

## 2. SYNOPSIS

<b>Sponsor:</b> Shionogi & Co., Ltd.	<b>Individual Study Table Referring to Part of the Dossier</b>	<i>(For National Authority Use only)</i>
<b>Name of Finished Product</b> Lusutrombopag	<b>Volume:</b>	
<b>Name of Active Ingredient:</b> S-888711	<b>Page:</b>	
<b>Study Title:</b> A Clinical Pharmacology Study of S-888711 in Thrombocytopenic Patients with Child-Pugh Class C Liver Disease		
<b>Investigators and Study Centers:</b> This was a multicenter study conducted at 35 centers in Japan.		
<b>Publication (reference):</b> None		
<b>Study Period:</b> ■ July 2016 (date of the first patient consent) through ■ March 2017 (date of the final observation for the last patient)		
<b>Phase of Development:</b> 1/2		
<b>Objectives:</b> <b>Primary Objective:</b> <ul style="list-style-type: none"> <li>To evaluate the safety and pharmacokinetics (PK) of S-888711 in Child-Pugh class C patients with thrombocytopenia due to chronic liver disease (CLD).</li> </ul> <b>Secondary Objective:</b> <ul style="list-style-type: none"> <li>To assess the platelet count in Child-Pugh class C patients with thrombocytopenia due to CLD receiving S-888711.</li> </ul>		
<b>Methodology:</b> This multicenter, open-label study was conducted in thrombocytopenic patients with CLD.  The study consisted of 3 study periods: a Screening Period of up to 28 days, a Treatment Period of 7 days, and a Post-treatment Period of 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 on Day 1 of the Treatment Period. Patients received S-888711 for up to 7 days. After the final administration of study drug, patients underwent specified study assessments through Day 35 (until the end of the Post-treatment Period). Platelet count on Days 3 to 7 was measured before administration of study drug, and the investigator or subinvestigator was to stop administration of study drug if platelet count was $\geq 50,000/\mu\text{L}$ with an increase of $\geq 20,000/\mu\text{L}$ from baseline. Invasive procedures were permitted between Days 9 and 14.		

### **Number of Patients Planned and Analysed:**

Planned sample size: Up to 15 patients (patient enrollment was allowed to be terminated when the number of patients necessary for the PK assessment was enrolled). Enrollment of eligible patients was difficult, with only 5 patients enrolled between [REDACTED] July 2016 and [REDACTED] February 2017. When 5 patients were enrolled, PK analysis was made, which showed that intra-individual variation was smaller than expected. Based on the finding, the sponsor judged that the sample size was adequate for PK assessment and terminated further patient enrollment to complete the study.

Enrolled: 5

Analysed for PK:

- PK concentration population: 5
- PK parameter population: 5

Analysed for safety:

- Safety analysis population: 5

Analysed for platelet count assessment:

- Full analysis set (FAS): 5

### **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 with any of the following criteria:
  - Patients with Child-Pugh class C liver disorder at screening
  - Patients whose Child-Pugh score was 9 points at screening and who had been diagnosed within 1 year before informed consent as having Child-Pugh class C liver disease more than once or for over a month
- Patients with the Eastern Cooperative Oncology Group (ECOG) performance status grade 0 or 1

#### **Exclusion Criteria:**

- Patients with any of hematopoietic tumor, aplastic anemia, myelodysplastic syndrome, myelofibrosis, congenital thrombocytopenia, drug-induced thrombocytopenia, generalized infection requiring treatment except for viral liver disease, or immune thrombocytopenia
- Patients with malignant tumors other than the treatment target of the primary invasive procedure (if applicable) in the study
- Patients with any of the following at the screening examination:
  - symptoms of hepatic encephalopathy which were comparable to occasional coma (3 points) for the Child-Pugh encephalopathy score, with or without medication for hepatic encephalopathy
  - uncontrollable ascites with drugs
  - total bilirubin of  $> 3 \text{ mg/dL}$

<ul style="list-style-type: none"><li>• Patients with portal vein tumor embolism or past or present thrombosis</li><li>• Patients for whom no hepatopetal portal blood flow was demonstrated</li></ul>
<b>Test Product, Dose and Mode of Administration, Lot Number:</b> S-888711 3-mg tablet for oral administration once daily. Bulk lot number: [REDACTED] (expiration date: November 2017).
<b>Duration of Treatment:</b> Up to 7 days
<b>PK Assessments:</b> Blood sampling was performed for the determination of plasma drug concentrations in all patients. The following PK parameters were calculated: maximum plasma concentration ( $C_{max}$ ), time to maximum plasma concentration ( $T_{max}$ ), area under the concentration-time curve from time zero to the dosing interval time ( $AUC_{0-\tau}$ ), terminal elimination rate constant ( $\lambda_z$ ), terminal elimination half-life ( $t_{1/2,z}$ ), and apparent total clearance (CL/F).
<b>Safety Assessments:</b> Physical examinations, diagnostic imaging to assess portal vein thrombosis (computed tomography [CT] or magnetic resonance imaging [MRI]), Doppler ultrasonography to assess portal blood flow, electrocardiography, and clinical laboratory tests (hematology, blood chemistry, and blood coagulation/fibrinolysis assay) were performed. Vital signs (blood pressure and pulse rate) were measured, and adverse events (AEs) were recorded.
<b>Platelet Count Assessments:</b> <ul style="list-style-type: none"><li>• Time course of platelet count</li><li>• Responder rate (ie, the proportion of patients for whom the platelet count reached <math>\geq 50,000/\mu\text{L}</math> with an increase of <math>\geq 20,000/\mu\text{L}</math> from baseline)</li><li>• Duration of the increase in platelet count, including:<ul style="list-style-type: none"><li>○ The number of days during which the platelet count was maintained at <math>\geq 50,000/\mu\text{L}</math></li><li>○ The number of days during which the platelet count was maintained at <math>\geq 70,000/\mu\text{L}</math></li><li>○ The number of days during which the platelet count was maintained at <math>\geq 50,000/\mu\text{L}</math> with an increase of <math>\geq 20,000/\mu\text{L}</math> from baseline</li></ul></li><li>• Frequency of platelet transfusion and dose (units) of platelets transfused during the study</li></ul>
<b>Statistical Methods:</b> <b>Pharmacokinetic Analysis:</b> To compare the PK of S-888711 between Child-Pugh class A, B, and C, PK parameters for patients with Child-Pugh class A and class B treated with S-888711 in the open-label phase 3b study (1338M0633, the A/B-1 and A/B-2 groups) were compared with PK parameters for patients in this study. The analysis of variance including Child-Pugh class as a fixed effect was performed for the following PK parameters of S-888711: the ln-transformed values for $C_{max}$ , $AUC_{0-\tau}$ , $\lambda_z$ , $t_{1/2,z}$ and CL/F. The ratios of the geometric least squares means and the corresponding 90% confidence intervals (CIs) were estimated by exponentiating the differences in means and the corresponding 90% CIs in the logarithm.

### **Safety Analysis**

- Treatment-emergent adverse events (TEAEs):
  - The number and proportion of patients with at least 1 TEAE, treatment-related AE, death, serious TEAE, significant TEAE (defined as any TEAE that led to discontinuation of the study drug or was severe, excluding serious TEAEs) and TEAE leading to discontinuation of study drug were summarised. 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), with separate summaries by severity and outcome.
  - The number and proportion of patients who experienced bleeding-related TEAEs, per the Standardised MedDRA Query (SMQ) “haemorrhage terms (except laboratory terms)”, were calculated.
  - AEs of special interest in the study included thrombosis- or 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”. The number and proportion of patients who experienced thrombosis- or thromboembolism-related TEAEs were calculated by SOC and PT.
- Clinical laboratory tests:
  - Summary statistics were provided for absolute values and changes from baseline at each scheduled time point.

In addition, vital signs, electrocardiograms (ECGs), and assessments of portal vein thrombosis and portal blood flow were summarized at each scheduled time point.

### **Analysis of Platelet Count:**

- Time course of platelet count (the analyses were performed separately for patients who received platelet transfusion and patients who did not receive platelet transfusion)
  - Summary statistics were provided for platelet count at each scheduled time point. The change in platelet count from baseline was also summarized.
  - Maximum platelet count and maximum change in platelet count for each patient were summarized.
- Proportion of responders
  - The number and proportion of patients who met the responder criterion at least once during the study and at each scheduled time point were summarized. For the proportion of responders during the study, the 95% CI was also calculated by the Clopper-Pearson method.
- Duration of the increase in platelet count to  $\geq 50,000/\mu\text{L}$ ,  $\geq 70,000/\mu\text{L}$ , and  $\geq 50,000/\mu\text{L}$  with an increase of  $\geq 20,000/\mu\text{L}$  from baseline
  - Summary statistics for the duration of increased platelet count were calculated in patients who received and patients who did not receive platelet transfusion.

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

### Results

**Results on Platelet Count:** Platelet transfusion was administered to 1 of the 5 patients during the study.

- Platelet count reached maximum values between Days 12 and 21 in the 5 patients. The mean (range) maximum platelet count in the 4 patients who did not receive platelet transfusion was  $8.40 (5.4 \text{ to } 10.5) \times 10^4/\mu\text{L}$ . The maximum platelet count in the 1 patient who received platelet transfusion was  $3.50 \times 10^4/\mu\text{L}$ . No patients had an increase in platelet count of  $> 20 \times 10^4/\mu\text{L}$  during the study.
- Three of the 4 patients who did not receive platelet transfusion met the responder criterion at least once during the study. The 3 patients met the responder criterion on Days 12 to 21.
- In 3 of the 4 patients without platelet transfusion, the mean number of days during which the platelet count was  $\geq 50,000/\mu\text{L}$  was 13.8 days; the mean number of days during which the platelet count was  $\geq 70,000/\mu\text{L}$  was 6.6 days; and the mean number of days during which the patient met the criterion for responder was 9.2 days.

### PK Results:

- The geometric mean  $C_{\max}$  and  $AUC_{0-\tau}$  of S-888711 for thrombocytopenic patients with Child-Pugh class C liver disease following 3 mg once daily multiple dosing were 163 ng/mL and 3233 ng·hr/mL (CV% Geometric Mean: 31.2% and 27.1%), respectively.
- The mean  $C_{\max}$  and  $AUC_{0-\tau}$  of S-888711 in patients with Child-Pugh class C liver disease were 29% and 21% lower compared to those in patients with Child-Pugh class A liver disease, and 21% both lower compared to those in patients with Child-Pugh class B liver disease, respectively. However, the ranges of  $C_{\max}$  and  $AUC_{0-\tau}$  observed overlapped among the patients with Child-Pugh class A, B, and C.  $C_{\max}$  and  $AUC_{0-\tau}$  of all patients with Child-Pugh class C did not exceed the maximum values from Child-Pugh class A and class B.
- The geometric mean  $t_{1/2,z}$  was 49.7 hours for patients with Child-Pugh class C liver disease, which was about 14 and 10 hours longer than that in patients with Child-Pugh class A and class B liver disease, respectively.

### Safety Results:

- A total of 9 TEAEs were reported in 4 of the 5 patients in the safety analysis population. No treatment-related AEs were reported. All TEAEs were moderate or mild in severity, except for one severe TEAE of neutrophil count decreased.
- No deaths or TEAEs leading to discontinuation of study drug occurred. The only serious TEAE was a severe decrease in neutrophil count, which was considered not related to the study drug by the investigator.
- A thrombosis- or thromboembolism-related TEAE occurred in 2 patients. One non-serious mild portal vein thrombosis was found based on CT as predefined in the protocol to be conducted between 3 and 10 days after the

invasive procedure and was considered not related to the study drug by the investigator because of a small increase in platelet (the maximum platelet count prior to the onset of the event,  $3.5 \times 10^4/\mu\text{L}$ ) and platelet transfusion was also performed. One non-serious mild mesenteric vein thrombosis was found based on CT as predefined in the protocol to be conducted between Days 12 and 28 and was considered not related to the study drug by the investigator because of no increase in platelet count (the maximum platelet count prior to the onset of the event,  $4.7 \times 10^4/\mu\text{L}$ ) and other reasons (a possible side effect of the concomitant prednisolone and the patient's predisposition to thrombosis at screening).

- One bleeding-related TEAE of haematochezia was reported in 1 patient. It was mild, non-serious, and considered not related to the study drug by the investigator.
- No unknown safety concerns were noted in laboratory tests, vital signs, or ECGs.

**Conclusions:**

The study was conducted in Child-Pugh class C patients, including those with slight fluctuation in Child-Pugh score. When 5 patients were enrolled, PK analysis was made, which showed that intra-individual variation was smaller than expected. Based on the finding, the sponsor judged that the sample size was adequate for PK assessment and terminated further patient enrollment to complete the study.

- The ranges of observed  $C_{\text{max}}$  and  $\text{AUC}_{0-\tau}$  overlapped among the patients with Child-Pugh class A, B, and C liver disease.
- The change in platelet count over time in patients with Child-Pugh class C liver disease was similar to that in patients with Child-Pugh class A and class B liver disease.
- No new or unique safety findings were noted.

**Final Report Date:** 21 Aug 2017