2. SYNOPSIS

English Translation (The original report was written in Japanese)

Name of Sponsor: Shionogi & Co., Ltd. **Name of Finished Product:** Not determined **Name of Active Ingredient:** S-888711	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	(For National Authority Use Only)
Title of Study: A phase 2 study of S-888711 in thrombocytopenic patients with chronic liver disease		
Investigators: [redacted], and other investigators (Total, 27 investigators)		
Study Centers: [redacted] and other study centers (Total, 27 study centers)		
Publication: None		
Study Period: Eleven months between January [redacted] (the date of first administration of study drug to the first patient) and November [redacted], 2011 (the date of final observation for the last patient)		
Phase of Development: 2		

Objectives:

To assess the efficacy, safety, and pharmacokinetics of S-888711 after a 7-day multiple oral administration as pretreatment for percutaneous liver ablation and explore the optimal dose of S-888711 in thrombocytopenic patients with chronic liver disease in a multicenter, open-label, randomized, parallel manner.

Primary objective:

To explore the optimal dose of S-888711 based on the time course of the platelet count after a 7-day multiple oral administration at several doses.

Secondary objectives:

- To evaluate the safety of S-888711 after a 7-day multiple oral administration.
- To assess the pharmacokinetics of S-888711 after a 7-day multiple oral administration.

Methodology:

S-888711 was administered orally at a dose of 0.25, 0.5, 0.75, 1, 1.5 or 2 mg once daily for 7 days to thrombocytopenic patients with chronic liver disease undergoing percutaneous liver ablation. The platelet count on Days 5, 6, and 7 was measured before administration on that day and S-888711 was administered after confirmation of platelet count measured on the day. If a patient had a platelet count of $\geq$ 50000/μL with an increase of $\geq$ 20000/μL from baseline, the patient was withdrawn from the study treatment at that time.

Target sample size was 12 patients per dose group. Doses of 0.25, 0.5, and 1 mg were initially administered in the study. Interim reviews were performed when interim results were obtained from approximately 6 patients per each dose group tested and determined whether other dose groups (0.75, 1.5, or 2 mg) were needed after assessing whether the

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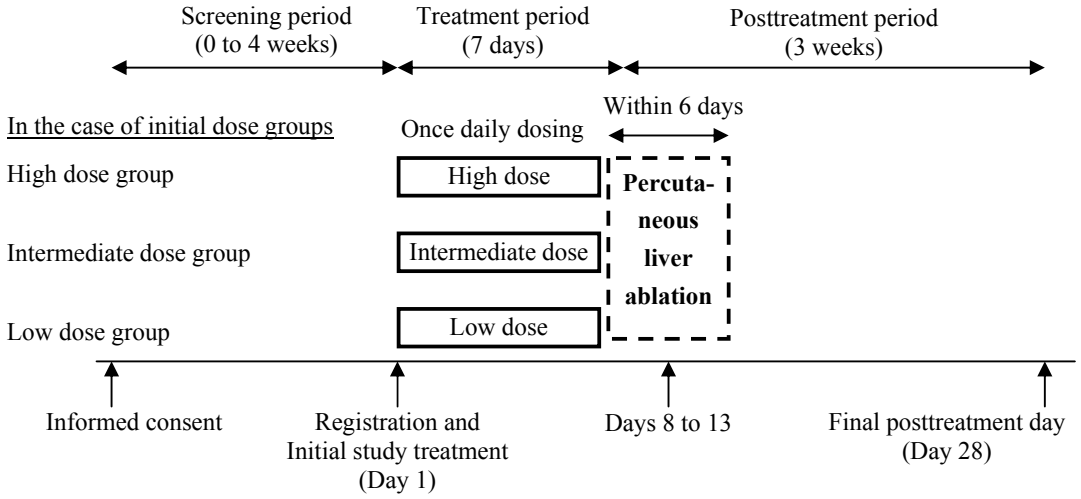
efficacy was sufficient or issues in safety were found at the dose tested. As a result, for the initial dose groups (0.25, 0.5, and 1 mg), no efficacy was shown and no issues in safety were observed. Thus, enrollment of patients was discontinued in the initial dose groups and additional higher doses (1.5 and 2 mg) were selected. In the 1.5-mg group, no patients achieved the primary endpoint on Day 8 suggesting insufficient efficacy. Thus, enrollment of patients was terminated in the 1.5-mg group. In the 2-mg group, some of the patients achieved the primary endpoint on Day 8 with no safety issues. Therefore, a total of 12 patients were enrolled in the 2-mg group. As shown above, the study was conducted at 5 doses comprised of the initial 3 doses (0.25, 0.5, and 1 mg) and the additional 2 higher doses (1.5 and 2 mg).



Number of Patients:

Target sample size was 12 patients per group (up to 54 patients in total [Note in translation: the maximum sample size is calculated at the assumption of 6 patients in 3 dose groups and 12 patients in 3 dose groups]); 35 patients were enrolled in the study. Patients included in the analysis population were 34 patients.

- Efficacy analysis population:
  - Full analysis set (FAS): 34 patients (5 in the 0.25-mg group, 6 in the 0.5-mg group, 5 in the 1-mg group, 6 in the 1.5-mg group, 12 in the 2-mg group)
  - Per protocol set (PPS): 28 patients (4 in the 0.25-mg group, 5 in the 0.5-mg group, 4 in the 1-mg group, 6 in the 1.5-mg group, 9 in the 2-mg group)

- Safety analysis population: 34 patients (5 in the 0.25-mg group, 6 in the 0.5-mg group, 5 in the 1-mg group, 6 in the 1.5-mg group, 12 in the 2-mg group)

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Diagnosis and Main Eligibility Criteria:

Inclusion criteria:

1. Patients aged 20 years or older at the time informed consent is 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 hospital between 5 and 14 days after the initiation of study treatment
8. Patients who were able to take appropriate contraceptive measures from enrollment to completion of posttreatment 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)

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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 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 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 hepatic arterial chemoembolization [TACE] and lipiodolization), interferon preparations, radiation therapy, thoracotomy, laparotomy, partial splenic embolization, hepatectomy, or transhepatic 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 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
Dose:
0.25 mg group: once-daily dose of 1 tablet

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0.5 mg group: once-daily dose of 2 tablets
1.0 mg group: once-daily dose of 4 tablets
1.5 mg group: once-daily dose of 6 tablets
2.0 mg group: once-daily dose of 8 tablets

Method of Administration:
Once-daily oral dose of S-888711 0.25 mg tablet(s)

4. Lot Number (Manufacturing Number)
S-888711 0.25 mg tablet, [redacted].

Duration of Administration: Seven days.

Control Drug, Dose and Mode of Administration, Lot Number: No control drug was used in the study.

Criteria for Evaluation:
Primary endpoints:
Proportion of patients who have platelet count of ≥ 50000/μL on Day 8 with an increase of ≥ 20000/μL from baseline.
Secondary endpoints:
1. Proportion of patients who have received platelet transfusion, frequency of platelet transfusion, and dose (units) of platelets transfused
2. Proportion of patients who have platelet count of ≥ 50000/μL during the study with an increase of ≥ 20000/μL from baseline
3. Platelet count during the study
4. Incidence of bleeding-related adverse events (AEs)
5. Incidence of thrombus-related AEs
6. Incidence of any AEs and adverse drug reactions (ADRs)
7. Plasma concentration of S-888711

Efficacy Assessment:
The primary endpoint of the study was the proportion of patients who had platelet count of ≥ 50000/μL on Day 8 with an increase of ≥ 20000/μL from baseline. The proportion of patients who achieved the primary endpoint was calculated by the sponsor.
The secondary endpoints of the study were as follows:
1. Proportion of patients who have received platelet transfusion, frequency of platelet transfusion, and dose (unit) of platelets transfused
2. Proportion of patients who have platelet count of ≥ 50000/μL at least once during the study with an increase of ≥ 20000/μL from baseline
3. Platelet count during the study
4. Plasma concentration of S-888711

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Safety Assessment:
AEs reported in the study period (for 28 days) including the treatment period and posttreatment 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, and electrocardiograms were assessed, if any.
The secondary endpoints for safety were as follows:

1. Incidence of AEs and ADRs
2. Incidence of bleeding-related AEs
3. Incidence of thrombus-related AEs

Statistical Methods:
Efficacy Analyses:
FAS was used as the primary efficacy analysis population, and "per-protocol set (PPS)" was used for the sensitivity analysis of the primary endpoint.

- The primary endpoint (ie, the proportion of patients who had platelet count of ≥ 50000/μL on Day 8 with an increase of ≥ 20000/μL from baseline) was calculated as follows:
  - The number of patients who achieved the primary endpoint in each dose group and its percentage in the analysis population.
  - The number of patients who achieved the primary endpoint by Child-Pugh or by baseline platelet count (< 20000, ≥ 20000 to < 30000, ≥ 30000 to < 40000, ≥ 40000 to < 50000)

- The secondary endpoints were calculated as follows:
  - The number and proportion of patients who have received platelet transfusion, frequency of platelet transfusion, and dose (unit) of platelets transfused in each dose group
  - Proportion of patients who have platelet count of ≥ 50000/μL with an increase of ≥ 20000/μL from baseline during the study
  - Platelet count, amount and percentage of change from the baseline by time point, time course of count during the study period, the maximum platelet count, and the time points at which reached the maximum platelet count

Pharmacokinetic Analyses
For the plasma concentration of S-888711 measured in the patients who completed 7 days 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 each time point. The following pharmacokinetics parameters were calculated using non-compartmental analysis method.

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- 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. 14.0) terms, and tabulated by system organ class and by preferred term.

- 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. For AEs, severity, outcome, time of onset, and causal relationship with the test drug were summarized by system organ class and by 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.

- 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.
- For electrocardiogram, the frequency and percentage of abnormal finding in electrocardiogram (12-lead electrocardiography) were calculated by time point.
- For portal vein thrombosis and portal vein blood flow were as follows:
  - The number and percentage 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.

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Summary - Conclusions

Efficacy Results:

Responders were defined as patients who achieved platelet count of ≥ 50000/μL with an increase of ≥ 20000/μL from baseline.

- In the FAS, the proportion of patients who achieved primary endpoint was 0% in the 1.5-mg or less dose groups and 33.3% (4/12) in the 2-mg group and responders were found only in the 2-mg group. Similar results were obtained for the PPS.
- The proportion of patients who received platelet transfusion was 80.0% in the 0.25-mg group (4/5), 50.0% in the 0.5-mg group (3/6), 60.0% (3/5) in the 1-mg group, 33.3% (2/6) in the 1.5-mg group, and 16.7% in the 2-mg group (2/12), indicating that the percentage decreased with increasing dose of S-888711.
- The proportion of responders during the study (ie, patients who achieved primary endpoint at least once during the study) was 60.0% (3/5) in the 0.25-mg group, 0% (0/6) in the 0.5-mg group, 20.0% (1/5) in the 1-mg group, 66.7% (4/6) in the 1.5-mg group, and 83.3% (10/12) in the 2-mg group. With excluding platelet counts measured after platelet transfusion, the proportion was 0% in the 1-mg or less dose groups, 50.0% (3/6) in the 1.5-mg group, and 75.0% (9/12) in the 2-mg group, indicating that the percentage increased with dose of S-888711 at 1.5 mg or higher.
- Platelet count increased over time in the 1.5- and 2-mg groups. In the 2-mg group, platelet count distinctly increased from Day 5 and reached a peak at Day 14 with excluding those after platelet transfusion. The mean maximum platelet count was 58300/μL at mean 10.0 days after the initial administration in the 1.5-mg group and 73500/μL at mean 12.1 days after the initial administration in the 2-mg group.
- Three patients in the 2-mg group met withdrawal criterion for platelet increase (ie, platelet count of ≥ 50000/μL with an increase of ≥ 20000/μL from baseline): 2 patients receiving S-888711 for 5 days and 1 patient receiving S-888711 for 6 days. Two patients receiving the drug for 5 days achieved primary endpoint at Day 8. The maximum platelet counts in the 3 patients were within the range of those in patients receiving 2 mg of S-888711 for 7 days.
- The geometric mean (GeoCV%) of C_{max} was 14.3 to 115 ng/mL (20.6% to 53.2%) and that of $AUC_{0-\tau}$ was 266.6 to 2146 ng·hr/mL (23.6% to 52.1%) within the dose range of 0.25 to 2 mg. C_{max} and $AUC_{0-\tau}$ increased dose-proportionally. The $t_{1/2,z}$ and CL/F were relatively constant regardless of dose.

Safety Results:

- Most of the patients experienced AEs and 266 AEs occurred in 33 of 34 patients (97.1%) in the safety analysis population: 41 AEs in 5 of 5 patients (100%) in the 0.25-mg group, 41 AEs in 6 of 6 patients (100%) in the 0.5-mg group, 25 AEs in 5 of 5 patients (100%) in the 1-mg group, 63 AEs in 6 of 6 patients (100%) in the 1.5-mg

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group, and 96 AEs in 11 of 12 patients (91.7%) in the 2-mg group. No dose-related increase in the incidence of AEs was noted. 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; no dose-related increases in severity of AEs were found. Most of the AEs were resolved or relieved.

- SAEs occurred in 1 patient in the 0.5-mg group and 1 patient in the 2-mg group; 1 patient in the 0.5-mg group died. The SAEs were pleural hemorrhage and procedural complication in the 0.5-mg group (Patient, [redacted]) and hepatic infarction and postoperative fever in the 2-mg group (Patient, [redacted]). All SAEs were caused by percutaneous liver ablation and hence considered not related to the study drug. No AEs leading to withdrawal from the study treatment occurred.
- Six significant AEs, which were severe, occurred in 4 of 5 patients (80.0%) in the 0.25-mg group, 9 significant AEs in 4 of 6 patients (66.7%) in the 0.5-mg group, 5 significant AEs in 3 of 5 patients (60.0%) in the 1-mg group, 4 significant AEs in 2 of 6 patients (33.3%) in the 1.5-mg group, and 9 significant AEs in 5 of 12 patients (41.7%) in the 2-mg group. Frequent significant AEs (incidence, $\geq$ 5%) were AST increased, blood pressure increased, procedural hypertension, ALT increased, WBC count decreased, and hypertension. Most of the AEs were clinically significant changes in the vital sign or laboratory test caused by percutaneous liver ablation and considered not related to the study drug.
- Frequent AEs (incidence, $\geq$ 10%) were pyrexia, AST increased, fibrin D-dimer increased, puncture site pain, ALT increased, blood pressure increased, nausea, oxygen saturation decreased, diarrhea, procedural hypertension, abdominal pain, malaise, musculoskeletal pain, blood lactate dehydrogenase increased, fibrin degradation products increased, ascites, and WBC count decreased.
- No thrombus-related AEs attributable to blood coagulation were reported.
- Seventeen bleeding-related AEs occurred in 13 (38.2%) of the patients receiving S-888711; no dose-related increase in the incidences of the AEs was noted.
- No dose-related increase in the incidence of ADRs was noted: 3 events in 2 of 5 patients (40.0%) in the 0.25-mg group, 1 event in 1 of 6 patients (16.7%) in the 0.5-mg group, 0 event (0%) in the 1-mg group, 3 events in 2 of 6 patients (33.3%) in the 1.5-mg group, and 0 event occurred (0%) in the 2-mg group. The following ADRs were reported in 1 patient each: malaise, ALT increased, AST increased, blood fibrinogen decreased, blood potassium increased, WBC count decreased, and rash. All ADRs were resolved or relieved.
- 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.

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Conclusions:

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The proportion of responders, which were patients with sufficient platelet increase for the pretreatment of percutaneous liver ablation, increased dose-dependently within the dose range of 0.25 to 2 mg of S-888711 dosed once daily for 7 days in thrombocytopenic patients with chronic liver disease.
Both C_{max} and $AUC_{0-\tau}$ increased dose-proportionally within the dose range tested and both $t_{1/2,z}$ and CL/F were relatively constant regardless of dose.
Dose-related increase in the incidence of Aes, ADRs, or severe Aes were not noted in the study, indicating that S-888711 has no significant safety concerns up to 2 mg in thrombocytopenic patients with chronic liver disease.

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<tr><td colspan="3">Date of the Report: June 11, 2012. November 07, 2012 (revision of Appendix 16.2.4).</td></tr>
<tr><td colspan="3">Date of Amendment 2: 16 Nov 2017</td></tr>
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