

2. SYNOPSIS

Sponsor: Shionogi & Co., Ltd.	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use only)</i>
Name of Finished Product Lusutrombopag	Volume:	
Name of Active Ingredient: S-888711	Page:	
Study Title: A Phase 3b Open-label Study of S-888711 in Thrombocytopenic Patients with Chronic Liver Disease		
Investigators and Study Centers: This was a multicenter study conducted at 82 sites in Japan.		
Publication (reference): None		
Study Period: ■ October 2015 (date of the first subject consent) and ■ September 2016 (date of the final observation for the last patient)		
Phase of Development: 3		
Objectives: Primary Objective: <ul style="list-style-type: none"> To assess the significance of platelet count measurement during administration of S-888711 to thrombocytopenic patients with chronic liver disease (CLD) receiving S-888711 as a pretreatment of invasive procedures. Secondary Objectives: <ul style="list-style-type: none"> To evaluate the safety, pharmacokinetics (PK), and efficacy of S-888711 in thrombocytopenic patients with CLD receiving S-888711 as a pretreatment of invasive procedures. To evaluate the safety, PK, and efficacy of S-888711 in thrombocytopenic patients with CLD receiving S-888711 among patients who have previously received S-888711. 		
Methodology: The multicenter, open-label study was conducted in thrombocytopenic patients with CLD. The study consisted of 3 study periods: a Screening Period for 1 to 28 days, a Treatment Period for 7 days, and a Post-treatment Period for 28 days. Potential patients who provided written informed consent were screened to assess their eligibility in the Screening Period. Eligible patients were enrolled in the study and started receiving 3 mg of S-888711 once daily (Day 1 of the Treatment Period). Patients received S-888711 for up to 7 days. After the final administration of study treatment, patients underwent specified study assessments through Day 35 (until the end of Post-treatment		

Period). The planned invasive procedure was performed between Days 9 and 14. Determination of the need for platelet transfusion was performed after Day 8 and immediately before performing the primary invasive procedure (ie, within 2 days before the day of the invasive procedure). Preoperative platelet transfusion was performed only when the platelet count was < 50,000/ μ L.

The study was conducted in 3 treatment groups (the A/B-1 group, the A/B-2 group, and the non-naive A/B group). Patients who had received S-888711 previously were assigned to the non-naive A/B group. Patients who had not previously received S-888711 were enrolled in the A/B-1 group or the A/B-2 group. The platelet count-related criteria for stopping the study treatment as shown in the table below were applied to each group. Of the A/B-1 and A/B-2 groups, the patient recruitment started with the A/B-1 group (Step 1). When the number of patients who had experienced platelet count of $\geq 200,000/\mu$ L was less than 2 in the A/B-1 group, which consisted of the target sample size of 45 patients, the A/B-2 group (Step 2) could be initiated.

Group	Step	Child-Pugh Class/ History of S-888711	Method for Applying the Platelet Count-related Criteria for Stopping the Study Treatment	Target Sample Size
A/B-1	1	A or B/ No	The investigator or subinvestigator will stop the study treatment if platelet count $\geq 50,000/\mu$ L with an increase of $\geq 20,000/\mu$ L from baseline on Day 6 or if platelet count increase of $> 40,000/\mu$ L from baseline on Day 5, Day 6, or Day 7.	45
A/B-2	2	A or B/ No	The investigator or subinvestigator will NOT stop the study treatment even if platelet count $\geq 50,000/\mu$ L with an increase of $\geq 20,000/\mu$ L from baseline. The investigator or subinvestigator will stop the study treatment if platelet count increase of $> 40,000/\mu$ L from baseline on Day 5, Day 6, or Day 7.	45
Non-naive A/B	—	A or B/ Yes	The investigator or subinvestigator will stop the study treatment if platelet count $\geq 50,000/\mu$ L with an increase of $\geq 20,000/\mu$ L from baseline on Day 3, Day 5, Day 6, or Day 7 or if platelet count increase of $> 40,000/\mu$ L from baseline on Day 3, Day 5, Day 6, or Day 7.	5

Aside from the non-naive A/B group, patients treated in the A/B-1 group or the A/B-2 group could be retreated with S-888711 during the Post-treatment Period, provided platelet count was < 50,000/ μ L, an additional invasive procedure was determined to be necessary, and there was no portal vein thrombosis based on imaging evaluation performed between 3 and 10 days after the previous invasive procedure. The retreatment was initiated between Days 14 and 35 and continued for up to 7 days with the original patient ID in the group in which the patient had been enrolled initially. The day of the initial retreatment was counted as Day 1 of the retreatment. The same study procedures followed during the Treatment Period and Post-treatment Period of the first treatment were repeated, and the additional invasive procedure was performed on Day 9 to 14 of the retreatment. Actually one patient was treated in the case in the A/B-1

group but the patient was counted as 1 patient in the A/B-1 group.

Number of Patients Planned and Analysed:

Planned target sample size: 95 (45 for the A/B-1 group, 45 for the A/B-2 group, 5 for the non-naive A/B group)

Enrolled: 102 (47 for the A/B-1 group*, 47 for the A/B-2 group, 8 for the non-naive A/B group*)

* Of the non-naive A/B patients, 1 patient had been enrolled initially in the A/B-1 group (patient ID 3LF001) and after the completion of the study, the patient was newly enrolled as a non-naive patient in the non-naive A/B group (patient ID 3LF003). The patient was counted in both groups.

Analysed for efficacy:

- Full analysis set (FAS): 102 (47 for the A/B-1 group, 47 for the A/B-2 group, 8 for the non-naive A/B group)

Analysed for PK:

- PK concentration population: 100 (46 for the A/B-1 group, 46 for the A/B-2 group, 8 for the non-naive A/B group)
- PK parameter population: 23 (15 for the A/B-1 group, 8 for the non-naive A/B group)

Analysed for safety:

- Safety analysis population: 102 (47 for the A/B-1 group, 47 for the A/B-2 group, 8 for the non-naive A/B group)

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

- Male or female patients aged 20 years or older at the time of signing the informed consent form
- Thrombocytopenic patients due to CLD
- Patients with a platelet count of $< 50,000/\mu\text{L}$ at screening
- Patients undergoing invasive procedures fulfilling the following criteria:
 - procedures being completed between 9 and 14 days after the initiation of the study treatment
 - procedures which do not include any of the following: laparotomy, thoracotomy, craniotomy, open-heart surgery, organ resection, or partial organ resection (except for procedures comparable to tissue resection)
- Patients with the Eastern Cooperative Oncology Group (ECOG) performance status grade 0 or 1

Exclusion Criteria:

- Patients with malignant tumours other than the treatment target of the primary invasive procedure in the study
- Patients with severe hepatic impairment (Child-Pugh class C)
- Patients with portal vein tumour embolism and past or present thrombosis
- Patients for whom no hepatopetal portal blood flow was demonstrated

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

S-888711 3-mg tablet for oral administration once daily.

Bulk lot number: [REDACTED] (expiration date: September 2016).

Duration of Treatment: Up to 7 days

Criteria for Evaluation:

Efficacy Assessments:

Efficacy Endpoints:

- The proportion of patients who required no platelet transfusion:
 - The proportion of patients who received no platelet transfusion prior to the initial invasive procedure, ie, the primary invasive procedure for the patient in this study, in the analysis population.
 - The proportion of patients who received no platelet transfusion until 7 days after the primary invasive procedure in the analysis population
 - The proportion of patients who required no platelet transfusion during the study, ie, the proportion of patients who received no platelet transfusion during the study in the analysis population
- Responder rate (ie, the proportion of patients for whom the platelet count reached $\geq 50,000/\mu\text{L}$ with an increase of $\geq 20,000/\mu\text{L}$ from baseline)
- Duration of the increase in platelet count, which was defined as follows:
 - The number of days during which platelet count was maintained as $\geq 50,000/\mu\text{L}$
 - The number of days during which platelet count was maintained as $\geq 70,000/\mu\text{L}$
 - The number of days during which platelet count was maintained as $\geq 50,000/\mu\text{L}$ with an increase of $\geq 20,000/\mu\text{L}$ from baseline
- Time course of platelet count
- Frequency of platelet transfusion and the dose (unit) transfused

PK Assessments:

Blood sampling was performed for the determination of plasma drug concentrations in all patients. Intensive blood sampling was performed in 16 patients of the A/B-1 group and all patients of the non-naive A/B group, and sparse blood sampling was performed in the remaining patients.

Safety Assessments:

Physical examinations, diagnostic imaging to assess portal vein thrombosis (ultrasonography, computed tomography [CT], or magnetic resonance imaging [MRI]), portal blood flow (Doppler ultrasonography), electrocardiography, and clinical laboratory tests (haematology, blood chemistry and blood coagulation/fibrinolysis assay) were performed, vital signs (blood pressure and pulse rate) were determined, and adverse events (AEs) were recorded.

Statistical Methods:

Efficacy Analysis:

- The proportion of patients who required no platelet transfusion
 - The number and proportion of patients who required no platelet transfusion were summarized by treatment group, along with 95% confidence intervals (CIs) calculated using the Clopper-Pearson method.
 - The proportion of patients who required no platelet transfusion was summarized for subgroups defined based on baseline platelet count, type of performed primary invasive procedure, Child-Pugh class, presence or absence of ascites, and Model for End-Stage Liver Disease (MELD) score.
- Responder rate
 - The number and proportion (with 95% CIs using the Clopper-Pearson method) of responders during the study and at each scheduled time point were calculated by treatment group.
- Duration of the increase in platelet count
 - Summary statistics for the duration of increased platelet count were calculated by treatment group in patients who received or did not receive platelet transfusions.
- Time course of platelet count
 - Summary statistics were provided for platelet count at each scheduled time point by treatment group. The change in platelet count from baseline, and the percent change in platelet count from baseline were also summarized.
 - Maximum platelet count and maximum change in platelet count for each patient were summarized by treatment group.
 - The number and proportion of patients with a decreased platelet count compared to baseline value at the end of the study were summarized by treatment group.
 - For patients who required no platelet transfusion, the time point of the maximum platelet count was summarized by treatment group.
 - Summary statistics for platelet count were calculated for patients without platelet transfusion in the A/B-1 and A/B-2 groups at each scheduled time point for the following 6 subgroups, which were determined based on application of a responder criterion (platelet count of $\geq 50,000/\mu\text{L}$ with an increase of $\geq 20,000/\mu\text{L}$ from baseline). Change from baseline in platelet count was also summarized as the following subgroups:
 1. Patients did not meet the predefined platelet count-related criteria for stopping the study treatment but the platelet count at Day 5 achieved $\geq 50,000/\mu\text{L}$ and increased $\geq 20,000/\mu\text{L}$ from baseline
 2. Patients did not meet the predefined platelet count-related criteria for stopping the study treatment but the platelet count at Day 6 achieved $\geq 50,000/\mu\text{L}$ and increased $\geq 20,000/\mu\text{L}$ from baseline (excluding the patients who included in subgroup 1)

3. Patients did not meet the predefined platelet count-related criteria for stopping the study treatment but the platelet count at Day 7 achieved $\geq 50,000/\mu\text{L}$ and increased $\geq 20,000/\mu\text{L}$ from baseline (excluding the patients who included in subgroups 1 and 2)
4. Patients did not meet the predefined platelet count-related criteria for stopping the study treatment or the responder criterion (excluding the patients who included in subgroups 1, 2 and 3)
5. Patients who met the predefined use of the responder criterion at Day 6 and stopped the study treatment
6. Patient who stopped the study treatment due to platelet count increased $> 40,000/\mu\text{L}$ from baseline

- Frequency of platelet transfusion and the dose (unit) transfused
- Summary statistics of the number and dose (unit) of platelet transfusion during the study were summarized for patient who received platelet transfusion.

Pharmacokinetic Analysis:

For patients who had not previously received S-888711 in the A/B-1 and A/B-2 groups, individual plasma S-888711 concentrations were summarized by Child-Pugh class (A or B) and regardless of Child-Pugh class and compared between Child-Pugh classes. For patients who had previously received S-888711 in the non-naïve A/B group, individual plasma S-888711 concentrations were summarized regardless of Child-Pugh class and compared with those in patients who had not received S-888711 in the A/B-1 and A/B-2 groups. Individual PK parameters of S-888711 for patients who had not previously received S-888711 were summarized by Child-Pugh class and regardless of Child-Pugh class. Individual PK parameters of S-888711 for patients who had previously received S-888711 (the non-naïve A/B group) were summarized regardless of Child-Pugh class.

Safety Analysis

- Treatment-emergent adverse events (TEAEs):
 - The number of patients who experienced at least 1 TEAE, treatment-related AE, death, serious TEAE, significant TEAE (defined as any TEAE that led to discontinuation of the study treatment or was severe excluding serious TEAEs) and TEAE leading to discontinuation of the study treatment were summarised by treatment group. The number of TEAEs was also presented.
 - TEAEs and treatment-related AEs were summarised by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) by treatment group, with separate summaries by severity, outcome and timing in relation to the primary invasive procedure (before, after).
 - The number and proportion of patients who experienced bleeding-related TEAEs, per the Standardised MedDRA Query (SMQ) “haemorrhage terms (except laboratory terms)”, were calculated by treatment group.
 - AEs of special interest in the study included thrombotic/thromboembolic

complications 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”. The number and proportion of patients who experienced thrombotic/thromboembolic TEAEs were calculated by SOC and PT by treatment group.

- Clinical laboratory tests:
 - Summary statistics were provided for absolute values and changes from baseline at each scheduled time point.
 - The number and proportion of patients classified as having laboratory test results of Grade 2 or higher per the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 were calculated at each scheduled time point and after the initiation of the study drug by treatment group.
 - The number and proportion of patients 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.

In addition, vital signs, electrocardiograms, and assessments of portal vein thrombosis and portal blood flow were summarized at each scheduled time point by treatment group.

Results

Efficacy Results:

- The proportion of patients who required no preoperative platelet transfusion was 80.9% (38/47 patients) in the A/B-1 group and 83.0% (39/47 patients) in the A/B-2 group. In the non-naive A/B group, the proportion of patients who required no preoperative platelet transfusion was 75.0% (6/8 patients).
- The proportion of responders during the study was 83.0% (39/47 patients) in the A/B-1 group and 85.1% (40/47 patients) in the A/B-2 group. The proportion of responders exceeded 50% on Day 10 to 21 in the A/B-1 and A/B-2 groups and was the greatest on Day 12 in the A/B-1 group and Day 14 in the A/B-2 group. No meaningful difference was found between the A/B-1 and A/B-2 groups. In the non-naive A/B group, the proportion was 75.0% (6/8 patients), exceeded 50% on Day 10 to Day 14, and was the greatest on Days 12 and 14 in the same value.
- The mean number of days during which the platelet count was $\geq 50,000/\mu\text{L}$ in patients without platelet transfusion was 20.7 days in the A/B-1 group and 20.3 days in the A/B-2 group. The mean number of days during which the platelet count was $\geq 70,000/\mu\text{L}$ in patients without platelet transfusion was 8.7 days in the A/B-1 group and 7.7 days in the A/B-2 group. The mean number of days during which the platelet count met the criterion for responder in patients without platelet transfusion was 12.8 days in the A/B-1 group and 13.3 days in the A/B-2 group. No meaningful difference in these criteria in patients without platelet transfusion was found between the A/B-1 and A/B-2 groups. In the non-naive A/B group, the mean number of days during which the platelet count was $\geq 50,000/\mu\text{L}$ in patients without platelet transfusion was 22.8 days, the

mean number of days during which the platelet count was $\geq 70,000/\mu\text{L}$ in patients without platelet transfusion was 7.8 days, and the mean number of days during which the platelet count met the criterion for responder in patients without platelet transfusion was 14.3 days.

- The mean (range) maximum platelet count in patients without platelet transfusion was $9.26 (5.5 \text{ to } 17.3) \times 10^4/\mu\text{L}$ in the A/B-1 group and $8.54 (5.9 \text{ to } 11.5) \times 10^4/\mu\text{L}$ in the A/B-2 group. The mean (range) time to reach the maximum platelet count in patients without platelet transfusion was 14.53 (10.0 to 28.0) days in the A/B-1 group and 13.90 (10.0 to 28.0) days in the A/B-2 group. No meaningful difference was found between the A/B-1 and A/B-2 groups. In the non-naive A/B group, the mean (range) maximum platelet count in patients without platelet transfusion was $8.45 (7.5 \text{ to } 9.8) \times 10^4/\mu\text{L}$, the mean (range) time to reach the maximum platelet count in patients without platelet transfusion was 13.33 (12.0 to 14.0) days.
- The maximum of the mean platelet counts was $10.22 \times 10^4/\mu\text{L}$ on Day 12 in subgroup 1, $9.27 \times 10^4/\mu\text{L}$ on Day 12 in subgroup 2, $10.81 \times 10^4/\mu\text{L}$ on Day 14 in subgroup 3, $7.26 \times 10^4/\mu\text{L}$ on Day 14 in subgroup 4, and $10.80 \times 10^4/\mu\text{L}$ on Day 10 in subgroup 5, showing that each profile on platelet increase resembled each other among subgroups.
- For the analysis by baseline platelet count ($< 35,000/\mu\text{L}$, $\geq 35,000/\mu\text{L}$), the proportion of patients who required no platelet transfusion tended to be lower in the subgroup with lower platelet count at screening. This tendency was found both in the A/B-1 and A/B-2 groups ($< 35,000/\mu\text{L}$, 46.2% in the A/B-1 group and 66.7% in the A/B-2 group; $\geq 35,000/\mu\text{L}$, 94.1% in the A/B-1 group and 90.6% in the A/B-2 group).

PK Results:

- The PK of S-888711 was similar between Child-Pugh class A and B. The effect of previous experience of S-888711 treatment on the PK of S-888711 was minimal.

Safety Results:

- A total of 204 TEAEs in 43 of 47 patients (91.5%) in the A/B-1 group, 141 TEAEs in 41 of 47 patients (87.2%) in the A/B-2 group, and 26 TEAEs in 6 of 8 patients (75.0%) in the non-naive A/B group were reported in the safety analysis population.
- No deaths or AEs leading to discontinuation of the study treatment occurred. Serious TEAEs were reported in 3 patients (1 event of blood glucose increased, 1 event of colon cancer, and 1 event of herpes zoster) in the A/B-1 group and 2 patients (1 event of portal vein thrombosis, and 1 event each [in the same patient] of ventricular tachycardia, sinus node dysfunction and cellulitis) in the A/B-2 group. Except for the portal vein thrombosis in the A/B-2 group, all serious TEAEs were considered not related to the study drug by the investigators.
- Thrombus-related TEAEs occurred in 1 of 47 patients (2.1%) in the A/B-1 group, and 2 of 47 patients (4.3%) in the A/B-2 group, and none in the non-

naive A/B group: 1 event of moderate tumour thrombosis in the A/B-1 group and 2 events of mild or severe portal vein thrombosis in the A/B-2 group. Of the reported portal vein thromboses in the A/B-2 group, the severe portal vein thrombosis was found in ultrasonography planned before invasive procedure and was considered to be serious and related to the study drug (the maximum platelet prior to and on the onset day, $7.5 \times 10^4/\mu\text{L}$); and the mild portal vein thrombosis was found in MRI after invasive procedures and was considered to be non-serious and not related to the study drug (the maximum platelet prior to the onset day, $8.6 \times 10^4/\mu\text{L}$; the platelet on the onset day, $7.7 \times 10^4/\mu\text{L}$). Patients with the events indicated no excessive increase in platelet counts.

- Bleeding-related TEAEs were reported for 5 of 47 patients (10.6%) in the A/B-1 group and 2 of 47 patients (4.3%) in the A/B-2 group, and none in the non-naive A/B group. All the events were mild and non-serious, and were considered not related to the study drug by investigators.
- Five treatment-related AEs were reported in 5 of 102 patients (4.9%): mild rash and moderate erythema multiforme in 1 each patient in the A/B-1 group; and severe portal vein thrombosis, mild white blood cell count decreased, and mild somnolence in 1 patient each in the A/B-2 group. There were no treatment-related AEs in the non-naive A/B group.
- No unknown safety concerns were noted for laboratory tests, vital signs or electrocardiograms.

Conclusions:

- No clinically-significant difference in the efficacy and safety was suggested when thrombocytopenic patients with CLD undergoing elective invasive procedures received S-888711 3 mg with the following methods: (1) S-888711 was stopped if platelet count on Day 6 met the responder criterion, platelet count $\geq 50,000/\mu\text{L}$ with an increase of $\geq 20,000/\mu\text{L}$ from baseline; (2) S-888711 was administered for a fixed 7-day period regardless of whether platelet count on Day 5, 6, or 7 met the responder criterion.
- Similar efficacy and safety was shown in the 8 patients who had previously received S-888711 and the S-888711 naive patients.
- No new or unique safety findings were reported.
- The PK of S-888711 was similar between Child-Pugh class A and B. The effect of previous experience of S-888711 treatment on the PK of S-888711 was minimal.

Final Report Date: 22 February 2017

Date of Amendment 1: 16 Nov 2017