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Lusutrombopag for the Treatment of Thrombocytopenia in Patients With Chronic Liver Disease Undergoing Invasive Procedures (L-PLUS 2)

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Thrombocytopenia may be associated with increased bleeding risk impacting timing and outcome of invasive procedures in patients with chronic liver disease (CLD). Lusutrombopag, a small-molecule, thrombopoietin (TPO) receptor agonist, was evaluated as a treatment to raise platelet counts (PCs) in patients with thrombocytopenia and CLD undergoing invasive procedures. L-PLUS 2 was a global, phase 3, randomized, double-blind, placebo-controlled study. Adults with CLD and baseline PCs < 50 × 10^9/L were randomized to receive once-daily lusutrombopag 3 mg or placebo ≤ 7 days before an invasive procedure scheduled 2-7 days after the last dose. The primary endpoint was avoidance of preprocedure platelet transfusion and avoidance of rescue therapy for bleeding. A key secondary endpoint was number of days PCs were ≥ 50 × 10^9/L throughout the study. Safety analysis was performed on patients who received at least one dose of study drug. This study occurred between June 15, 2015, and April 19, 2017, with a total of 215 randomized patients (lusutrombopag, 108; placebo, 107); 64.8% (70/108) of patients in the lusutrombopag group versus 29.0% (31/107) in the placebo group met the primary endpoint (P < 0.0001; difference of proportion 95% confidence interval [CI], 36.7 [24.9, 48.5]). The median duration of PCs ≥ 50 × 10^9/L was 19.2 days with lusutrombopag (without platelet transfusion) compared with 0.0 in the placebo group (with platelet transfusion) (P = 0.0001). Most adverse events were mild or moderate in severity, and rates were similar in the lusutrombopag and placebo groups (47.7% and 48.6%, respectively). *Conclusion:* Lusutrombopag was superior to placebo for reducing the need for platelet transfusions and achieved durable PC response in patients with thrombocytopenia and CLD undergoing invasive procedures, with a safety profile similar to placebo. (Hepatology 2019;70:1336-1348).

Thrombocytopenia, the most common hematologic complication of chronic liver disease (CLD), is an indicator of advanced disease and is associated with poorer prognosis.[1-3] Severe thrombocytopenia (platelet count [PC] < 50-75 × 10^9/L) is of particular clinical concern as it complicates management of patients with CLD; these patients often require numerous medical and/or surgical diagnostic and therapeutic procedures.[2-5]

The presence of severe thrombocytopenia in patients with CLD may aggravate bleeding associated

Abbreviations: AE, adverse event; CI, confidence interval; CLD, chronic liver disease; ITT, intent-to-treat; IVRS/IWRS, Interactive Voice/Web Response System; PC, platelet count; PP, per-protocol; TEAE, treatment-emergent AE; TPO, thrombopoietin.

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with procedures and can also significantly complicate routine patient care and result in delayed or canceled procedures, as reviewed in Poordad and others.[3,5-8] Although controversial, prophylactic platelet transfusions are commonly used to reduce the risk of bleeding due to severe thrombocytopenia in patients with CLD requiring invasive procedures.[2,3] The controversy on the need for platelet transfusion is based on several studies that suggested that the risk of bleeding is related to factors other than PC, such as the type of procedure and the underlying Child-Pugh class,[9-11] whereas other evidence shows a correlation between degree of thrombocytopenia and procedure-associated bleeding incidence.[4]

Despite the controversy around the relationship between thrombocytopenia and bleeding risk, and the lack of definitive evidence that prophylactic platelet transfusion improves hemostatic potential and reduces bleeding risk, current expert opinion recommends consideration of platelet transfusion in patients with cirrhosis and thrombocytopenia before invasive procedures, as noted in recent literature reviews.[12,13] Interestingly, even with a lack of consensus on the use of platelet transfusions in patients with PCs < 50×10^9/L, this threshold is commonly used in clinical practice as the standard of care.[2,3,12] Adding to the controversial nature of their use, prophylactic platelet transfusions have several limitations, including short duration of efficacy, risk of transfusion reactions, platelet refractoriness due to alloimmunization, and cost.[2,3,14] Hence, there is an unmet need for effective therapies that increase PCs by stimulating endogenous production of functional platelets. Thrombopoietin (TPO) plays an important role in regulating thrombopoiesis and is a proven therapeutic target to stimulate production of platelets.[2,15,16]

Lusutrombopag is a second-generation, oral TPO receptor agonist.[17,18] Previous studies have demonstrated that lusutrombopag raises PCs and that there are no required food restrictions and no clinically significant drug-drug interactions.[18,19] Lusutrombopag was approved in Japan in 2015 for use in patients with thrombocytopenia and CLD undergoing invasive procedures.[20] This approval was based on the results of L-PLUS 1, a phase 3, double-blind, placebo-controlled trial conducted in Japan.[21]

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The present phase 3 global study, L-PLUS 2, a double-blind, placebo-controlled trial, evaluated the ability of lusutrombopag to increase PCs and reduce the need for platelet transfusions in non-Japanese patients with severe thrombocytopenia and CLD undergoing an elective invasive procedure.

Patients and Methods

TRIAL DESIGN

This was a multinational, phase 3, randomized, double-blind, placebo-controlled study that assessed the efficacy and safety of lusutrombopag for the treatment of thrombocytopenia in patients with CLD undergoing invasive procedures. The investigators conducted the study in 22 countries across 138 sites, of which 102 sites screened patients and 88 sites randomized at least 1 patient: Argentina (2), Australia (2), Austria (3), Belgium (2), Canada (3), Czech Republic (2), France (2), Germany (3), Hungary (2), Israel (9), Italy (7), Poland (3), Republic of Korea (8), Romania (3), Russian Federation (3), Spain (5), Taiwan (3), Thailand (4), Turkey (4), Ukraine (5), United Kingdom (2), and the United States of America (11). The study was approved by institutional review boards in accordance with International Conference on Harmonisation Good Clinical Practices, the ethical principles outlined in the Declaration of Helsinki, and local requirements.

PATIENTS

Patients were men or women ≥18 years of age with a clinical diagnosis of CLD (Child-Pugh class A or B) and PCs < 50×10^9/L at baseline before randomization who were scheduled to undergo an invasive procedure 9-14 days after randomization and were likely to require administration of platelets to raise the PC above 50×10^9/L. Some procedures were excluded, such as laparotomy, thoracotomy, craniotomy, open-heart operation, or organ resection. Patients were excluded if they had hematopoietic tumors; aplastic anemia; myelodysplastic syndrome; myelofibrosis; or congenital, immune, or drug-induced thrombocytopenia or CLD Child-Pugh class C, among other conditions (for a full list of inclusion and exclusion criteria, see Supporting Table 1). All patients provided written informed consent before any study procedures.

RANDOMIZATION AND MASKING

Patients were randomly assigned 1:1 on day 1 to lusutrombopag (3-mg tablet once daily for up to 7 days) or matching placebo using the Interactive Voice/Web Response System (IVRS/IWRS). The randomization scheme and medication identification number schedule were generated by Cenduit (IVRS/IWRS vendor; Allschwil, Switzerland). All patients, investigators, and study site and Shionogi personnel were blinded to the assigned treatment at randomization until database lock. Unblinding at the investigators' request was allowed only in the event of an emergency to determine an appropriate course of therapy. Only the sponsor's drug supply management staff, unblinded statisticians on the data and safety monitoring board, and drug safety personnel reporting unexpected serious adverse reactions had access to the randomization schedule as required by local regulations. Randomization was stratified by primary invasive procedure (liver ablation/coagulation or other invasive procedures) and baseline PC (< 35×10^9/L or ≥ 35×10^9/L).

PROCEDURES

The study consisted of three periods: a screening period (up to 28 days before randomization), a treatment period of 7 days (days 1-7, during which the study drug was to be administered for 4-7 days), and a posttreatment period of 28 days. The invasive procedure was performed in the posttreatment period between days 9 and 14. The study duration for any patient was to be up to 63 days (Fig. 1). A 3-mg tablet of lusutrombopag (S-888711; QS Pharma, LLC, Boothwyn, PA) or matching placebo was administered orally once daily. Administration of the study drug on day 2 was to be performed ≥12 hours after administration on day 1 and on subsequent days at the same time, as much as practical.

Blood samples for PCs were collected and analyzed on day 1 before randomization and on days 5-8, 10, 12, 14, 17, 21, 28, and 35 (or at drug interruption and/or early termination). On days 5, 6, and 7, the PC was to be measured before administration of the study drug. If the PC was ≥ 50×10^9/L with an increase of ≥ 20×10^9/L, no additional dose of the study drug was administered. A preoperative platelet transfusion was required if the PC was < 50×10^9/L as determined on

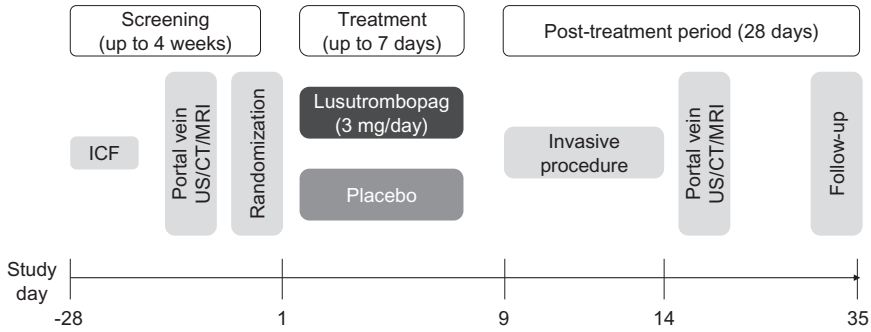

FIG. 1. L-PLUS 2 trial design. Abbreviations: CT, computed tomography; ICF, informed consent form; MRI, magnetic resonance imaging; US, ultrasonography.

or after day 8, but no more than 2 days before the invasive procedure. Any necessary platelet transfusion was given between day 8 and the period immediately before performing the invasive procedure (i.e., within 2 days before the day of the procedure).

Rescue therapy for bleeding events, independent of PCs, included platelet preparations, other blood preparations, including red blood cells and plasma, and volume expanders. Antithrombotic drugs could be administered as rescue therapy for thrombotic events when the PC was ≥ 200 × 10^9/L or when, in the opinion of the investigator, formation of a thrombus was highly suspected.

Adverse events (AEs) were recorded throughout the study period. Treatment-emergent AEs (TEAEs) of special interest included thrombosis-related and thromboembolism-related events. Therefore, imaging studies were included in the protocol to prospectively assess portal vein thrombosis (ultrasonography, computed tomography, or magnetic resonance imaging) and portal blood flow (Doppler ultrasonography) during screening, 3-10 days after the invasive procedure, and at stopping the study drug or early termination. Severity of bleeding was assessed according to the World Health Organization Bleeding Scale at each of the following time points: during the screening period; at randomization; day 8; 3-10 days after the procedure; and day 35 (at stopping the study drug or early termination).

EFFICACY ENDPOINTS

The primary endpoint was the proportion of patients who required no platelet transfusions before the primary invasive procedure and no rescue therapy for bleeding, as assessed from randomization through 7 days after the procedure. This composite endpoint was considered an appropriate primary endpoint for examining the sustainability of the response and fulfilling regulatory requirements. The primary endpoint was also assessed for each of the following subgroups: baseline PC (< 35 × 10^9/L, ≥ 35 × 10^9/L), primary invasive procedure, sex, age (< 65 years, ≥ 65 years), baseline body weight (< 75 kg, ≥ 75 kg), race, and Child-Pugh class. Key secondary endpoints included the proportion of patients who required no platelet transfusion during the study; the proportion of responders, defined as the proportion of patients who achieved a PC ≥ 50 × 10^9/L with an increase of ≥ 20 × 10^9/L from baseline at any time during the study; and the number of days during which the PC was maintained at ≥ 50 × 10^9/L. Other secondary endpoints included the proportion of patients who required rescue therapy for bleeding during the study, frequency of platelet transfusions, and PC over time.

STATISTICAL ANALYSIS

The planned sample size was 200 patients. Based on the results of L-PLUS 1, it was assumed that the proportion of patients meeting the primary endpoint would be 20% in the placebo group and 70% in the lusutrombopag group; 100 patients per group would provide 99% power to detect a difference of 50% between the lusutrombopag and placebo groups at a two-sided significance level of 0.05. For the safety analysis, 100 patients per group ensured that there

was at least a 95% probability of detecting AEs with an incidence of 3% or more. A data safety monitoring board oversaw the study, and the trial registration number was NCT02389621.

The intent-to-treat (ITT) population included all randomized patients and was the primary population for the efficacy analysis. The per-protocol (PP) population included all randomized patients who had no major protocol deviations pertaining to the efficacy evaluation. The safety population included all randomized patients who received at least one dose of the study drug.

The primary endpoint was analyzed using a Cochran-Mantel-Haenszel test adjusted by stratification factors. Secondary efficacy endpoints were summarized by treatment group, and key secondary endpoints were analyzed using a gatekeeping strategy. Sequential testing for the secondary endpoints was carried out in the following order: (1) proportion of patients requiring no platelet transfusion during the study, (2) proportion of responders, (3) duration of PC ≥ 50 × 10^9/L (with platelet transfusion), and (4) duration of PC ≥ 50 × 10^9/L (lusutrombopag without platelet transfusion and placebo with platelet transfusion). All significance testing was two-sided with 0.05 as the accepted level for significance. All analyses and listings were performed using SAS (version 9.2; SAS Institute Inc., Cary, NC) and WinNonlin (version 6.2.1; Certara, Princeton, NJ).

Results

A total of 322 patients were assessed for eligibility (Supporting Table 1), and 215 patients were randomized (108 to lusutrombopag, 107 to placebo) (Fig. 2) for the L-PLUS 2 study, which took place between June 15, 2015, and April 19, 2017. Demographic and clinical characteristics are summarized in Table 1. There were no substantial differences between groups in terms of demographic or clinical characteristics; surgical procedures were also balanced between

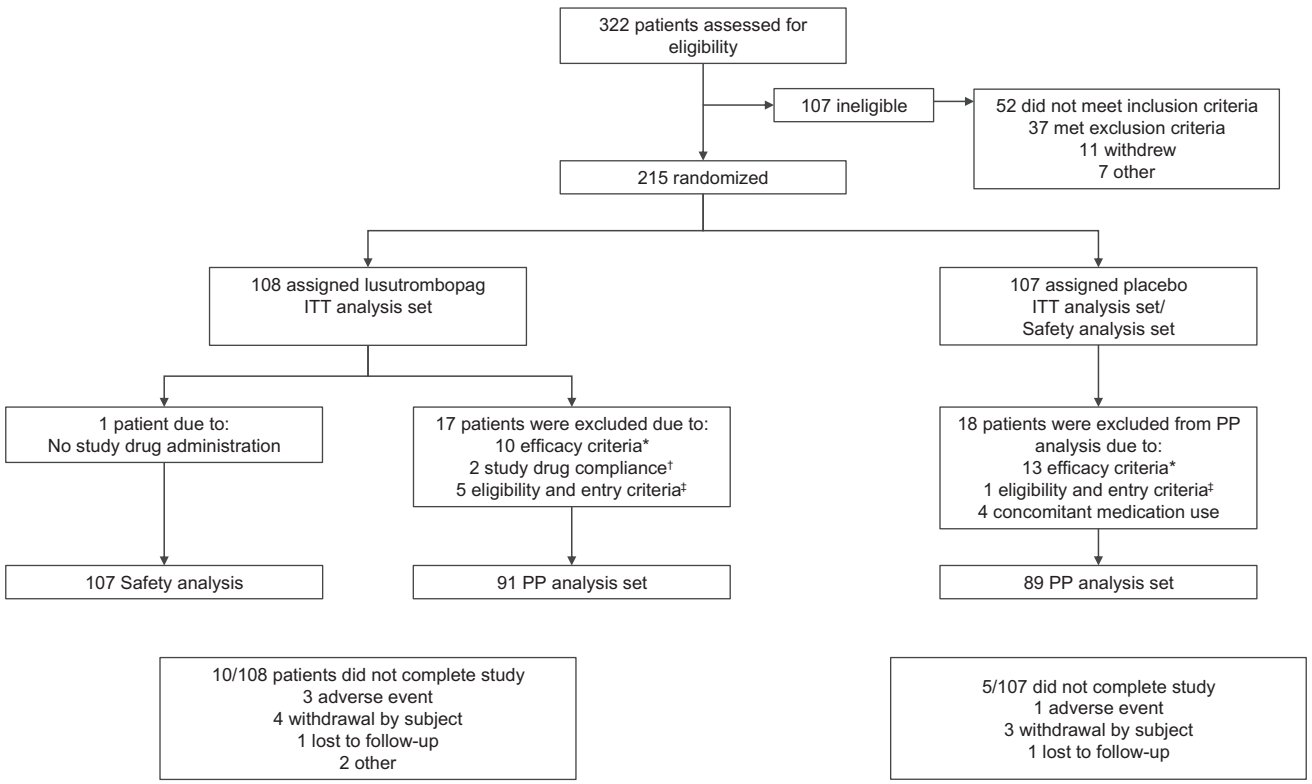

FIG. 2. Trial profile. *Includes noncompliance with preprocedure platelet transfusion instructions or out of window of preprocedure platelet transfusion assessment. †Includes subjects receiving less than 5 days of study drug but did not fulfill the stopping criterion for study drug or no study drug administration. ‡Includes Child-Pugh class C, received other TPO receptor agonist, or PC > 50 × 10^9/L at baseline on day 1 before randomization.

TABLE 1. Demographic and Clinical Characteristics for ITT and PP Populations

		ITT (n = 215)		PP (n = 180)	
		LUSU (n = 108)	PBO (n = 107)	LUSU (n = 91)	PBO (n = 89)
Sex, n (%)	Male	65 (60.2)	69 (64.5)	51 (56.0)	57 (64.0)
	Female	43 (39.8)	38 (35.5)	40 (44.0)	32 (36.0)
Mean age, years (SD)		55.2 (11.6)	56.1 (11.0)	55.7 (11.0)	55.5 (11.6)
Type of CLD, n (%)*	Hepatitis B	24 (22.2)	21 (19.6)	18 (19.8)	17 (19.1)
	Hepatitis C	51 (47.2)	51 (47.7)	45 (49.5)	39 (43.8)
	Alcoholic	24 (22.2)	26 (24.3)	21 (23.1)	21 (23.6)
	NASH	12 (11.1)	15 (14.0)	9 (9.9)	14 (15.7)
	Autoimmune	5 (4.6)	5 (4.7)	5 (5.5)	4 (4.5)
Child-Pugh class, n (%)	A	72 (66.7)	63 (58.9)	59 (64.8)	52 (58.4)
	B	33 (30.6)	43 (40.2)	32 (35.2)	36 (40.4)
	C	3 (2.8)	0	0	0
Baseline PC ($\times 10^9$/L), n (%)	Mean (SD)	37.7 (9.0)	37.4 (7.8)	37.5 (8.9)	36.9 (7.6)
	< 35	36 (33.3)	38 (35.5)	31 (34.1)	31 (34.8)
	≥ 35	71 (65.7)	68 (63.6)	60 (65.9)	58 (65.2)
Surgical procedure received, n (%)†	Percutaneous RFA/MCT	4 (3.7)	1 (0.9)	3 (3.3)	1 (1.1)
	TACE	11 (10.2)	9 (8.4)	9 (9.9)	7 (7.9)
	Liver biopsy	3 (2.8)	6 (5.6)	3 (3.3)	5 (5.6)
	Other liver-related procedure	2 (1.9)	4 (3.7)	2 (2.2)	3 (3.4)
	EVL	32 (29.6)	29 (27.1)	28 (30.8)	26 (29.2)
	EIS	1 (0.9)	1 (0.9)	1 (1.1)	0
	GI endoscopy	28 (25.9)	30 (28.0)	25 (27.5)	22 (24.7)
	Diagnostic	20 (18.5)	25 (23.4)	18 (19.8)	18 (20.2)
	Operative	8 (7.4)	5 (4.7)	7 (7.7)	4 (4.5)
	Dental extraction	13 (12.0)	11 (10.3)	11 (12.1)	9 (10.1)
	Other‡	8 (7.4)	7 (6.5)	8 (8.8)	7 (7.9)
	Procedure not received	6 (5.6)	9 (8.4)	1 (1.1)	9 (10.1)

*Patients could be counted in more than one category.
†Primary invasive procedures were reclassified after unblinding by reviewing the case report form details because of a greater than expected number of "Other" reported.
‡Surgical procedure classified as "Other" defined in Supporting Table S2.
Abbreviations: EIS, endoscopic injection sclerotherapy; EVL, endoscopic variceal ligation; GI, gastrointestinal; LUSU, lusutrombopag; MCT, microwave coagulation therapy; NASH, nonalcoholic steatohepatitis; PBO, placebo; RFA, radiofrequency ablation; SD, standard deviation; TACE, transcatheter arterial chemoembolization.

groups (Table 1; for a list of surgical procedures classified as "Other," see Supporting Table 2). A total of 35 patients (16.3%) in the ITT population, including 17 (15.7%) in the lusutrombopag group and 18 (16.8%) in the placebo group, were excluded from the PP population. The most common reason for exclusion was noncompliance with the preprocedure platelet transfusion instructions, such as not receiving platelet transfusions when they should have been administered (3 lusutrombopag, 10 placebo) and receiving platelet transfusions that should not have been administered (5 lusutrombopag) (Supporting Table 3). Overall, 15 patients withdrew from the study (10 lusutrombopag, 5 placebo).

A total of 45 patients did not require the full 7 days of the study drug (35 lusutrombopag, 10 placebo), among whom 36 (30 lusutrombopag, 6 placebo) met the criteria for treatment withdrawal (PC of ≥ 50 × 10^9/L with an increase of ≥ 20 × 10^9/L from baseline). Additionally, 3 patients in the placebo group missed 1 day of dosing, with the reasons cited being diarrhea and vomiting, IVRS/IWRS not functional, and missed dose. A total of 15 patients (6 lusutrombopag, 9 placebo) did not undergo the planned procedure, primarily because of study withdrawal or PC < 50 × 10^9/L (Supporting Table 4).

Significantly more patients who were randomly assigned to lusutrombopag than placebo in the ITT

population avoided platelet transfusion before the primary invasive procedure and did not require rescue therapy for bleeding from randomization through 7 days after the primary procedure (Fig. 3); 64.8% (70/108; 95% confidence interval [CI], 55.0, 73.8) and 29.0% (31/107; 95% CI, 20.6, 38.5) of patients randomly assigned to lusutrombopag and placebo, respectively, met this primary endpoint ($P < 0.0001$; difference of proportion 95% CI, 36.7 [24.9, 48.5]). For the patients who received a platelet transfusion, the majority occurred on the day of the primary invasive procedure: 76.5% (26/34) for the lusutrombopag arm and 64.4% (47/73) for the placebo arm. In a sensitivity analysis using the PP population, 72.5% (66/91; 95% CI, 62.2, 81.4) and 20.2% (18/89; 95% CI, 12.4, 30.1) of patients met the primary endpoint ($P < 0.0001$; difference of proportion 95% CI, 53.3 [42.1, 64.5]; Fig. 3).

A statistical analysis for each component of the primary endpoint was not planned *a priori*. However, the proportion of patients who avoided preprocedure platelet transfusion was significantly greater in the lusutrombopag group compared with the placebo group (64.8% vs. 29.9%, $P < 0.0001$). Only 2 patients required rescue therapy for bleeding in the 7-day period after the procedure, and both events occurred in the placebo group. The first patient underwent polypectomy as the primary invasive procedure and received preprocedure platelet transfusions on days 8 and 9 because the PC was $< 50 \times 10^9$/L. On day 10, the patient had a large intestinal hemorrhage and received a platelet transfusion. The second patient underwent mastoidectomy plus tympanoplasty as the primary invasive procedure with preprocedure platelet transfusion on day 11 because the PC was $< 50 \times 10^9$/L. On day 12, the patient experienced a large hemorrhage from the ear requiring both platelet and blood transfusions. Both bleeding events that resulted in administration of rescue therapy were considered by the investigator to be not related to the study drug.

A subgroup analysis favored lusutrombopag over placebo for the primary endpoint consistently across subgroups for both the ITT and PP populations (Fig. 4A,B); however, the analysis was not powered to detect statistical differences between subgroups. Additionally, the proportion of patients meeting the primary efficacy endpoint according to the primary invasive procedure was greater in the lusutrombopag group compared with placebo in all but two procedures. One of these procedures was endoscopic injection sclerotherapy, which was equal to placebo in the ITT population, and the other was liver biopsy, which was equal to placebo in the ITT population and greater in the placebo group compared with lusutrombopag in the PP population (Supporting Table 5).

Lusutrombopag was superior to placebo for the secondary endpoints of the proportion of patients

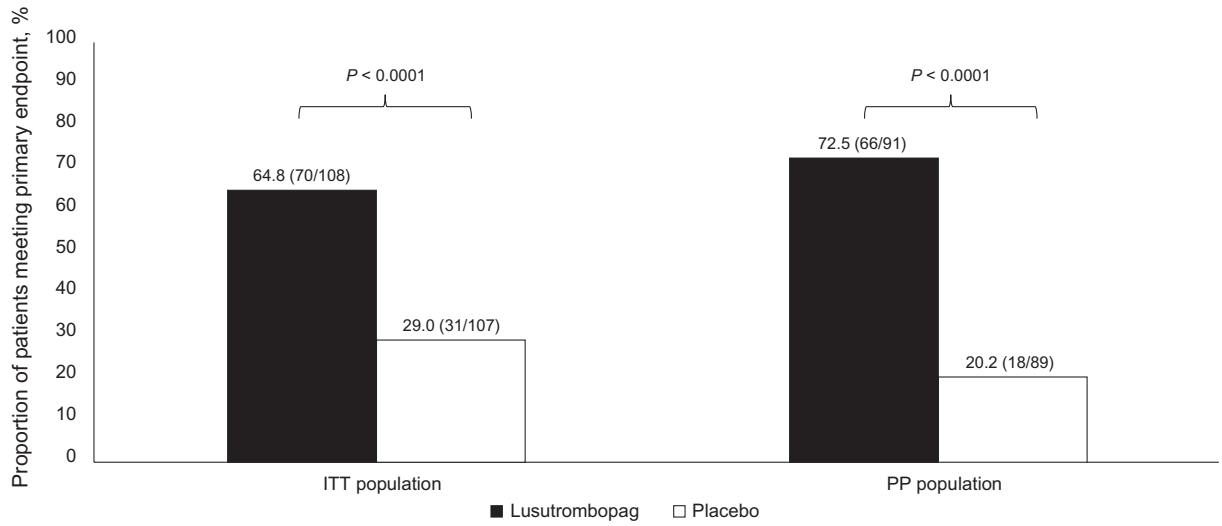

FIG. 3. Proportion of patients in the lusutrombopag and placebo groups meeting the primary efficacy endpoint in ITT and PP populations.

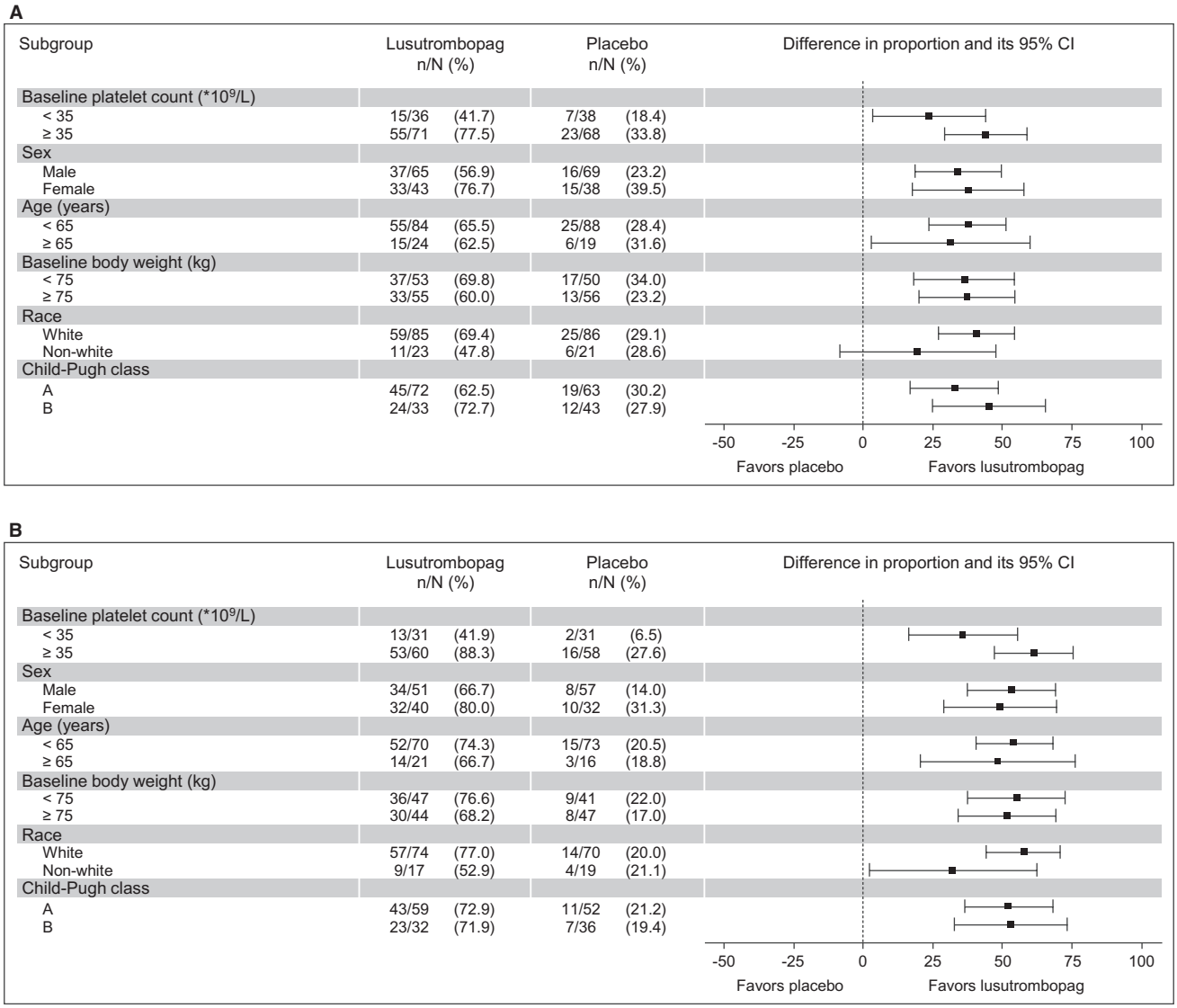

FIG. 4. Subgroup analysis for the difference in the proportion of patients in the lusutrombopag and placebo groups meeting the primary efficacy endpoint for (A) ITT (prespecified analysis) and (B) PP (post hoc analysis) populations. Primary endpoint is proportion of patients who required no platelet transfusion before invasive procedure and no rescue therapy for bleeding from randomization through 7 days after the procedure. In addition to patients who received platelet transfusion, patients who did not receive an invasive procedure regardless of the reason were considered as receiving platelet transfusion. The Wald-type CIs were calculated.

who avoided platelet transfusion during the study and of those who achieved a PC ≥ 50 × 10^9/L and an increase ≥ 20 × 10^9/L from baseline at any time during the study (P < 0.0001 for both; Table 2). In addition, the median duration of time that PCs remained ≥ 50 × 10^9/L for patients who received lusutrombopag and no platelet transfusions (n = 74) was 19.2 days versus 0.0 days for patients who received placebo and platelet transfusions (n = 73) (P < 0.0001; Table 2). The change in PCs over time for patients treated with lusutrombopag who did not receive a platelet transfusion versus patients treated with placebo who did receive a platelet transfusion is presented in Fig. 5. Median maximum change from baseline was over 4 times higher for patients treated with lusutrombopag who did not receive platelet transfusions than for patients treated with placebo who did receive platelet transfusions (45 × 10^9/L vs. 11 × 10^9/L). Results for other secondary endpoints and additional analyses are summarized in Table 2.

TABLE 2. Secondary Endpoints and Additional Assessments (ITT Population)

	LUSU (n = 108)	PBO (n = 107)	*P* Value
Secondary endpoints			
Avoided platelet transfusion during the study			
n (%)*	68 (63.0)	31 (29.0)	< 0.0001
95% CI	53.1, 72.1	20.6, 38.5	34.8 (22.8, 46.8)
Responder rate			
n (%)†	70 (64.8)	14 (13.1)	< 0.0001
95% CI	55.0, 73.8	7.3, 21.0	52.5 (42.0, 62.9)
Duration of PC ≥ 50×10^9/L, median, days‡	19.2	0.0	< 0.0001**
Mean time to reach maximum PC, days (SD)§	12.4 (4.7)	18.2 (10.4)	—
Required rescue therapy for bleeding, n (%)	0	2 (1.9)	—
Frequency of platelet transfusion, n (%)			
1 transfusion	34 (31.5)	61 (57.0)	—
2 transfusions	0	6 (5.6)	—
3 transfusions	0	5 (4.7)	—
4 transfusions	0	0	—
5 transfusions	0	1 (0.9)	—
Additional assessments			
Required antithrombotic agent for thrombotic events, n (%)	2 (1.9)	2 (1.9)	—
PC ≥ 50×10^9/L before invasive procedure, n (%)‖	73 (67.6)	21 (19.6)	< 0.0001
Maximum (median) PC × 10^9/L§	85.0	57.5	—
Maximum (median) increase from baseline in PC × 10^9/L‡	45.0	11.0	—
Maximum PC × 10^9/L§	219¶	167	—
Met treatment completion criterion,# n (%)	30 (27.8)	6 (5.6)	—

*Proportion of subjects who required no platelet transfusion and underwent the invasive procedure during the study; Cochran-Mantel-Haenszel test adjusted by stratification factors.
†Responders: patients who achieved a PC of ≥ 50×10^9/L with an increase of ≥ 20×10^9/L from baseline at any time during the study. Patients who met the responder criteria only after platelet transfusion were considered nonresponders. Cochran-Mantel-Haenszel test adjusted by stratification factors.
‡Value without platelet transfusion for lusutrombopag (n = 74) and with platelet transfusion for placebo (n = 73).
§Value for patients without platelet transfusion (n = 74 for lusutrombopag, and n = 34 placebo).
‖PC at platelet transfusion assessment regardless of preprocedure platelet transfusion provided the patient underwent invasive procedure, the patient did not receive a platelet transfusion within 7 days of procedure, and the patient received no rescue therapy from randomization through 7 days after the procedure; Cochran-Mantel-Haenszel test adjusted by stratification factors.
¶The 1 patient with an excessive PC (maximum count of 219×10^9/L on day 10) was self-medicating with eltrombopag during the study. A protocol-specified assessment for PVT after the treatment period indicated no symptoms of PVT.
#PC ≥ 50×10^9/L with an increase of ≥ 20×10^9/L from baseline.
**Wilcoxon rank sum test.
Abbreviations: LUSU, lusutrombopag; PBO, placebo; PVT, portal vein thrombosis; SD, standard deviation.

Overall, 47.7% (51/107) of patients in the lusutrombopag group and 48.6% (52/107) in the placebo group had at least one TEAE (Table 3). Most were mild or moderate in severity. Only 1 patient in the placebo group had TEAEs leading to discontinuation of the study drug (dehydration, hypokalemia, nausea, and vomiting); no patient in the lusutrombopag group had a TEAE leading to discontinuation of the study drug.

Serious TEAEs with an outcome of death occurred in 3 patients, all in the lusutrombopag group: 1 patient with Child-Pugh class C liver disease, a protocol deviation, died of multiorgan failure and cardiac arrest; a second patient died because of progression of hepatic cirrhosis; and a third died because of procedurally related vessel perforation. None of these deaths were judged by the investigator to be related to treatment with lusutrombopag.

There were four treatment-emergent thrombotic events found as per prespecified protocol-defined or routine imaging, with no accompanying symptoms documented related to the thrombotic episode: two in the lusutrombopag group and two in the placebo group. One of the lusutrombopag-treated patients had a thrombosis in a branch of the left intrahepatic

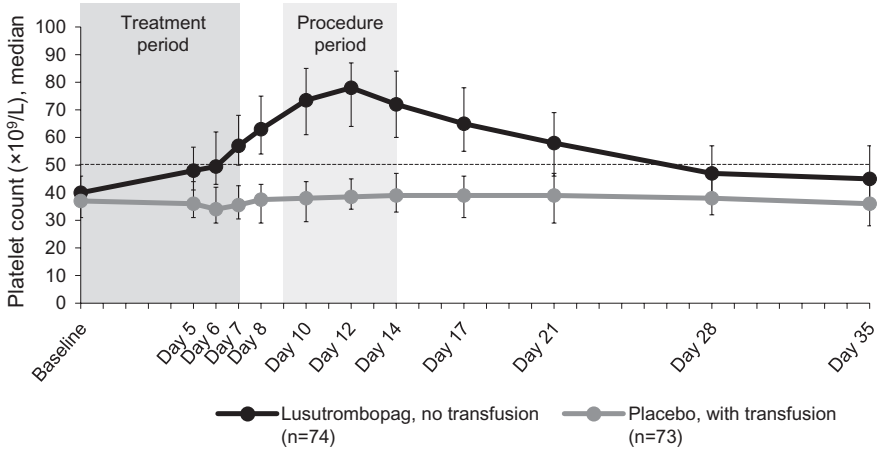

FIG. 5. Median PCs over time for patients treated with lusutrombopag (without platelet transfusion) or placebo (with platelet transfusion). Error bars indicate 25th percentile and 75th percentile.

artery; this event was not considered to be related to lusutrombopag. The other lusutrombopag-treated patient experienced a cardiac left ventricular thrombosis; however, a prior history of coronary artery disease and previously documented cardiac ventricular thrombosis should have excluded this patient from the study. Maximum PCs for these 2 patients were 62×10^9/L and 119×10^9/L, respectively, indicating no excessive increase in PCs. In the placebo group, 1 patient had an incomplete thrombosis of the superior portal vein, and the second had a nonocclusive thrombosis in the right branch of the portal vein. All splanchnic thrombotic events were asymptomatic and discovered by the predefined imaging criteria.

Few bleeding-related TEAEs were reported in this study (Table 3). Overall, there were three bleeding events in 3 patients in the lusutrombopag group (2.8%) and seven bleeding events in 6 patients in the placebo group (5.6%). All three bleeding-related events in the lusutrombopag group were mild in severity. In the placebo group, two bleeding events were considered to be mild, four were moderate, and one was severe.

Discussion

L-PLUS 2 results demonstrated that in patients with severe thrombocytopenia and CLD, lusutrombopag 3 mg given once daily for up to 7 days, with or without food, was superior to placebo in reducing the need for platelet transfusions before an invasive procedure ($P < 0.0001$). Although the primary endpoint was met, it is likely the underlying driver was the number of patients who avoided platelet transfusion before an invasive procedure, as there were only two bleeding events in the 7-day period after the procedure. Lusutrombopag achieved the clinical benefit of avoiding platelet transfusion before an invasive procedure through a predictable and durable effect on PC increase over the threshold of 50×10^9/L for a median 19.2 days. Overall, lusutrombopag demonstrated a safety profile comparable with that of placebo, with no increase in the risk of thrombotic events.

The beneficial effect of lusutrombopag over placebo was consistent across all evaluated subgroups (baseline PC, primary invasive procedure, sex, age, baseline body weight, race, and Child-Pugh class). Although consistent with the primary efficacy analysis, data for the subgroup analyses should be interpreted with caution because of the small number of patients in some subgroups and the fact that the study was not powered to show differences between the subgroups.

The results of this global study are consistent with an earlier phase 3 study, L-PLUS 1, conducted in Japan.[21] In L-PLUS 1, lusutrombopag treatment significantly decreased the requirement for preprocedure platelet transfusions compared with placebo in Japanese patients with CLD undergoing invasive procedures (79.2% vs. 12.5%, respectively, $P < 0.0001$).[21] The most common invasive procedure included percutaneous liver ablation (42.7%).[21]

TABLE 3. Overall Summary of AEs

	LUSU (n = 107) n (%)	PBO (n = 107) n (%)
TEAEs	51 (47.7)	52 (48.6)
Treatment-related AEs	6 (5.6)	13 (12.1)
Deaths	3 (2.8)	0
Serious TEAEs	7 (6.5)	7 (6.5)
TEAEs in > 3% of patients		
Headache	6 (5.6)	2 (1.9)
Abdominal pain	5 (4.7)	5 (4.7)
Fatigue	3 (2.8)	7 (6.5)
Peripheral edema	3 (2.8)	4 (3.7)
Nausea	2 (1.9)	5 (4.7)
Any event related to bleeding*	3 (2.8)	6 (5.6)
Mild, n	3	2
Moderate, n	0	4
Severe, n	0	1
Specific events		
Eyelid hematoma	0	1 (0.9)†
Ear hemorrhage	0	1 (0.9)‡
Hematoma	1 (0.9)§	1 (0.9)‖
Pharyngeal hemorrhage	0	1 (0.9)¶
Esophageal varices hemorrhage	0	1 (0.9)#
Rectal hemorrhage	1 (0.9)**	0
Large intestinal hemorrhage	0	1 (0.9)††
Ecchymosis	1 (0.9)‡‡	0
Traumatic hemorrhage	0	1 (0.9)§§

*There were seven events in 6 patients in the placebo group.
†Occurred after EVL.
‡Occurred after mastoidectomy + tympanoplasty.
§Right and left arm hematomas occurred before colonoscopy.
‖Leg hematoma occurred before EVL.
¶Pharynx bleeding occurred after gastroscopy.
#Esophageal varices with bleeding occurred after EVL.
**Rectal bleeding occurred after diagnostic laparocentesis.
††Lower gastrointestinal colonic bleeding occurred after polypectomy.
‡‡Ecchymosis on left posterior forearm occurred after EGD.
§§Bruising due to minor trauma occurred after gastroscopy.
Abbreviations: EGD, esophagogastroduodenoscopy; EVL, endoscopic variceal ligation; LUSU, lusutrombopag; PBO, placebo.

The number of days PCs were ≥ 50 × 10^9/L was significantly greater with lusutrombopag treatment (median, 22.1 days, without platelet transfusion) than placebo (median, 3.3 days, with platelet transfusion) (P < 0.0001).[21] Importantly, the incidence of bleeding-related AEs in the lusutrombopag arm was approximately half that of the placebo arm (14.6% vs. 27.1%, respectively).[21] Interestingly, the bleeding rate in L-PLUS 1 was higher than that in the current study, likely because of the increased number of higher-risk invasive procedures in the L-PLUS 1 study, such as radiofrequency ablation. Lusutrombopag was well tolerated, with a safety profile comparable with that of placebo.[21]

Platelet growth factors for raising the PC in CLD have been used for patients receiving interferon therapy[22] and for those undergoing invasive procedures.[23] The ability to increase the PC has been well documented in patients with CLD,[23,24] but controversy still exists as to whether this increase in PC is necessary to prevent bleeding complications, as no studies have been adequately powered to determine this benefit. However, procedures in clinical practice have been delayed because of thrombocytopenia,[1,3] and many institutions have predefined platelet thresholds.[25,26] Use of TPO receptor agonists has a clear role in this situation clinically, but each physician has to evaluate the risk-benefit ratio to use these agents in CLD.

Lusutrombopag has been available in Japan since 2015, providing real-world clinical experience. Postmarketing data show that of the ~4,000 patients exposed to lusutrombopag as of April 30, 2018, a total of 99 AEs were reported, and 46 AEs were considered serious (data on file). A review of all spontaneous AE reporting suggests lusutrombopag is well tolerated, with a safety profile consistent with L-PLUS 1 and L-PLUS 2 clinical trial data.

Thrombotic events are a key safety concern with the use of either platelet transfusion or administration of a TPO receptor agonist to raise PCs in patients with CLD. A unique strength of the L-PLUS 2 study was inclusion of prospective imaging before randomization and after the study to accurately capture the occurrence and resolution of portal vein thrombosis in this patient population. There were four thrombotic TEAEs in this study, two in each group; all were asymptomatic and found as per prespecified, protocol-defined, or routine imaging. These findings are consistent with a recently published meta-analysis revealing the prevalence of portal vein thrombosis to be 2.8% in patients with liver disease and thrombocytopenia who were undergoing an elective invasive procedure and treated with TPO receptor agonists.[27] The median maximum PC in patients treated with lusutrombopag was 85.0 × 10^9/L, with only 1 patient in this study reporting a PC ≥ 200 × 10^9/L. It should be noted that this patient self-medicated

with eltrombopag during the screening period and from day 18 through the remainder of the study (a protocol violation) and was omitted from the PP population. The small number of thrombotic AEs observed with lusutrombopag contrasts with results from the Eltrombopag Evaluated for Its Ability to Overcome Thrombocytopenia and Enable Procedures (ELEVATE) trial, which was terminated early because of an increased risk of portal vein thromboses, possibly due to excessive PCs (i.e., > 200 × 10^9/L), despite effectively increasing PCs.[23] In this eltrombopag trial, 6/143 patients randomly assigned to eltrombopag experienced symptomatic portal vein or splanchnic vein thromboses compared with 2/145 patients randomly assigned to placebo.[23] In the ADAPT-1 and ADAPT-2 trials, treatment with avatrombopag, a recently approved TPO receptor agonist studied in patients with thrombocytopenia and CLD, resulted in 2 patients developing portal vein thrombosis (one was a partial portal vein thrombosis and one was assessed to be serious but not related).[24,28] However, because of the lack of prospective imaging for thrombosis in the ELEVATE and ADAPT trials, only symptomatic occurrences were detected, unlike the current trial that accounted for asymptomatic occurrences. Although the present trial included a study treatment completion criterion as a safety measure (i.e., PC ≥ 50 × 10^9/L with an increase of ≥ 20 × 10^9/L from baseline), internal data from previous studies suggest that the probability of reaching excess PCs (i.e., ≥ 200 × 10^9/L) at the 3-mg dose were low in Japanese and non-Japanese patients (1.52% and 0.43%, respectively). Taking into account all the PC data from this trial and because the only patient in this study who had a PC ≥ 200 × 10^9/L was also taking eltrombopag in violation of the protocol, the utility of the once-daily, 3-mg dose of lusutrombopag in achieving optimal responses without excessive increases in PC is further established.

Recent research reports suggest that patients with cirrhosis may not have primary hemostatic defects and that a low PC does not predict unprovoked major or minor bleeding or postprocedure bleeding. These reports have questioned the standard practice of infusing platelets when counts are < 50 × 10^9/L, as these patients are in a "rebalanced hemostatic state." However, evidence suggests that thrombin production is impaired in patients with cirrhosis as platelet levels decrease to less than 50 × 10^9/L[29] and that the feeble rebalanced hemostatic state of patients with cirrhosis could be challenged during invasive procedures.[30] In the current study, a numerical reduction in bleeding-related AEs was observed in the lusutrombopag arm (three events) compared with placebo (seven events); this was also consistent with the previous L-PLUS 1 study.[21]

A potential limitation of this study is that it did not take into consideration comorbidities and confounders for risk of bleeding as it pertains to investigator-directed administration of platelet transfusions, and this could have influenced adaptation of local thresholds, thereby leading to protocol violations. Another limitation includes the severity of liver disease and the degree of portal hypertension and bleeding of patients in this study. Lastly, because of the extremely low number of postprocedure bleeding events in both arms, with only 2 placebo patients requiring platelet transfusion, the second component of the primary endpoint, the proportion of patients who required no rescue therapy for bleeding, was not powered to determine significance. Although further studies are needed to fully elucidate the reduction in bleeding risk associated with the use of TPO receptor agonists in this setting, the necessary inclusion of a pure placebo arm would present investigators with overwhelming ethical hurdles.

In conclusion, the results of this completed global study, L-PLUS 2, demonstrate that lusutrombopag is a safe and effective treatment option for raising PCs and reducing the need for platelet transfusions in the management of patients with CLD and thrombocytopenia undergoing invasive procedures. The clinical benefits of lusutrombopag provided by 3-mg dosing, coupled with the flexibility of a 7-day procedural window for scheduling or repeating procedures as necessary, provide physicians with an alternative therapeutic option to help manage patients with CLD and thrombocytopenia undergoing an invasive procedure.

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