2. SYNOPSIS

Sponsor: Shionogi	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: Lusutrombopag	**Volume:**	
Name of Active Ingredient: S-888711 (international nonproprietary name [INN], lusutrombopag)	**Page:**	

Study Title:
A Phase 3 randomised, double-blind, placebo-controlled study to assess the safety and efficacy of S-888711 (lusutrombopag) for the treatment of thrombocytopenia in patients with chronic liver disease undergoing elective invasive procedures (L-PLUS 2)

Investigators and Study Centers: This was a multicenter study conducted at 138 sites in 22 countries.

Publication (reference): None

Studied Period: █ Jun 2015 (first subject informed consent) and █ Apr 2017 (last subject last observation)

Phase of Development: 3

Objectives:

Primary Objective:

- To compare the efficacy of S-888711 with placebo for the treatment of thrombocytopenia in subjects with chronic liver disease (CLD) who are undergoing elective invasive procedures.

Secondary Objectives:

- To assess the safety and tolerability of S-888711 treatment compared with placebo
- To assess the platelet response following treatment with S-888711 compared with placebo
- To assess the pharmacodynamics (PD) and pharmacokinetics (PK) of S-888711

Methodology:

This was a Phase 3, multinational, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of lusutrombopag for the treatment of thrombocytopenia in subjects with CLD undergoing elective invasive procedures. The study consisted of 3 periods: a screening period (up to 28 days prior to randomization), a treatment period of 7 days (Days 1 to 7 during which study drug was to be administered for 4 to 7 days), and a posttreatment period (through 28 days posttreatment). Thus, the study duration for any subject was to be up to 63 days.

Eligible subjects, who had provided written informed consent, were to be randomized in a 1:1 ratio to treatment with either lusutrombopag (3 mg) or placebo once daily for up to 7 days. Randomization was stratified by the primary invasive procedure (ie, liver ablation/coagulation or other invasive procedures) and baseline platelet count ($< 35 \times 10^9$/L or $\geq 35 \times 10^9$/L).

Once-daily treatment with lusutrombopag 3 mg or placebo was to commence on Day 1 and continue for up to 7 days. Platelet count was to be determined on Days 5, 6, and 7 prior to administration of study drug; if a subject met the administration stopping criterion (ie, platelet count $\geq 50 \times 10^9$/L with an increase of $\geq 20 \times 10^9$/L from baseline), no additional dose of study drug was to be administered. The planned invasive procedure was to be performed in the posttreatment period between Days 9 and 14. Platelet count for determination of the need for platelet transfusion was to be determined on or after Day 8, but no more than 2 days prior to the invasive procedure; a platelet transfusion was required if the platelet count was $< 50 \times 10^9$/L.

Number of Subjects Planned and Analyzed:

Planned: 200 (100 per treatment group)

Randomized: 215 (lusutrombopag, 108; placebo, 107)

Analyzed for efficacy:

- Intention-to-treat (ITT) Population: 215 (lusutrombopag, 108; placebo, 107)
- Per-protocol (PP) Population: 180 (lusutrombopag, 91; placebo, 89)

Analyzed for PK:

- PK Concentration Population: 81 (lusutrombopag)
- PK Parameter Population: 9 (lusutrombopag)

Analyzed for safety:

- Safety Population: 214 (lusutrombopag, 107; placebo, 107)

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

- Male or female subjects 18 years of age or older at the time of signing informed consent form
- CLD limited to Child-Pugh class A and class B disease
- Platelet count $< 50 \times 10^9$/L at baseline on Day 1 prior to randomization
- Undergoing an elective invasive procedure that:
  - o Was likely to require administration of platelets
  - o Was expected to be performed between Days 9 and 14
  - o Did not include laparotomy, thoracotomy, craniotomy, open-heart surgery, or organ resection
  - o Did not include partial organ resection (however, biopsy and other types of tissue removal were allowed if the risk of bleeding and invasiveness was considered comparable or lower than that of those procedures in the list of example procedures)

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- Eastern Cooperative Oncology Group (ECOG) performance status (PS) grade of 0 or 1

Exclusion Criteria:

- Any solid malignant tumor, with exceptions including a malignant tumor that was the treatment target of the primary invasive procedure

- History of splenectomy

- History of liver transplantation

- Portal vein tumor embolism

- History or presence of thrombotic disease

- History or presence of disease associated with a risk of bleeding (eg, coagulation factor deficiency or von Willebrand factor deficiency)

- Absence of hepatopetal blood flow in the main trunk of the portal vein as demonstrated by Doppler ultrasonography within 28 days prior to randomization

Test Product, Dose and Mode of Administration, Lot Number:

Lusutrombopag 3-mg tablet for oral administration once daily. Bulk lot number: ▮▮▮▮▮ (expiration date: Nov 2017)

Duration of Treatment: Up to 7 days

Reference Therapy, Dose and Mode of Administration, Lot Number:

Placebo tablet for oral administration once daily. Bulk lot number: ▮▮▮▮ (expiration date: Nov 2017)

Criteria for Evaluation:

Primary Efficacy Endpoint:

The primary endpoint was the proportion of subjects who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomization through 7 days after the primary invasive procedure.

Secondary Efficacy Endpoints:

Secondary endpoints included the following:

- Proportion of subjects who required no platelet transfusion during the study

- Proportion of responders: subjects who achieved a platelet count of $\geq 50 \times 10^9$/L with an increase of $\geq 20 \times 10^9$/L from baseline at any time during the study

- Duration of the increase in platelet count, defined as the number of days during which the platelet count was maintained as $\geq 50 \times 10^9$/L

- Proportion of subjects who required rescue therapy for bleeding at any time during the study

- Frequency of platelet transfusions and dose (unit) transfused during the study

- The change from baseline in platelet count over time (time course of platelet count)

Pharmacokinetics Assessments:

A total of 272 plasma lusutrombopag concentrations were determined for the 81 subjects

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who received lusutrombopag and were included in the sparse PK sampling group (PK Concentration Population). A total of 63 plasma lusutrombopag concentrations were determined for the 9 subjects who received lusutrombopag and were included in the intensive PK sampling group (PK Parameter Population).

Safety Assessments:

Adverse events (AEs) were to be recorded and physical examinations, imaging studies to assess portal vein thrombosis (ultrasonography, computed tomography [CT], or magnetic resonance imaging [MRI]) and portal blood flow (Doppler ultrasonography), electrocardiography [ECG] and clinical laboratory tests (hematology, blood chemistry, and blood coagulation/fibrinolysis assay) were to be performed, and vital signs (blood pressure and pulse rate) and severity of any bleeding (according to the World Health Organization [WHO] Bleeding Scale) were to be determined.

Statistical Methods:

Analysis Populations:

- **ITT Population**: includes all randomized subjects. Subjects were analyzed according to the treatment to which they were randomized.

- **PP Population**: includes all randomized subjects who had no major protocol deviations pertaining to the efficacy evaluation. Deviations were determined prior to unblinding of the study data.

- **Safety Population**: includes all randomized subjects who received at least 1 dose of the study drug. This population was analyzed according to the treatment that subjects actually received, rather than the treatment to which they were randomized.

- **PK Concentration Population**: includes all subjects who underwent plasma PK sampling and who had at least 1 evaluable PK assay result for lusutrombopag.

- **PK Parameter Population**: includes all subjects with at least 1 PK parameter estimated in the intensive PK sampling group.

Efficacy Analysis:

The ITT Population was the primary population for the analysis of efficacy. The PP Population was used in a sensitivity analysis of the primary endpoint.

Primary Endpoint Analysis

- The number and proportion of subjects who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from the date of randomization through 7 days after the primary invasive procedure were summarized by treatment group, along with 95% confidence intervals (CIs) calculated using the Clopper-Pearson method. The treatment groups were compared using the Cochran-Mantel-Haenszel (CMH) test, adjusted using the stratification factors of platelet count at randomization ($< 35 \times 10^9$/L, $\geq 35 \times 10^9$/L) and the planned primary invasive procedure (liver ablation/coagulation, other invasive procedure).

- As a sensitivity analysis, the primary efficacy analysis was repeated using the PP Population. Additionally, to explore the impact of missing data, discontinuations, subjects who did not undergo an invasive procedure, and

protocol deviations pertaining to platelet transfusion, 2 additional sensitivity analyses of the primary endpoint were performed using 2 modified definitions of success criteria.

- The primary endpoint was analyzed for the subgroups of baseline platelet count ($< 35 \times 10^9$/L, $\geq 35 \times 10^9$/L), performed primary invasive procedure (percutaneous radiofrequency ablation [RFA]/ microwave coagulation therapy [MCT], laparoscopic RFA/MCT, endoscopic variceal ligation [EVL], endoscopic injection sclerotherapy [EIS], transcatheter arterial chemoembolization [TACE], transcatheter arterial embolization [TAE], other, and not performed), sex, age (< 65 years, ≥ 65 years), baseline body weight (< 75 kg, ≥ 75 kg), race (white, nonwhite), and Child-Pugh class (class A, B, and C). The number and proportion of subjects were summarized by treatment group, and the treatment groups were compared using the Fisher's exact test. The interaction between subgroup and treatment group was tested using the Breslow-Day test.

Secondary Endpoint Analyses

A gatekeeping strategy was employed for sequentially testing the important secondary endpoints, identified as being most clinically relevant. If the primary endpoint was statistically significant, the secondary endpoints were tested sequentially in the following order:

- Number and proportion of subjects who required no platelet transfusion during the study
- Number and proportion of responders: subjects who achieved a platelet count of $\geq 50 \times 10^9$/L, with an increase of $\geq 20 \times 10^9$/L from baseline at any time during the study
- Duration of platelet count $\geq 50 \times 10^9$/L
- Duration of the platelet count $\geq 50 \times 10^9$/L (lusutrombopag without platelet transfusion and placebo with platelet transfusion)

Other secondary endpoints included:

- Number and proportion of subjects who required rescue therapy for bleeding events
- Frequency of platelet transfusion and dose (unit) transfused
- Time course of platelet count

Pharmacokinetic Analysis:

Plasma lusutrombopag concentrations were summarized for subjects who completed at least 5 days of study drug administration. Time-course profiles for plasma concentration data were presented graphically. Based on plasma concentration data on Days 5 and 6 and using noncompartmental methods, the following PK parameters were calculated, whenever possible, for each subject who completed at least 5 days of study drug administration in the intensive PK sampling group: maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), area under the plasma concentration-time curve over the dosing interval τ (ie, 24 hours; $AUC_{0-\tau}$) and apparent total clearance (CL/F).

Safety Analysis

- Treatment-emergent adverse events (TEAEs):

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- Adverse events were classified by system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) Version 18.0. Of the AEs reported, TEAEs (defined as those reported after administration of the first dose of study drug) were used for the analysis of safety.

- The number and proportion of subjects with at least 1 TEAE, treatment-related TEAEs, TEAEs with an outcome of death, serious TEAE, and TEAE leading to discontinuation of study drug were summarized by treatment group. The number of TEAEs was also presented. Treatment-emergent AEs and treatment-related TEAEs were summarized by MedDRA SOC and preferred term for each treatment group, with separate summaries by severity, outcome and timing in relation to the primary invasive procedure (before, after).

- Bleeding-related TEAEs, per the Standardised MedDRA Query (SMQ) "haemorrhage terms (except laboratory terms)", were summarized.

- Treatment-emergent adverse events of special interest in the study included thrombosis- and thromboembolism-related events per the SMQs "embolic and thrombotic events, arterial", "embolic and thrombotic events, venous", and "embolic and thrombotic events, vessel type unspecified and mixed arterial and venous". These were summarized by SOC and preferred term.

- Clinical laboratory tests:

  - Summary statistics were provided for absolute values and changes from baseline at each scheduled time point.

  - The number and proportion of subjects with abnormalities classified as Grade 2 or higher per the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 were calculated at each scheduled time point by treatment group.

  - The number and proportion of subjects who met the prespecified criteria for liver function abnormalities were calculated at each scheduled time point and after the initiation of study drug by treatment group.

- The recordings of WHO Bleeding Scale, vital signs, ECG, portal vein thrombosis and portal blood flow were summarized at each scheduled time point by treatment group.

Summary of Results

Efficacy:

In the ITT Population, the proportion of subjects who met the primary endpoint (ie, required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomization through 7 days after the primary invasive procedure) was statistically significantly greater in the lusutrombopag group than in the placebo group (64.8% [70/108 subjects] vs. 29.0% [31/107 subjects]; p < 0.0001). The sensitivity analysis using the PP Population were consistent with the primary analysis based on the ITT Population, with the proportion of subjects meeting the primary endpoint statistically significantly greater in the lusutrombopag group than in the placebo

group (72.5% [66/91 subjects] vs. 20.2% [18/89 subjects]; p < 0.0001). Furthermore, 2 additional sensitivity analyses of the primary endpoint using the ITT Population, performed to explore the impact of missing data, discontinuations, subjects who did not undergo an invasive procedure, and protocol deviations pertaining to platelet transfusion, were also consistent with the primary analysis based on the ITT Population, supporting the robustness of the data.

Each of the prespecified important secondary efficacy endpoints, identified as the most clinically relevant for this subject population, showed statistical significance under sequential testing using a gatekeeping procedure:

- The proportion of subjects who received no platelet transfusion during the study was statistically significantly greater in the lusutrombopag group than in the placebo group (63.0% [68/108 subjects] vs. 29.0% [31/107 subjects]; p < 0.0001).

- The proportion of responders (ie, subjects who achieved a platelet count of $\geq 50 \times 10^9$/L with an increase of $\geq 20 \times 10^9$/L from baseline at any time during the study) was also statistically significantly greater in the lusutrombopag group than in the placebo group (64.8% [70/108 subjects] vs. 13.1% [14/107 subjects]; p < 0.0001). The proportion of responders exceeded 50% on Days 10, 12, and 14 in the lusutrombopag group and reached the highest value on Day 12. The proportion of responders did not exceed 10% in the placebo group on any study day.

- The number of days during which the platelet count was $\geq 50 \times 10^9$/L was significantly greater in the lusutrombopag group compared with the placebo group (the median duration, 15.11 days vs. 0.98 days; p = 0.0002).

- The number of days during which the platelet count was $\geq 50 \times 10^9$/L was significantly greater in the lusutrombopag group without platelet transfusion than in the placebo group with platelet transfusion (the median duration, 19.21 days vs. 0 days; p < 0.0001).

For the other secondary efficacy endpoints, the overall numbers of subjects requiring rescue therapy for bleeding events were low (0 [0%] and 2 [1.9%] in the lusutrombopag and placebo groups, respectively). Lusutrombopag had benefits in terms of both reducing the need for platelet transfusion, as well as reducing the number of platelet transfusions in subjects who required a platelet transfusion. In the lusutrombopag group for subjects without platelet transfusion (N = 74), the mean (range) maximum platelet count in subjects was 86.9 (25 to 219) $\times 10^9$/L and the mean maximum increase from baseline in platelet count was 47.1 $\times 10^9$/L. In comparison, for subjects with platelet transfusion in the lusutrombopag group (N = 34), the mean (range) maximum platelet count in subjects was 60.3 (26 to 149) $\times 10^9$/L and the mean maximum increase from baseline in platelet count was 27.2 $\times 10^9$/L. For subjects with platelet transfusion in the placebo group (N = 73), the mean (range) maximum platelet count was 49.3 (15 to 100) $\times 10^9$/L and the mean maximum increase from baseline in platelet count was 13.1 $\times 10^9$/L.

The maximum platelet count in the 30/108 subjects (27.8%) in the lusutrombopag group who discontinued study drug because they met the administration stopping criterion (ie, platelet count $\geq 50 \times 10^9$/L with an increase of $\geq 20 \times 10^9$/L from baseline) ranged from 59×10^9/L to 219×10^9/L, and 1 of the 30 subjects had a maximum platelet count

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$> 200 \times 10^9$/L. The value of 219×10^9/L was attributed to a subject with a protocol deviation that led to their exclusion from the PP Population (ie, took another thrombopoietin [TPO] receptor agonist). Among the 29 of 30 subjects remaining, the maximum platelet count was 150×10^9/L, indicating no excessive increase in platelet count (ie, $> 200 \times 10^9$/L).

Although data should be interpreted with caution due to the small number of subjects in some subgroups and the fact that the study was not powered to show differences between the subgroups, prespecified subgroup analysis of the primary endpoint demonstrated generally consistent results with the primary efficacy analysis, with a treatment benefit in favor of lusutrombopag suggested over placebo for most of the subgroups analyzed. No statistically significant differences were found in the subgroup-by-treatment interaction for any factor. The treatment effect was numerically lower and the difference was deemed to be clinically relevant in subjects with lower baseline platelet count ($< 35 \times 10^9$/L vs. $\geq 35 \times 10^9$/L). However, almost half of subjects with a platelet count of $< 35 \times 10^9$/L at baseline in the lusutrombopag group still showed favorable responses (15/36 subjects [41.7%]).

Pharmacokinetics:

With respect to lusutrombopag PK, the geometric mean values (coefficient of variation [CV%] geometric mean) for C_{max}, $AUC_{0-\tau}$, and CL/F were 157 ng/mL (34.7%), 2737 ng·hr/mL (36.1%), and 1.10 L/hr (36.1%), respectively, based on the intensive PK sampling group. The median T_{max} was 5.95 hours. The C_{max} and $AUC_{0-\tau}$ exhibited a moderate interindividual variability.

Safety:

A total of 109 TEAEs were reported in 51 of 107 subjects (47.7%) in the lusutrombopag group and 134 TEAEs were reported in 52 of 107 subjects (48.6%) in the placebo group. Headache was the only TEAE that occurred at an incidence of 5% or more in the lusutrombopag group. Furthermore, serious TEAEs, irrespective of outcome, were reported at an identical incidence in the lusutrombopag and placebo groups (6.5%), and in the lusutrombopag group, all serious TEAEs were reported in single subjects, and only 1 serious TEAE was considered by the investigator to be related to study drug (cardiac ventricular thrombosis; in a subject with a prior history of coronary artery disease and prior cardiac ventricular thrombus, against the eligibility criteria). Three subjects (2.8%), all in the lusutrombopag group, had TEAEs with an outcome of death (multiorgan failure, cardiac arrest, hepatic cirrhosis, and vessel perforation), but none of these events with a fatal outcome were considered by the investigator to be related to study drug. Additionally, no subjects in the lusutrombopag group had a TEAE leading to discontinuation of study drug. Severe TEAEs were reported at a low and comparable incidence in both treatment groups ($< 5\%$) and no severe TEAEs were considered by the investigator to be related to study drug.

Thrombosis- and thromboembolism-related TEAEs occurred in 2 of 107 subjects (1.9%) each in both the lusutrombopag group and the placebo group. This included TEAEs of cardiac ventricular thrombosis and portal vein thrombosis in the lusutrombopag group and 2 cases of portal vein thrombosis in the placebo group. All portal vein thromboses were found on protocol-specified ultrasonography between 3 and 10 days after the planned invasive procedure and the event of cardiac ventricular thrombosis was identified

on a routine CT scan of the abdomen. One subject (1.2%) in each treatment group had hepatofugal portal blood flow and 1 subject (1.2%) in the placebo group had portal blood flow stasis after the invasive procedure. Bleeding-related TEAEs were reported in 3 of 107 subjects (2.8%) in the lusutrombopag group and 6 of 107 subjects (5.6%) in the placebo group.

No clinically significant trend in mean or median values for laboratory tests was found in the lusutrombopag group compared with the placebo group for the majority of parameters. Although some subjects had changes from baseline in alanine aminotransferase (ALT), aspartate aminotransferase (AST), or prothrombin time-international normalized ratio (PT-INR), these changes may be associated with the background CLD and raise no safety concerns regarding worsening liver function after treatment with lusutrombopag. Although the mean changes from baseline in ALT and AST were higher in the lusutrombopag group than the placebo group on Day 14, by Day 35, values had returned to normal in the lusutrombopag group. No clinically significant findings were noted for vital signs or ECGs, and no clinically significant shifts in grade on the WHO Bleeding Scale were recorded throughout the study.

Conclusions:

- Oral administration of lusutrombopag 3 mg once daily for up to 7 days was effective at increasing platelets to at least 50×10^9/L and thus avoiding the need for platelet transfusion prior to an elective invasive procedure in thrombocytopenic subjects with CLD, with a statistically significant treatment benefit in favor of lusutrombopag consistently demonstrated across all primary and important secondary endpoints, across the ITT and PP Populations.

- No safety concerns for lusutrombopag 3 mg compared with placebo were raised.

- Thus, based on the data presented herein, the efficacy of lusutrombopag 3 mg administered once daily for up to 7 days prior to an elective invasive procedure has been established in thrombocytopenic subjects with CLD, with no additional safety concerns raised in this study.

Final Report Date: 04 October 2017