2. SYNOPSIS

English Translation (The original report was written in Japanese)

Name of Sponsor: Shionogi & Co., Ltd. **Name of Finished Product:** To be determined **Name of Active Ingredient:**	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	(For National Authority Use Only)
Title of Study: A phase 2 higher-dose study of S-888711 in thrombocytopenic patients with chronic liver disease		
Investigators: [redacted], and other investigators (22 investigators in total)		
Study Centers: [redacted], and other study centers (22 study centers in total)		
Publication: None		
Study Period: Nine months between October [redacted], 2011 (date of the first administration of the study drug to the first patient) and June [redacted], 2012 (date of the final observation for the last patient)		
Phase of Development: 2		
Study Objectives: To assess the safety, pharmacokinetics, and efficacy of S-888711 after a 7-day multiple oral administration as a pretreatment for percutaneous liver ablation in thrombocytopenic patients with chronic liver disease. **Primary Objective:** To assess the safety and pharmacokinetics of S-888711 after a 7-day multiple oral administration. **Secondary Objectives:** 1. To assess the change in platelet count after a 7-day multiple oral administration of S-888711. 2. To assess the proportion of patients who received platelet transfusion after a 7-day multiple oral administration of S-888711.		
Methodology: In this study, multiple oral dose of S-888711 was administered once daily for 7 days to thrombocytopenic patients with chronic liver disease undergoing percutaneous liver ablation. The study was conducted with the following dose groups and initiated from the 2.5-mg group (Step 1); the Step was planned to be directly shifted to either the Step 3 or the Step 4 based on the safety data for the Step 1 and Step 2: • 2.5-mg group (multiple oral dose of 2.5 mg of S-888711 per day for 7 days) in the Step 1 • 3-mg group (multiple oral dose of 3 mg of S-888711 per day for 7 days) in the Step 2 • 3.5-mg group (multiple oral dose of 3.5 mg of S-888711 per day for 7 days) in the		

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Step 3

- 4-mg group (multiple oral dose of 4 mg of S-888711 per day for 7 days) in the Step 4

The planned sample size was 6 patients per dose group. The sponsor determined appropriateness of dose escalation by discussing with medical officers and other persons based on platelet count and safety data (eg, reported adverse events) in all patients receiving S-888711 in the dose group according to the criteria for dose escalation.

After the Step 1, no safety issue or excess increase in platelets was suggested in the 2.5-mg group and the interim review meeting determined initiating the next step (3-mg group, Step 2) after confirming no safety issues were found in 2 patients who did not complete the post-treatment period at the time of the interim review meeting.

After the Step 2, no safety issue or excess increase in platelets was suggested in the 3-mg group. The degree of increase in platelets was suggested to be similar between the 2-mg and 3-mg groups based on the time course of platelet count in patients who showed the maximum platelet count in each group, the maximum rate of change in platelets per day, or the time course of platelet count after completion of study drug administration. The interim review meeting determined initiating the Step 4 (4-mg group).

The study was conducted for 3 dose groups of 2.5-mg, 3-mg, and 4-mg groups according to the following schedule. On Day 3 to 7, S-888711 was administered after confirmation of the platelet count, which was measured before the administration on each day. A patient was withdrawn from the study treatment if platelet count meets the withdrawal criterion, which is platelet count $\geq$ 50,000/μL with an increase of $\geq$ 20,000/μL from baseline. Percutaneous liver ablation was performed between Day 8 (after the completion of Day 8 procedures) and Day 13. After the treatment period, patients underwent study procedures until Day 35 in the post-treatment period.

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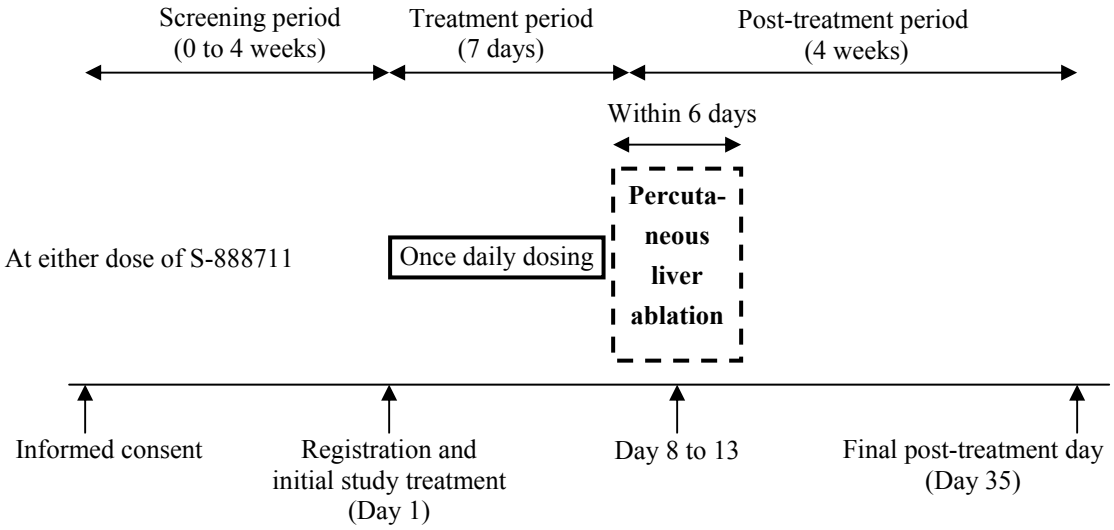

Number of Patients:

Planned target sample size: 6 patients per group (up to 24 patients in total).

Enrolled patients: 21 patients.

Analysis population: 21 patients as follows:

- Efficacy analysis population (Full analysis set [FAS]): 21 patients (6 in the 2.5-mg group, 7 in the 3-mg group, and 8 in the 4-mg group)
- Safety analysis population: 21 patients (6 in the 2.5-mg group, 7 in the 3-mg group, and 8 in the 4-mg group)

Diagnosis and Main Eligibility Criteria:

Inclusion Criteria:

1. Patients aged 20 years or older at the time informed consent was obtained
2. Patients who were able to provide written consent in person
3. Patients with past or present chronic liver disease caused by hepatitis B or C virus
4. Patients who would be undergoing percutaneous liver ablation for primary hepatic cancer
5. Patients with platelet count < 50000/μL at the screening
6. Patients with the Eastern Cooperative Oncology Group (ECOG) performance status grade 0 or 1
7. Patients who were able to stay in the hospital between 5 and 14 days after the initiation of the study treatment
8. Patients who were able to take appropriate contraceptive measures from enrollment to

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completion of the post-treatment assessment

Exclusion Criteria:

1. Patients who had undergone splenectomy
2. Patients with any of the following diseases:
   - Hematopoietic tumor
   - Aplastic anemia
   - Myelodysplastic syndrome
   - Myelofibrosis
   - Congenital thrombocytopenia
   - Drug-induced thrombocytopenia
   - Generalized infection requiring treatment except for viral liver disease
   - Immune thrombocytopenia
3. Patients who had undergone liver transplantation
4. Patients with any of the following at the screening examination:
   - Child-Pugh class C liver disorder
   - Uncontrollable hepatic encephalopathy with drugs
   - Uncontrollable ascites with drugs
   - Prothrombin activity < 50%
   - Bilirubin level > 3 mg/dL
5. Patients with malignant tumor other than primary hepatic cancer or with a history of malignant tumor other than primary hepatic cancer within 5 years
6. Patients with extrahepatic lesions of primary hepatic cancer
7. Patients with past or present thrombosis (eg, cerebral infarction, myocardial infarction, angina pectoris, pulmonary thromboembolism, deep vein thrombosis, disseminated intravascular coagulation syndrome)
8. Patients with portal vein thrombosis based on imaging evaluation within 28 days prior to enrollment or with a history of portal vein thrombosis
9. Patients complicated with or with a history of any of the following diseases:
   - Congenital thrombotic disease (eg, antithrombin deficiency, protein C deficiency, protein S deficiency, coagulation factor [Factor V Leiden] mutation)
   - Acquired thrombotic disease (eg, antiphospholipid antibody syndrome, paroxysmal nocturnal hemoglobinuria, hyperhomocysteinemia, increased factor VIII)
   - Budd-Chiari syndrome
10. Patients for whom hepatofugal portal blood flow or portal blood flow stasis was demonstrated by Doppler ultrasonography within 28 days prior to enrollment
11. Patients who required antithrombotic drugs within 7 days prior to enrollment and thereafter
12. Patients with untreated gastroesophageal varices from which had bleeding or which

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were found to require treatment based on upper gastrointestinal endoscopy within 6 months prior to enrollment
13. Patients with past or present disease associated with a risk of bleeding (eg, coagulation factor deficiency, von Willebrand factor deficiency)
14. Patients with Grade 2 or more severe bleeding at screening according to the World Health Organization (WHO) Bleeding scale
15. Patients who received anticancer drugs (except for transcatheter arterial chemoembolization [TACE] and lipiodolization), interferon preparations, radiation therapy, thoracotomy, laparotomy, partial splenic embolization, hepatectomy, or transcatheter arterial infusion chemotherapy (TAI) (except for lipiodolization) within 90 days prior to enrollment
16. Patients who received percutaneous liver ablation, percutaneous ethanol injection therapy, TACE, lipiodolization with anticancer drugs (ie, Lip-TAI), or transcatheter arterial embolization (TAE), excluding Lipiodol infusion for marking, to treat hepatic cancer within 14 days prior to enrollment
17. Patients who received blood transfusions (except for red blood cell products) within 14 days prior to enrollment
18. Patients who previously received thrombopoietin (TPO) receptor agonists
19. Female patients who were pregnant, possibly pregnant, or lactating
20. Patients who received other investigational products within 90 days prior to enrollment
21. Patients who were considered ineligible for the study by the investigator or subinvestigator for any other reasons

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

Test Drug (S-888711):

- S-888711 0.25-mg tablet
- S-888711 2-mg tablet

Dose:

- For the 2.5-mg group, one 2-mg tablet and two 0.25-mg tablets of S-888711
- For the 3-mg group, one 2-mg tablet and four 0.25-mg tablets of S-888711
- For the 3.5-mg group, one 2-mg tablet and six 0.25-mg tablets of S-888711
- For the 4-mg group, two 2-mg tablets of S-888711

Method of Administration:

Once-daily oral dose of S-888711 0.25-mg tablet(s) or S-888711 2-mg tablet(s)

Lot Number (Manufacturing Number):

- S-888711 0.25-mg tablet, [redacted]
- S-888711 2-mg tablet, [redacted]

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Duration of Administration: Seven days.

Control Drug, Dose and Mode of Administration, Lot Number: Not applicable

Criteria for Evaluation:

Efficacy Assessment:

The following efficacy assessments were performed based on the results on measurements of platelet count and platelet transfusion:

1. The proportion of patients who had platelet count of ≥ 50000/μL on Day 8 with an increase of ≥ 20000/μL from baseline
2. The number and proportion of patients who received platelet transfusion, frequency of platelet transfusion, and dose (unit) of platelets transfused
3. The proportion of patients who had platelet count of ≥ 50000/μL at least once during the study with an increase of ≥ 20000/μL from baseline
4. Platelet count during the study

Pharmacokinetic Assessment:

- Plasma concentration and pharmacokinetic parameters of S-888711

Safety Assessment:

Adverse events (AEs) reported in the study period (for 35 days), including the treatment period and post-treatment period, were investigated. Preferred terms, seriousness, severity, outcome, and causal relationship with S-888711 were assessed for AEs. Abnormal findings for laboratory tests, vital signs (blood pressure, pulse rate), and electrocardiograms were assessed, if any. Portal vein thrombosis and portal blood flow were assessed. The following safety assessments were performed:

1. Incidence of AEs and adverse drug reactions (ADRs)
2. Incidence of bleeding-related AEs
3. Incidence of thrombus-related AEs

Statistical Methods:

Efficacy Analyses:

FAS was used as the efficacy analysis population.

1. The proportion of patients whose platelet count on Day 8 was ≥ 50,000/μL with an increase of ≥ 20,000/μL from baseline was calculated by dose group and as follows:
   - by Child-Pugh Class (A or B)
   - by baseline platelet count (< 20000, ≥ 20000 to < 30000, ≥ 30000 to < 40000, or ≥ 40000 to < 50000)
2. The number and proportion of patients who underwent platelet transfusion, as well as the frequency and the dose (unit) were calculated by dose group.
3. The proportion of patients whose platelet count reached ≥ 50,000/μL at least once

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during the study with an increase of ≥ 20,000/μL from baseline was calculated by dose group.

4. The following summary statistics of platelet count were calculated by dose group and scheduled time points:
   - the change and percent change in platelet count from baseline
   - the time course of platelet count
- the maximum platelet count and the time point when the maximum platelet count was reached
- the maximum increase in platelet count and the time point when the maximum platelet count was reached

Pharmacokinetic Analyses

For the plasma concentration of S-888711 measured in the patients who completed 7-day administration, arithmetic mean, standard deviation, coefficient of variation (CV%), geometric mean, coefficient of variation of geometric mean (GeoCV%), minimum, median and maximum were calculated for each dose group and for each time point. The following pharmacokinetic parameters were calculated using non-compartmental analysis method.

- C_{max} (ng/mL): Maximum plasma drug concentration
- T_{max} (hr): Time to maximum plasma drug concentration
- $AUC_{0-\tau}$ (ng·hr/mL): Area under the plasma concentration-time curve over the dosing interval time (24 hours)
- $t_{1/2,z}$ (hr): Terminal elimination half-life
- CL/F (L/hr): Apparent total clearance, calculated from formula: $CL/F = dose/AUC_{0-\tau}$

Safety Analyses:

Reported AEs were coded to the Medical Dictionary for Regulatory Activities (MedDRA, ver. 14.1) terms, and tabulated by system organ class and by preferred term.

1. Incidence of AEs and ADRs
   - The number of the patients experiencing AEs or ADRs and the number of the events of AEs and ADRs were summarized for each dose group to calculate incidence and its 95% confidence interval. The incidence was defined as percentage of patients experiencing AEs in the analysis population, and the confidence interval of the incidence was calculated based on the Clopper-Pearson method.
   - The number of the patients experiencing AEs or ADRs and the number of the events of AEs and ADRs were summarized for each dose group to calculate incidence by system organ class and by preferred term. The number of the patients in each category (severity, outcome, time of onset, and causal relationship with the test drug) were also summarized to calculate incidence by system organ class and by

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preferred term. ADRs were summarized in a similar manner (excluding causal relationship with the study drug).
- Bleeding-related or thrombus-related AEs were summarized to calculate the incidence by system organ class and by preferred term.

2. For laboratory tests and vital signs (blood pressure, pulse rate), summary statistics were calculated for each dose group and for each time point. The change from the baseline was calculated and analyzed in a similar manner.
3. For electrocardiogram, the frequency and percentage of abnormal finding in electrocardiogram (12-lead electrocardiography) were calculated by time point.
4. For portal vein thrombosis and portal vein blood flow were as follows:
   - The number and proportion of patients experiencing portal vein thrombosis were calculated.
   - The number of patients classified in several categories for direction of portal vein blood flow (hepatofugal, hepatopetal, portal blood stasis) after percutaneous liver ablation was calculated. For hepatofugal or hepatopetal flow, summary statistics of postoperative portal vein blood flow rate were calculated.

Summary - Conclusions

Efficacy Results:

- In the FAS, the proportion of responders (ie, patients who achieved platelet count of ≥ 50000/μL with an increase of ≥ 20000/μL from baseline) on Day 8 was 66.7% (4/6) in the 2.5-mg group, 42.9% (3/7) in the 3-mg group, and 50.0% (4/8) in the 4-mg group.
- Only 1 patient in each group received platelet transfusion and no difference in the proportion of the patients was found among dose groups: 16.7% (1/6) in the 2.5-mg group, 14.3% (1/7) in the 3-mg group, and 12.5% (1/8) in the 4-mg group.
- The proportion of responders during the study was 83.3% (5/6) in the 2.5-mg group, 85.7% (6/7) in the 3-mg group, 100.0% (8/8) in the 4-mg group. With excluding platelet counts measured after platelet transfusion, the proportion was 66.7% (4/6) in the 2.5-mg group, 85.7% (6/7) in the 3-mg group, 87.5% (7/8) in the 4-mg group, indicating that the percentage increased with increasing dose of S-888711.
- Platelet count increased from Day 4 over time in all groups. With excluding platelet counts measured after platelet transfusion, the mean maximum platelet count was 85700/μL at mean 10.0 days after the initial administration in the 2.5-mg group, 80600/μL at mean 13.1 days after the initial administration in the 3-mg group, and 82300/μL at mean 13.3 days after the initial administration in the 4-mg group. The trend of slightly extending time to reach the maximum platelet count was shown with increasing dose of S-888711.
- Five patients met withdrawal criterion for platelet increase (ie, platelet count of ≥

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50000/μL with an increase of ≥ 20000/μL from baseline): 3 patients in the 2.5-mg group and 2 in the 4-mg group. Of these patients, 1 patient each received S-888711 for 2 days (4-mg group), 4 days (4-mg group), and 5 days (2.5-mg group); 2 patients received S-888711 for 6 days (2.5-mg group). All 5 patients achieved platelet count of ≥ 50000/μL with an increase of ≥ 20000/μL from baseline on Day 8. The maximum platelet counts of the patients were the same or less than those of patients receiving S-888711 for 7 days in each group.

- The geometric mean (GeoCV%) of C_{max} was 182 ng/mL (25.0%) in the 2.5-mg group, 250 ng/mL (32.0%) in the 3-mg group, and 342 ng/mL (27.1%) in the 4-mg group; that of $AUC_{0-\tau}$ was 3540 ng·hr/mL (24.5%) in the 2.5-mg group, 4799 ng·hr/mL (32.9%) in the 3-mg group, and 6264 ng·hr/mL (34.7%) in the 4-mg group. C_{max} and $AUC_{0-\tau}$ appeared to increase dose-proportionally. CL/F was relatively constant regardless of dose.

Safety Results:

- A total of 187 AEs occurred in 21 of 21 patients (100%) in the safety analysis population: 56 AEs in 6 of 6 patients (100%) in the 2.5-mg group, 58 AEs in 7 of 7 patients (100%) in the 3-mg group, and 73 AEs in 8 of 8 patients (100%) in the 4-mg group. Most of the AEs were moderate or severe since eligible patients for the study had chronic liver disease with liver cancer and underwent percutaneous liver ablation during the study period. Most of the AEs resolved or relieved.
- Two serious AEs (SAEs) were reported in 2 patients: aspiration in the 2.5-mg group (patient ID, [redacted]) and pyrexia in the 4.0-mg group (patient ID, [redacted]). Aspiration was caused by aging and was considered not related to the study drug and pyrexia was considered related to the percutaneous liver ablation and was considered not related to the study drug. No AEs leading to withdrawal from the study treatment occurred.
- Significant AEs, which were severe, occurred: 7 events in 3 of 6 patients (50.0%) in the 2.5-mg group, 5 events in 4 of 7 patients (57.1%) in the 3-mg group, and 10 events in 6 of 8 patients (75.0%) in the 4-mg group. For each of the significant AEs, no dose-related increase in the incidences of the AEs was noted.
- Frequent AEs (incidence, ≥ 10%) were pyrexia, aspartate aminotransferase (AST) increased, fibrin D-dimer increased, alanine aminotransferase (ALT) increased, procedural hypertension, oxygen saturation decreased, puncture site pain, nausea, blood lactate dehydrogenase (LDH) increased, fibrin degradation products increased, blood bilirubin increased, blood pressure increased, antithrombin III decreased, constipation, malaise, prothrombin level decreased, and musculoskeletal pain. Only for the events of pyrexia and fibrin D-dimer increased, the incidence of the AEs increased with increasing dose of S-888711; all the AEs resolved or relieved. All the AEs except for the event of pyrexia reported in the 3-mg group were considered not related to the study

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drug. Most of the event of pyrexia and all events of fibrin D-dimer increased occurred after percutaneous liver ablation. The event of fibrin D-dimer increased was caused by percutaneous liver ablation because no mean values of fibrin D-dimer (including values which were considered as clinically significant changes) increased dose-dependently.

- No thrombus-related AEs were reported.
- Thirteen bleeding-related AEs occurred in 7 (33.3%) patients in all groups; no dose-related increase in the incidences of the AEs was noted.
- One ADR, which was mild pyrexia in the 3-mg group, was noted in 1 of 21 patients (4.8%). The event of pyrexia resolved on the next day after onset without treatment.
- No clinically significant changes in laboratory tests were found other than those due to percutaneous liver ablation.
- No clinically significant findings were noted for vital signs or electrocardiogram.

Conclusions:

- Efficacy of S-888711 as pretreatment for percutaneous liver ablation was found with 2.5, 3 and 4 mg of doses once daily for 7 days in thrombocytopenic patients with chronic liver disease.
- Both C_{max} and $AUC_{0-\tau}$ appeared to increase dose-proportionally and CL/F was relatively constant within the dose range tested of S.888711.
- No trend of dose-related increase was noted for the incidence of AEs or ADRs in the study, indicating that S-888711 has no significant safety concerns up to 4 mg in thrombocytopenic patients with chronic liver disease.

Date of the Report: 01 February 2013

Date of Amendment 1: 16 Nov 2017