Lusutrombopag Is Safe and Efficacious for Treatment of Thrombocytopenia in Patients With and Without Hepatocellular Carcinoma

Naim Alkhouri,[*] Michio Imawari,[‡] Namiki Izumi,[§] Yukio Osaki,[‖] Toshimitsu Ochiai,[¶] Takeshi Kano,[#] Roy Bentley,[**] and Franco Trevisani[‡‡]

[*]Department of Metabolic Center, Texas Liver Institute, San Antonio, Texas; [‡]Institute for Gastrointestinal and Liver Disease, Shin-Yurigaoka General Hospital, Kawasaki, Japan; [§]Department of Gastroenterology and Hepatology, Musashino Red Cross Hospital, Tokyo, Japan; [‖]Meiwa Hospital, Nishinomiya, Japan; [¶]Biostatistics Center, [#]Global Project Management Department, Shionogi & Co, Ltd, Osaka, Japan; [**]Global Market Access, Shionogi, Inc, Florham Park, New Jersey; [‡‡]Department of Medical and Surgical Sciences, Alma Mater Studiorum, University of Bologna, Bologna, Italy

BACKGROUND & AIMS: **Patients with hepatocellular carcinoma (HCC) secondary to chronic liver disease often require invasive procedures but frequently have thrombocytopenia. Lusutrombopag is an agonist of the thrombopoietin receptor that activates platelet production.**

METHODS: **We performed an integrated analysis of data from 2 phase 3 trials (L-PLUS 1, Japan, October 2013 to May 2014, and L-PLUS 2, global, June 2015 to April 2017) that compared the efficacy and safety of lusutrombopag with placebo in patients with chronic liver disease, with and without HCC. Our analysis included patients with Eastern Cooperative Oncology Group grades of 0 or 1, Child–Pugh classes A or B, and a platelet count less than 50×10^9/L who were scheduled to undergo invasive procedures in 9 to 14 days. Patients received lusutrombopag (3 mg) or placebo daily for 7 days or fewer before an invasive procedure. Imaging studies assessed treatment-emergent adverse events, including asymptomatic portal vein thrombosis. The primary end point was no requirement for platelet transfusion before the invasive procedure and rescue therapies for bleeding 7 days or fewer after the invasive procedure.**

RESULTS: **The per-protocol population included 270 patients (95 with HCC). A significantly higher proportion of patients with HCC who received lusutrombopag achieved the primary end point (68.0%) vs patients who received placebo (8.9%) ($P < .0001$); in patients without HCC, these proportions were 77.0% vs 21.6% ($P < .0001$). Lusutrombopag reduced the need for platelet transfusions, increased platelet counts for 3 weeks, and reduced the number of bleeding events in patients with and without HCC compared with placebo. Risk of thrombosis was similar to that of placebo.**

CONCLUSIONS: **Patients with and without HCC receiving lusutrombopag had a reduction in the number of platelet transfusions before invasive procedures compared with patients receiving placebo, with no increase in thrombosis or bleeding. L-PLUS 1: JapicCTI-132323; L-PLUS 2: ClinicalTrials.gov number no: NCT02389621.**

Keywords: Hepatocellular Carcinoma; Chronic Liver Disease; Thrombopoietin Receptor Agonist; Invasive Procedure.

Hepatocellular carcinoma (HCC) is the fifth most common cancer in men, the ninth most common cancer in women, and the second most common cause of cancer deaths worldwide.[1] HCC frequently is secondary to chronic liver disease (CLD) owing to infection with hepatitis viruses or inappropriate alcohol consumption.[2] In developed countries, nonalcoholic fatty liver, particularly, nonalcoholic steatohepatitis, is an emerging risk factor accounting for a rapidly growing proportion of HCC.[2]

Abbreviations used in this paper: **CLD, chronic liver disease; HCC, hepatocellular carcinoma; PP, per-protocol; PVT, portal vein thrombosis; TCP-CLD, thrombocytopenia associated with chronic liver disease; TEAE, treatment-emergent adverse event; TPO-RA, thrombopoietin receptor agonist.**

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Thrombocytopenia frequently is present in patients with cirrhosis who require an invasive procedure as part of their routine clinical care. Preoperative thrombocytopenia is associated with unfavorable outcomes and worse overall survival of patients with HCC.[3,4] Cirrhotic patients have an increased risk of vein thrombosis, particularly portal vein thrombosis (PVT), which is increased further by the development of HCC.[5–7]

Patients with HCC frequently require invasive diagnostic (liver biopsy) and therapeutic procedures (eg, variceal band ligation, liver resection percutaneous ablation, and transarterial chemoembolization).[8–10] Because the vast majority of HCC develops in a setting of cirrhosis, patients with this tumor have a higher risk of bleeding with invasive procedures.[11]

In patients with thrombocytopenia associated with CLD (TCP-CLD) undergoing invasive procedures, platelet transfusion is the mainstay of treatment to increase the platelet count to reduce the bleeding risk.[12,13] However, platelet transfusions have several limitations, including a short duration of effectiveness and complications such as platelet refractoriness resulting from alloimmunization.[14] Moreover, in patients with CLD, platelet transfusions do not always result in maintenance of desired hemostatic platelet levels.[12,13] Approximately 22% of platelet transfusions are not effective, with liver disease being a significant risk factor (odds ratio, 1.84; 95% CI, 1.24–2.73).[15]

Lusutrombopag (Shionogi & Co, Ltd, Osaka, Japan) is an oral thrombopoietin receptor agonist (TPO-RA) that activates the signal transduction pathway in the same fashion as endogenous thrombopoietin to induce platelet production.[16,17] Lusutrombopag has been approved globally (EU in 2019, Japan in 2015, and the United States in 2018) for the treatment of TCP-CLD (EU approval for severe thrombocytopenia) in adults scheduled to undergo an invasive procedure.[16–19] Clinical trials have shown the efficacy and safety of lusutrombopag in patients with TCP-CLD.[20–22] In this integrated analysis of 2 trials, the efficacy and safety of lusutrombopag in patients with TCP-CLD and HCC was assessed in comparison with those without HCC.

What You Need to Know

Background

Patients with hepatocellular carcinoma (HCC) secondary to chronic liver disease often require invasive procedures, but frequently have thrombocytopenia. Lusutrombopag is an agonist of the thrombopoietin receptor that activates platelet production.

Findings

Patients with and without HCC receiving lusutrombopag had a reduction in the number of platelet transfusions before invasive procedures compared with patients receiving placebo, with no increase in thrombosis or bleeding.

Implications for patient care

Lusutrombopag can increase platelet counts in patients with chronic liver disease, with or without HCC, before they undergo invasive procedures minimizing need for platelet transfusions, transfusion-related complications, delays in procedures, and bleeding events.

Methods

Study Design and Treatment

L-PLUS 1 and L-PLUS 2 were 2 phase 3, multicenter, randomized, double-blind, placebo-controlled studies with similar end points and the same study design (Figure 1). The trials were conducted according to good practice guidelines and were approved by the Institutional Review Board at each site.[21,22] This manuscript was reviewed and approved by all the authors who had access to all study data.

After a screening period of 28 days, eligible patients were randomized in a 1:1 ratio to receive either lusutrombopag 3 mg or placebo once daily for 7 days or fewer before an invasive procedure performed 9 to 14 days after randomization.[21,22] Patients were stratified based on the type of primary invasive procedure (liver ablation/coagulation or other invasive procedure) and the platelet count at the time of screening for L-PLUS 1 ($<35 \times 10^9$/L, 35–$<45 \times 10^9$/L, and $\geq 45 \times 10^9$/L) and at baseline (day 1) for L-PLUS 2 ($<35 \times 10^9$/L or $\geq 35 \times 10^9$/L). Treatment completion criteria was satisfied if the patient reached a platelet count of $\geq 50 \times 10^9$/L with an increase of $\geq 20 \times 10^9$/L from baseline. A preoperative platelet transfusion was required if the platelet count was less than 50×10^9/L as determined on or after day 8, but no more than 2 days before the procedure.

Treatment-emergent adverse events (TEAEs) of special interest, including asymptomatic PVT and portal blood flow, were assessed prospectively by imaging studies.[21,22] Computed tomography, magnetic resonance imaging, or ultrasonography were performed during screening, 3 to 10 days after the procedure, and at cessation of the study drug.[21,22]

Participants

The key inclusion criteria included adult patients with Child–Pugh class A or B CLD with a platelet count less than 50×10^9/L at baseline who were scheduled to undergo an invasive procedure 9 to 14 days after randomization.[21,22] Key exclusion criteria included the following: patients undergoing major surgical procedures; patients with splenectomy, liver transplantation, uncontrolled ascites, or hepatic encephalopathy; patients with PVT, hematopoietic tumors, aplastic anemia,

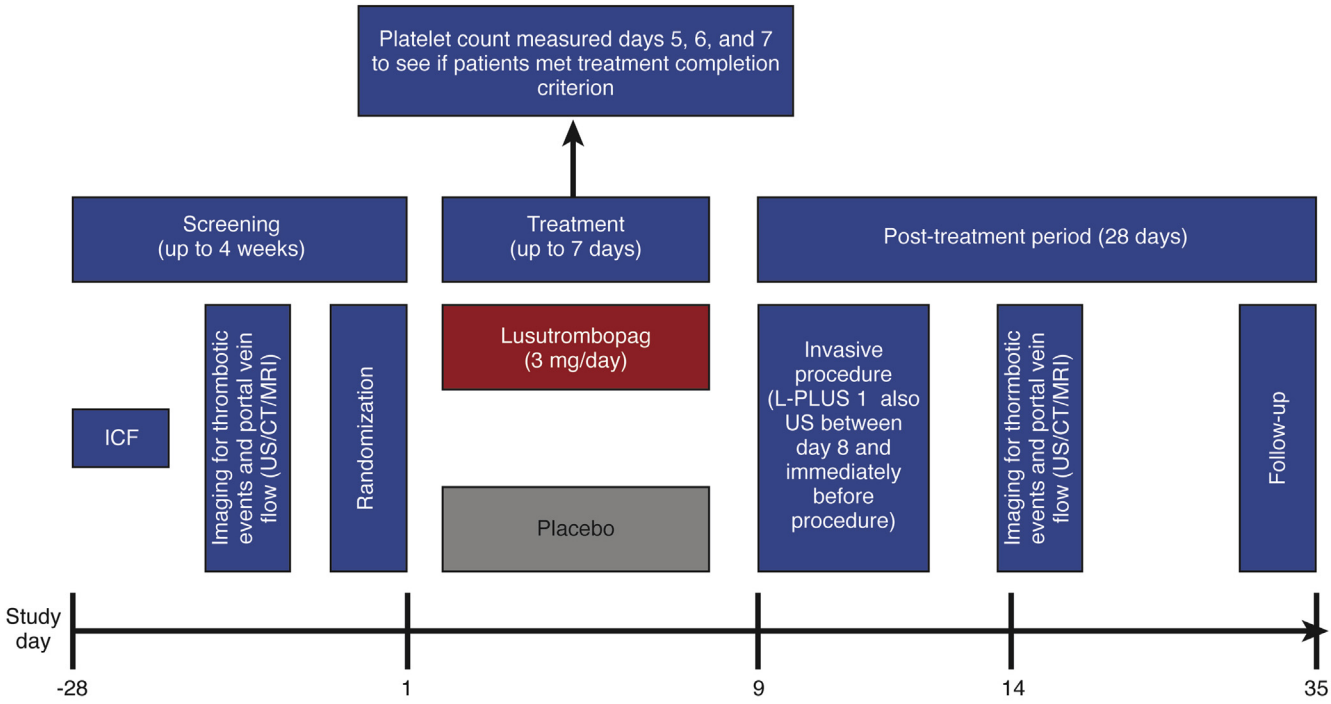

Figure 1. Study design. CT, computed tomography; ICF, informed consent; MRI, magnetic resonance imaging; US, ultrasonography.

myelodysplastic syndrome, myelofibrosis, congenital, immune, or drug-induced thrombocytopenia; and patients with malignancies other than HCC. Exceptions were made if the tumor was the treatment target of the primary invasive procedure or nonmelanoma skin cancer, intramucosal cancer, or carcinoma in situ not requiring any treatment during the study. Patients were considered to have HCC if they reported a medical history of hepatocellular carcinoma (as Medical Dictionary for Regulatory Activities preferred term).

Key Outcome Measures of Post Hoc Analysis

The primary end point for this post hoc analysis was the proportion of patients who did not require a platelet transfusion before the primary invasive procedure and/or no rescue therapy for bleeding from randomization through 7 days after the procedure in the per-protocol (PP) population. Secondary end points included the maximum platelet count, duration of the increase in platelet count $\geq 50 \times 10^9$/L, and the time course of platelet counts. The safety of lusutrombopag in patients with HCC was compared with those without HCC by assessing the incidence of bleeding and thrombosis-related TEAEs and overall TEAEs.

Study Population and Statistical Analysis

For this analysis, the PP population included all patients who were randomized and had no major protocol deviations pertaining to the efficacy evaluation. The safety analysis included all randomized patients who received at least 1 dose of study drug.

The primary end point was compared between treatment groups using the Cochran–Mantel–Haenszel test stratified by baseline platelet count and study. *P* value and CIs were calculated using the Wald method. The duration of the increase in platelet count $\geq 50 \times 10^9$/L in the lusutrombopag group (without platelet transfusion) was compared with that in the placebo group (with platelet transfusion) by using the Wilcoxon rank-sum test.

Results

Patients and Baseline Characteristics

A total of 312 patients with TCP-CLD were randomized from the L-PLUS trials, of whom 310 received treatment. Forty-two patients were excluded from the intention-to-treat population for a total of 270 patients comprising the PP population (Supplementary Table 1). Of the 270 patients in the PP population, 95 had HCC and 175 did not have HCC. Of the 95 patients with HCC, 50 received lusutrombopag and 45 received placebo. Of the 175 patients without HCC, 87 received lusutrombopag and 88 patients received placebo.

The demographic and baseline characteristics for patients in this integrated post hoc analysis are shown in Table 1. Sex, Child–Pugh class, and baseline platelet counts had a similar distribution between patients with HCC and those without HCC, and between those treated

Table 1. Demographics and Baseline Characteristics: L-PLUS 1 and L-PLUS 2; PP Population

Characteristic	Patients with HCC			Patients without HCC		
	LUSU 3 mg (n = 50)	PBO (n = 45)	Total (N = 95)	LUSU 3 mg (n = 87)	PBO (n = 88)	Total (N = 175)
Sex, n (%)						
Male	28 (56.0)	30 (66.7)	58 (61.1)	43 (49.4)	54 (61.4)	97 (55.4)
Female	22 (44.0)	15 (33.3)	37 (38.9)	44 (50.6)	34 (38.6)	78 (44.6)
Age, *y*						
Mean	65.0	66.3	65.6	57.2	55.6	56.4
SD	8.1	11.0	9.5	12.1	11.6	11.8
Child–Pugh class, n (%)						
A	25 (50.0)	27 (60.0)	52 (54.7)	59 (67.8)	47 (53.4)	106 (60.6)
B	25 (50.0)	18 (40.0)	43 (45.3)	28 (32.2)	40 (45.5)	68 (38.9)
Baseline platelet count, 10^9/L						
Mean	38.3	39.1	38.7	38.8	37.1	37.9
SD	8.8	7.7	8.3	8.0	7.3	7.7
<35, n (%)	14 (28.0)	10 (22.2)	24 (25.3)	24 (27.6)	31 (35.2)	55 (31.4)
≥35, n (%)	36 (72.0)	35 (77.8)	71 (74.7)	63 (72.4)	57 (64.8)	120 (68.6)

HCC, hepatocellular carcinoma; LUSU, lusutrombopag; PBO, placebo; PP, per protocol.

with lusutrombopag or placebo. The mean platelet counts at baseline for patients with HCC and those without HCC were 38.7 ± 8.3 (10^9/L) and 37.9 ± 7.7 (10^9/L), respectively. Among patients with HCC, most (88.4%) of the invasive procedures performed were liver related. The most common liver-directed interventions in patients with HCC were ablations and transcatheter arterial chemoembolizations. For patients without HCC, 65.1% underwent gastrointestinal/endoscopic procedures; 20% underwent other procedures, including dental procedures; 9.7% underwent liver procedures; and 5.1% did not undergo a procedure (Table 2).

Efficacy

There was a significantly greater proportion of lusutrombopag-treated patients achieving the primary end point of no platelet transfusions before the primary invasive procedure and no rescue therapy for bleeding for 7 days or fewer after the procedure compared with the corresponding placebo-treated patients, regardless of HCC status. In the HCC group, the primary end point was met in 68.0% of lusutrombopag-treated and 8.9% of placebo-treated patients (difference of proportion, 60.5%; $P < .0001$). In the group of patients without HCC, 77.0% of lusutrombopag-treated and 21.6% of placebo-treated patients met the primary end point (difference of proportion, 52.6%; $P < .0001$) (Figure 2). Platelet transfusion was administered in 15 lusutrombopag-treated and 41 placebo-treated patients in the HCC group. In patients without HCC, a platelet transfusion was provided to 21 lusutrombopag-treated and 66 placebo-treated patients. The maximum platelet count achieved in patients with and without HCC regardless of whether the patient received platelet transfusion during the study was 145 × 10^9/L and 150 × 10^9/L in the lusutrombopag treatment groups vs 102 × 10^9/L and 167 × 10^9/L in the placebo groups, respectively. In patients with HCC, platelet counts remained ≥50 × 10^9/L for a median of 23.2 days (Q1, Q3: 12.2 d, 28.0 d) in the lusutrombopag group (without platelet transfusion; n = 35) compared with 3.3 days (Q1, Q3: 0.0 d, 9.7 d) for placebo (with platelet transfusion; n = 41; $P < .0001$). In patients without HCC, platelet counts remained ≥50 × 10^9/L for a median of 21.0 days (Q1, Q3: 15.5 d, 28.8 d) in the lusutrombopag group (without platelet transfusion; n = 66) compared with 0.0 days (Q1, Q3: 0.0 d, 2.6 d) for placebo (with platelet transfusion; n = 66; $P < .0001$). As shown in Figure 3, treatment with lusutrombopag led to a prolonged improvement in platelet count compared with placebo regardless of HCC status.

Safety

The incidence of patients with at least 1 TEAE was higher in the HCC group (n = 79 of 106; 74.5%) compared with the group without HCC (n = 117 of 204; 57.4%). However, in both groups, patients treated with lusutrombopag did not have an increased incidence of TEAEs compared with those receiving placebo (Supplementary Table 2). The incidence of thrombosis-related AEs was similar in patients with and without HCC. In patients with HCC, 1 patient receiving lusutrombopag developed a PVT and 1 patient receiving placebo developed a mesenteric vein thrombosis. In patients without HCC receiving lusutrombopag, 1 patient had a PVT and 1 patient had a cardiac ventricular thrombosis. In patients without HCC receiving placebo,

Table 2. Types of Procedures Performed for Patients With and Without HCC: PP Population

Primary received procedure	Patients with HCC			Patients without HCC		
	LUSU 3 mg (n = 50)	PBO (n = 45)	Total (N = 95)	LUSU 3 mg (n = 87)	PBO (n = 88)	Total (N = 175)
Liver-related procedures, n (%)	44 (88.0)	40 (88.9)	84 (88.4)	10 (11.5)	7 (8.0)	17 (9.7)
Percutaneous RFA/MCT	21 (42.0)	20 (44.4)	41 (43.2)	3 (3.4)	0	3 (1.7)
TACE	20 (40.0)	16 (35.6)	36 (37.9)	1 (1.1)	1 (1.1)	2 (1.1)
Liver biopsy	2 (4.0)	2 (4.4)	4 (4.2)	4 (4.6)	5 (5.7)	9 (5.1)
Liver-related other procedures	1 (2.0)	2 (4.4)	3 (3.2)	2 (2.3)	1 (1.1)	3 (1.7)
GI/endoscopy-related procedures, n (%)	5 (10.0)	5 (11.1)	10 (10.5)	58 (66.7)	56 (63.6)	114 (65.1)
EVL	2 (4.0)	4 (8.9)	6 (6.3)	31 (35.6)	30 (34.1)	61 (34.9)
EIS	0	0	0	3 (3.4)	1 (1.1)	4 (2.3)
GI endoscopy[a]	3 (6.0)	1 (2.2)	4 (4.2)	24 (27.6)	25 (28.4)	49 (28.0)
Other procedures, n (%)	0	0	0	19 (21.8)	16 (18.2)	35 (20.0)
Dental extraction	0	0	0	11 (12.6)	9 (10.2)	20 (11.4)
Others	0	0	0	8 (9.2)	7 (8.0)	15 (8.6)
Procedure not received, n (%)	1 (2.0)	0	1 (1.1)	0	9 (10.2)	9 (5.1)

NOTE. The presented categories for invasive procedures were determined by sponsor after unblinding. There were 5 patients without HCC who had percutaneous RFA/MCT or TACE. Of these, 3 had a history of hepatic cancer different from HCC, 1 had a hyperechoic liver lesion, and for 1 patient, the reason for TACE remained unknown because a history of liver cancer was not reported.

EIS, endoscopic injection sclerotherapy; EVL, endoscopic variceal ligation; GI, gastrointestinal; HCC, hepatocellular carcinoma; LUSU, lusutrombopag; MCT, microwave coagulation therapy; PBO, placebo; PP, per protocol; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization.

[a]Regardless of polypectomy or biopsy, except EVL and EIS.

there were 2 patients with PVTs. All PVTs were asymptomatic and found during imaging required by protocol.

The incidence of patients with at least 1 bleeding-related TEAE was lower in the lusutrombopag group compared with the placebo group, regardless of HCC status (Table 3). Among patients with HCC, 9.1% of patients receiving lusutrombopag had at least 1 bleeding-related AE compared with 15.7% of patients receiving placebo. Among patients without HCC, 5% of those receiving lusutrombopag had at least 1 bleeding-related event compared with 10.6% of placebo-treated patients.

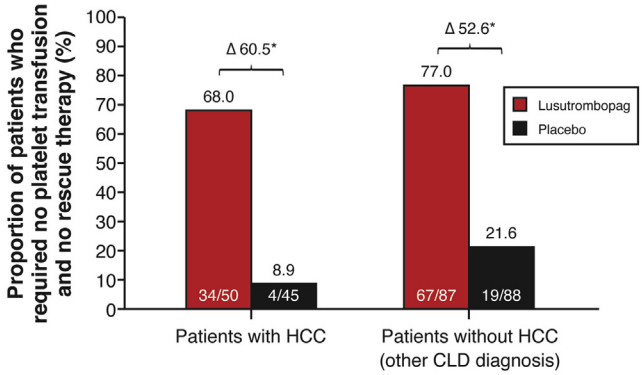

Figure 2. Efficacy of lusutrombopag was similar in patients with and without hepatocellular carcinoma (HCC) (per-protocol population). Patients who received platelet transfusion were counted as having the transfusion even if they did not undergo a procedure. Difference of proportion of patients statistical analysis: Cochran–Mantel–Haenszel test with baseline platelet count and study as stratum. The *P* value and CI were calculated using the Wald method. Δ difference of proportion of lusutrombopag patients vs placebo patients. *$P < .0001$. CLD, chronic liver disease.

Discussion

In this post hoc analysis, lusutrombopag was efficacious for the treatment of patients with TCP-CLD undergoing invasive procedures, with comparable efficacy in those with and without HCC. Patients receiving lusutrombopag without platelet transfusion maintained a platelet count level above the threshold required for safely undergoing an invasive procedure for a median of 23.2 days for patients with HCC and a median of 21.0 days for patients without HCC. The 21.0- to 23.2-day duration of the efficacy of lusutrombopag in maintaining a platelet count $\geq 50 \times 10^9$/L provides an important clinical benefit for patients with TCP-CLD undergoing a planned procedure.

In these studies, lusutrombopag was well tolerated. It is clinically remarkable that in patients with HCC, who are particularly prone to develop PVT, lusutrombopag did not increase the incidence of thrombosis-related AEs compared with patients receiving placebo. Approximately 88% of patients with HCC underwent a liver-related procedure compared with approximately 10% of patients without HCC. This is significant because ablations or transcatheter arterial chemoembolizations can be associated with serious bleeding complications.[23,24] It is clinically important that given the greater number of liver-related procedures, the incidence of bleeding-related AEs was lower in patients treated with lusutrombopag than placebo.

The results of this integrated post hoc analysis further support the overall results of lusutrombopag phase 3 trials and a phase 2b trial in patients with TCP-

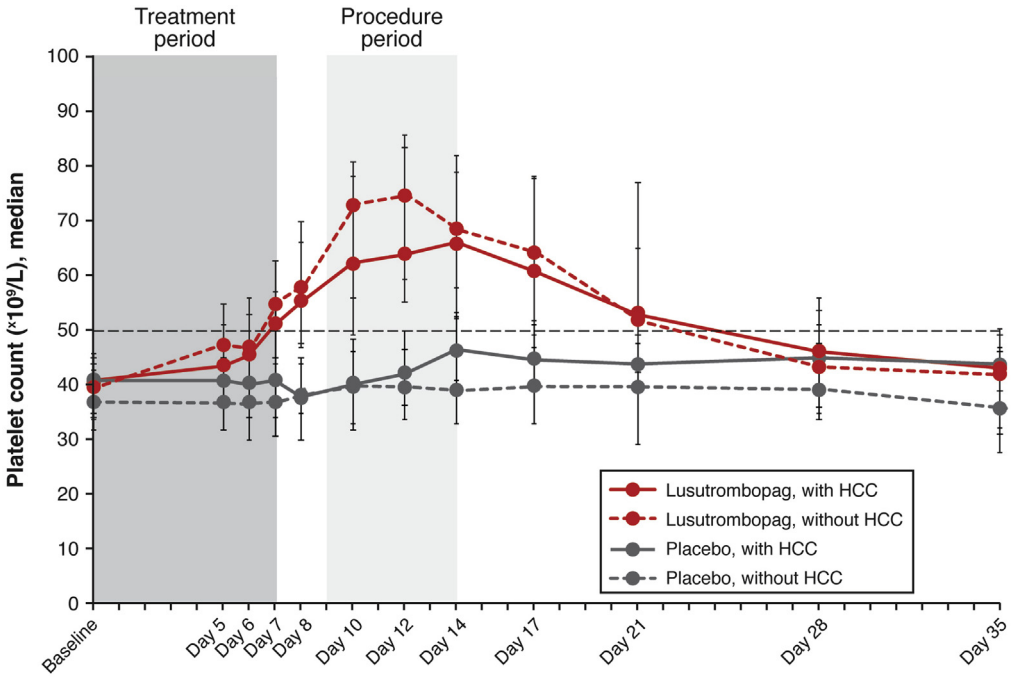

Figure 3. Median platelet count over time in chronic liver disease patients with or without hepatocellular carcinoma (HCC) (per-protocol population). Summarized platelet count regardless of platelet transfusion during the study. Data point reflects the median, error bars are 25th and 75th percentiles.

CLD and show benefit in patients with and without HCC.[21,22,25] A separate post hoc analysis showed lusutrombopag is efficacious compared with placebo regardless of the underlying etiology of the CLD, further showing its utility in patients with TCP-CLD.[26]

A limitation of this study was the high rate of protocol violations related to platelet transfusions. A number of patients were excluded from the PP population owing to receipt of unnecessary platelet transfusions or because they did not receive a needed platelet transfusion.

Two additional oral TPO-RAs, eltrombopag and avatrombopag, have been studied for treating TCP-CLD before undergoing an invasive procedure.

The Eltrombopag Evaluated for Its Ability to Overcome Thrombocytopenia and Enable Procedures study assessed the efficacy and safety of eltrombopag in TCP-CLD patients but did not report results in patients with HCC.[27] In this trial, 292 patients with CLD and a platelet count of less than 50×10^9/L received daily eltrombopag or placebo for 14 days before a planned procedure. Results showed a significant reduction in the need for a platelet transfusion before, during, or within 7 days after the procedure, compared with placebo (72% vs 19%; $P < .001$). The secondary end point of noninferiority (margin, 10%) of the difference in the incidence of bleeding-related AEs between patients receiving eltrombopag (17%) or placebo (23%) was met with an absolute difference of −6% (95% CI, −15% to 3%). However, 6 patients receiving eltrombopag developed PVT compared with 1 patient receiving placebo.[27] The increased incidence of thrombosis-related AEs led to termination of the trial.

The ADAPT-1 and ADAPT-2 studies evaluated the safety and efficacy of avatrombopag and included a low-platelet (platelets $<40 \times 10^9$/L) (cohort 1) and a high-platelet cohort (platelets 40 to $<50 \times 10^9$/L) (cohort 2).[28] In these trials, patients receiving avatrombopag had a reduction in the need for platelet transfusions before a procedure or rescue therapy after a procedure compared with placebo. Unlike the integrated analysis reported here, patients in the ADAPT trials could have a screening or baseline platelet count $\leq 60 \times 10^9$/L, as long as the mean platelet count was less than 50×10^9/L. Platelet transfusion was at the discretion of the investigator and not based on prespecified criteria. Patients receiving avatrombopag or placebo had a similar incidence of AEs, including thrombosis-related or bleeding-related events. However, unlike the L-PLUS trials, there was no preplanned imaging to assess for PVT, and therefore asymptomatic PVT was not captured. Across ADAPT-1 and ADAPT-2, there was a comparable incidence of bleeding events in avatrombopag-treated vs placebo-treated patients (3.8% vs 3.3% and 2.6% vs 4.6%, respectively).[28] Lusutrombopag-treated patients experienced approximately 50% fewer bleeding related events compared with placebo in L-PLUS 1 (14.6% vs 27.1%, respectively) and L-PLUS 2 (2.8% vs 5.6%, respectively).[29] Of note, bleeding events may have been recorded differently in the ADAPT vs L-PLUS studies.

The ADAPT-1 and ADAPT-2 trials included 117 patients with HCC (27% of patients) compared with 35% of patients in the L-PLUS trials.[28] Results of a subanalysis of the ADAPT trials showed that avatrombopag was more efficacious than placebo regardless of HCC status.[30] The proportion of patients not requiring a platelet transfusion or rescue procedure was similar between patients with or without HCC (cohort 1: no HCC: avatrombopag, 68.4%; placebo, 34.9%; HCC: avatrombopag, 64.3%,

Table 3. Bleeding-Related TEAEs in Patients With or Without HCC (Safety Analysis Population)

	Patients with HCC			Patients without HCC		
	LUSU 3 mg (n = 55)	PBO (n = 51)	Total (N = 106)	LUSU 3 mg (n = 100)	PBO (n = 104)	Total (N = 204)
Patients with at least 1 AE	5 (9.1)	8 (15.7)	13 (12.2)	5 (5.0)	11 (10.6)	16 (7.8)
Treatment-emergent adverse event, n (%)						
Eye disorders	0	0	0	0	1 (1.0)	1 (0.5)
Eyelid hematoma	0	0	0	0	1 (1.0)	1 (0.5)
Ear and labyrinth disorders	0	0	0	0	1 (1.0)	1 (0.5)
Ear hemorrhage	0	0	0	0	1 (1.0)	1 (0.5)
Vascular disorders	0	1 (2.0)	1 (0.9)	1 (1.0)	1 (1.0)	2 (1.0)
Hematoma	0	1 (2.0)	1 (0.9)	1 (1.0)	1 (1.0)	2 (1.0)
Respiratory, thoracic, and mediastinal disorders	0	4 (7.8)	4 (3.8)	0	2 (1.9)	2 (1.0)
Epistaxis	0	3 (5.9)	3 (2.8)	0	1 (1.0)	1 (0.5)
Hemoptysis	0	1 (2.0)	1 (0.9)	0	0	0
Pharyngeal hemorrhage	0	0	0	0	1 (1.0)	1 (0.5)
Gastrointestinal disorders	0	1 (2.0)	1 (0.9)	1 (1.0)	3 (2.9)	4 (2.0)
Esophageal varices hemorrhage	0	0	0	0	2 (1.9)	2 (1.0)
Gingival bleeding	0	1 (2.0)	1 (0.9)	0	0	0
Rectal hemorrhage	0	0	0	1 (1.0)	0	1 (0.5)
Large intestinal hemorrhage	0	0	0	0	1 (1.0)	1 (0.5)
Skin and subcutaneous tissue disorders	1 (1.8)	1 (2.0)	2 (1.9)	2 (2.0)	0	2 (1.0)
Purpura	1 (1.8)	0	1 (0.9)	1 (1.0)	0	1 (0.5)
Ecchymosis	0	0	0	1 (1.0)	0	1 (0.5)
Hemorrhage subcutaneous	1 (1.8)	0	1 (0.9)	0	0	0
Petechiae	0	1 (2.0)	1 (0.9)	0	0	0
General disorders and administration site conditions	0	1 (2.0)	1 (0.9)	0	1 (1.0)	1 (0.5)
Injection site hemorrhage	0	1 (2.0)	1 (0.9)	0	1 (1.0)	1 (0.5)
Injury, poisoning, and procedural complications	5 (9.1)	2 (3.9)	7 (6.6)	1 (1.0)	3 (2.9)	4 (2.0)
Postprocedural hemorrhage	2 (3.6)	1 (2.0)	3 (2.8)	0	1 (1.0)	1 (0.5)
Procedural hemorrhage	2 (3.6)	0	2 (1.9)	1 (1.0)	1 (1.0)	2 (1.0)
Contusion	0	1 (2.0)	1 (0.9)	0	0	0
Traumatic hemorrhage	0	0	0	0	1 (1.0)	1 (0.5)
Postprocedural contusion	1 (1.8)	0	1 (0.9)	0	0	0

NOTE. A bleeding-related event was defined as an adverse event that belonged to the standard MedDRA queries "Hemorrhage terms (except laboratory terms)."
AE, adverse event; HCC, hepatocellular carcinoma; LUSU, lusutrombopag; PBO, placebo; TEAE, treatment-emergent adverse event.

placebo 12%; cohort 2: no HCC: avatrombopag, 91.7%; placebo, 36.7%; HCC: avatrombopag, 81.3%; placebo, 33.3%). Similar results were observed for the proportion of patients achieving a platelet count $\geq 50 \times 10^9$/L on the day of the procedure.[30]

Given the concern for thromboembolic events raised with other TPO-RAs,[27,28] patients in the L-PLUS studies were assessed prospectively for asymptomatic thrombosis-related events with imaging. A recent meta-analysis evaluated the risk of PVT with eltrombopag, avatrombopag, and lusutrombopag in TCP-CLD. In an analysis of 3 studies (n = 514), there was no statistical difference (odds ratio, 2.6; 95% CI, 0.6–11.6; $P = .212$) in the incidence of PVT in patients treated with TPO-RAs vs placebo before undergoing an invasive procedure. Eltrombopag was the only TPO-RA found to have an association with PVT (odds ratio, 3.8; 95% CI, 1.14–13.2; $P = .03$) in the analysis of 4 studies (the additional study included CLD patients with hepatitis C virus infection who received eltrombopag, n = 1953).[31] This may be because the eltrombopag dose administered in the CLD study was the same as that indicated for the treatment of immune thrombocytopenic purpura, leading to excessive ($\geq 200 \times 10^9$/L) increases in platelet count and PVTs.[27,31,32] In the ADAPT trials, 3 avatrombopag-treated patients experienced an excessive increase in platelet count, without thrombotic events.[28] In our study, only 1 lusutrombopag-treated patient who also self-administered eltrombopag had a platelet count $\geq 200 \times 10^9$/L. In the L-PLUS trials, doses of study drug were not administered if treatment completion criterion was met. This additional safety criterion was included to prevent an excessive increase in platelet count. Pharmacokinetic and pharmacodynamic simulations and a subsequent open-label study confirmed it is not necessary to discontinue lusutrombopag before completion of 7 days of therapy or monitor platelets during lusutrombopag administration. Based on the simulation study, the

probability of surpassing a platelet count $\geq 200 \times 10^9$/L was low (1.2%) and in the open-label study no patients had an increase in platelet count greater than 200×10^9/L.[33]

Thrombocytopenia associated with HCC is common and imposes a significant impact on the management of these patients, including the cost of therapies, missed or delayed procedures, additional laboratory work and hospitalizations, and complications from transfusions.[13] In patients with and without HCC, lusutrombopag was efficacious in increasing platelet count before a planned invasive procedure, thereby avoiding the number of platelet transfusions compared with placebo, with no increase in the incidence of TEAEs including thrombosis. Therefore, lusutrombopag represents an efficacious and safe therapy to prepare TCP-CLD patients, regardless of HCC presence, for invasive procedures by minimizing delays in procedures, transfusion-related complications, and bleeding events, without increasing thrombotic events.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2020.03.032.

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Reprint requests
Address requests for reprints to: Naim Alkhouri, MD, Texas Metabolic Center, 607 Camden Street, Suite 101, San Antonio, Texas 78215. e-mail: alkhouri@txliver.com; fax: (210) 227-6951.

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CRediT Authorship Contributions
Naim Alkhouri (Conceptualization: Equal; Formal analysis: Equal; Writing – original draft: Equal; Writing – review & editing: Equal); Michio Imawari (Formal analysis: Equal; Writing – original draft: Equal; Writing – review & editing: Equal); Namiki Izumi (Data curation: Equal; Formal analysis: Equal; Writing – original draft: Equal; Writing – review & editing: Equal); Yukio Osaki (Data curation: Equal; Formal analysis: Equal; Writing – original draft: Equal; Writing – review & editing: Equal); Toshimitsu Ochiai (Formal analysis: Equal; Writing – original draft: Equal; Writing – review & editing: Equal; Statistical analysis: Lead); Takeshi Kano (Formal analysis: Equal; Writing – original draft: Equal; Writing – review & editing: Equal; Administrative, technical, or material support: Lead); Roy Bentley (Conceptualization: Equal; Formal analysis: Equal; Writing – original draft: Equal; Writing – review & editing: Equal); Franco Trevisani (Formal analysis: Equal; Writing – original draft: Equal; Writing – review & editing: Equal).

Conflicts of interest
The authors disclose the following: Naim Alkhouri is an advisor for Dova Pharma and Shionogi and serves on the speakers bureau for Dova Pharma; Michio Imawari is an advisor for Shionogi & Co, Ltd and EA Pharma Co, Ltd, and a consultant for Japan Bio Products Co, Ltd; Namiki Izumi serves on the speakers bureau for AbbVie, Shionogi, Bayer, Gilead Science, Otsuka, and Eisai; Yukio Osaki serves on the speakers bureau and teaches for Gilead Sciences, Inc, Bayer Yakuhin, Ltd, MSD Co, Inc, Shionogi & Co, Ltd, AbbVie GK, and Eisai Co, Ltd; Toshimitsu Ochiai and Takeshi Kano are employees of Shionogi & Co, Ltd; Roy Bentley is an employee of Shionogi, Inc; and Franco Trevisani is an advisor for Bayer, Sirtex, Alfasigma, and Bristol-Myers Squibb, and a consultant for Bayer.

Supplementary Table 1. Major Reasons for Exclusion From the Per-Protocol Population by Treatment Group

Reason for exclusion	Overall (N = 312)	
	LUSU 3 mg	Placebo
Noncompliance with preprocedural platelet transfusion instructions[a]	8	10
Out of window of preprocedure platelet transfusion assessment	3	3
Incomplete study drug administration	3	1
Not fulfilling eligibility criteria	5	1
Use of prohibited concomitant medication	1	5
Other treatment violation	0	2
Noncompliance	0	0
Total	20	22

LUSU, lusutrombopag.
[a]There were 5 patients in the lusutrombopag group who received a platelet transfusion but should not have, and 3 patients in the lusutrombopag group and 10 patients in the placebo group who did not receive a platelet transfusion but should have.

Supplementary Table 2. TEAEs in Patients With or Without HCC: Incidence ≥5%

	Patients with HCC			Patients without HCC		
	LUSU 3 mg (n = 55)	PBO (n = 51)	Total (N = 106)	LUSU 3 mg (n = 100)	PBO (n = 104)	Total (N = 204)
Patients with at least 1 AE, n (%)	41 (74.5)	38 (74.5)	79 (74.5)	55 (55.0)	62 (59.6)	117 (57.4)
Treatment-emergent adverse event, n (%)						
Nasopharyngitis	2 (3.6)	3 (5.9)	5 (4.7)	5 (5.0)	2 (1.9)	7 (3.4)
Influenza	0	3 (5.9)	3 (2.8)	0	1 (1.0)	1 (0.5)
Insomnia	4 (7.3)	2 (3.9)	6 (5.7)	0	1 (1.0)	1 (0.5)
Headache	2 (3.6)	1 (2.0)	3 (2.8)	5 (5.0)	4 (3.8)	9 (4.4)
Pleural effusion	2 (3.6)	3 (5.9)	5 (4.7)	0	0	0
Epistaxis	0	3 (5.9)	3 (2.8)	0	1 (1.0)	1 (0.5)
Ascites	2 (3.6)	3 (5.9)	5 (4.7)	4 (4.0)	4 (3.8)	8 (3.9)
Abdominal pain	3 (5.5)	1 (2.0)	4 (3.8)	3 (3.0)	4 (3.8)	7 (3.4)
Nausea	3 (5.5)	0	3 (2.8)	1 (1.0)	6 (5.8)	7 (3.4)
Constipation	4 (7.3)	4 (7.8)	8 (7.5)	1 (1.0)	0	1 (0.5)
Pyrexia	4 (7.3)	5 (9.8)	9 (8.5)	1 (1.0)	1 (1.0)	2 (1.0)
Fatigue	2 (3.6)	0	2 (1.9)	1 (1.0)	7 (6.7)	8 (3.9)
Aspartate aminotransferase increased	11 (20.0)	15 (29.4)	26 (24.5)	1 (1.0)	2 (1.9)	3 (1.5)
Alanine aminotransferase increased	8 (14.5)	10 (19.6)	18 (17.0)	1 (1.0)	0	1 (0.5)
Oxygen saturation decreased	2 (3.6)	7 (13.7)	9 (8.5)	1 (1.0)	0	1 (0.5)
Blood bilirubin increased	4 (7.3)	4 (7.8)	8 (7.5)	1 (1.0)	0	1 (0.5)
Fibrin degradation products increased	2 (3.6)	4 (7.8)	6 (5.7)	0	2 (1.9)	2 (1.0)
Fibrin D dimer increased	1 (1.8)	3 (5.9)	4 (3.8)	0	2 (1.9)	2 (1.0)
White blood cell count decreased	0	4 (7.8)	4 (3.8)	0	1 (1.0)	1 (0.5)
C-reactive protein increased	1 (1.8)	3 (5.9)	4 (3.8)	0	0	0
Blood calcium decreased	3 (5.5)	0	3 (2.8)	0	0	0
Postoperative fever	16 (29.1)	19 (37.3)	35 (33.0)	3 (3.0)	9 (8.7)	12 (5.9)
Procedural pain	17 (30.9)	14 (27.5)	31 (29.2)	8 (8.0)	8 (7.7)	16 (7.8)
Procedural hypertension	15 (27.3)	14 (27.5)	29 (27.4)	5 (5.0)	4 (3.8)	9 (4.4)
Procedural nausea	3 (5.5)	5 (9.8)	8 (7.5)	3 (3.0)	3 (2.9)	6 (2.9)
Procedural vomiting	6 (10.9)	5 (9.8)	11 (10.4)	1 (1.0)	1 (1.0)	2 (1.0)
Postprocedural discomfort	0	1 (2.0)	1 (0.9)	4 (4.0)	6 (5.8)	10 (4.9)

AE, adverse event; HCC, hepatocellular carcinoma; LUSU, lusutrombopag; PBO, placebo; TEAE, treatment-emergent adverse event.