Received: 25 November 2020 | Revised: 22 January 2021 | Accepted: 26 January 2021

DOI: 10.1111/eci.13503

RESEARCH LETTER

WILEY

Bleeding events in lusutrombopag-treated thrombocytopenic patients

1 | INTRODUCTION

Patients with advanced chronic liver disease are characterised by the presence of thrombocytopenia in a proportion ranging from 15% to 84%, depending on the threshold used to define this abnormality and the degree of severity of liver disease.[1-3] In these patients, thrombocytopenia is multifactorial and may be associated with an increased risk of bleeding following invasive procedures.[4,5] Indeed, although the platelet count threshold associated with an increased risk of bleeding is debated, current practice guidelines suggest platelet transfusions, or the use of thrombopoietin receptor agonists (TPO-RA), prior to high-risk planned invasive procedures, in patients with chronic liver disease and a platelet count $<50 \times 10^9$/L.[6-9] In this setting, TPO-RA proved to be a solid treatment option to safely and consistently raise platelet counts, thereby significantly decreasing the number of platelet transfusions.[9-13] However, from the physician's point of view, avoidance of platelet transfusions may be considered just a proxy for more clinically relevant endpoints, such as the reduction of procedural and post-procedural bleeding.[14]

Lusutrombopag is an orally available, small-molecule TPO-RA that, in a phase 2b study carried out in patients with severe thrombocytopenia and chronic liver disease undergoing radiofrequency ablation for hepatocellular carcinoma, reduced the proportion of patients needing pre-procedure platelet transfusion relative to placebo (Figure 1 [15-17]).[11] These findings were subsequently replicated in two larger studies that enrolled patients with chronic liver disease and severe thrombocytopenia who were scheduled to undergo various types of planned invasive procedures, and where clinicians were expected to transfuse platelets based on guidelines in order to decrease the likelihood of post-procedural bleeding.[11,13] The results of these trials led to the approval of lusutrombopag in Japan and in the USA for the treatment of thrombocytopenia, and in the EU for severe thrombocytopenia associated with chronic liver disease in patients undergoing an invasive procedure.[15,18,19]

The aim of this secondary analysis of the lusutrombopag studies (phase 2b, L-PLUS 1 and L-PLUS 2) was to evaluate procedural and post-procedural bleeding rates in patients who received lusutrombopag or placebo—and specifically, those who received lusutrombopag without platelet transfusion or placebo with platelet transfusion—so as to explore the potential of a treatment strategy based on TPO-RA administration rather than platelet transfusion in decreasing the rate of bleeding events.

2 | MATERIALS AND METHODS

This retrospective safety analysis included data pooled from three randomised clinical trials of patients with chronic liver disease and thrombocytopenia undergoing a planned invasive procedure. Patients were randomised to receive 3 mg lusutrombopag or placebo; patients received treatment for up to 7 days and initiated treatment 9-14 days prior to an invasive procedure. If a patient's platelet count was $<50 \times 10^9$/L no more than 2 days prior to the procedure, a platelet transfusion was mandated. Bleeding-related adverse events that occurred during and after the procedure were summarised descriptively. Additional details are included under Supplementary Materials, Materials and Methods.

3 | RESULTS

3.1 | Patient characteristics

The pooled analysis included a total of 341 patients (lusutrombopag, n = 171; placebo, n = 170). Of these, 124 (72.5%) patients received lusutrombopag without platelet transfusion, and 126 received placebo with platelet transfusion (74.1%). Patients receiving lusutrombopag without platelet transfusion were split evenly between males (n = 62, 50%) and females (n = 62, 50%); patients receiving placebo

with platelet transfusion were prevalently males (n = 81, 64.3%). The mean ages were 60.9 (standard deviation [SD], 11.8) and 61.0 (SD, 12.4) years for patients treated with lusutrombopag without platelet transfusion and placebo with platelet transfusions, respectively. The most common cause of chronic liver disease was hepatitis C (lusutrombopag without platelet transfusion, n = 74, 59.7%; placebo with platelet transfusion, n = 72, 57.1%). The mean baseline platelet counts were well below the 50×10^9/L threshold in both patients who received lusutrombopag without platelet transfusion (41.0×10^9/L) and those who received placebo with platelet transfusion (37.6×10^9/L) (Table S1).

3.2 | Patients with bleeding events according to study subgroups

Overall, the proportion of patients with procedural and post-procedural bleeding events was numerically higher in the placebo with platelet transfusion group as compared to the lusutrombopag without platelet transfusion group (15/126, 11.9% *versus* 8/124, 6.5%, Figure 2A), and this result was consistent when bleeding events were considered both during (6/126, 4.8% *versus* 4/124, 3.2%) and after (9/126, 7.1% *versus* 5/124, 4.0%) the invasive procedure (Figure 2B). In terms of the main baseline characteristics of patients who experienced a bleeding event, 7 (63.6%) patients were male in the lusutrombopag without platelet transfusion subgroup, compared to 10 (40.0%) in those who received placebo with platelet transfusion; mean age was 65.2 (SD, 13.7) and 70.3 (SD, 11.0) years, respectively. Additional baseline characteristics of patients who experienced a bleeding event are reported in Table S2.

3.3 | Bleeding events according to study type of invasive procedure and study subgroups

For this analysis, procedural and post-procedural bleeding event rates were subdivided according to the type of invasive procedure and by treatment arm. In patients undergoing liver-related invasive procedures, a greater proportion of patients with at least one bleeding event was observed among those who received placebo with platelet transfusion (9/56, 16.1%) as compared to lusutrombopag without platelet transfusion (6/54, 11.1%), while a larger difference was observed in patients undergoing gastrointestinal-related invasive procedures (5/56, 8.9% *versus* 1/50, 2.0%). These differences were consistent when the bleeding events were considered during (4/56 [7.1%] *versus* 1/50 [2.0%]) and after (1/56 [1.8%] *versus* 0) the gastrointestinal-related invasive procedures in patients who received placebo with platelet transfusion as compared to those who received lusutrombopag without platelet transfusion, respectively (Table S3).

3.4 | Timing of bleeding events in relation to platelet counts

In this analysis, we included patients who had a platelet count of either $<50 \times 10^9$/L or $\geq 50 \times 10^9$/L at least once at any time

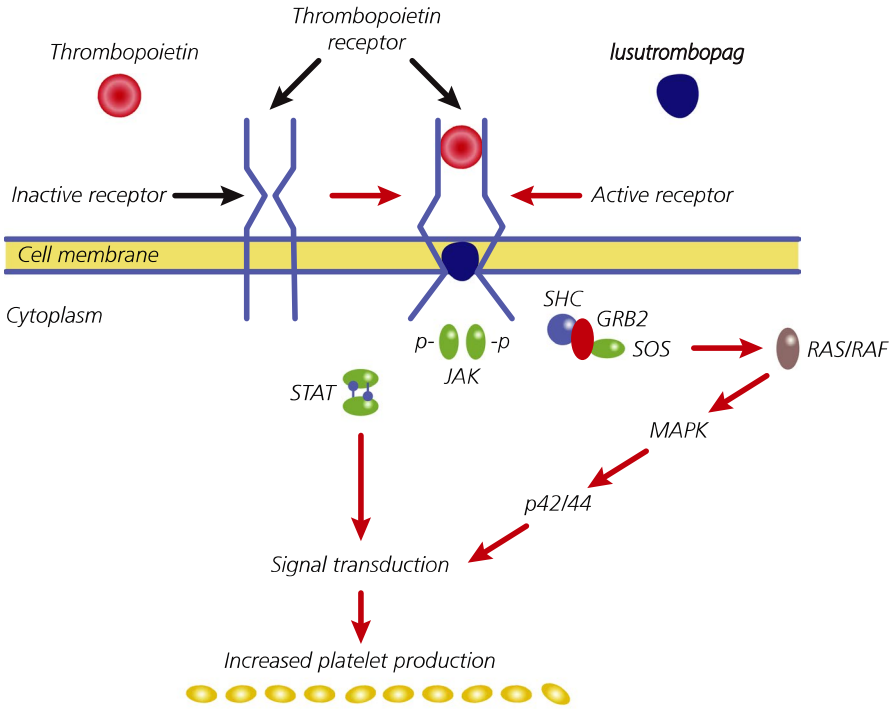

FIGURE 1 Lusutrombopag mechanism of action. Thrombopoietin (TPO) acts on the TPO receptor, activates JAK and STAT pathways, and leads to an upregulation of megakaryocytes and platelet production.[16] Lusutrombopag triggers increased platelet production by activating signal transduction in a manner similar to endogenous TPO.[15,17] Adapted with permission from Kuter D. *Int J Hematol* 2013;98:10-23

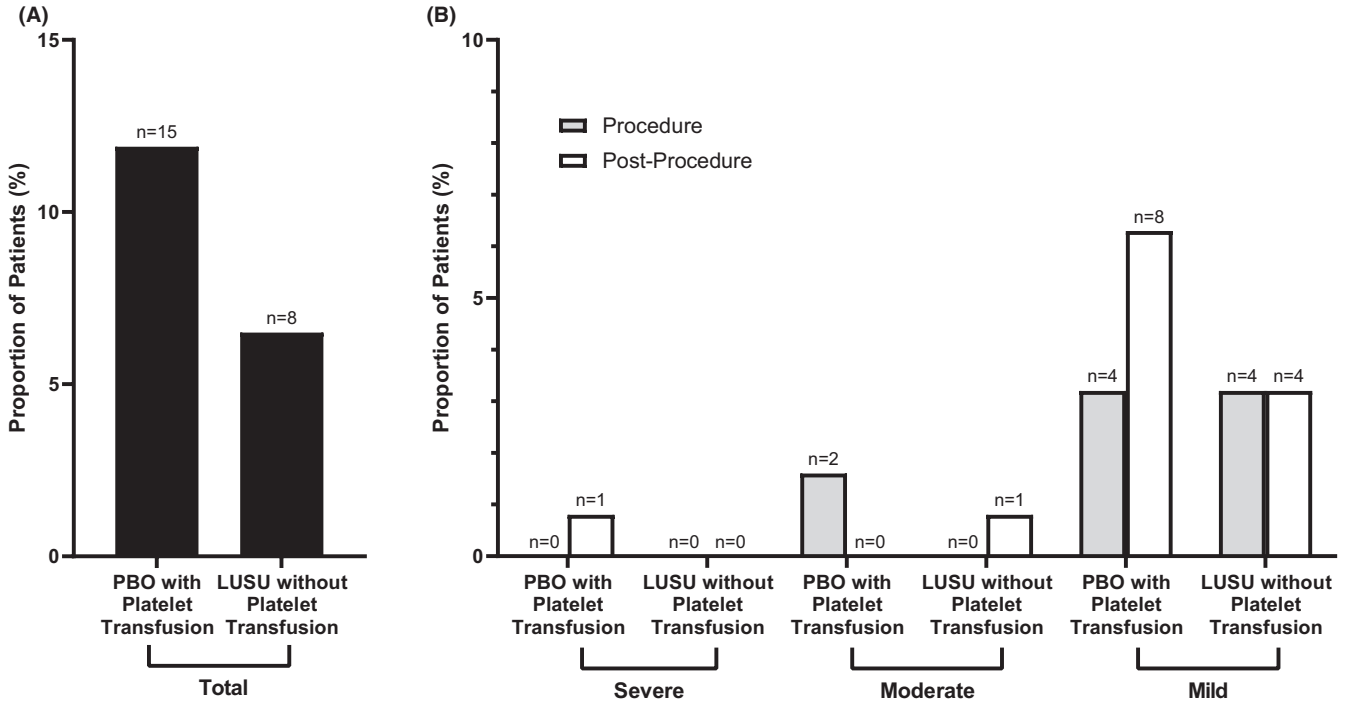

FIGURE 2 Patients with bleeding events (A), further subdivided by severity and timing of onset (B) (pooled safety data)[a]. LUSU, lusutrombopag; PBO, placebo. Pre-procedural bleeding events are not shown. [a]Patients could be counted >1× in the same time period if they experienced 2 bleeding events with different severities but only 1× if severity was the same; the same patient could be counted >1× if they experienced bleeding events in different time periods

point after the primary invasive procedure, including platelet counts which were the last platelet counts checked prior to the primary invasive procedure. In patients who had a platelet count $\geq 50 \times 10^9$/L, the proportions of procedural bleeding events were similar between patients who received lusutrombopag without platelet transfusion (3.4%) as compared to patients who received placebo with platelet transfusion (3.3%), while the post-procedural bleeding event rate was more than double in the latter group (9.8% *versus* 4.2%). In contrast, among patients who received placebo with platelet transfusion and who had a platelet count $<50 \times 10^9$/L after the primary invasive procedure, the event rates were 6.8% and 5.1% for procedural and post-procedural bleeding, respectively (Table S4).

4 | DISCUSSION

The association between bleeding risk and thrombocytopenia in patients with liver disease undergoing procedures has been debated at length, and while some studies have not identified a link between platelet counts and procedural bleeding,[20] there is consistent evidence that low platelet count can be considered a risk factor for bleeding in patients undergoing liver biopsy, percutaneous ablation of liver tumours, and several other invasive procedures.[4,6-8,21-23] In this regard, the most recent consensus conference on coagulation in liver disease stated that platelet count values $<50 \times 10^9$/L may be associated with higher risk of bleeding, but cautioned that platelet counts alone do not provide a complete characterisation of bleeding event risk.[6] Further, both American College of Gastroenterology and American Gastroenterology Association practice guidelines highlight that, in patients with liver disease and thrombocytopenia undergoing invasive procedures, a platelet count $\geq 50 \times 10^9$/L may optimise clot formation and that higher platelet levels may be more appropriate for high-risk procedures, although this may probably require high doses of platelet infusions; therefore, in planned procedures, the use of TPO-RA may be more appropriate.[7,8] Recent studies have shown that the administration of TPO-RA safely and consistently raises platelet counts, obviating the need for platelet transfusions in patients with thrombocytopenia and chronic liver disease undergoing invasive procedures, although it remains to be established whether their use may lead to a decrease in procedural and post-procedural bleeding events.[14]

The current study reported the results of a secondary analysis of pooled data from three lusutrombopag randomised clinical trials and aimed to explore whether the effects of its administration might be associated with lower rates of procedural and post-procedural bleeding in patients with chronic liver disease and severe thrombocytopenia. In this post hoc analysis, bleeding events in patients who

received lusutrombopag without platelet transfusion were compared to those in patients who received placebo with platelet transfusion, considered as the current standard of care, so as to mirror more closely the scenario of the expected use of lusutrombopag in clinical practice.

Overall, the results of this exploratory analysis show that the percentage of patients with procedural and post-procedural bleeding events tended to be lower among patients who received lusutrombopag without platelet transfusion as compared to those who received placebo with platelet transfusion (6.5% *versus* 11.9%). Moreover, this lower tendency of bleeding was observed consistently in both the procedural (3.2% *versus* 4.8%) and post-procedural (4.0% *versus* 7.1%) subgroups. This tendency was confirmed in the subgroup of patients undergoing liver-related procedures (11.1% *versus* 16.1%) and was even more pronounced in patients undergoing gastrointestinal-related (2.0% *versus* 8.9%) procedures. The present exploratory analysis was not designed to detect statistically significant differences in the rate of bleeding events; while this analysis may be suggestive that there is less occurrence of bleeding events in patients with lusutrombopag versus patients without lusutrombopag as it relates to an invasive procedure, these initial findings need to be confirmed through appropriately designed studies, sufficiently powered to confirm such a treatment benefit.

Platelet function may have a role in the observed bleeding events. Platelet function is dependent in part on the quality of platelets being received through the transfusion, the effectiveness of which can be impacted by the age of the platelets being transfused and the quality of the platelets provided from the donor.[24-26] Conversely, TPO-RAs lead to endogenous platelet production; however, the functionality of those platelets compared to platelets received through a platelet transfusion has not been studied. Although platelet dysfunction may be a factor in the observed differences of bleeding events, platelet function in patients receiving lusutrombopag as compared to platelet transfusions remains to be investigated.

Among patients who achieved a platelet count $\geq 50 \times 10^9$/L at least once at any time point after the primary invasive procedure, patients who received placebo with platelet transfusion had a post-procedural bleeding event rate double that observed in patients treated with lusutrombopag without platelet transfusion (9.8% *versus* 4.2%). In this regard, it has to be emphasised that due to the timing of data collection, actual platelet count at the time of bleeding was not available, although it could be inferred that platelet count values at the time of the procedure were greater in the lusutrombopag without platelet transfusion subgroup compared to the placebo with platelet transfusion subgroup, as lusutrombopag has been shown to maintain a platelet count greater than 50×10^9/L for approximately three weeks post-administration as compared to the limited magnitude of effect of platelet transfusions.[11]

All in all, the preliminary results reported here seem to suggest that in this clinical setting, the increase in platelet count determined by the use of lusutrombopag may be associated not only with a significant reduction in the need for platelet transfusions but also with a tendency towards a decreased bleeding rate. This tendency was consistent for patients undergoing liver-related and gastrointestinal procedures and was even more evident following the procedures, and may be explained by the fact that the increase in platelet count induced by lusutrombopag is superior and more persistent than the effect achieved by platelet transfusion, and may therefore induce a greater haemostatic effect.[11,13]

Similar to the trend observed in the use of lusutrombopag, the ELEVATE trial reported a decreased rate of bleeding events in the eltrombopag cohort as compared to the placebo cohort (17% and 23%, respectively).[9] In the ADAPT 2 trial, the rate of bleeding events in avatrombopag-treated patients as compared to placebo-treated patients was 2.6% *versus* 4.6%, while in ADAPT 1 the bleeding events were comparable in the two arms (avatrombopag 3.8% *versus* placebo 3.3%).[12,14] However, comparisons are complicated by the different definition of bleeding events used among studies and by the timing of bleeding events reported.

This study has a number of limitations, which are mainly related to the nature of the analyses of trial results. Individually, the clinical studies were not powered to detect a statistically significant difference in bleeding events between study arms, and by comparing the lusutrombopag without platelet transfusion and placebo with platelet transfusion subgroups, these data no longer constitute a randomised population. As this was a post hoc analysis, calculation of P-values was not appropriate for these analyses, and therefore, tests of significance were not included. Additionally, this post hoc analysis is based on bleeding events defined as a safety endpoint, as opposed to an efficacy endpoint.

To conclude, these preliminary results infer that the effects of administration of lusutrombopag may be associated with a lower bleeding rate as compared to the standard of care, represented by platelet transfusion, in patients with liver disease and thrombocytopenia undergoing planned invasive procedures, and should be considered thought-provoking while stimulating further research in this patient population. Although we are fully aware of the limitations of the study results, we feel that what we observed may represent a signal that is worth being explored in future clinical trials, or using real-world evidence, so as to confirm these exploratory initial results, and to assess whether the use of TPO-RA may represent not only a safe and valid alternative to platelet transfusions but also a more efficacious and effective treatment option to reduce bleeding events.

KEYWORDS
bleeding, invasive procedures, liver disease, platelets, thrombocytopenia

ACKNOWLEDGEMENTS
These studies were funded by Shionogi & Co., Ltd. (Osaka, Japan).

CONFLICT OF INTEREST
EGG is a consultant for Shionogi. TK, TO and RB are employees of Shionogi. PS was an employee of Shionogi at the time of the study. NA is a consultant/advisory board member for Gilead, Echosens, Ligand, Janssen, Shionogi, SpringBank and Trio Healthcare. NA has stock with SpringBank and Allurion and stock options with SpringBank.

AUTHOR CONTRIBUTIONS
This study was a collaborative effort of all authors. Medical writing assistance was provided by Meghan Sullivan, PhD, of MedVal Scientific Information Services, LLC (Princeton, NJ, USA), and was funded by Shionogi Inc. (Florham Park, NJ, USA).

TRIAL REGISTRATION NUMBER
Phase 2b: M0626 [JapicCTI-121944]; phase 3: L-PLUS 1 [JapicCTI-132323], global L-PLUS 2 study [NCT02389621].

DATA AVAILABILITY STATEMENT
Shionogi Inc has a data sharing policy, and requests can be submitted for anonymised patient-level data.

Edoardo Giovanni Giannini[1]
Takeshi Kano[2]
Toshimitsu Ochiai[3]
Roy Bentley[4]
Pomy Shrestha[5]
Nezam Afdhal[6]

[1]*Gastroenterology Unit, Department of Internal Medicine, University of Genoa, IRCCS-Ospedale Policlinico San Martino, Genoa, Italy*
[2]*Global Project Management Department, Shionogi & Co., Ltd., Osaka, Japan*
[3]*Biostatistics Center, Shionogi & Co., Ltd., Osaka, Japan*
[4]*US Global Market Access, Shionogi Inc., Florham Park, NJ, USA*
[5]*Product Safety and Pharmacovigilance, Shionogi Inc., Florham Park, NJ, USA*
[6]*Liver Center, Beth Israel Deaconess Medical Center, Boston, MA, USA*

Correspondence
Edoardo Giovanni Giannini, Gastroenterology Unit, Department of Internal Medicine, University of Genoa, Viale Benedetto XV, no. 6, Genoa 16132, Italy.
Email: egiannini@unige.it

ORCID
Edoardo Giovanni Giannini https://orcid.org/0000-0001-8526-837X

REFERENCES

1. Giannini EG. Review article: thrombocytopenia in chronic liver disease and pharmacologic treatment options. *Aliment Pharmacol Ther*. 2006;23:1055-1065.
2. Mitchell O, Feldman DM, Diakow M, Sigal SH. The pathophysiology of thrombocytopenia in chronic liver disease. *Hepat Med*. 2016;8:39-50.
3. Giannini EG, Marenco S, Fazio V, Pieri G, Savarino V, Picciotto A. Peripheral blood cytopaenia limiting initiation of treatment in chronic hepatitis C patients otherwise eligible for antiviral therapy. *Liver Int*. 2012;32:1113-1119.
4. Under the auspices of the Italian Association for the Study of Liver Diseases (AISF) and the Italian Society of Internal Medicine (SIMI). Hemostatic balance in patients with liver cirrhosis: report of a consensus conference. *Dig Liver Dis*. 2016;48:455-467.
5. 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.
6. Intagliata NM, Argo CK, Stine JG, et al. Concepts and controversies in haemostasis and thrombosis associated with liver disease: proceedings of the 7th International Coagulation in Liver Disease Conference. *Thromb Haemost*. 2018;118:1491-1506.
7. O'Leary JG, Greenberg CS, Patton HM, Caldwell SH. AGA clinical practice update: coagulation in cirrhosis. *Gastroenterology*. 2019;157(1):34-43.e1.
8. Simonetto DA, Singal AK, Garcia-Tsao G, Caldwell SH, Ahn J, Kamath PS. ACG clinical guideline: disorders of the hepatic and mesenteric circulation. *Am J Gastroenterol*. 2020;115:18-40.
9. Afdhal NH, Giannini EG, Tayyab G, et al. Eltrombopag before procedures in patients with cirrhosis and thrombocytopenia. *N Engl J Med*. 2012;367:716-724.
10. 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;54:171-181.
11. 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;17:1192-1200.
12. Terrault N, Chen YC, Izumi N, et al. Avatrombopag before procedures reduces need for platelet transfusion in patients with chronic liver disease and thrombocytopenia. *Gastroenterology*. 2018;155:705-718.

13. 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;70:1336-1348.
14. Olson SR, Koprowski S, Hum J, McCarty OJT, DeLoughery TG, Shatzel JJ. Chronic liver disease, thrombocytopenia and procedural bleeding risk; are novel thrombopoietin mimetics the solution? *Platelets*. 2018;30:796-798.
15. *MULPLETA® (lusutrombopag tablets) for oral use* [prescribing information]. Florham Park, NJ: Shionogi Inc.; 2018.
16. Kuter DJ. New thrombopoietic growth factors. *Blood*. 2007;109:4607-4616.
17. Yoshida H, Yamada H, Nogami W, et al. Development of a new knock-in mouse model and evaluation of pharmacological activities of lusutrombopag, a novel, nonpeptidyl small-molecule agonist of the human thrombopoietin receptor c-Mpl. *Exp Hematol*. 2018;59:30-39.e2.
18. 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 December 20, 2020.
19. European Commission. Lusutrombopag [product information]. 2019; Available at: https://www.ema.europa.eu/en/documents/product-information/mulpleo-previously-lusutrombopag-shionogi-epar-product-information_en.pdf. Accessed January 22, 2021.
20. Napolitano G, Iacobellis A, Merla A, et al. Bleeding after invasive procedures is rare and unpredicted by platelet counts in cirrhotic patients with thrombocytopenia. *Eur J Intern Med*. 2017;38:79-82.
21. Goto E, Tateishi R, Shiina S, et al. Hemorrhagic complications of percutaneous radiofrequency ablation for liver tumors. *J Clin Gastroenterol*. 2010;44:374-380.
22. Cocero N, Bezzi M, Martini S, Carossa S. Oral surgical treatment of patients with chronic liver disease: assessments of bleeding and its relationship with thrombocytopenia and blood coagulation parameters. *J Oral Maxillofac Surg*. 2017;75:28-34.
23. Seeff LB, Everson GT, Morgan TR, et al. Complication rate of percutaneous liver biopsies among persons with advanced chronic liver disease in the HALT-C trial. *Clin Gastroenterol Hepatol*. 2010;8:877-883.
24. Schiffer CA, Anderson KC, Bennett CL, et al. Platelet transfusion for patients with cancer: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol*. 2001;19:1519-1538.
25. Stroncek DF, Rebulla P. Platelet transfusions. *Lancet*. 2007;370:427-438.
26. Slichter SJ, Davis K, Enright H, et al. Factors affecting post-transfusion platelet increments, platelet refractoriness, and platelet transfusion intervals in thrombocytopenic patients. *Blood*. 2005;105:4106-4114.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Giannini EG, Kano T, Ochiai T, Bentley R, Shrestha P, Afdhal N. Bleeding events in lusutrombopag-treated thrombocytopenic patients. *Eur J Clin Invest*. 2021;51:e13503. https://doi.org/10.1111/eci.13503