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:** S-888711	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	(For National Authority Use Only)
Title of Study: Evaluation of platelet functions in thrombocytopenic patients with chronic liver disease treated with S-888711		
Investigators: [redacted] (13 investigators in total)		
Study Centers: [redacted]s (13 medical institutions in total)		
Publication: None		
Study Period: Five months between March [redacted], 2014 (date of the first administration of the study drug to the first patient) and July [redacted], 2014 (date of the final observation for the last patient)		
Phase of Development: 1		
Study Objectives: **Primary Objective:** To evaluate the platelet functions in thrombocytopenic patients with chronic liver disease following multiple doses of 3 mg of S-888711. **Secondary Objectives:** To evaluate the efficacy, safety, and pharmacokinetics of S-888711 in thrombocytopenic patients with chronic liver disease following multiple doses of 3 mg of S-888711.		
Methodology: The multicenter, open-label study was conducted in 8 thrombocytopenic patients with chronic liver disease. The study consisted of 3 study periods: the Screening Period for 1 to 28 days, the Treatment Period for 7 days, and the Post-treatment Period for 28 days. Potential patients who provide written informed consent were screened to assess the eligibility in the Screening Period. Eligible patients were enrolled in the study and the patients started receiving 3 mg of S-888711 once daily (the initial administration of S-888711 was on Day 1). The duration of the treatment was for 7 days (Treatment Period). After the final study treatment, patients underwent specified post-treatment study assessments (Post-treatment Period). The platelet function tests were performed 3 times in the Screening Period (baseline), once between Days 9 and 14, and on Day 35. If any invasive procedure was performed, the invasive procedure was permitted after completion of platelet function tests and between Days 9 and 14.		

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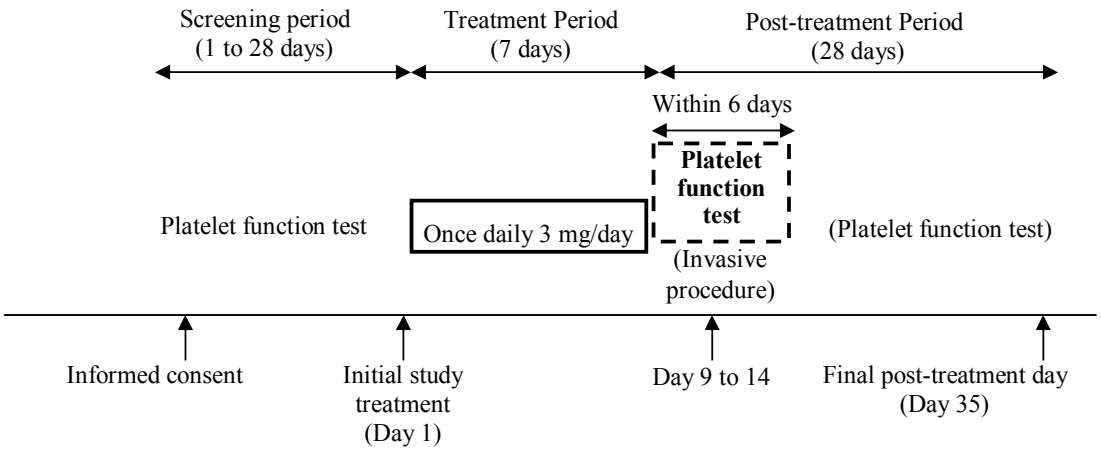

Number of Patients:

Planned target sample size: 6 patients

Enrolled patients: 8 patients

Analysis population: 8 patients

- Safety analysis population: 8 patients
- Pharmacokinetic concentration population: 8 patients
- Pharmacokinetic parameter population: 8 patients

Diagnosis and Main Eligibility Criteria:

Inclusion Criteria:

1. Patients who were able to understand the study and comply with all study procedures, and were willing to provide written informed consent prior to screening
2. Male or female patients aged 20 years or older at the time of signing the informed consent form
3. Thrombocytopenic patients due to chronic liver disease
4. Patients with a platelet count of < 50,000/μL at screening
5. Patients with the Eastern Cooperative Oncology Group (ECOG) performance status grade 0 or 1
6. For male patients, patients who were sterile or who agreed to use an appropriate method of contraception (including use of a condom with spermaticide) from enrollment to completion of the post-treatment assessment
7. For female patients, postmenopausal patients for at least 2 years since their last regular menstrual periods

Exclusion Criteria:

1. Patients with any of the following diseases:
   – hematopoietic tumor

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  - aplastic anemia
  - myelodysplastic syndrome
  - myelofibrosis
  - congenital thrombocytopenia
  - drug-induced thrombocytopenia
  - generalized infection requiring treatment except for viral liver disease
  - immune thrombocytopenia
2. Patients with any of the following concomitant malignant tumors other than the treatment target of the primary invasive procedure in the study:
  - malignant tumors which were not included in the categories of skin cancer (except for melanoma), intramucosal cancer, or carcinoma in situ
  - malignant tumors involving nodal metastasis, distant metastasis, or invasion to the surrounding organ
  - malignant tumors requiring any treatment during the study
3. Patients who had undergone splenectomy
4. Patients who had undergone liver transplantation
5. 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
6. Patients with portal vein tumor embolism
7. Patients with a complication or with a history of any of the following diseases:
  - thrombosis (eg, cerebral infarction, myocardial infarction, angina pectoris, pulmonary thromboembolism, deep vein thrombosis, disseminated intravascular coagulation syndrome)
  - 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
  - disease associated with a risk of bleeding (eg, coagulation factor deficiency, von Willebrand factor deficiency)
  - platelet dysfunction (eg, thrombasthenia, Bernard-Soulier syndrome, Storage pool disease)
8. Patients with portal vein thrombosis based on ultrasonography or imaging evaluation within 28 days prior to enrollment or with a history of portal vein thrombosis
9. Patients for whom no hepatopetal portal blood flow was demonstrated by Doppler ultrasonography within 28 days prior to enrollment
10. Patients with untreated gastroesophageal varices which were bleeding or found to require treatment based on upper gastrointestinal endoscopy within 180 days prior to

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enrollment (except for patients who underwent procedure for the treatment of gastroesophageal varices in the study)

11. Patients with Grade 2 or more severe bleeding at screening according to the World Health Organization (WHO) Bleeding scale
12. Patients with alcohol abuse
13. Patients who had received any of the following drugs or therapies within 90 days prior to enrollment:
    - anticancer drugs except for transcatheter arterial chemoembolization (TACE) and lipiodolization
    - interferon preparations
    - radiation therapy
    - exsanguination
14. Patients who had received any of the following invasive procedures within 90 days prior to enrollment:
    - procedures involving laparotomy, thoracotomy, craniotomy, or open-heart surgery
    - procedures involving any organ resection or any partial organ resection
    - partial splenic embolization
15. Patients who had received any of the following treatments within 28 days prior to enrollment:
    - blood transfusions (except for red blood cell preparations and albumin preparations)
    - antithrombotics
    - TPO receptor agonists (including S-888711)
    - any invasive procedures (except for the treatment of gastroesophageal varices)
16. Patients who had received other investigational products within 90 days prior to enrollment
17. 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: Not applicable

Test Drug (S-888711):
S-888711 3-mg tablet

Dose:
One 3-mg tablet of S-888711

Method of Administration:
Once-daily oral dose

Lot Number (Manufacturing Number):
S-888711 3-mg tablet, [redacted]

Duration of Administration: Seven days.

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

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Criteria for Evaluation:

Platelet Functions Assessment:

Platelet functions were evaluated with platelet aggregation, platelet release reaction, and peripheral blood smear. The platelet aggregation test is a standard test for diagnosis of platelet dysfunction. The platelet release reaction is a test used for diagnosis of dysfunction on platelet activation or platelet release. Peripheral blood smear was performed for differentiating whether the abnormal finding was caused by morphological defect of platelet if any abnormal finding was shown on platelet aggregation. The platelet functions were evaluated by comparing platelet functions between before and after administration of S-888711. Platelet counts were monitored from baseline to after administration of S-888711.

Pharmacokinetic Assessment:

plasma concentration, 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 ($AUC_{0-\tau}$), apparent total clearance (CL/F)

Safety Assessment:

Adverse events (AEs) reported from the time of informed consent through completion of the Post-treatment Period (or at drug withdrawal and/or early termination of assessment) 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. Any test results which were considered to be clinically significant by the investigator or subinvestigator were recorded as AEs. Portal vein thrombosis and portal blood flow were assessed. The following safety assessments were performed:

1. Incidence of AEs and adverse drug reactions (ADRs [ie, treatment-related AEs])
2. Incidence of bleeding-related AEs
3. Incidence of thrombus-related AEs

Statistical Methods:

Platelet Functions (platelet aggregation, platelet release reaction, peripheral blood smear):

For the platelet aggregation, summary statistics for the maximum aggregation rate and its change from baseline were calculated at each scheduled time point (baseline, one point between Days 9 and 14, and on Day 35) by agonist and its concentration. Shift table for the number of patients with or without the secondary aggregation was presented at each scheduled time point (before and after administration of the study drug). For the platelet release reaction, summary statistics for the expression rate of the platelet activation marker and its change from baseline were calculated at each scheduled time point (baseline, one point between Days 9 and 14, and on Day 35) by agonist and its concentration. For the peripheral blood smear, the finding in each category (normal or abnormal) was summarized

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at each scheduled time point. When both assessments of morphology and granules were normal, the patient finding was categorized as "normal". When either of assessments of morphology or granules was abnormal, the patient finding was categorized as "abnormal". Summary statistics for platelet count were calculated for confirming the increase in platelet by administration of S-888711.

Pharmacokinetic Analyses:
Individual plasma S-888711 concentrations were listed and summarized by nominal time. Summary statistics included number of non-missing observations (N), arithmetic mean (Mean), SD, coefficient of variation (CV%, calculated by SD/Mean × 100), geometric mean and coefficient of variation for geometric mean (CV% Geometric Mean), and median, minimum and maximum values at each sampling time. The CV% Geometric Mean was calculated according to a formula, CV% Geometric Mean = $[\exp(sd^2)-1]^{1/2} \times 100$, where sd was the standard deviation for natural logarithmic (ln) transformed data. Pharmacokinetic parameters except for T_{max} were summarized by treatment with N, Mean, SD, CV%, geometric mean, CV% Geometric Mean, median, minimum and maximum values. The T_{max} was summarized by treatment with N, Mean, SD, CV%, median, minimum and maximum values.

Safety Analyses:
1. Incidence of Treatment-emergent Adverse Events and Adverse Drug Reactions
Reported AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA, ver. 17.0) terms, and tabulated by system organ class and by preferred term. Treatment-emergent AEs (TEAEs), which were AEs reported after the initial dosing of study drug, were used for safety analyses.

- The number of patients experiencing TEAEs or ADRs and the number of TEAEs and ADRs were summarized to calculate the incidence and its 95% confidence interval. The incidence was defined as the percentage of patients experiencing TEAEs in the analysis population, and the confidence interval of the incidence was calculated based on the Clopper-Pearson method.
- The number of patients experiencing TEAEs or ADRs and the number of TEAEs and ADRs were summarized to calculate the incidence by system organ class and by preferred term. The number of patients in each category (severity) was summarized to calculate the incidence by system organ class and by preferred term.
- Bleeding-related or thrombus-related TEAEs were summarized to calculate the incidence by system organ class and by preferred term.

2. Laboratory tests and vital signs (blood pressure, pulse rate)

- Summary statistics of platelet and other laboratory tests were calculated for each time point. The change from the baseline was calculated and analyzed in a similar manner.

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- Summary statistics of blood pressure (systolic and diastolic) and pulse rate were calculated for each time point. The change from the baseline was calculated and analyzed in a similar manner.

3. Electrocardiogram

- The frequency and percentage of abnormal findings in electrocardiogram (ECG, 12-lead ECG) were calculated by time point.

4. Portal vein thrombosis and portal vein blood flow

- The number and proportion of patients experiencing portal vein thrombosis at least once after the initial administration of the study drug were calculated.
- The direction of portal vein blood flow (hepatofugal, hepatopetal, portal blood stasis) was assessed by Doppler ultrasonography.

Summary - Conclusions

Results on Platelet Functions:

- The mean platelet count increased from Day 5, reached the peak on Day 14, and then decreased. The mean platelet count was $7.93 \times 10^4/\mu L$ (the mean change in platelet count from baseline, $3.94 \times 10^4/\mu L$) on Day 14. The maximum platelet count throughout the study was $12.4 \times 10^4/\mu L$ (the change in platelet count from baseline, $8.4 \times 10^4/\mu L$) on Day 10; the increase in platelet count was within the range of notinfluencing the safety of patients.
- For platelet aggregation test using agonists (ADP and collagen), no abnormal result on platelet aggregation was found with either of agonists after administration of S-888711 and the maximum aggregation rate was almost the same before and after administration of S-888711.
- For platelet release test in the presence and absence of agonist (ADP), the expression rate of P-selectin in the presence of ADP was higher than that in the absence of ADP after administration of S-888711, indicating that the platelet release was found. No large change in platelet release was found before and after administration of S-888711.
- As a result of morphological assessment of platelet, no tendency of increasing in morphologically abnormal platelet was shown after administration of S-888711.

Pharmacokinetic Results:

- After administration of S-888711 for 5 days (after 5-day oral multiple dose), the geometric mean (CV% Geometric Mean) of pharmacokinetic parameters was 244 ng/mL (27.0%) for C_{max}, 4645 ng·hr/mL (30.2%) for $AUC_{0-\tau}$, and 0.646 L/hr (30.2%) for CL/F.

Safety Results:

- A total of 39 TEAEs occurred in all of the 8 patients (100.0%) in the safety analysis population. No ADRs were reported since all TEAEs were considered not related to the study drug by investigator or subinvestigator. No deaths, serious TEAEs, or TEAEs leading to withdrawal from the study treatment occurred in the study. Nine severe

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TEAEs occurred in 4 of 8 patients (50.0%): procedural hypertension (4 events), blood pressure increased (2 events), neutropenia (1 event), blood glucose increased (1 event), and hyperuricaemia (1 event). All of the events other than neutropenia were resolved without any treatment. Neutropenia occurred 26 days after completion of administration of the study drug. The event was monitored for 29 days but was considered no problem with follow-up within usual care after that by investigator or subinvestigator. Follow-up of the event was stopped with no resolution.

- No clinically significant changes were found for laboratory tests (except for platelet count), blood pressure, pulse rate, and ECG. No patients with thrombosis in the portal vein were found.

Conclusions:
S-888711 increased platelet count and had no effect on platelet functions at multiple doses of 3 mg of S-888711 in thrombocytopenic patients with chronic liver disease. No clinically significant concerns were found for the safety or the tolerability at multiple doses of 3 mg of S-888711 in thrombocytopenic patients with chronic liver disease.

Date of the Report: November 11, 2014