Original Article

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

Kazushi Numata,1 Katsuaki Tanaka,1,2 Takayuki Katsube,3 Toshimitsu Ochiai,4 Takahiro Fukuhara,5 Takeshi Kano,6 Yukio Osaki,7,8 Namiki Izumi9 and Michio Imawari10

1Gastroenterological Center, Yokohama City University Medical Center, Yokohama, 2Gastroenterological Center, Japanese Red Cross Hadano Hospital, Hadano, 3Clinical Pharmacology and Pharmacokinetics, 4Biostatistics Center, 5Clinical Development, and 6Project Management, Shionogi & Co., Ltd., and 7Department of Gastroenterology and Hepatology, Japanese Red Cross Society Osaka Hospital, Osaka, 8Department of Gastroenterology and Hepatology, Meiwa Hospital, Nishinomiya, 9Department of Gastroenterology and Hepatology, Japanese Red Cross Society Musashino Hospital, Musashino, 10Institute for Gastrointestinal and Liver Diseases, Shin yurigaoka General Hospital, Kawasaki, Japan

Aim: Lusutrombopag is approved for thrombocytopenia in chronic liver disease patients planned to undergo invasive procedures. In previous clinical studies, lusutrombopag treatment was stopped in patients with an increase in platelet count (PC) of ≥20×10^9/L from baseline and whose PC was ≥50×10^9/L (discontinuation criteria). We assessed the influence of platelet monitoring during lusutrombopag treatment in lusutrombopag naïve patients.

Methods: In this open label study, Child–Pugh class A and B (A/B) patients were enrolled and treated with lusutrombopag (3 mg/day) for 7 days. In the treatment naïve A/B 1 group, the discontinuation criteria were applied on day 6. In the treatment naïve A/B 2 group, the criteria were not applied. In a non naïve A/B group, the criteria were applied on days 3 and 5–7. The main efficacy end point was the proportion of patients without platelet transfusion (PT) before the primary invasive procedure.

Results: In the A/B 1, A/B 2, and non naïve A/B groups, the proportions of patients without PT were 80.9% (38/47), 83.0% (39/47), and 75.0% (6/8), respectively. The mean durations of PC ≥50×10^9/L without PT were 20.7, 20.3, and 22.8 days, respectively. Excessive PC increases (≥200×10^9/L) were not detected in any group. Treatment related adverse events occurred in 4.3%, 6.4%, and 0% of A/B 1, A/B 2, and non naïve A/B patients, respectively. Severe portal vein thrombosis occurred in one A/B 2 patient (PC 75×10^9/L at onset).

Conclusions: No meaningful efficacy and safety differences were observed among the groups with or without discontinuation criteria and the non naïve group. These findings support lusutrombopag treatment without platelet monitoring and retreatment with lusutrombopag.

Key words: liver disease, lusutrombopag, monitoring, physiologic, platelet count, pre exposure prophylaxis, thrombocytopenia

Correspondence: Dr Kazushi Numata, Gastroenterological Center, Yokohama City University Medical Center, Urafune-cho 4-57, Minami-ku, Yokohama 232-0024, Japan. Email: kz-numa@urahp.yokohama-cu.ac.jp

Conflict of interest: KN and KT have no conflict of interest to disclose. T Katsube, TO, TF, and T Kano are employees of the study sponsor, Shionogi & Co., Ltd., Osaka, Japan. YO has received honoraria from Shionogi & Co., Ltd., Gilead Sciences, and AbbVie. NI has received honoraria from Shionogi & Co., Ltd. MI has received honoraria from Shionogi & Co., Ltd. and Japan Bio Products Co.

Financial support: This study was funded by Shionogi & Co., Ltd.

Received 26 November 2019; revision 16 June 2020; accepted 24 June 2020.

© 2020 The Authors. Hepatology Research published by John Wiley & Sons Australia, Ltd on behalf of Japan Society of Hepatology. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
INTRODUCTION

THROMBOCYTOPENIA IS A common hematologic abnormality in patients with chronic liver disease (CLD). In CLD, thrombocytopenia is generally the result of decreased platelet production, splenic sequestration, and increased platelet destruction.1 Thrombocytopenia is associated with a greater risk of postoperative bleeding, which could affect the ability of CLD patients to undergo planned invasive diagnostic or therapeutic procedures (e.g., percutaneous, transjugular, or laparoscopic liver biopsy; paracentesis; thoracentesis; radiofrequency ablation [RFA]; or transarterial chemoembolization [TACE]), or surgical procedures (e.g., partial hepatectomy for hepatocellular carcinoma).2

Preoperative platelet transfusions (PTs) have not been shown to be effective in preventing postoperative bleeding due to their lack of effectiveness in increasing or maintaining platelet count (PC) levels at medically appropriate levels (≥50 × 10⁹/L). Furthermore, PTs are associated with a high rate of immunologically mediated reactions or bacterial contamination.3–5 Repeated PTs could result in refractoriness (i.e., failure to obtain an adequate response to PTs).6,7 Platelet refractoriness is associated with several negative outcomes, such as increased risk of bleeding,8 decreased survival,9 extended hospitalizations, and higher inpatient costs.10 In patients with CLD, PTs have been shown to be ineffective in achieving a hemostatic level.11

Lusutrombopag is an orally administered, small-molecule thrombopoietin (TPO) receptor agonist that acts on the transmembrane domain of human TPO receptors, activates the signal transduction pathway in a manner similar to endogenous TPO, and leads to upregulation of platelet production.12 Lusutrombopag is currently approved in Japan (2015) and the USA (2018) for the treatment of thrombocytopenia, and in the EU (2019) for the treatment of severe thrombocytopenia in adults with CLD scheduled for planned invasive procedures.12,13

Previous clinical trial data have established the efficacy of lusutrombopag in CLD patients with thrombocytopenia. In a phase IIb dose-finding study in Japan, fewer patients who were treated with lusutrombopag (2, 3, or 4 mg) before RFA required PT compared with the placebo group (P < 0.01).14 Similarly, in the Japanese L-PLUS 1 phase III study, fewer patients in the lusutrombopag group required preoperative PT before the primary invasive procedure compared with the placebo group (P < 0.0001).15 The global L-PLUS 2 phase III study also revealed that lusutrombopag was superior to placebo with regard to the primary end-point: the proportion of patients who required no PT prior to the primary invasive procedure and no rescue therapy for bleeding from randomization through 7 days after the primary invasive procedure (P < 0.0001).16

A study of the oral TPO-receptor agonist eltrombopag in patients with thrombocytopenia and CLD reported that the risk of thrombosis increases in patients with a PC exceeding 200 × 10⁹/L.17 Based on this observation, all three of the previous lusutrombopag clinical trials incorporated platelet monitoring and applied treatment discontinuation criteria (lusutrombopag treatment was stopped in patients with an increase in PC of ≥20 × 10⁹/L from baseline and whose PC was ≥50 × 10⁹/L) in the last 3 days of treatment. This methodology is reflected in the Japanese package insert for lusutrombopag, which recommends treatment discontinuation in patients with liver cirrhosis who achieve these PC levels, in order to avoid portal vein thrombosis (PVT), although similar recommendations are not applied in other regions such as Europe and the USA. However, strict application of these criteria can be burdensome and unpleasant for patients, as platelet monitoring requires repeated hospital visits and blood sampling. There is currently insufficient information to determine whether platelet monitoring using these discontinuation criteria during a 7-day lusutrombopag treatment period is necessary for all patients, or if platelet monitoring could be reduced or omitted in suitable patients without negatively impacting safety or efficacy outcomes.18 Furthermore, only a few reports describe the effect of lusutrombopag in patients being retreated with lusutrombopag.19,20 This open-label study aimed to determine whether platelet monitoring and the discontinuation criteria could be applied at a reduced frequency without affecting clinical outcomes. Additionally, the efficacy, safety, and pharmacokinetics (PK) were evaluated in lusutrombopag-naïve and lusutrombopag retreatment (non-naïve) CLD patients with thrombocytopenia undergoing planned invasive procedures.

METHODS

Study design, treatment, and ethics

This was a multicenter, open-label phase IIIb study undertaken between October 2015 and September 2016 at 82 sites in Japan. The study consisted of screening, lusutrombopag treatment (3 mg once daily on days 1–7), and post-treatment periods (Fig. 1).

Initially, lusutrombopag-naïve patients were enrolled into the A/B-1 group; platelets were monitored on days 5–7 during the treatment period. Lusutrombopag treatment had to be stopped in patients with an increase in
platelets of at least \( \geq 20 \times 10^9/L \) from baseline and whose PC was at least \( \geq 50 \times 10^9/L \) (defined as the discontinuation criteria) on day 6 (Table 1). Subsequently, after confirming that no more than one patient in the A/B-1 group experienced a platelet count (PC) \( \geq 200 \times 10^9/L \), patients who had previously received lusutrombopag were enrolled into the non-naive A/B group, and the discontinuation criteria were applied on day 3 and days 5–7.

It should be noted that the timing of platelet monitoring in our study was not identical to that recommended in the Japanese lusutrombopag prescribing information (in which PC is measured at least once on or around day 5 after treatment with lusutrombopag and, subsequently, as needed according to the results obtained). If the PC increased by more than \( 40 \times 10^9/L \) from baseline in both A/B-1 and A/B-2 on days 5–7, and in non-naive A/B on day 3 and days 5–7, discontinuation criteria were deemed to be satisfied and no further lusutrombopag treatment was given; this precaution was implemented to prevent excessive PC increases.\(^{17}\)

The study timeline allowed for invasive procedures to be undertaken between days 9 and 14. The need for PT was determined after day 8 and immediately before undertaking the primary planned invasive procedure (but not more than 2 days prior to the invasive procedure). Preoperative PT was undertaken only when the PC was found to be \( < 50 \times 10^9/L \).

The use of platelet preparations (except for preoperative use and as rescue therapy) and other blood product preparations, anticancer drugs, interferon, macrophage colony-stimulating factor, granulocyte colony-stimulating factor, erythropoietin, other TPO receptor agonists, antithrombotic agents (except as rescue therapy), desmopressin, monoethanolamine oleate, and other investigational products were prohibited. Therapeutic phlebotomy, radiotherapy, and any other procedure, except for the planned invasive procedure, were prohibited.

---

**Figure 1** Study design to determine the need for platelet monitoring during 7-day lusutrombopag treatment in chronic liver disease patients with thrombocytopenia undergoing planned invasive procedures. \( ^{†} \) Platelet count measurements were made as follows: days 5, 6, and 7 for the A/B-1 and A/B-2 groups; and days 3, 5, 6, and 7 for the non-naive A/B group. PK, pharmacokinetic.

**Table 1** Study groups of chronic liver disease patients with thrombocytopenia treated with lusutrombopag

| Treatment group | Lusutrombopag treatment status | Study day on which discontinuation criteria were applied\(^{‡}\) |
|-----------------|-------------------------------|-------------------------------------------------|
| A/B-1\(^{†}\)   | Naïve                         | Day 6                                           |
| A/B-2\(^{†}\)   | Naïve                         | Not applied                                    |
| Non-naive A/B   | Previously treated            | Days 3, 5, 6, and 7                            |

\(^{†}\) lusutrombopag-naïve patients were initially enrolled into the A/B-1 group. Enrollment into the A/B-2 group was allowed only after confirming that no more than one patient in the A/B-1 group experienced a platelet count (PC) \( \geq 200 \times 10^9/L \).

\(^{‡}\) An increase in platelets of \( \geq 20 \times 10^9/L \) from baseline and PC \( \geq 50 \times 10^9/L \) during lusutrombopag treatment.
The protocol (1338 M0633) was approved by the Institutional Review Board at each study site. The study was carried out in accordance with the current International Conference on Harmonization Good Clinical Practice guidelines, and the ethical principles outlined in the Declaration of Helsinki. All patients gave written informed consent before entering the study. The study was registered at the Japan Pharmaceutical Information Center under the identification number JapicCTI-153023.

Patients

Patients with CLD aged ≥20 years with severe thrombocytopenia (PC < 50 × 10^9/L), who were scheduled to undergo a planned invasive procedure between 9 and 14 days after the initiation of lusutrombopag treatment, and had an Eastern Cooperative Oncology Group performance status of 0 or 1 were eligible for enrollment.

Patients with any of the following hematological disorders were excluded from the study: hematopoietic tumor; aplastic anemia; myelodysplastic syndrome; myelofibrosis; immune, congenital or drug-induced thrombocytopenia; or generalized infection (other than viral liver disease) requiring treatment. Other key exclusion criteria were: severe hepatic impairment (Child–Pugh class C liver disease); portal vein tumor thrombosis; patients with past or present thrombosis (e.g., cerebral infarction, myocardial infarction, angina pectoris, pulmonary thromboembolism, deep vein thrombosis, or disseminated intravascular coagulation syndrome); and lack of hepatopetal portal blood flow.

Efficacy assessments

The efficacy end-points were as follows: the proportion of patients who did not require preoperative PT (main end-point); the responder rate during the study (i.e., the proportion of patients with an increase in platelets of ≥20 × 10^9/L from baseline and PC≥20 × 10^9/L); duration of the increase in PC≥50 × 10^9/L, ≥70 × 10^9/L, and ≥50 × 10^9/L with an increase of ≥20 × 10^9/L from baseline; and time course of PC.

Safety assessments

Adverse events (AEs) were recorded using the Medical Dictionary for Regulatory Activities version 18.0. Treatment-emergent AEs (TEAEs), treatment-related AEs (TRAEs), and thrombosis-related and bleeding-related AEs were evaluated and summarized.

Diagnostic imaging to assess PVT and portal blood flow (Doppler ultrasonography, computed tomography, or magnetic resonance imaging) were carried out three times during the screening period, between day 8 and immediately before the procedure, and 3–10 days after the procedure.

Pharmacokinetic assessments

Intensive blood sampling was carried out for the determination of plasma drug concentrations in 16 patients in A/B-1 and all patients in non-naïve A/B, and sparse blood sampling was carried out in the rest of the patients. Further details of PK assessments based on plasma drug concentrations from intensive blood samples are provided in Data S1.

Statistical methods

The target sample size of this study was 95 patients with Child–Pugh class A or B. The inclusion of 45 patients each into the A/B-1 and A/B-2 groups allowed for the comparison of efficacy and safety end-points with the confirmatory L-PLUS 1 study, which included similar patient numbers per treatment group. An additional five patients were included in the non-naïve A/B group based on the expected feasibility of patient accrual. The full analysis set (FAS) included all enrolled patients who received at least one dose of the study drug and had a baseline PC measurement and at least one measurement of PC after the initiation of study drug administration. The analysis of efficacy was undertaken in the FAS population. The 95% confidence intervals for patient proportions were calculated using the Clopper–Pearson method. All the analyses and listings were undertaken using SAS (version 9.2) (SAS Institute Inc., Cary, NC, USA) and Phoenix WinNonlin (version 6.2.1) (Cartera L. P., Princeton, NJ, USA).

RESULTS

Patients

A TOTAL OF 102 patients were enrolled in the study. As no patients in A/B-1 experienced PC≥200 × 10^9/L, enrollment into A/B-2 was allowed to proceed as planned. All enrolled patients were included in the FAS: 47 each in A/B-1 and A/B-2 and eight in non-naïve A/B. Overall, two patients were withdrawn in the post-treatment period after the 7-day drug treatment was completed, one patient in A/B-1 at the patient’s request and one patient in A/B-2 because of a severe PVT. In total, 100 patients completed the study through to the end of the post-treatment period (Fig. 2).

Three patients in A/B-1 met the discontinuation criteria on day 6 (an increase in platelets of ≥20 × 10^9/L from baseline and PC≥50 × 10^9/L), and thus, received treatment for 5 days. One patient in A/B-2 forgot to take the study drug on day 4. No excessive increases in PC,
which would have triggered treatment cessation, were observed during the treatment (i.e., none of the patients in any group experienced PC $\geq 200 \times 10^9/L$, and none in any group had an increase of $\geq 40 \times 10^9/L$ from baseline). Thus, 44/47 patients (93.6%) in A/B-1 and 46/47 patients (97.9%) in A/B-2 received the study drug for 7 days. The baseline characteristics of the three groups are shown in Table 2.

![Diagram](image)

**Figure 2** Patient disposition among chronic liver disease subjects with thrombocytopenia treated with lusutrombopag for 7 days. †Lusutrombopag-naïve patients were initially enrolled into the A/B-1 group. ‡Enrollment into the A/B-2 group was allowed only after confirming that no more than one patient in the A/B-1 group experienced a platelet count $\geq 200 \times 10^9/L$.

**Table 2** Characteristics of chronic liver disease (CLD) patients with thrombocytopenia treated with lusutrombopag ($N=102$)

|                        | A/B-1, $N=47$ | A/B-2, $N=47$ | Non-naïve A/B, $N=8$ |
|------------------------|---------------|---------------|----------------------|
| Sex, $n$ ( %)          |               |               |                      |
| Male                   | 26 (55.3)     | 26 (55.3)     | 4 (50.0)             |
| Female                 | 21 (44.7)     | 21 (44.7)     | 4 (50.0)             |
| Age (years), mean (SD) | 71.0 (7.8)    | 67.1 (8.7)    | 73.6 (6.0)           |
| History of CLD, $n$ ( %) |             |               |                      |
| Hepatitis B            | 5 (10.6)      | 4 (8.5)       | 0 (0.0)              |
| Hepatitis C            | 31 (66.0)     | 32 (68.1)     | 4 (50.0)             |
| Alcoholic hepatitis    | 10 (21.3)     | 4 (8.5)       | 3 (37.5)             |
| Non-alcoholic hepatitis| 0 (0.0)       | 6 (12.8)      | 0 (0.0)              |
| Autoimmune hepatitis   | 1 (2.1)       | 1 (2.1)       | 0 (0.0)              |
| Child–Pugh class, $n$ ( %) |             |               |                      |
| A                      | 25 (53.2)     | 35 (74.5)     | 4 (50.0)             |
| B                      | 22 (46.8)     | 12 (25.5)     | 4 (50.0)             |
| Baseline PC            |               |               |                      |
| Median (range), $\times 10^9/L$ | 40.0 (21–53) | 39.0 (24–54) | 39.0 (31–47)         |
| $\leq 35 \times 10^9/L, n$ (%) | 13 (27.7)   | 15 (31.9)     | 3 (37.5)             |
| $\geq 35 \times 10^9/L, n$ (%) | 34 (72.3)   | 32 (68.1)     | 5 (62.5)             |
| Splenomegaly, $n$ (%)   | 44 (93.6)     | 42 (89.4)     | 8 (100.0)            |
| Thrombopoietin (pg/mL) at screening, mean (SD) | 105.40 (133.30) | 76.54 (116.73) | 142.09 (161.06) |

†Splenomegaly was confirmed by ultrasonography, computed tomography, or magnetic resonance imaging during the screening phase.

PC, platelet count; SD, standard deviation.
Table 3 Proportion of chronic liver disease patients with thrombocytopenia, treated with lusutrombopag, who did not require platelet transfusion (PT) before invasive procedure

| Procedure | A/B-1, N=47 | A/B-2, N=47 | Non-naïve A/B, N=8 |
|-----------|-------------|-------------|-------------------|
| Proportion of patients who did not require PT | 80.9 (38/47) | 83.0 (39/47) | 75.0 (6/8) |
| Exact 95% CI | (66.7, 90.9) | (69.2, 92.4) | (34.9, 96.8) |
| Baseline PC | | | |
| <35×10^9/L | 46.2 (6/13) | 66.7 (10/15) | - |
| ≥35×10^9/L | 94.1 (32/34) | 90.6 (29/32) | - |
| Child–Pugh class | | | |
| A | 88.0 (22/25) | 80.0 (28/35) | - |
| B | 72.7 (16/22) | 91.7 (11/12) | - |

Data were calculated as % (100 x number of patients who did not require PT/[number of patients who required PT and did not require PT])
†One patient was withdrawn from each group after the 7-day drug treatment.
‡Angiography, endoscopic mucosal resection, endoscopic mucosal dissection, lipiodol-transcatheter arterial infusion, liver biopsy, balloon-occluded retrograde transvenous obliteration, endoscopic injection sclerotherapy, argon plasma coagulation.
- not applicable; CI, confidence interval; EVL, esophageal varices ligation; MCT, microwave coagulation therapy; PC, platelet count; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization.

Non-naïve A/B included seven patients who had previously received lusutrombopag in a previous clinical study and one patient who had been previously treated in A/B-1. The interval (minimum to maximum) between the initiation of the first treatment and that of the second treatment was 92 to 1543 days in non-naïve A/B. All eight non-naïve A/B patients were responders on their first lusutrombopag treatment. These eight patients (100%) received the study drug for 7 days.

Efficacy
The proportions of patients who did not require PT prior to the primary invasive procedure in A/B-1, A/B-2, and non-naïve A/B were 80.9% (38/47), 83.0% (39/47), and 75.0% (6/8), respectively. No meaningful differences were observed in the main efficacy end-point among these groups. Moreover, there were no differences between A/B-1 and A/B-2 in the proportion of patients who did not require PT before the invasive procedure (Table 3).

The proportions of responders (an increase in platelets of ≥20×10^9/L from baseline and PC≥50×10^9/L) during the study in A/B-1, A/B-2, and non-naïve A/B were 83.0% (39/47), 85.1% (40/47), and 75.0% (6/8), respectively.

The time course of the median PC in A/B-1, A/B-2, and non-naïve A/B is shown in Figure 3. The mean (range) number of days to reach the maximum PC in patients without PT were 14.53 (10.0 to 28.0), 13.90 (10.0 to 28.0), and 13.33 (12.0 to 14.0) days in A/B-1, A/B-2, and non-naïve A/B, respectively. The median (range) maximum PC in patients without PT was 89.5×10^9/L (55 to 173) in the A/B-1 group, 81.0×10^9/L (59 to 115) in the A/B-2 group, and 81.0×10^9/L (75 to 98) in the non-naïve A/B group. The respective median (range) maximum increases in PC from baseline in patients without PT were 44.5×10^9/L (13 to 123) in the A/B-1 group, 43.0×10^9/L (23 to 83) in the A/B-2 group, and 42.0×10^9/L (34 to 59) in the non-naïve A/B group.

Regarding the duration of PC increase, patients in A/B-1 (n=34), A/B-2 (n=37), and non-naïve A/B (n=6) who did not undergo PT maintained PC≥50×10^9/L for a mean of 20.7, 20.3, and 22.8 days, PC≥70×10^9/L for a mean of 8.7, 7.7, and 7.8 days, and PC≥50×10^9/L with an increase of ≥20×10^9/L from baseline for a mean of 12.8, 13.3, and 14.3 days, respectively.

Safety
A total of 204 TEAEs in 43 of 47 patients (91.5%) in A/B-1, 141 TEAEs in 41 of 47 patients (87.2%) in A/B-2, and 26 TEAEs in six of eight patients (75.0%) in non-naïve A/B were observed. Treatment-emergent AEs occurring at an incidence of 10% or more in either the A/B-1 or A/B-2 were constipation, pyrexia, any procedural complication events, and any clinical laboratory parameters (Table 4).
Figure 3  Time course of median platelet count in chronic liver disease patients with thrombocytopenia treated with lusutrombopag, who did not undergo platelet transfusion. Error bars show inter-quartile range. BL, baseline.

Table 4  Treatment-emergent adverse events (TEAE) with an incidence $>$10% among chronic liver disease patients with thrombocytopenia treated with lusutrombopag

| Type of TEAE, n (%) | Total of A/B-1 and A/B-2, N=94 | A/B-1, N=47 | A/B-2, N=47 | Non-naive A/B, N=8 |
|---------------------|---------------------------------|-------------|-------------|--------------------|
| Constipation        | 12 (12.8)                       | 9 (19.1)    | 3 (6.4)     | 1 (12.5)           |
| Pyrexia             | 7 (7.4)                         | 6 (12.8)    | 1 (2.1)     | 0 (0.0)            |
| Musculoskeletal stiffness | 0 (0.0)  | 0 (0.0)     | 0 (0.0)     | 1 (12.5)           |
| Skin exfoliation    | 0 (0.0)                         | 0 (0.0)     | 0 (0.0)     | 1 (12.5)           |
| Hypoglycemia        | 0 (0.0)                         | 0 (0.0)     | 0 (0.0)     | 1 (12.5)           |
| Infections and infestations |         |             |             |                    |
| Nasopharyngitis     | 4 (4.3)                         | 3 (6.4)     | 1 (2.1)     | 1 (12.5)           |
| Gastroenteritis     | 0 (0.0)                         | 0 (0.0)     | 0 (0.0)     | 1 (12.5)           |
| Tinea cruris        | 0 (0.0)                         | 0 (0.0)     | 0 (0.0)     | 1 (12.5)           |
| Investigations      |                                 |             |             |                    |
| AST increased       | 23 (24.5)                       | 14 (29.8)   | 9 (19.1)    | 4 (50.0)           |
| ALT increased       | 15 (16.0)                       | 12 (25.5)   | 3 (6.4)     | 2 (25.0)           |
| C-reactive protein increased | 7 (7.4)  | 6 (12.8)    | 1 (2.1)     | 1 (12.5)           |
| Blood pressure increased | 6 (6.4)  | 4 (8.5)     | 2 (4.3)     | 1 (12.5)           |
| Oxygen saturation decreased | 2 (2.1)  | 1 (2.1)     | 1 (2.1)     | 1 (12.5)           |
| Blood albumin decreased | 1 (1.1)  | 1 (2.1)     | 0 (0.0)     | 1 (12.5)           |
| Procedural complications |                             |             |             |                    |
| Postoperative fever | 35 (37.2)                       | 18 (38.3)   | 17 (36.2)   | 5 (62.5)           |
| Procedural hypertension | 35 (37.2) | 19 (40.4)  | 16 (34.0)   | 1 (12.5)           |
| Procedural pain     | 28 (29.8)                       | 14 (29.8)   | 14 (29.8)   | 1 (12.5)           |
| Procedural nausea   | 5 (5.3)                         | 2 (4.3)     | 3 (6.4)     | 1 (12.5)           |
| Incision site pruritus | 0 (0.0)  | 0 (0.0)     | 0 (0.0)     | 1 (12.5)           |

ALT, alanine aminotransferase; AST, aspartate aminotransferase.
TRAEs were reported in five of 102 patients: mild rash and moderate erythema multiforme in one patient each in A/B-1 (4.3%), and severe PVT, mild white blood cell count decreased, and mild somnolence in one patient each in A/B-2 (6.4%). No TRAEs were reported in non-naïve A/B.

Thrombosis- and bleeding-related AEs are summarized in Table 5. Moderate thrombosis (n=1) occurred in A/B-1, and severe PVT (n=1) and mild PVT (n=1) occurred in A/B-2. The patient with severe PVT reached the maximum PC (PC=75×10⁹/L) on the day of onset (day 11) after 7 days of treatment. The patients who experienced thrombosis-related AEs showed no excessive increase in PC. Bleeding-related events were mild and non-serious and were considered to not be related to lusutrombopag.

**Pharmacokinetic analysis**

Among the patients who underwent intensive PK sampling, the plasma concentration profiles of lusutrombopag were similar between lusutrombopag-naive and non-naïve patients (Fig. S1). The mean plasma concentration profiles of lusutrombopag were similar between lusutrombopag-naive Child–Pugh class A and B patients (Fig. S2). Table S1 shows the summary statistics of the PK parameters of lusutrombopag in lusutrombopag-naive and non-naïve patients, respectively. Table S2 shows that the PK parameters of lusutrombopag were similar between Child–Pugh class A and B patients, and the effect of previous lusutrombopag treatment on the PK of lusutrombopag was not clinically relevant.

**DISCUSSION**

THIS PHASE IIIIB open-label study evaluated the efficacy and safety of once-daily, 3 mg lusutrombopag treatment up to 7 days with (A/B-1 group) or without (A/B-2 group) application of the discontinuation criteria (an increase in platelets of ≥20×10⁹/L from baseline and PC≥50×10⁹/L) in lusutrombopag-naive Japanese CLD patients (Child–Pugh class A/B) with thrombocytopenia undergoing planned invasive procedures. Regarding efficacy, more than 80% of patients did not require preoperative PT and more than 83% of patients were responders in A/B-1 and A/B-2; the proportions were similar in both groups. The maximum PC and mean durations of PC≥50×10⁹/L were similar between the A/B-1 and A/B-2 groups. The incidences of TEAEs were also relatively similar between these two groups (43 patients [91.5%] in A/B-1 and 41 patients [87.2%] in A/B-2). These results suggest that there were no clinically significant differences in efficacy or safety, regardless of the application of the discontinuation criteria. When comparing the present study with L-PLUS 1, a Japanese phase III study with application of the discontinuation criteria on days 5–7 of treatment, there were no major differences in patient characteristics, such as Child–Pugh class, hepatitis B, hepatitis C, or main procedures (RFA/microwave coagulation and TACE total). Moreover, the transfusion avoidance rate (79.2% [38/48]) and responder rate (77.1%) in the lusutrombopag group in L-PLUS 1 were comparable to those observed in A/B-1 (PT avoidance rate 80.9%)

### Table 5  Thrombosis-related and bleeding-related adverse events (AEs) among chronic liver disease patients with thrombocytopenia treated with lusutrombopag

| Thrombosis-related AEs, † n (%) | Total of A/B-1 and A/B-2, N=94 | A/B-1, N=47 | A/B-2, N=47 | Non-naïve A/B, N=8 |
|---------------------------------|---------------------------------|-------------|-------------|-------------------|
| Patients with any thrombosis-related AE | 3 (3.2) | 1 (2.1) | 2 (4.3) | 0 (0.0) |
| Portal vein thrombosis | 2 (2.1) | 0 (0.0) | 2 (4.3) | 0 (0.0) |
| Tumor thrombosis | 1 (1.1) | 1 (2.1) | 0 (0.0) | 0 (0.0) |
| Bleeding-related AEs, † n (%) | 7 (7.4) | 5 (10.6) | 2 (4.3) | 0 (0.0) |
| Epistaxis | 2 (2.1) | 1 (2.1) | 1 (2.1) | 0 (0.0) |
| Hematoma | 1 (1.1) | 1 (2.1) | 0 (0.0) | 0 (0.0) |
| Hemorrhoidal hemorrhage | 1 (1.1) | 1 (2.1) | 0 (0.0) | 0 (0.0) |
| Traumatic hematoma | 1 (1.1) | 1 (2.1) | 0 (0.0) | 0 (0.0) |
| Post-procedural hemorrhage | 1 (1.1) | 1 (2.1) | 0 (0.0) | 0 (0.0) |
| Hemorrhage subcutaneous | 1 (1.1) | 0 (0.0) | 1 (2.1) | 0 (0.0) |

† Including thrombotic/thromboembolic complications per the standard Medical Dictionary for Regulatory Activities query “embolic and thrombotic events, arterial”, “embolic and thrombotic events, venous”, and “embolic and thrombotic events, vessel type unspecified and mixed arterial and venous”.

© 2020 The Authors.

Hepatology Research published by John Wiley & Sons Australia, Ltd on behalf of Japan Society of Hepatology
Regarding safety, there was no major difference in TEAE incidence between the present study and the lusutrombopag arm of L-PLUS 1 (93.8%). Moreover, the numbers of bleeding-related events were lower in the present study (10.6% and 4.3% in A/B-1 and A/B-2, respectively) compared with that in the lusutrombopag arm of L-PLUS 1 (14.6%), especially for procedure-related hemorrhage. The incidence of treatment-related severe thrombotic events was similar in A/B-1 (0/47), A/B-2 (1/47), and the lusutrombopag arm of L-PLUS 1 (1/48). The PC in the single case of severe PVT in each of the A/B-2 and L-PLUS 1 lusutrombopag groups was comparable (i.e., ≥70×10^9/L but <80×10^9/L). Furthermore, no patient in the present study presented a PC exceeding 200×10^9/L, which was found to be the threshold leading to an increased number of PVTs in the ELEVATE study. Overall, our data show that the PC level was not as high in patients with thrombocytopenia in the current study as in the L-PLUS studies. Considering the target population for this study had CLD, and patients were planned to undergo invasive procedures, moderate or severe TEAEs related to the pre-existing disease or invasive procedure were expected. Notably, the case of PVT in A/B-2 was the only severe and serious TEAE considered potentially related to the study drug. It is possible that the patient was already at an increased risk of PVT, as cirrhosis is a well-known risk factor.

Overall, comparable safety and no excessive platelet increase were observed with lusutrombopag treatment for 7 days regardless of the timing of the discontinuation criteria application. These findings suggest that the role of platelet monitoring in lusutrombopag discontinuation might be limited to helping to ensure treatment safety, such as avoiding thrombosis due to excessive increase of platelets.

Additionally, this study evaluated the efficacy, safety, and PK of once-daily 3 mg lusutrombopag treatment in non-naive A/B, including seven patients who had been treated with lusutrombopag in previous clinical trials and one patient in A/B-1 who had received lusutrombopag for 7 days. In non-naive A/B, all patients completed 7 days of treatment. The proportions of patients not requiring PT and of responders were both 75.0% (6/8). The time course of PC in the non-naive patients was similar to the profiles in lusutrombopag-naïve patients from previous reports. The incidence of TEAEs was 75.0%. There were no thrombosis-related or bleeding-related AEs in non-naive patients. Furthermore, the PK analysis did not identify any notable differences in plasma lusutrombopag concentrations or other PK parameters between non-naive and naïve patients, or differences based on Child-Pugh class. These results indicate that promising efficacy and safety findings might be observed in patients who were previously treated with lusutrombopag, similar to the results observed in lusutrombopag-naïve patients.

The data from our study indicated that endogenous TPO concentrations were highest in the non-naive A/B group, compared with patients in A/B-1 and A/B-2 who had not previously received lusutrombopag. However, the relationship between the progression of liver disease and decreases in endogenous TPO concentration is controversial. A post hoc analysis of the L-PLUS 1 study showed that endogenous TPO concentration did not affect the thrombopoietic efficacy of lusutrombopag. In the current study, the results suggest that the efficacy was not influenced by endogenous TPO concentration in patients retreated with lusutrombopag.

This study had several limitations, such as the open-label design, the non-randomized allocation of patients to each group, the limited number of retreatment patients available for the evaluation of efficacy and safety, and the varying types of invasive procedures. In conclusion, there were no clinically significant differences in the efficacy and safety of lusutrombopag treatment with or without discontinuation criteria in lusutrombopag-naïve thrombocytopenic patients with CLD undergoing planned invasive procedures. Furthermore, similar efficacy, safety, and PK results were also observed in patients who had previously received lusutrombopag. These results suggested that lusutrombopag might be safe and effective in CLD patients with thrombocytopenia undergoing planned invasive procedures without platelet monitoring.

**ACKNOWLEDGMENTS**

This study was funded by Shionogi & Co., Ltd. The authors thank Keyra Martinez Dunn, MD, of Edanz Medical Writing for providing medical writing support, which was funded by Shionogi & Co., Ltd. through EMC in accordance with Good Publication Practice guidelines (http://www.ismpp.org/gpp3).

**REFERENCES**

1. Mitchell O, Feldman DM, Diakov M, Sigal SH. The pathophysiology of thrombocytopenia in chronic liver disease. *Hepat Med* 2016; 8: 39–50.
2 Saab S, Brown RS Jr. Management of thrombocytopenia in patients with chronic liver disease. Dig Dis Sci 2019; 64: 2757–68.

3 Kiefel V. Reactions induced by platelet transfusions. Transfus Med Hemother 2008; 35: 354–8.

4 McCullough J. Current issues with platelet transfusion in patients with cancer. Semin Hematol 2000; 37(2 Suppl 4): 3–10.

5 Perrotta PL, Snyder EL. Non-infectious complications of transfusion therapy. Blood Rev 2001; 15: 69–83.

6 Stanworth SJ, Navarrete C, Escourt L, Marsh J. Platelet refractoriness – practical approaches and ongoing dilemmas in patient management. Br J Haematol 2015; 171: 297–305.

7 Murphy M. Managing the platelet refractory patient. ISBT Sci Ser 2014; 9: 234–8.

8 Toor AA, Choo SY, Little JA. Bleeding risk and platelet transfusion refractoriness in patients with acute myelogenous leukemia who undergo autologous stem cell transplantation. Bone Marrow Transplant 2000; 26: 315–20.

9 Kerkhoffs JL, Eikenboom JC, van de Watering LM et al. The clinical impact of platelet refractoriness: correlation with bleeding and survival. Transfusion 2008; 48: 1959–65.

10 Meekan KR, Matias CO, Rathore SS et al. Platelet transfusions: utilization and associated costs in a tertiary care hospital. Am J Hematol 2000; 64: 251–6.

11 Tripodi A, Primignani M, Chantarangkul V et al. Global hemostasis tests in patients with cirrhosis before and after prophylactic platelet transfusion. Liver Int 2013; 33: 362–7.

12 Kim ES. Lusutrombopag: first global approval. Drugs 2016; 76: 155–8.

13 Miller JB, Figueroa EJ, Haug RM, Shah NL. Thrombocytopenia in chronic liver disease and the role of thrombopoietin agonists. Gastroenterol Hepatol (NY) 2019; 15: 326–32.

14 Tateishi R, Seike M, Kudo M et al. A randomized controlled trial of lusutrombopag in Japanese patients with chronic liver disease undergoing radiofrequency ablation. J Gastroenterol 2019; 54: 171–81.

15 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.

16 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.

17 Afghal NH, Giannini EG, Tayyab G et al. Eltrombopag before procedures in cirrhosis and thrombocytopenia. N Engl J Med 2012; 367: 716–24.

18 Katsube T, Shimizu FT, Kano T, Wajiima 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.

19 Ishikawa T, Okoshi M, Tomiyoshi K et al. Efficacy and safety of repeated use of lusutrombopag prior to radiofrequency ablation in patients with recurrent hepatocellular carcinoma and thrombocytopenia. Hepatol Res 2019; 49: 590–3.

20 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.

21 Zocco MA, Di Stasio E, De Cristofaro R et al. Thrombosis risk factors in patients with liver cirrhosis: correlation with MELD scoring system and portal vein thrombosis development. J Hepatol 2009; 51: 682–9.

22 Then EO, Are VS, Lopez-Luciano M et al. Elevated international normalized ratio: a risk factor for portal vein thrombosis in cirrhotic patients. Gastroenterology Res 2019; 12: 135–40.

23 Matsutani S, Fukuzawa T, Watanabe Y, Mizumoto H, Yokosuka O. Pathophysiological view of the management of portal vein thrombosis. Kan tan sui 2010; 6: 259–68. (In Japanese.)

24 Tschoatsiz EA, Senzolo M, Germani G, Gatt A, Burroughs AK. Systematic review: portal vein thrombosis in cirrhosis. Aliment Pharmacol Ther 2010; 31: 366–74.

25 Temel T, Cansu DU, Temel HE, Ozakyol AH. Serum thrombopoietin levels and its relationship with thrombocytopenia in patients with cirrhosis. Hepat Mon 2014; 14: e18556.

26 Schöffski P, Tack F, Trautwein C et al. Thrombopoietin serum levels are elevated in patients with hepatitis B/C infection compared to other causes of chronic liver disease. Liver 2002; 22: 114–20.

27 Koruk M, Onuk MD, Akçay F, Savas MC. Serum thrombopoietin levels in patients with chronic hepatitis and liver cirrhosis, and its relationship with circulating thrombocyte counts. Hepatogastroenterology 2002; 49: 1645–8.

SUPPORTING INFORMATION

ADDITIONAL SUPPORTING INFORMATION may be found online in the Supporting Information section at the end of the article.

Data S1 Supplementary methods.

Table S1 Summary statistics of pharmacokinetic parameters of lusutrombopag in lusutrombopag-naïve and non-naïve patients.

Table S2. Comparison of pharmacokinetic parameters by Child–Pugh class and lusutrombopag-naïve vs non-naïve patients.

Figure S1 Mean (standard deviation) plasma concentration of lusutrombopag in lusutrombopag-naïve and non-naïve patients. (a) Linear scale. (b) Semi-logarithmic scale.

Figure S2 Mean (standard deviation) plasma concentration of lusutrombopag in lusutrombopag-naïve patients according to Child–Pugh class. (a) Linear scale. (b) Semi-logarithmic scale.