelosuppression, and alterations in haematopoietic and coagulation factors.[1–3] For example, the risk of bleeding in CLD may be affected by decreased thrombin production when platelet counts fall below approximately 50 × 10^9/L,[4] yet this is countered by an increase in von Willebrand factor.[1,2]

Notwithstanding, TCP influences clinical decisions in CLD patients, in particular when weighing the risks *vs.* benefits of certain diagnostic or therapeutic interventions.[1–3] Most clinicians and society guidelines recommend that a patient has a

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platelet count ≥50 × 10^9/L before an invasive procedure.[5–11] Platelet transfusion has been the standard of care to reduce the risk of bleeding in patients with TCP-CLD undergoing invasive procedures.[12–15] However, platelet transfusions have limitations, including low effectiveness of platelet response, short duration of effectiveness, and refractoriness as a result of alloimmunisation.[12,13] Further, CLD patients are less likely to have an increase in platelet count ≥50 × 10^9/L after platelet transfusion.[16]

Lusutrombopag is an oral, thrombopoietin receptor agonist approved in Japan (2015) and the United States (2018) for the treatment of TCP, and in the European Union (2019) for severe TCP, associated with CLD in patients undergoing planned invasive procedures.[17–19] Two phase III, randomised, placebo-controlled trials (L-PLUS 1, JapicCTI-132323, M0631; L-PLUS 2, NCT02389621, M0634) demonstrated the efficacy and safety of lusutrombopag 3 mg orally daily for ≤7 days in patients with TCP-CLD.[20,21] In the intention-to-treat (ITT) and per-protocol (PP) populations, 68.2% and 73.7% of lusutrombopag patients met the primary endpoint (proportion of patients who did not require platelet transfusion before the primary invasive procedure and did not require rescue therapy for bleeding from randomisation through 7 days after the invasive procedure) *vs.* 23.9% and 17.3% of placebo patients for a difference of proportion of 44.4% and 55.8% (p <0.0001), respectively, in the integrated analysis of the L-PLUS studies.[22]

Non-randomised, observational studies have explored factors that may impact platelet response after lusutrombopag administration in TCP-CLD. A multivariate analysis identified that a subset of patients with a baseline platelet count <30 × 10^9/L (n = 58) were less likely to reach a maximum platelet count >50 × 10^9/L (hazard ratio [HR] 0.026; 95% CI 0.00–0.17; p <0.001) or have an increase >20 × 10^9/L (HR 0.11; CI 0.02–0.55; p = 0.007).[23] In another study, the maximum platelet count was 86 ± 26 × 10^9/L compared with 50 ± 20 × 10^9/L in patients with a baseline platelet count >30 × 10^9/L and ≤30 × 10^9/L (p <0.01), respectively.[24] The response rate, characterised as a platelet count ≥50 × 10^9/L the day before the procedure, was 94% (16/17 patients) in patients with a baseline platelet count >30 × 10^9/L and 63% (5/8 patients) in patients with a baseline platelet count ≤30 ×10^9/L (p = 0.08).[24] The first study found that patients with a higher splenic volume were less likely to have an increase in platelet count >20 × 10^9/L (HR 0.06; CI 0.00–0.67; p = 0.023);[23] the second study saw that patients with a higher splenic volume had a lower response rate with a baseline platelet count ≤30 × 10^9/L (p = 0.02).[24] A third study examined splenic volume in lusutrombopag non-responders (n = 10) and responders (n = 40), defined as patients who had a platelet count ≥50 ×10^9/L with an increase >20 × 10^9/L from baseline.[25] Responders had a lower splenic volume compared to non-responders (653.0 ± 267 ml *vs.* 1,092 ± 314 ml, p <0.0001). Splenic volume was found to be an independent factor that predicted platelet response in a multivariate analysis (odds ratio [OR] 11.2; CI 1.354–103.0; p = 0.025).[25]

However, predictors of successful treatment with lusutrombopag and the time course of platelet changes have not been well described. This analysis was undertaken to help clinicians better understand the platelet count response to lusutrombopag in comparison with placebo, including the increase in and time course of the platelet count, in patients with TCP-CLD before planned invasive procedures. The outcomes between lusutrombopag without platelet transfusion and placebo with platelet transfusion were also compared. The information presented here supplements the data from the pivotal phase III studies. It provides further details for clinicians regarding the expected magnitude, timing, and duration of the increase in platelet count with lusutrombopag that was not published in the primary L-PLUS 1 and L-PLUS 2 publications and will assist in procedural planning. With this knowledge, clinicians can make more informed and precise clinical decisions for patients with TCP-CLD, including those with low baseline platelet counts, before invasive procedures.

Patients and methods

Study design

This was a *post-hoc* analysis of data combined from the L-PLUS 1 and L-PLUS 2 studies. Full details of the individual studies are published in Hidaka *et al.*[20] and Peck-Radosavljevic *et al.*[21] Both studies were conducted in accordance with local and national regulatory requirements and under the protocols approved by respective institutional review boards or independent ethics committees in accordance with Good Clinical Practice (GCP) guidelines, the International Conference on Harmonisation (ICH), and Guideline for Good Clinical Practice (E6). All patients provided written informed consent. Patients were included in L-PLUS 1 if they were ≥20 years old with a platelet count <50 ×10^9/L at screening and in L-PLUS 2 if they were ≥18 years old with a platelet count <50 × 10^9/L at baseline on day 1 before randomisation. Other inclusion criteria for both studies included: patients who had TCP-CLD, defined as Child-Pugh class A or B cirrhosis; scheduled to undergo an invasive procedure 9–14 days after randomisation; and would likely require administration of platelets to increase the platelet count to ≥50 × 10^9/L. Exclusion criteria included high-risk procedures such as laparotomy, thoracotomy, craniotomy, open-heart surgery, organ resection, partial organ resection, and partial splenic embolisation. Patients who were diagnosed with conditions such as haematopoietic tumours, aplastic anaemia, myelodysplastic syndrome or myelofibrosis, or congenital, immune, or drug-induced TCP, or who were Child-Pugh class C were also excluded. Additional exclusion criteria included: history or presence of thrombotic disease, including portal vein thrombosis; diagnosis of malignancies other than the treatment target of the primary invasive procedure in the study; malignant tumours requiring any systemic treatment or radiotherapy during the study or were associated with metastasis or invasion of surrounding organs; history or presence of disease associated with a risk of bleeding; or splenectomy or liver transplant.

The L-PLUS studies had comparable endpoints and similar study design (Fig. 1[26]).[20,21] Patients were randomised in a 1:1 ratio to receive lusutrombopag 3 mg or matching placebo once daily for ≤7 days before an invasive procedure planned 9–14 days after randomisation. A preoperative platelet transfusion was required if the platelet count was <50 × 10^9/L on or after day 8, but no more than 2 days before the procedure.

Post-hoc analysis

The ITT population included all randomised patients. The PP population included all randomised patients who had no major protocol deviations. After platelet transfusion, platelet counts for those patients that received platelet transfusions were included in all groups for this analysis. Data were evaluated descriptively.

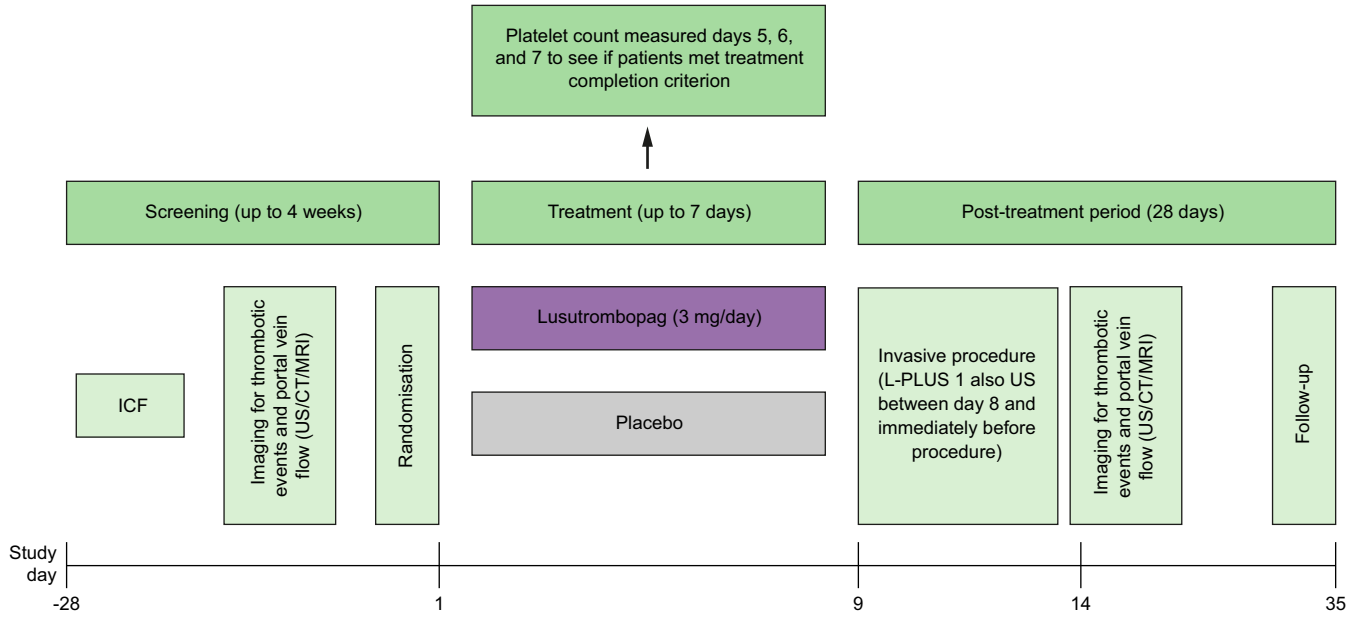

Fig. 1. Study design. CT, computerised tomography; ICF, informed consent form; US, ultrasonography; MRI, magnetic resonance imaging; Reprinted from Alkhouri N, Imawari M, Izumi N, Osaki Y, Ochiai T, Kano T, *et al.* Clin Gastroenterol Hepatol 2020;18:2600-2608. https://doi.org/10.1016/j.cgh.2020.03.032. [Epub ahead of print]; under Creative Commons Attribution-NonCommercial-No Derivatives License (CC BY NC ND) (https://creativecommons.org/licenses/by-nc-nd/4.0/)

The *post-hoc* assessments evaluating patients in the PP population who received lusutrombopag *vs.* placebo included the proportion of patients who achieved a platelet count ≥50 × 10^9/L, had an increase ≥1.5-fold from baseline, and experienced at least a doubling from baseline at least once during the study; the earliest day patients achieved a platelet count of ≥50 × 10^9/L after the initial dose of study drug; the average maximum, and the maximum change in platelet count in each group stratified according to baseline platelet count (<30 × 10^9/L, ≥30 × 10^9/L to <40 × 10^9/L, and ≥40 × 10^9/L); and the proportion of patients who achieved a platelet count ≥50 × 10^9/L in the lusutrombopag-treated compared with the placebo-treated patients at the platelet transfusion assessment, which occurred on or after day 8, but no more than 2 days before the invasive procedure.

A subgroup analysis of the proportion of patients in the lusutrombopag without platelet transfusion group and placebo with platelet transfusion group assessed the achievement of a platelet count increase ≥50 × 10^9/L, ≥1.5-fold from baseline, and at least a doubling from baseline at least once during the study and the maximum and maximum change in platelet count by baseline value. An additional subgroup analysis of the platelet count over time in 4 subgroups, lusutrombopag without platelet transfusion, lusutrombopag with platelet transfusion, placebo without platelet transfusion, and placebo with platelet transfusion, was also performed.

Safety

Safety data, assessed as treatment-emergent adverse events (TEAEs) in all randomised patients who received at least 1 dose of study drug, were collected from the signing of informed consent through completion of the post-treatment period or early termination. Investigators characterised the relationship of TEAEs to treatment and coded the severity of adverse events (AEs) as mild (minor, did not interfere with usual daily activities), moderate (discomfort, interfered with usual daily activity or affected clinical status), or severe (caused interruption of usual daily activities or had a clinically significant effect). Any AE resulting in death, a life-threatening condition, hospitalisation or prolongation of hospitalisation, persistent or significant disability/incapacity, congenital anomaly/birth defect, or other medically important condition that could jeopardise the patient and may require medical intervention to prevent 1 of the outcomes listed in this definition was deemed a serious AE. Ultrasonography, computerised tomography, and magnetic resonance imaging were performed prospectively during screening, 3–10 days after the procedure, and at cessation of study drug or early termination. These imaging studies were performed at these specified time points (in L-PLUS 1, ultrasonography was also performed between day 8 and immediately before the procedure) to prospectively assess for thrombotic and thromboembolic events, which were considered TEAEs of special interest. Evaluations for asymptomatic portal vein thrombosis and portal blood flow direction were completed before and after therapy.[20,21]

Results

A total of 312 patients with TCP-CLD were randomised for the ITT population in the integrated study. The PP population consisted of 137 lusutrombopag-treated patients and 133 placebo-treated patients. A total of 20 lusutrombopag-treated and 22 placebo-treated patients were excluded from the PP population. The most common reason for exclusion was non-compliance with pre-procedural platelet transfusion instructions (see Fig. S1, for patient disposition). Demographics and baseline characteristics for the ITT and PP populations were similar (Table 1).

In the *post-hoc* analysis, the proportion of patients who achieved a platelet count ≥50 × 10^9/L at least once during the study was 88.3% in the lusutrombopag group *vs.* 58.6% in the placebo

Table 1. Integrated demographics and baseline characteristics for the intention-to-treat and per-protocol population.

Characteristic		ITT population		PP population	
		LUSU 3 mg n = 157 n (%)	PBO n = 155 n (%)	LUSU 3 mg n = 137 n (%)	PBO n = 133 n (%)
Sex	Male	87 (55.4)	99 (63.9)	71 (51.8)	84 (63.2)
	Female	70 (44.6)	56 (36.1)	66 (48.2)	49 (36.8)
Age (years)	Mean	59.4	59.4	60.0	59.2
	SD	12.1	11.8	11.4	12.4
Race	White	85 (54.1)	86 (55.5)	74 (54.0)	70 (52.6)
	Asian	64 (40.8)	65 (41.9)	57 (41.6)	59 (44.4)
	American Indian or Alaska Native	2 (1.3)	0	2 (1.5)	0
	African American	1 (0.6)	0	1 (0.7)	0
	Other	3 (1.9)	0	2 (1.5)	0
	Not provided	2 (1.3)	4 (2.6)	1 (0.7)	4 (3.0)
Region	North America	19 (12.1)	11 (7.1)	17 (12.4)	8 (6.0)
	Europe	44 (28.0)	50 (32.3)	39 (28.5)	39 (29.3)
	Asia	62 (39.5)	65 (41.9)	56 (40.9)	59 (44.4)
	Rest of world	32 (20.4)	29 (18.7)	25 (18.2)	27 (20.3)
BMI (kg/m^2)	Mean	26.4	26.7[a]	26.1	26.5[b]
	SD	5.2	5.5	5.0	5.4
Aetiology of cirrhosis	Hepatitis C	91 (58.0)	83 (53.5)	84 (61.3)	69 (51.9)
	Hepatitis B	28 (17.8)	29 (18.7)	22 (16.1)	25 (18.8)
	Alcoholic hepatitis	27 (17.2)	32 (20.6)	22 (16.1)	26 (19.5)
	Non-alcoholic hepatitis	15 (9.6)	19 (12.3)	11 (8.0)	17 (12.8)
	Autoimmune hepatitis	5 (3.2)	5 (3.2)	5 (3.6)	4 (3.0)
	Other hepatitis	16 (10.2)	7 (4.5)	13 (9.5)	7 (5.3)
History of any transfusion[c]		76 (48.4)	88 (56.8)	67 (48.9)	74 (55.6)
Child-Pugh class	A	99 (63.1)	85 (54.8)	84 (61.3)	74 (55.6)
	B	55 (35.0)	69 (44.5)	53 (38.7)	58 (43.6)
	C	3 (1.9)[d]	0	0	0
WHO Bleeding Scale	Grade 0	144 (91.7)	139 (89.7)	126 (92.0)	119 (89.5)
	Grade 1	12 (7.6)	16 (10.3)	11 (8.0)	14 (10.5)
Baseline platelet count ($10^9/L$)[e]	Mean	38.8[f]	38.2[a]	38.6	37.8
	SD	8.5	7.6	8.3	7.5
	<35	43 (27.4)	48 (31.0)	38 (27.7)	41 (30.8)
	≥35	113 (72.0)	106 (68.4)	99 (72.3)	92 (69.2)
Splenomegaly[g]		141 (89.8)	141 (91.0)	124 (90.5)	121 (91.0)
Ascites		33 (21.0)	39 (25.2)	31 (22.6)	34 (25.6)
Hepatic encephalopathy	None/no encephalopathy	124 (79.0)	125 (80.6)	109 (79.6)	109 (82.0)
	Grade I–II/encephalopathy controlled medically	33 (21.0)	30 (19.4)	28 (20.4)	24 (18.0)

CLD, chronic liver disease; ITT, intent-to-treat; LUSU, lusutrombopag; PBO, placebo; PP, per protocol; SD, standard deviation; WHO, World Health Organization. Data are shown as mean and standard deviation or absolute numbers and percentages.

[a] Calculated for 154 out of 155 patients.

[b] Calculated for 132 out of 122 patients.

[c] Including whole blood, red blood cells, platelets, other transfusion, or transfusion type unspecified.

[d] Three patients with Child-Pugh class 3 liver disease were erroneously enrolled and were excluded from the per protocol population.

[e] The value observed on day 1 before the initial dose of study drug. If this value was missing, the most recent value obtained before day 1 within the 7 preceding days was used.

[f] Calculated for 156 out of 157 patients.

[g] Splenomegaly was confirmed by ultrasonography, computerised tomography, or magnetic resonance imaging in the screening phase.

group. The proportion of patients who achieved a platelet count increase of ≥1.5-fold from baseline and at least a doubling in the platelet count from baseline at least once was 86.9% and 52.6% in the lusutrombopag group and 32.3% and 6.0% in the placebo group, respectively (Fig. 2). Patients who received lusutrombopag reached a platelet count ≥50 × 10^9/L more rapidly than those who received placebo (Fig. 3). Lusutrombopag-treated patients who achieved a platelet count ≥50 × 10^9/L did so in a median of 6 days whereas placebo-treated patients attained this in a median of 10 days. The median maximum platelet count in each group stratified according to the baseline platelet count (<30 × 10^9/L, ≥30 × 10^9/L to <40 × 10^9/L, and ≥40 × 10^9/L) was higher in lusutrombopag-treated patients compared with placebo-treated patients (Fig. 4). The median maximum change in platelet count by baseline platelet count in lusutrombopag-treated patients was 24 × 10^9/L, 42 × 10^9/L, and 40 × 10^9/L, whereas in placebo-treated patients it was 8 × 10^9/L, 14 × 10^9/L, and 12 × 10^9/L. At the platelet transfusion assessment, the proportion of patients who achieved a platelet count ≥50 × 10^9/L was 75.0% for lusutrombopag-treated patients, compared with 17.7% for patients who received placebo (Fig. 5). Five patients had a baseline platelet count <20 × 10^9/L, of these, 4 received lusutrombopag (see Table S1, for summary information for patients with baseline platelet counts <20 × 10^9/L in the PP population). Three of the 4 lusutrombopag-treated patients had a platelet count that more than doubled from baseline (2 reached a maximum platelet count ≥50 × 10^9/L without platelet transfusion and 1 had an increase 3-fold above baseline before platelet transfusion). One lusutrombopag-treated patient achieved a maximum platelet count approximately 2.5-fold above baseline 1 day after receiving a platelet transfusion.

Subgroup analyses were performed in the lusutrombopag without platelet transfusion and placebo with platelet transfusion groups. More patients in the lusutrombopag without

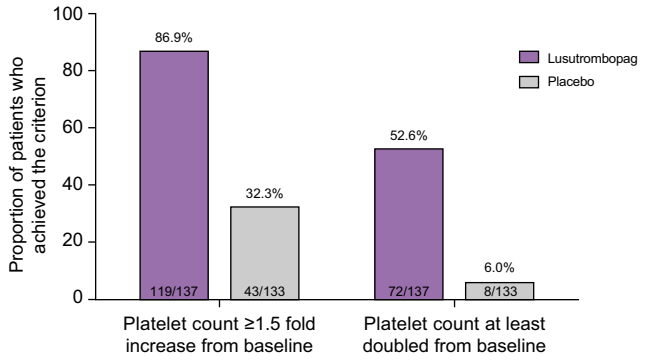

Fig. 2. Proportion of patients who achieved a platelet count increase ≥1.5-fold from baseline and platelet count that at least doubled from baseline in the per-protocol population.

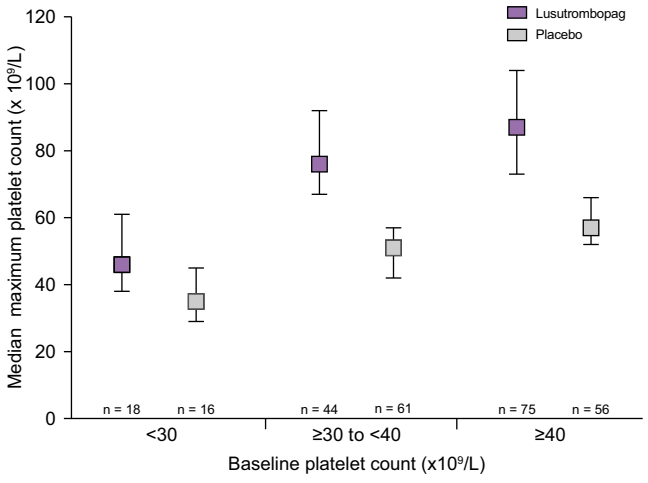

Fig. 4. Median maximum platelet count in each group stratified according to the baseline platelet count in the per-protocol population. Purple and grey boxes, median; error bars, 25th and 75th percentiles.

platelet transfusion group (99.0%) reached a platelet count ≥50 × 10^9/L *vs.* the placebo with platelet transfusion group (51.4%). [Note: The minimum maximum platelet count value for this cohort (and the overall cohort) was 48 × 10^9/L. This patient, whose platelet count was measured on study day 8 before the planned invasive procedure, prematurely discontinued from the study on day 11 hence the invasive procedure was cancelled and no platelet transfusion was administered.] In addition, more patients in the lusutrombopag without platelet transfusion group achieved a platelet count increase ≥1.5-fold from baseline and at least a doubling from baseline (92.1% and 61.4%) as compared with the placebo with platelet transfusion group (29.0% and 2.8%) (Fig. 6). The overall median platelet count in the lusutrombopag without platelet transfusion group was 87 × 10^9/L (IQR 73 × 10^9/L, 100 × 10^9/L) compared with 50 × 10^9/L (IQR 42 × 10^9/L, 57 × 10^9/L) in the placebo with platelet transfusion group. When stratified by the baseline platelet count, the single maximum platelet counts were higher in each of the baseline platelet count groups (<30 × 10^9/L, ≥30 × 10^9/L to <40 × 10^9/L, ≥40 × 10^9/L) in the lusutrombopag without platelet transfusion group as compared with the placebo with platelet transfusion group (see Table S2 for subgroup summary statistics for maximum platelet count by baseline value in the PP population). The overall median maximum change in platelet count in the lusutrombopag without platelet transfusion group was 47 × 10^9/L (IQR 34 × 10^9/L, 61 × 10^9/L) compared with 12 × 10^9/L (IQR 6 × 10^9/L, 19 × 10^9/L) in the placebo with platelet transfusion group. When stratified by the baseline platelet count, the single maximum change in platelet counts were higher in each of the baseline platelet count groups in the lusutrombopag without platelet transfusion group as compared with the placebo with platelet transfusion group (see Table S3 for subgroup summary statistics for maximum change in platelet count by baseline value in the PP population).

The platelet count over time was evaluated in 4 subgroups. This analysis showed that patients who received lusutrombopag

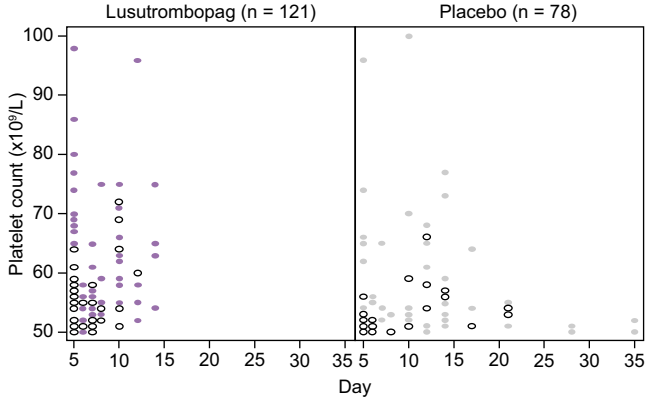

Fig. 3. Earliest day when patients achieved a platelet count of ≥50 × 10^9/L after initial dose of study drug in the per-protocol population. Solid coloured circles represent 1 patient and black outlined circles represent more than 1 patient.

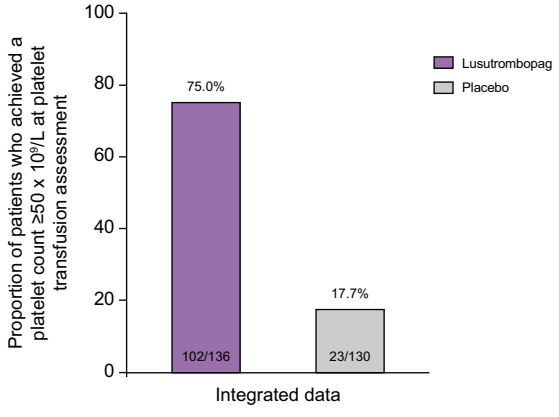

Fig. 5. Proportion of patients who achieved a platelet count ≥50 × 10^9/L at platelet transfusion assessment in the per-protocol population. The study protocol required to measure a platelet count on or after day 8, but no more than 2 days before the primary invasive procedure, to assess the need for a pre-operative platelet transfusion before the procedure. One patient in the lusutrombopag group and 3 patients in the placebo group did not have a platelet count recorded in the case form at the platelet transfusion assessment and were excluded from this analysis.

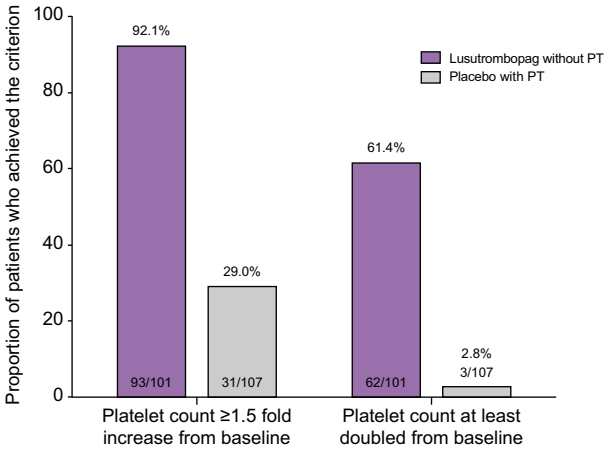

Fig. 6. Subgroup analysis of the proportion of patients in the lusutrombopag without platelet transfusion group and placebo with platelet transfusion group who achieved platelet count increase ≥1.5-fold from baseline and platelet count that at least doubled from baseline in the per-protocol population. PT, platelet transfusion.

without platelet transfusion achieved median platelet counts >50 × 10^9/L during the procedure period and for nearly 3 weeks in total during the study as compared with patients in the lusutrombopag with platelet transfusion, placebo without platelet transfusion, and placebo with platelet transfusion groups (Fig. 7).

Safety

Lusutrombopag was well tolerated with few serious adverse events. Patients in both groups reported ≥1 TEAE (61.9% in lusutrombopag group, 64.5% in placebo group), but most were mild in severity and deemed not related to treatment. TEAEs that occurred in ≥10% of patients in either group were postoperative fever (12.3% lusutrombopag, 18.1% placebo), procedural pain (16.1% lusutrombopag, 14.2% placebo), procedural hypertension (12.9% lusutrombopag, 11.6% placebo), and elevation in aspartate aminotransferase (7.7% lusutrombopag, 11.0% placebo). There were 25 (16.1%) TEAEs in the lusutrombopag group and 28 (18.1%) in the placebo group that were deemed severe, of which 1 (0.6%) in the lusutrombopag group was deemed treatment related. AEs that were deemed treatment-related occurred in 6.5% and 9.0% of lusutrombopag- and placebo-treated patients, respectively. Treatment-related AEs that occurred in ≥2 patients in either group included headache (1.9% lusutrombopag), nausea (1.9% lusutrombopag, 1.3% placebo), abdominal pain (1.9% placebo), diarrhoea (0.6% lusutrombopag, 1.3% placebo), vomiting (1.3% placebo), fatigue (1.3% placebo), aspartate aminotransferase increased (1.3% placebo), and international normalised ratio increased (1.3% placebo). Eight (5.2%) serious AEs occurred in the lusutrombopag group and 11 (7.1%) occurred in the placebo group, of which 2 (1.3%) and 1 (0.6%) were deemed treatment-related, respectively. Thrombotic and thromboembolic events were extremely rare, with 1 asymptomatic portal vein thrombosis and 1 cardiac ventricular thrombosis (the patient had a history of cardiac ventricular thrombosis) in the lusutrombopag group and 1 asymptomatic portal vein thrombosis in the placebo group were considered treatment-related. There were bleeding-related events in 6.5% of lusutrombopag-treated patients and 12.3% of placebo-treated patients. There were 3 deaths, considered not related to the study drug, in the lusutrombopag group and none in the placebo group. The full details of safety analyses for the L-PLUS 1 and L-PLUS 2 studies have been published in Hidaka *et al.*[20] and Peck-Radosavljevic *et al.*,[21] respectively.

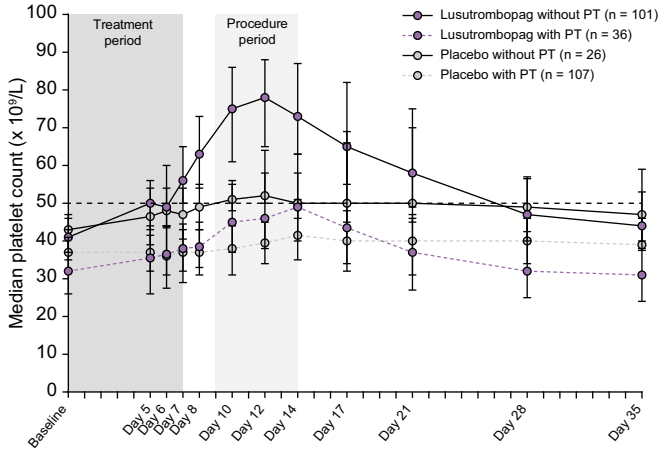

Fig. 7. Subgroup analysis of the platelet count over time in the lusutrombopag without platelet transfusion, lusutrombopag with platelet transfusion, placebo without platelet transfusion, and placebo with platelet transfusion in the per-protocol population. PT, platelet transfusion. Error bars represent 25th and 75th percentiles.

Discussion

Clinicians generally target a platelet count >50 × 10^9/L before planned invasive procedures to prevent bleeding in patients with TCP-CLD.[6,27] As discussed earlier, multiple factors, including potentially reduced thrombin production when platelet counts are <50 × 10^9/L,[4] contribute to the possibility of increased bleeding risk in CLD patients.[1–3] Studies have identified that the risk of procedure-related bleeding is increased when platelet counts fall below approximately 60 to 75 × 10^9/L, with the highest risk of bleeding occurring when the platelet count is <10 to 20 × 10^9/L.[28–30] In general, CLD patients with platelet counts ≤50 × 10^9/L are considered to be at high risk for procedure-related bleeding.[31]

In this analysis, more patients in the lusutrombopag group achieved a platelet count ≥50 × 10^9/L at least once during the study and at the platelet transfusion assessment. The majority of patients in the lusutrombopag group experienced a ≥1.5-fold increase and approximately 50% had at least a doubling in their platelet count from baseline, including those patients with baseline platelet counts <20 × 10^9/L. Lusutrombopag-treated patients who reached a platelet count ≥50 × 10^9/L did so sooner than placebo-treated patients and experienced average maximum platelet counts at or above this target. Altogether, this highlights that lusutrombopag-treated patients consistently experienced a clinically relevant response in platelet count as compared to placebo, even with low baseline platelet counts. This knowledge of the expected magnitude and timing of platelet count change with lusutrombopag will improve clinical planning and decision-making as well as potentially allow certain patients to undergo invasive procedures who were previously not considered candidates owing to the risk of procedure-related

bleeding. For instance, given that platelet counts will increase by ≥1.5-fold with lusutrombopag, patients with very low baseline platelet counts may qualify for procedures that have a target platelet count ≥20 × 10^9/L.[31] Further, patients for whom platelet transfusions are not anticipated to produce the target platelet count or would require high doses of platelet transfusions to reach the physician-determined target platelet count before the planned procedure may be able to achieve the target with lusutrombopag.[6,32]

The time course of the platelet count increase is also important for decreasing the risk of bleeding after the procedure.[27] The platelet count over time in the lusutrombopag without platelet transfusion group demonstrated that the increase in platelet count is maintained over the time course needed for planned invasive procedures. Patients in this subgroup had median platelet counts >50 × 10^9/L for approximately 3 weeks over the duration of the study period. The clinical implications of the duration of platelet count increase allows for optimising the timing of planned invasive procedures in patients with TCP-CLD.

This *post-hoc* analysis corroborates the ineffectiveness of platelet transfusions in TCP-CLD.[6] Patients in the placebo group were less likely to reach a platelet count ≥50 × 10^9/L, have a ≥1.5-fold increase, or a doubling in platelet count from baseline even after receiving platelet transfusions, whereby those who received lusutrombopag without platelet transfusion reached these criteria a majority of the time. Real-world observational studies support these findings. In a study of 15 patients who received lusutrombopag before radiofrequency ablation, the platelet count increased from 38 × 10^9/L to 72 × 10^9/L.[33] Another study found that the difference in the increase in platelet count with lusutrombopag *vs.* platelet transfusion was 46 × 10^9/L *vs.* 10 × 10^9/L, respectively (p <0.0001).[34] The response rate, defined as an increase in platelet count >10 × 10^9/L, was 100% (33/33 patients) with lusutrombopag as opposed to 51.4% (19/37 patients) with platelet transfusion (p <0.0001).

One limitation of this *post-hoc* analysis is that additional factors that may confound response to lusutrombopag or platelet transfusion, such as splenic volume, were not evaluated. Studies are needed to elucidate why there is variability in responses. Other limitations are that patients undergoing higher-risk procedures, such as neurosurgical interventions or major cardiac, intra-abdominal, and orthopaedic surgeries,[7,31] and those with the most decompensated cirrhosis (Child-Pugh class C) were not included in the L-PLUS 1 and L-PLUS 2, which limits the generalisability of these findings to CLD patients with the highest risk of bleeding. Lastly, both platelet transfusions and thrombopoietin agonists are considered options to increase platelet counts in patients with TCP-CLD before invasive procedures[8] but their impact on procedural and post-procedural related bleeding events is still controversial.[7,32,35] The effect of lusutrombopag on bleeding events has not been fully elucidated, however, numerically fewer bleeding events occurred in patients receiving lusutrombopag 3 mg/day compared with placebo in the two phase III and phase IIb studies[20,21,36] and a *post-hoc* analysis of their pooled data suggests that patients treated with lusutrombopag who did not receive platelet transfusions had fewer bleeding events compared with placebo patients who received platelet transfusions.[37]

In closing, the magnitude of the platelet count change experienced in TCP-CLD patients receiving lusutrombopag provides a clinically relevant increase in platelets. Lusutrombopag reliably produces an increase in platelet count ≥50 × 10^9/L, in a median of 6 days in most patients, that is maintained for 3 weeks, thus providing a safe and efficacious alternative to platelet transfusion to decrease the potential risk of bleeding associated with invasive procedures.

Abbreviations

AE, adverse event; CLD, chronic liver disease; GCP, Good Clinical Practice; HR, hazard ratio; ICH, International Conference on Harmonisation; ICF, informed consent form; ITT, intention-to-treat; LUSU, lusutrombopag; PBO, placebo; PP, per protocol; PT, platelet transfusion; TCP, thrombocytopaenia; TEAE, treatment-emergent adverse event; US, ultrasonography; WHO, World Health Organization; CT, computerised tomography; MRI, magnetic resonance imaging.

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Conflicts of interest

Robert S. Brown, Jr: Consultant and research support from AbbVie, Shionogi, Dova, Gilead, Intercept. Michio Imawari: Advisor for Shionogi, Japan Bio Products and EA Pharma. Namiki Izumi: Funding for speakers bureau from AbbVie, Shionogi, Bayer, Gilead, Otsuka, and Eisai. Yukio Osaki: Speaking and teaching for Gilead, Bayer Yakuhin, MSD, Shionogi, AbbVie GK, and Eisai. Roy Bentley: Shionogi employee. Toshimitsu Ochiai: Shionogi employee. Takeshi Kano: Shionogi employee. Markus Peck-Radosavljevic: Personal fees from Shionogi during the conduct of this study.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conceptualisation: MI. Data curation: YO. Formal analysis: All authors. Project administration: TK. Supervision: MI. Writing – original draft: All authors. Writing – review & editing: All authors. Other: Statistical analysis: TO. All authors had access to all of the data and can vouch for the integrity of the data analyses. All authors have reviewed the manuscript and approved the final submitted version.

Data availability statement

Shionogi Inc. has a data sharing policy and requests can be submitted for anonymised patient level data.

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Supplementary data

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Author names in bold designate shared co-first authorship

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