Adv Ther (2022) 39:4285–4298
https://doi.org/10.1007/s12325-022-02237-8

ORIGINAL RESEARCH

Pharmacokinetic Assessment and Treatment Effect of Lusutrombopag in Child–Pugh Class C Patients: Review of Patient Data from Two Clinical Studies and Post-Marketing Surveillance

Steven L. Flamm · Markus Peck-Radosavljevic · Takahiro Fukuhara · Roy Bentley · Takayuki Katsube · Toshimitsu Ochiai · Takeshi Kano · Eri Tsukimura · Ritsue Sasaki · Yukio Osaki

Received: May 12, 2022 / Accepted: June 20, 2022 / Published online: July 29, 2022

ABSTRACT

Introduction: Patients with thrombocytopenia and chronic liver disease are at increased risk of bleeding during invasive procedures due to low platelet counts. Lusutrombopag, an orally active thrombopoietin receptor agonist, increases platelet count and reduces the need for platelet transfusion in chronic liver disease patients with thrombocytopenia undergoing a planned invasive procedure. The safety of lusutrombopag in patients with Child–Pugh class C chronic liver disease is not known. The present analysis was performed to determine the pharmacokinetics, efficacy, and safety of lusutrombopag in patients with Child–Pugh class C chronic liver disease.

Methods: Data for patients with Child–Pugh class C chronic liver disease were collected from three data sets: a phase 1/2 Child–Pugh class C study (n = 5) (JapicCTI-163289 [Japan Pharmaceutical Information Center]), a phase 3 pivotal study (L-PLUS 2, n = 3) (NCT02389621 [Clinicaltrials.gov]), and ongoing post-marketing surveillance (n = 27) (JapicCTI-163432 [Japan Pharmaceutical Information Center]). Patients received lusutrombopag at 3 mg for up to

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12325-022-02237-8.

S. L. Flamm (✉)
Department of Medicine (Gastroenterology and Hepatology) and Surgery, Northwestern University Feinberg School of Medicine, 676 North Saint Clair, Arkes 19-041, Chicago, IL 60611, USA
e-mail: s-flamm@northwestern.edu

M. Peck-Radosavljevic
Abteilung Innere Medizin & Gastroenterologie (IMuG), Mit Zentraler Aufnahme- & Erstversorgung (ZAE), Klinikum Klagenfurt am Wörthersee, Klagenfurt, Austria

T. Fukuhara
Clinical Research Development Department, Shionogi & Co., Ltd., Osaka, Japan

R. Bentley
US Global Market Access, Shionogi Inc., Florham Park, NJ, USA

T. Katsube · T. Kano
Global Project Management Department, Shionogi & Co., Ltd., Osaka, Japan

T. Ochiai
Biostatistics Center, Shionogi & Co., Ltd., Osaka, Japan

E. Tsukimura
Postmarketing Surveillance & Pharmacoepidemiology Department, Shionogi Pharmacovigilance Center Co., Ltd., Osaka, Japan

R. Sasaki
Pharmacovigilance Department, Shionogi & Co., Ltd., Osaka, Japan

Y. Osaki
Meiwa Hospital, Nishinomiya, Japan

7 days. Safety and efficacy assessments were collected from two clinical studies and the post-marketing surveillance; pharmacokinetic data were collected from the phase 1/2 study.

Results: Mean C_{max} and $AUC_{0-\tau}$ were lower in Child–Pugh class C patients than Child–Pugh class A and B; individual patients' C_{max} and $AUC_{0-\tau}$ values overlapped among Child–Pugh classes. In lusutrombopag patients who did not receive platelet transfusion ($n = 4$ in phase 1/2, $n = 1$ in phase 3, $n = 24$ in post-marketing surveillance), the median (range) maximum platelet count was 88.5 $\times$ 10^9/L (54–105 $\times$ 10^9/L), 80 $\times$ 10^9/L, and 91 $\times$ 10^9/L (41–186 $\times$ 10^9/L; $n = 23$), respectively. There were no treatment-related adverse events or treatment-related serious adverse events. One patient from the phase 1/2 study had a non-serious portal vein thrombosis, which was not considered treatment-related.

Conclusions: The analysis presented in this study suggests that lusutrombopag increases platelet counts in Child–Pugh class C patients and is safe and well tolerated in this patient population.

Trial Registration: L-PLUS 2: NCT02389621 (Clinicaltrials.gov). Phase 1/2: JapicCTI-163289 (Japan Pharmaceutical Information Center [JAPIC]). Post-marketing surveillance: JapicCTI-163432 (JAPIC).

Keywords: Chronic liver disease; Severe thrombocytopenia; Invasive procedure; Child–Pugh class C; Lusutrombopag; Thrombopoietin receptor agonist

Key Summary Points

Why carry out this study?

Patients with chronic liver disease (CLD) often experience thrombocytopenia, which puts them at increased risk of bleeding during invasive procedures.

Phase 3 studies have shown that the orally active thrombopoietin receptor agonist (TPO-RA) lusutrombopag is effective in increasing platelet count and reducing the need for platelet transfusions in patients with CLD and thrombocytopenia who are undergoing a planned invasive procedure, although lusutrombopag's efficacy and safety in patients with Child–Pugh (CP) class C CLD has not been established.

This analysis provides the first evaluation of the efficacy/effectiveness, safety, and pharmacokinetics of lusutrombopag in a subgroup of patients with CP class C CLD from three data sets: a phase 1/2 CP class C study ($n = 5$), a phase 3 pivotal study ($n = 3$), and post-marketing surveillance ($n = 27$).

What was learned from the study?

In the CP class C patients who were treated with lusutrombopag and did not receive platelet transfusions ($n = 4$ in phase 1/2, $n = 1$ in phase 3, $n = 24$ in post-marketing surveillance), median (range) maximum platelet counts were 88.5 $\times$ 10^9/L (54–105 $\times$ 10^9/L), 80 $\times$ 10^9/L, and 91 $\times$ 10^9/L (41–186 $\times$ 10^9/L; $n = 23$), respectively, and no treatment-related adverse events or treatment-related serious adverse events were observed.

The results of this analysis suggest that lusutrombopag increases platelet counts in CP class C patients and is safe and well tolerated in this patient population.

Although there is a need for interventions for patients with CP class C CLD, this population has been the target of few analyses; these data therefore present a valuable insight into the treatment of patients with CP class C disease undergoing planned invasive procedures.

INTRODUCTION

Thrombocytopenia is a common complication of patients with chronic liver disease (CLD), which arises because of decreased hepatic production of thrombopoietin (TPO) and splenic sequestration of platelets [1]. Because of the resulting low platelet counts, patients are at an increased risk of bleeding during invasive procedures [2, 3]. Platelet transfusions have been employed to raise platelet counts in patients with CLD and thrombocytopenia prior to invasive procedures, but there is controversy surrounding this practice. The effects of platelet transfusions are brief and may result in adverse transfusion reactions [4, 5]. Importantly, repeated use in patients also may result in platelet transfusion refractoriness due to alloimmunization. Furthermore, the costs associated with platelet transfusions are high [4, 6].

Second generation TPO receptor agonists (TPO-RAs) have emerged as an efficacious and safe therapeutic option in patients with thrombocytopenia. Lusutrombopag is a TPO-RA approved in Japan (2015) and the USA (2018) for treatment of thrombocytopenia, and in the European Union (2019) for severe thrombocytopenia, associated with CLD in patients undergoing a planned invasive procedure [7–9]. As an orally active, small molecule TPO-RA, lusutrombopag acts via TPO receptors on megakaryocytes, activating platelet production via the same signal cascade as endogenous TPO [9, 10].

Previous studies have confirmed that lusutrombopag is an efficacious treatment option that reduces the need for platelet transfusion in patients undergoing planned procedures. L-PLUS 1, a phase 3, double-blind study conducted in Japan demonstrated that 79.2% of patients did not require preoperative platelet transfusion compared to only 12.5% of placebo-treated patients ($P < 0.0001$). No significant safety concerns were identified [10]. Similarly, L-PLUS 2, a phase 3 double-blind study conducted globally, found that 64.8% of lusutrombopag-treated patients in the intent-to-treat population did not require a platelet transfusion and rescue therapy for bleeding 7 days after the primary procedure, compared to 29.0% of placebo-treated patients [11]. These findings were similar to those in the L-PLUS 2 per-protocol (PP) analysis set (72.5% and 20.2%, respectively). The safety profile was similar to placebo.

Although the efficacy and safety profile of lusutrombopag has been established in patients with CLD, it has not been established in patients with Child–Pugh (CP) class C CLD, as this patient population was excluded in previous studies [10, 11]. Furthermore, the pharmacokinetic/pharmacodynamic profile of lusutrombopag may be altered in patients with CP class C liver disease. Lusutrombopag is excreted mainly via feces in humans; fecal excretion accounts for 83% of the administered dose, with 16% of the dose excreted as unchanged lusutrombopag, and urinary excretion accounts for approximately 1% [9].

A pharmacokinetic/pharmacodynamic study demonstrated that patients with a CP score of 9 or higher had an increased slope relating plasma lusutrombopag concentrations and a lower median area under the curve (AUC) compared to patients with class A or B. This may be because patients with liver disease may have intestinal alterations that affect the extent of drug absorption [12]. This should be taken into consideration when treating this subset of patients.

The present analysis evaluated the efficacy/effectiveness, safety, and pharmacokinetics of lusutrombopag in a subgroup of patients with CP class C CLD, which has not been previously reported.

METHODS

Study Design

CP class C patient-level data were extracted from three data sets: a phase 1/2 CP class C study; a phase 3 pivotal study, despite CP class C exclusion criteria (L-PLUS 2, $n = 3$); and post-marketing surveillance (PMS), despite lusutrombopag being contraindicated in this population in Japan where the PMS is ongoing. Data from the L-PLUS 2 [11] and PMS were

previously published [13]. The planned PMS survey period was from October 2016 to May 2021, and the enrollment period was from October 2016 to September 2020; the date of data cutoff for the PMS data set for this analysis was September 27, 2019 (Japan Pharmaceutical Information Center [JAPIC], ID: JapicCTI-163432). The phase 1/2 study (JAPIC, ID: JapicCTI-163289) was an open-label, single-arm pharmacokinetic trial conducted in Japan from July 6, 2016 to March 23, 2017 and the phase 3 pivotal study (NCT02389621) was a double-blinded, placebo-controlled trial conducted globally from June 15, 2015 to April 19, 2017. A list of study investigators for the phase 1/2 and phase 3 studies is shown in Table S1 in the supplementary material. The authors confirm that all ongoing and related trials for this drug/intervention are registered.

In the phase 1/2 and phase 3 studies, patients with baseline platelet counts below 50×10^9/L received lusutrombopag 3 mg for no more than 7 days. In the phase 3 study, invasive procedures were scheduled 9–14 days after randomization; in the phase 1/2 study, an invasive procedure was not required. The PMS was conducted under routine clinical practice; patients received 3 mg lusutrombopag and were observed for 2 months from the start of the first lusutrombopag treatment.

Compliance with Ethics Guidelines

All patients provided written informed consent in the phase 1/2 and phase 3 studies. For these studies, the study protocol was approved by the institutional review boards of each participating center, shown in Table S2 in the supplementary material. According to exemptions under the Good Post-Marketing Study Practice ordinance by the Ministry of Health, Labour, and Welfare in Japan, institutional review board approval and informed consent were not required for the PMS. In the PMS data, patients were anonymized prior to analysis. All studies conformed to the ethical principles outlined in the Declaration of Helsinki and all revisions thereof.

Assessments

In the phase 1/2 study, pharmacokinetic assessments were performed using blood sampling to determine plasma drug concentration in all patients, and parameters were calculated using non-compartmental analyses (WinNonlin, Version 6.2.1, Princeton, NJ; AutoPilotToolkit, Version 2.0, Princeton, NJ). Endpoints included maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the concentration–time curve from time zero to the dosing interval time ($AUC_{0-\tau}$), terminal elimination rate constant (λ_z), terminal elimination half-life ($t_{1/2,z}$), and apparent total clearance (CL/F).

In the phase 3 study, the primary endpoint was the proportion of patients who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomization through 7 days after the primary invasive procedure.

Platelet counts were measured in both studies and the PMS. In the phase 1/2 study, platelet counts were assessed at screening (day -28), pre-dosing on day 1, and post-dosing on days 3–8, 10, 12, 14, 17, 21, 28, and 35. In the phase 3 study, platelet counts were assessed at screening (day -28), pre-dosing on day 1, and post-dosing on days 5–8, 10, 12, 14, 17, 21, 28, and 35. In the PMS, platelet count was assessed prior to first treatment, between initiation of first treatment and invasive procedure, and after invasive procedure.

In both the phase 1/2 and 3 studies, receipt of platelet transfusion, mean maximum increase in platelet count, and duration of platelet count $\geq 50 \times 10^9$/L were evaluated. In the phase 1/2 study, imaging for portal vein thrombosis was conducted via CT or MRI during screening and between study days 12 and 28; in the phase 3 study, imaging for portal vein thrombosis (via ultrasonography, CT, or MRI) took place during screening and following the invasive procedure.

The PMS assessed receipt of platelet transfusion and safety. When judged necessary by the physician, the presence of portal vein thrombosis was evaluated.

Statistical Analysis

Pharmacokinetics

In the phase 1/2 study, the analysis of variance for class A, B, and C patients, including CP class as a fixed effect, was performed for the following pharmacokinetic parameters: the ln-transformed values for C_{max}, $AUC_{0-\tau}$, λ_z, $t_{1/2,z}$, and CL/F. For this analysis, Child–Pugh class A and B patients were included from the open-label, phase 3b study (1338M0633) [14]. The ratios of the geometric least squares means and the corresponding 90% confidence intervals (CIs) were estimated by exponentiating the differences in means and the corresponding 90% CIs in the logarithm.

Efficacy

The phase 1/2 and 3 studies assessed maximum platelet count, maximum change from platelet count from baseline, and the duration of platelet count greater than or equal to 50×10^9/L. In the phase 1/2 study, the number of platelet transfusions received was summarized descriptively, with no statistical testing performed because of the small number of CP class C patients. In the phase 3 study, the primary endpoint (avoidance of pre-procedure platelet transfusion and avoidance of rescue therapy for bleeding through 7 days after primary procedure) was analyzed descriptively for the subgroups by CP class (class A, B, and C), with no statistical testing performed because of the small number of CP class C patients. Additionally, a pooled analysis of CP class A/B and C patients from the phase 1/2 and phase 3 trials was conducted.

In the PMS, the proportion of patients who did not require platelet transfusion was calculated, as well as the factors potentially affecting effectiveness.

Safety

In the phase 1/2 and phase 3 study, adverse events were reported according to Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Safety analysis for the two studies and the PMS included serious adverse events and thrombosis- and embolism-related adverse events.

RESULTS

Patients

Five CP class C patients were included from the phase 1/2 study, three from the phase 3 pivotal study (L-PLUS 2), and 27 from the PMS. CP class C patients from the phase 3 pivotal study were CP class C at baseline, and were treated despite eligibility criteria excluding CP class C status. CP class C patients from the PMS were also included in this report although lusutrombopag is contraindicated in this population in Japan where the PMS is ongoing. The median (range) baseline platelet counts for patients in the phase 1/2 study, phase 3 study, and the PMS were 40×10^9/L ($12–52 \times 10^9$/L), 24×10^9/L ($19–44 \times 10^9$/L), and 43.5×10^9/L ($17–92 \times 10^9$/L), respectively. All patients in the phase 1/2 and phase 3 studies received lusutrombopag for 7 days. In the PMS, 25/27 patients received lusutrombopag for 7 days (1 patient received lusutrombopag for 4 days and 1 for 6 days). Baseline characteristics and demographics are shown in Table 1. In a pooled analysis of the phase 1/2 and phase 3 trials, median (range) age (class A/B, 60 years [19–-81 years]; class C, 51 [31–74 years]) and baseline platelet counts were comparable between class A/B (41×10^9/L; $13–59 \times 10^9$/L) and class C patients (39×10^9/L; $12–52 \times 10^9$/L Table 2).

Pharmacokinetics

In the phase 1/2 CP class C study, C_{max} was lower for CP class C patients compared to CP class A patients (geometric least squares mean ratio, 0.715 [90% CI 0.543, 0.941]) and class B patients (0.792 [0.597, 1.051], Table 3; Fig. S1 in the supplementary material). This was also observed for $AUC_{0-\tau}$ (geometric least squares mean ratio, 0.793 [90% CI 0.589, 1.068] and 0.790 [0.582, 1.072], respectively, Table 3; Fig. S1). However, the distributions of C_{max} and

Table 1 Demographics and baseline characteristics of Child–Pugh class C patients

	Phase 1/2[a] (*n* = 5)	Phase 3 (*n* = 3)	PMS (*n* = 27)
Sex, *n* (%)			
Male	1 (20.0)	2 (66.6)	18 (66.7)
Female	4 (80.0)	1 (33.3)	9 (33.3)
Age, years			
Mean (SD)	62.0 (10.6)	38.0 (6.1)	63.6 (9.8)
Median (range)	65 (50–74)	41 (31–42)	66 (42–79)
Disease etiology[b]			
HBV	0	2 (66.6)	2 (7.4)
HCV	2 (40.0)	0	8 (29.6)
Alcoholic hepatitis	0	2 (66.6)	8 (29.6)
Non-alcoholic hepatitis	1 (20.0)	0	7 (25.9)
Other	2 (40.0)	0	3 (11.1)
Child–Pugh score, median (range)	10 (9–11)	10 (10–13)	11 (10–13)
Baseline platelet count ($\times 10^9$/L)			
n	5	3	26
Mean (SD)	37.8 (15.5)	29.0 (13.2)	46.2 (16.2)
Median (range)	40 (12–52)	24 (19–44)	43.5 (17–92)

HBV hepatitis B virus, *HCV* hepatitis C virus, *PMS* post-marketing surveillance, *SD* standard deviation

[a]One patient had Child–Pugh class B at enrollment, but as a result of fluctuations in score and a medical history of Child–Pugh class C disease, the patient was included in the Child–Pugh class C analysis

[b]Patients may have had more than one etiology

$AUC_{0-\tau}$ values for individual patients overlapped among CP classes. Terminal half-life was about 14 h and 10 h longer in CP class C (49.7 h) than CP class A (36.2 h) and B (39.5 h), respectively.

Table 2 Pooled analysis of demographics and baseline characteristics in phase 1/2 and phase 3 trials by Child–Pugh class

	Class A/B (*n* = 154)	Class C[a] (*n* = 8)
Sex, *n* (%)		
Male	85 (55.2)	3 (37.5)
Female	69 (44.8)	5 (62.5)
Age, years		
Mean (SD)	59.8 (11.8)	53.0 (15.1)
Median (range)	60 (19–81)	51 (31–74)
Disease etiology[b]		
HBV	26 (16.9)	2 (25.0)
HCV	91 (59.1)	2 (25.0)
Alcoholic hepatitis	25 (16.2)	2 (25.0)
Non-alcoholic hepatitis	15 (9.7)	1 (12.5)
Cholestatic hepatitis	5 (3.2)	1 (12.5)
Other	16 (10.4)	0
Child–Pugh score, median (range)	6 (5–9)	10 (9–13)
Baseline platelet count ($\times 10^9$/L)		
n	153	8
Mean (SD)	39.0 (8.3)	34.5 (14.4)
Median (range)	41 (13–59)	39 (12–52)

HBV hepatitis B virus, *HCV* hepatitis C virus, *SD* standard deviation

[a]One patient had Child–Pugh class B at enrollment, but as a result of fluctuations in score and a medical history of Child–Pugh class C disease, the patient was included in the Child–Pugh class C analysis

[b]Patients may have had more than one etiology

Efficacy and Effectiveness

The results for median maximum platelet count (class A/B, 78×10^9/L; class C, 73×10^9/L), median maximum increase from baseline (class A/B, 38.5×10^9/L; class C, 36.5×10^9/L), and the median duration of platelet count

Table 3 Comparison of pharmacokinetic parameters of lusutrombopag in patients with CP class A, B, and C in the phase 1/2 CP class C study

	Geometric least squares mean			Geometric least squares mean ratio (90% CI)	
	Child–Pugh A (n = 8)	Child–Pugh B (n = 7)	Child–Pugh C (n = 5)	Child–Pugh C/ Child–Pugh A	Child–Pugh C/ Child–Pugh B
C_{max} (ng/mL)	227	205	163	0.715 (0.543, 0.941)	0.792 (0.597, 1.051)
$AUC_{0-\tau}$ (ng·h/mL)	4075	4092	3233	0.793 (0.589, 1.068)	0.790 (0.582, 1.072)
λ_z (L/h)	0.0191	0.0176	0.0139	0.729 (0.603, 0.880)	0.795 (0.655, 0.965)
$t_{1/2,z}$ (h)	36.2	39.5	49.7	1.372 (1.136, 1.657)	1.259 (1.037, 1.528)
CL/F (L/h)	0.736	0.733	0.928	1.261 (0.936, 1.697)	1.266 (0.933, 1.717)

CI confidence interval, C_{max} maximum concentration, $AUC_{0-\tau}$ area under the concentration–time curve, λ_z terminal elimination rate constant, *CL/F* apparent total clearance, $t_{1/2,z}$ terminal elimination half-life

Table 4 Pooled efficacy analysis of phase 1/2 and phase 3 trials by Child–Pugh class

	Child–Pugh class A/B			Child–Pugh class C		
	Without PT (n = 112)	With PT (n = 42)	Total (N = 154)	Without PT (n = 5)	With PT (n = 3)	Total (N = 8)
Maximum PC ($\times 10^9$/L)						
Mean (SD)[a]	88.1 (25.6)	62.3 (23.4)	81.0 (27.5)	83.2	51.0	71.1
Median (range)	86.5 (25–219)	59.5 (26–149)	78 (25–219)	85 (54–105)	52 (35–66)	73 (35–105)
Maximum PC increase from baseline ($\times 10^9$/L)						
Mean (SD)	47.6 (24.4)	27.9 (19.5)	42.1 (24.7)	43.0	26.0	36.6
Median (range)	45 (− 9 to 173)	22.5 (− 1 to 113)	38.5 (− 9 to 173)	45 (7–67)	23 (22–33)	36.5 (7–67)
Duration of PC increase > 50 $\times 10^9$/L (days)						
n	110[b]	42	152[a]	5	3	8
Median (range)	21.0 (0–40.6)	6.1 (0–27.8)	17.6 (0–40.6)	16.1 (5.3–22.6)	0.5 (0–15.1)	14.6 (0–22.6)

PC platelet count, *PT* platelet transfusion, *SD* standard deviation
[a]Where $n \geq 10$
[b]Two patients did not have duration of PC increase available

Table 5 Efficacy endpoints in Child–Pugh class C patients in the phase 1/2, phase 3 studies, and post-marketing surveillance

	Phase 1/2 (n = 5)		Phase 3 (n = 3)		PMS (n = 27)	
	No PT (n = 4)	PT (n = 1)	No PT (n = 1)	PT (n = 2)	No PT[a] (n = 23)	PT (n = 3)
Maximum PC ($\times 10^9$/L)						
Mean (SD)[b]	84.0	35.0	80.0	59.0	101.6 (38.6)	53.3
Median (range)	88.5 (54–105)	35	80	59	91 (41–186)	53 (45–62)
Maximum PC increase from baseline ($\times 10^9$/L)						
Mean (SD)	39.8	23.0	56.0	27.5	53.6 (34.2)	20.7
Median (range)	42.5 (7–67)	23	56	27.5 (22–33)	45 (8–146)	16 (10–36)
Duration of PC increase > 50 $\times 10^9$/L (days), median (range)[c]	16.1 (5.3–19.9)	0[d]	14.1	7.8 (0.5–15.1)	NA	NA

NA not available, *PC* platelet count, *PMS* post-marketing surveillance, *SD* standard deviation

[a]One patient who did not receive a PT with lusutrombopag did not have platelet count data available and was not included in the analysis

[b]Where $n \geq 10$

[c]Time points in patients included in the PMS data set were not uniform; therefore, duration of PC increase is not available

[d]Patient's maximum PC did not exceed 50 $\times 10^9$/L during treatment

increase (class A/B, 17.6 days; class C; 14.6 days) for the patients in the pooled analysis of the phase 1/2 and 3 trials, regardless of platelet transfusion status, are shown in Table 4.

In the phase 1/2 study, four of five patients who received lusutrombopag did not receive a platelet transfusion. Among these patients, the median (range) maximum platelet count was 88.5 $\times 10^9$/L (54–105 $\times 10^9$/L), with a median (range) maximum increase of 42.5 $\times 10^9$/L (7–67 $\times 10^9$/L). Platelet count remained at least 50 $\times 10^9$/L for a median 16.1 days (range 5.3–19.9 $\times 10^9$/L) (Table 5).

Of the three patients with CP class C who received lusutrombopag in the phase 3 study, one patient did not receive a pre-procedure platelet transfusion and rescue therapy for bleeding through 7 days after procedure and responded to lusutrombopag treatment. The patient had a maximum platelet count of 80.0 $\times 10^9$/L with a change of 56.0 $\times 10^9$/L from baseline at day 12. The duration of platelet count greater than or equal to 50 $\times 10^9$/L was 14.1 days (Table 5). The other two lusutrombopag-treated patients received platelet transfusions. The first of these two patients had a baseline platelet count of 19 $\times 10^9$/L; at day 12, the patient had a platelet count of 21 $\times 10^9$/L, after which the patient was given a platelet transfusion. Following platelet transfusion, the maximum platelet count was 52 $\times 10^9$/L at day 28 (max platelet count change, 33 $\times 10^9$/L); the duration of platelet count greater than or equal to 50 $\times 10^9$/L was 0.5 days. In the second of these two patients, the baseline platelet count was 44 $\times 10^9$/L; at day 10, the platelet count was 49 $\times 10^9$/L, after which the patient received a platelet transfusion. Following platelet transfusion, the maximum platelet count was 66 $\times 10^9$/L at day 12 (max platelet count change, 22 $\times 10^9$/L), with a duration of platelet

Table 6 Summary of TEAEs occurring in at least 5% of patients in the clinical trials

	Phase 1/2		Phase 3		Overall
	Child–Pugh class C (n = 5)	Child–Pugh class A/B (n = 152)	Child–Pugh class C (n = 3)	Child–Pugh class C (n = 8)	Child–Pugh class A–C (N = 160)
Any TEAE, n (%)	4 (80.0)	93 (61.2)	3 (100.0)	7 (87.5)	100 (62.5)
Procedural pain	0	25 (16.4)	0	0 (0)	25 (15.6)
Procedural hypertension	0	20 (13.2)	0	0 (0)	20 (12.5)
Postoperative fever	0	19 (12.5)	0	0 (0)	19 (11.9)
Aspartate aminotransferase increased	0	12 (7.9)	0	0 (0)	12 (7.5)
Alanine aminotransferase increased	0	9 (5.9)	0	0 (0)	9 (5.6)
Ascites	0	5 (3.3)	1 (33.3)	1 (12.5)	6 (3.8)
Blood bilirubin increased	1 (20.0)	5 (3.3)	0	1 (12.5)	6 (3.8)
Constipation	1 (20.0)	5 (3.3)	0	1 (12.5)	6 (3.8)
Diarrhea	1 (20.0)	4 (2.6)	0	1 (12.5)	5 (3.1)
Anemia	0	1 (0.7)	2 (66.7)	2 (25)	3 (1.9)
Pleural effusion	1 (20.0)	2 (1.3)	0	1 (12.5)	3 (1.9)
Portal vein thrombosis	1 (20.0)	2 (1.3)	0	1 (12.5)	3 (1.9)
Pruritus	0	2 (1.3)	1 (33.3)	1 (12.5)	3 (1.9)
Acute kidney injury	0	0	2 (66.7)	2 (25)	2 (1.3)
Chest pain	0	1 (0.7)	1 (33.3)	1 (12.5)	2 (1.3)
Hepatic encephalopathy	1 (20.0)	1 (0.7)	0	1 (12.5)	2 (1.3)
Acute hepatic failure	0	0	1 (33.3)	1 (12.5)	1 (0.6)
Acute respiratory distress syndrome	0	0	1 (33.3)	1 (12.5)	1 (0.6)
Anal abscess	0	0	1 (33.3)	1 (12.5)	1 (0.6)
Cardiac arrest	0	0	1 (33.3)	1 (12.5)	1 (0.6)
Clostridium difficile colitis	0	0	1 (33.3)	1 (12.5)	1 (0.6)
Dyspnea	0	0	1 (33.3)	1 (12.5)	1 (0.6)

Table 6 continued

	Phase 1/2		Phase 3		Overall
	Child–Pugh class C (n = 5)	Child–Pugh class A/B (n = 152)	Child–Pugh class C (n = 3)	Child–Pugh class C (n = 8)	Child–Pugh class A–C (N = 160)
Encephalopathy	0	0	1 (33.3)	1 (12.5)	1 (0.6)
Fluid retention	0	0	1 (33.3)	1 (12.5)	1 (0.6)
Hematochezia	1 (20.0)	0	0	1 (12.5)	1 (0.6)
Mesenteric vein thrombosis	1 (20.0)	0	0	1 (12.5)	1 (0.6)
Multi-organ failure	0	0	1 (33.3)	1 (12.5)	1 (0.6)
Neutrophil count decreased	1 (20.0)	0	0	1 (12.5)	1 (0.6)
Sepsis	0	0	1 (33.3)	1 (12.5)	1 (0.6)

TEAE treatment-emergent adverse event

count increase greater than or equal to 50×10^9/L of 15.1 days.

In the PMS, 24 of 27 patients did not receive a platelet transfusion. In 23 patients who received lusutrombopag without platelet transfusion and had platelet count data available, the mean maximum platelet count was 101.6×10^9/L (range 41–186 $\times 10^9$/L) and the mean maximum platelet count increase from baseline was 53.6×10^9/L (range 8–146 $\times 10^9$/L) (Table 5). Duration of platelet count increase was not available for patients in the PMS. Data for the three patients who received platelet transfusion are shown in Table S3 in the supplementary material.

Safety

In both clinical studies and the PMS, all treatment-emergent adverse events (TEAE) and serious adverse events were determined by the study investigators or the reporting physicians to be not related to lusutrombopag treatment. In the phase 1/2 and phase 3 trials, 80.0% (n = 4) and 100.0% (n = 3) of CP class C patients experienced at least one TEAE. In the phase 3 studies, 61.2% (n = 93) of CP class A/B patients experienced at least one TEAE. No new safety signals emerged in the CP class C cohort. Among CP class C patients in the clinical trials, all TEAEs occurred in one patient each, with the exception of acute kidney injury and anemia, which occurred in two patients each (Table 6). In the PMS, adverse events occurred in 33% (n = 9) of patients with CP class C, of which the most common was pyrexia (n = 4, 14.8%; Table 7).

Increased transaminases were observed in a minority of A/B patients from the phase 3 trial and no CP class C patients from either the phase 1/2 or phase 3 trials (Table 6). Similarly, increases in transaminases were seen in both CP class A/B (AST, 2.6% [n = 14]; ALT, 2.2% [n = 12]) and CP class C (AST and ALT, 3.7% [each n = 1]) patients from the PMS (Table 7). The proportions of patients with increases in bilirubin between CP class A/B in the phase 3 trials and CP class C patients in the phase 1/2 study were 3.3% (n = 5) and 20.0% (n = 1), respectively, although the numbers are small and hence the percentages should only be taken as observational (Table 6). Hepatic encephalopathy and ascites, which are associated with decompensated cirrhosis, were infrequently observed in the phase 1/2 and 3

Table 7 Summary of adverse events occurring in more than 2% of patients in the PMS

	Child–Pugh Class A/B (n = 543)	Child–Pugh Class C (n = 27)
Any AE, n (%)	119 (21.9)	9 (33.3)
Pyrexia	23 (4.2)	4 (14.8)
Aspartate aminotransferase increased	14 (2.6)	1 (3.7)
Alanine aminotransferase increased	12 (2.2)	1 (3.7)
C-reactive protein increased	4 (0.7)	1 (3.7)
Hepatic function abnormal	11 (2.0)	0
Hypoalbuminemia	4 (0.7)	1 (3.7)
Hemoglobin decreased	3 (0.6)	1 (3.7)
Pleural effusion	2 (0.4)	1 (3.7)
Hypoprothrombinemia	1 (0.2)	1 (3.7)
Intra-abdominal hemorrhage	1 (0.2)	1 (3.7)
Acute kidney injury	0	1 (3.7)
Constipation	0	1 (3.7)
Decreased appetite	0	1 (3.7)
Hepatic cirrhosis	0	1 (3.7)
Edema due to hepatic disease	0	1 (3.7)
Pain	0	1 (3.7)
Peritonitis bacterial	0	1 (3.7)
Red blood cell count decreased	0	1 (3.7)
Portal vein thrombosis[a]	9 (1.7)	0

AE adverse event

[a]As an adverse event of special interest, portal vein thrombosis was included despite not reaching the threshold of 2% of patients in either the Child–Pugh class A/B or C subsets of patients

trials, and did not appear to be different between the CP class A/B and C populations (Table 6) [15]. A summary of additional adverse events in the phase 1/2 and 3 trials and the PMS is shown in Tables 6 and 7.

An adverse event of special interest was observed in one CP class C patient who received lusutrombopag in the phase 1/2 study and subsequently experienced portal vein thrombosis (PVT) on day 20 of the study, which did not resolve by the time of last follow-up (day 35). This was considered non-serious and unrelated to the study drug by the investigator and no action was taken related to the event. The thrombosis was not apparent on the day 3 diagnostic CT. The PVT was asymptomatic and found by diagnostic CT imaging as per protocol. Two additional cases of PVT occurred in CP class A/B patients from the phase 3 trial; PVT occurred in 1.7% (n = 9) CP class A/B patients from the PMS, but was not reported in any CP class C patients (Tables 6 and 7). No thrombotic adverse events were identified in CP class C patients in the PMS data.

DISCUSSION

Lusutrombopag, an orally active, second-generation, small molecule TPO-RA, has previously been demonstrated to reduce the need for platelet transfusion in patients with thrombocytopenia and CLD undergoing invasive procedures [10, 11]. However, despite the need for interventions for CP class C patients with chronic liver disease-related thrombocytopenia, there have been few analyses done in this population, necessitating post hoc descriptive analyses such as the present study to evaluate treatments in this underserved population. Here, we provide the first evaluation of a TPO-RA in a population of patients with CP class C disease. In both clinical studies and the PMS, patients with CP class C benefited from lusutrombopag treatment, as evident in the increase in platelet counts following treatment and avoidance of the need for platelet transfusion; treatment was safe and well tolerated with no treatment-related adverse events. In CP class A/B and class C patients from the phase 1/2 and phase 3 trials, baseline platelet count levels were comparable (CP class A/B, 39×10^9/L [SD, 8.3×10^9/L]; CP class C, 34.5×10^9/L [SD, 14.4×10^9/L]) and platelet count for the patients' treatment with lusutrombopag was increased (maximum platelet count, 81.0×10^9/L [range 25–219×10^9/L] and 71.1×10^9/L [range 35–105×10^9/L]; maximum change in platelet count from baseline, 42.1×10^9/L [range -9 to 173×10^9/L] and 36.6×10^9/L [range 7–67×10^9/L]).

In an analysis of hepatic impairment in the phase 1/2 study, the observed C_{max} in patients with CP class C decreased relative to CP class A (geometric least squares mean [GLS], 0.715) and B (GLS, 0.792; Table 3). A similar decrease was observed for $AUC_{0-\tau}$ (class A, GLS, 0.793; class B, GLS, 0.790), consistent with past observations in patients with a CP score of 9 or higher [12]. This indicates that the prolongation of the terminal half-life does not translate into an increased drug exposure, which would not call for a change in dosing in CP class C patients and adds reassurance to the safety data regarding platelet overshoot and potential for PVT. However, individual C_{max} and $AUC_{0-\tau}$ overlapped among CP classes.

Although the numbers in the phase 1/2 CP class C study were small ($n = 5$), there were no reports of increased AST/ALT and one report of an elevated bilirubin test; one patient had a PVT that was considered non-serious and unrelated to the study drug by the investigator. However, when safety data were compared from the PMS, which included 570 patients (CP class C, $n = 27$; CP class A/B, $n = 543$), the findings were comparable, with no PVTs reported in the CP class C patients. Additionally, among CP class C patients, ascites occurred in one of the three patients in the phase 3 trial and was not reported in the phase 1/2 trial or the PMS.

As the management of diagnostic and therapeutic procedures in patients with thrombocytopenia and CLD is a common issue faced by physicians, these data present a valuable insight into the treatment of patients with CP class C disease undergoing a planned invasive procedure.

A limitation of this study is the small sample size. As such, these findings should be taken as directional and confirmed by larger investigations in the future. Furthermore, the PMS data has the same limitations common to all observational studies, including the fact that data points were not necessarily obtained at the same time for all patients, and some baseline characteristics differed from the phase 1/2 and phase 3 trials, which may limit interpretation of the results.

CONCLUSION

This analysis suggests that lusutrombopag is safe and efficacious as well as effective in raising platelet counts in CP class C patients undergoing planned invasive procedures. Given the descriptive nature of analyzing the limited data currently available, confirmatory trials should be considered in the future.

ACKNOWLEDGEMENTS

We thank the patients and families who participated in the studies/PMS. We also thank the investigators who conducted the studies/PMS.

Funding. This analysis and the publisher's Rapid Service and Open Access Fees were funded by Shionogi & Co., Ltd.

Medical Writing, Editorial, and Other Assistance. The authors thank Meghan Sullivan, PhD, and Michelle Jones, PhD, MWC, of MedVal Scientific Information Services, LLC for medical writing and editorial assistance, which was funded by Shionogi & Co., Ltd. This manuscript was prepared according to the International Society for Medical Publication Professionals' "Good Publication Practice for Communicating Company-Sponsored Medical Research: GPP3."

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. Conception and design: all authors. Acquisition of data: all authors. Analysis and interpretation of the data: all authors. Drafting and critical revision of the article for important intellectual content: all authors.

Disclosures. Steven L. Flamm is a Consultant for Gilead, AbbVie, Salix, Intercept, and Shionogi; received research funding from Gilead and Intercept. Markus Peck-Radosavljevic consults and advises for Shionogi and Sobi. Yukio Osaki has completed speaking and teaching for Gilead Sciences Inc., Bayer Yakuhin, Ltd, MSD Co., Inc., Shionogi & Co., Ltd., AbbVie GK, and Eisai Co., Ltd. Takahiro Fukuhara, Roy Bentley, Takayuki Katsube, Toshimitsu Ochiai, Takeshi Kano, Eri Tsukimura and Ritsue Sasaki are all Shionogi employees.

Compliance with Ethics Guidelines. These studies were conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonisation. For the phase 1/2 and phase 3 studies, all patients provided written informed consent, and the study protocols were approved by the institutional review boards or independent ethics committee of each participating center. According to exemptions under the Good Post-Marketing Study Practice ordinance by the Ministry of Health, Labour, and Welfare in Japan, institutional review board approval and informed consent were not required for the PMS. In the PMS data, patients were anonymized prior to analysis.

Data Availability. All data generated or analyzed during this study are included in this published article or as supplementary information files.

REFERENCES

1. Hayashi H, Beppu T, Shirabe K, Maehara Y, Baba H. Management of thrombocytopenia due to liver cirrhosis: a review. World J Gastroenterol. 2014;20:2595–605.

2. Giannini EG, Peck-Radosavljevic M. Platelet dysfunction: status of thrombopoietin in thrombocytopenia associated with chronic liver failure. Semin Thromb Hemost. 2015;41:455–61.

3. Giannini EG, Greco A, Marenco S, Andorno E, Valente U, Savarino V. Incidence of bleeding following invasive procedures in patients with thrombocytopenia and advanced liver disease. Clin Gastroenterol Hepatol. 2010;8:899–902.

4. Peck-Radosavljevic M. Thrombocytopenia in chronic liver disease. Liver Int. 2017;37:778–93.

5. Maruyama T, Murata S, Takahashi K, et al. Platelet transfusion improves liver function in patients with chronic liver disease and cirrhosis. Tohoku J Exp Med. 2013;229:213–20.

6. Poordad F. Review article: thrombocytopenia in chronic liver disease. Aliment Pharmacol Ther. 2007;26(suppl 1):5–11.

7. Shionogi & Co., Ltd. Shionogi launches MULPLETA® tablets 3mg in Japan for improvement of thrombocytopenia. 2015. https://www.shionogi.com/content/dam/shionogi/global/news/pdf/2015/151201_e.pdf. Accessed 9 May 2022.

8. European Commission. Lusutrombopag [product information]. 2019. https://www.ema.europa.eu/en/medicines/human/EPAR/mulpleo. Accessed 9 May 2022.

9. MULPLETA® (lusutrombopag tablets) for oral use [prescribing information]. Florham Park, NJ: Shionogi Inc.; July 2018.

10. Hidaka H, Kurosaki M, Tanaka H, et al. Lusutrombopag reduces need for platelet transfusion in patients with thrombocytopenia undergoing invasive procedures. Clin Gastroenterol Hepatol. 2019;17:1192–200.

11. Peck-Radosavljevic M, Simon K, Iacobellis A, et al. Lusutrombopag for the treatment of thrombocytopenia in patients with chronic liver disease undergoing invasive procedures (L-PLUS 2). Hepatology. 2019;70:1336–48.

12. Katsube T, Shimizu R, Fukuhara T, Kano T, Wajima T. Pharmacokinetic/pharmacodynamic modelling and simulation of lusutrombopag, a novel thrombopoietin receptor agonist, for the treatment of thrombocytopenia in patients with chronic liver disease undergoing invasive procedures. Clin Pharmacokinet. 2019;58:1469–82.

13. Sasaki R, Shiino C, Imawari M, et al. Safety and effectiveness of lusutrombopag in Japanese chronic liver disease patients with thrombocytopenia undergoing invasive procedures: interim results of a postmarketing surveillance. Hepatol Res. 2019;49:1169–81.

14. Numata K, Tanaka K, Katsube T, et al. Is platelet monitoring during 7-day lusutrombopag treatment necessary in chronic liver disease patients with thrombocytopenia undergoing planned invasive procedures? A phase IIIb open-label study. Hepatol Res. 2020;50:1141–50.

15. Mansour D, McPherson S. Management of decompensated cirrhosis. Clin Med (Lond). 2018;18:s60–5.