

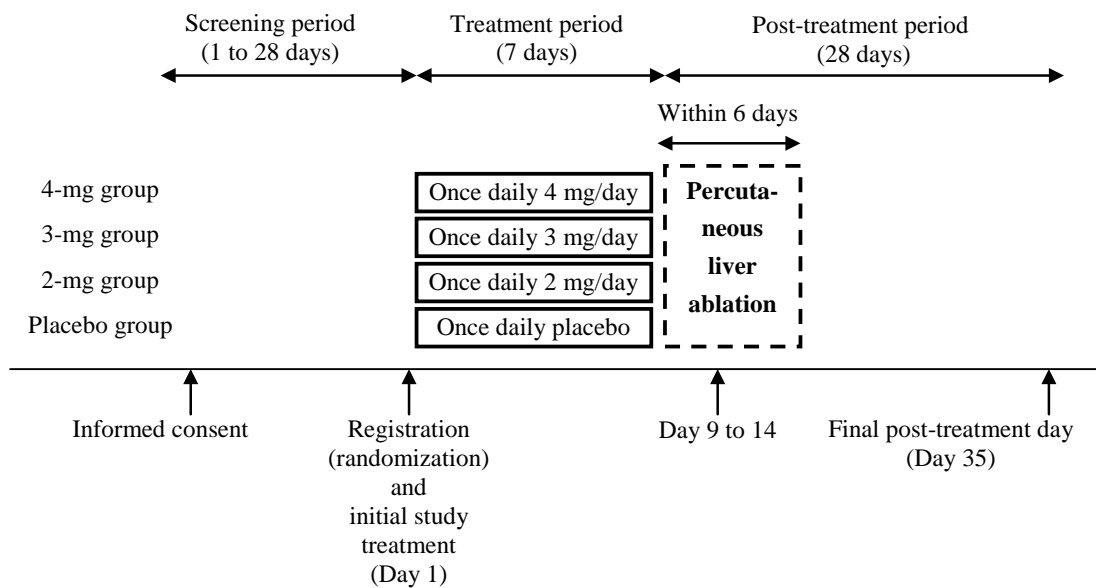
## 2. SYNOPSIS

English Translation (The original report was written in Japanese)

<b>Name of Sponsor:</b> Shionogi & Co., Ltd.	<b>Individual Study Table Referring to Part of the Dossier Volume:</b>  <b>Page:</b>	(For National Authority Use Only)
<b>Name of Finished Product:</b> To be determined		
<b>Name of Active Ingredient:</b>		
<b>Title of Study:</b> A phase 2b study of S-888711 in thrombocytopenic patients with chronic liver disease		
<b>Investigators:</b> [REDACTED] and other investigators (63 investigators in total)		
<b>Study Centers:</b> [REDACTED], and other study centers (63 study centers in total)		
<b>Publication:</b> None		
<b>Study Period:</b> Nine months between August [REDACTED], 2012 (date of the first administration of the study drug to the first patient) and April [REDACTED], 2013 (date of the final observation for the last patient)		
<b>Phase of Development:</b> 2		
<b>Study Objectives:</b> <b>Primary Objective:</b> To assess the optimal dose of S-888711 as a pretreatment for percutaneous liver ablation in thrombocytopenic patients with chronic liver disease based on the proportion of patients who required no platelet transfusion prior to percutaneous liver ablation. <b>Secondary Objectives:</b> To compare the efficacy, safety, and pharmacokinetics of S-888711 with those of placebo in thrombocytopenic patients with chronic liver disease as a pretreatment for percutaneous liver ablation based on the following variables: <ul style="list-style-type: none"><li>● Proportion of patients who required no platelet transfusion during the study</li><li>● Proportion of patients who have a platelet count of <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 maintenance of the increase in platelet count</li><li>● Time course of platelet count</li><li>● Adverse events (AEs) and adverse drug reactions (ADRs)</li><li>● Bleeding-related AEs</li><li>● Thrombosis-related AEs</li><li>● Assessment of portal vein thrombosis and portal blood flow</li><li>● Laboratory test, vital sign, and electrocardiogram</li><li>● Plasma S-888711 concentration</li></ul>		
<b>Methodology:</b> The multicenter, randomized, double-blind, placebo controlled study was conducted in thrombocytopenic patients with chronic liver disease.		

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The study consisted of 3 study periods: the Screening Period of 1 to 28 days, the Treatment Period of 7 days, and the Post-treatment Period of 28 days. Potential patients who provided written informed consent were screened to assess the eligibility in the Screening Period. Eligible patients were enrolled in the study and randomized to 1 of 4 treatment groups (Registration): the 2-mg group (S-888711 2 mg once daily), the 3-mg group (S-888711 3 mg once daily), the 4-mg group (S-888711 4 mg once daily), or the placebo group (placebo once daily). The randomization was performed in a ratio of 1:1:1:1 with a stochastic minimization method. Patients started receiving the assigned study drug once daily (Day 1) and received the study drug for 7 days (Treatment Period). After the final study treatment, patients underwent specified post-treatment study assessments (Post-treatment Period). Percutaneous liver ablation was performed between Days 9 and 14. The need for platelet transfusion was determined after completion of the study assessment on Day 8 and immediately before percutaneous liver ablation.



**Number of Patients:**

Planned target sample size: 60 patients

Enrolled patients: 61 patients

Analysis population is follows:

- Efficacy analysis population: full analysis set (FAS), 61 patients (15 in the 2-mg group, 16 in the 3-mg group, 15 in the 4-mg group, and 15 in the placebo group); per protocol set (PPS), 52 patients (15 in the 2-mg group, 12 in the 3-mg group, 13 in the 4-mg

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group, and 12 in the placebo group) ● Safety analysis population: 61 patients (15 in the 2-mg group, 16 in the 3-mg group, 15 in the 4-mg group, and 15 in the placebo group)		
<b>Diagnosis and Main Eligibility Criteria:</b>		
<b>Inclusion Criteria:</b>		
<ol style="list-style-type: none"> <li>1. Patients who were able to understand the study and comply with all study procedures, and willing to provide written informed consent prior to screening</li> <li>2. Male or female patients aged 20 years or older at the time of signing the informed consent form</li> <li>3. Thrombocytopenic patients due to chronic liver disease</li> <li>4. Patients with a platelet count of &lt; 50,000/<math>\mu</math>L at screening</li> <li>5. Patients who were undergoing percutaneous liver ablation for the primary hepatic cancer</li> <li>6. Patients with the Eastern Cooperative Oncology Group (ECOG) performance status grade 0 or 1</li> <li>7. Patients who were able to stay in the hospital between 5 and 14 days after the initiation of the study treatment</li> <li>8. Only for male patients who were sterile or who agreed to use an appropriate method of contraception (including use of a condom with spermicide) from enrollment to completion of the post-treatment assessment</li> <li>9. Patients who agreed to use barrier contraception (including condom, diaphragm, and cervical cap) with spermicide or to use highly-effective contraception (including contraceptive implant, injectable contraceptive, combination oral contraceptive, intrauterine contraceptive device, and vasectomized partner) from enrollment to completion of post-treatment assessment except for female patients who were postmenopausal or who were surgically sterile</li> </ol>		
<b>Exclusion Criteria:</b>		
<ol style="list-style-type: none"> <li>1. Patients who had undergone splenectomy</li> <li>2. Patients with any of the following diseases:                         <ul style="list-style-type: none"> <li>– hematopoietic tumor</li> <li>– aplastic anemia</li> <li>– myelodysplastic syndrome</li> <li>– myelofibrosis</li> <li>– congenital thrombocytopenia</li> <li>– drug-induced thrombocytopenia</li> <li>– generalized infection requiring treatment except for viral liver disease</li> <li>– immune thrombocytopenia</li> </ul> </li> <li>3. Patients who had undergone liver transplantation</li> <li>4. Patients in whom performing percutaneous liver ablation is considered to be difficult</li> </ol>		

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<ol style="list-style-type: none"> <li>5. Patients with any of the followings at the screening examination:                             <ul style="list-style-type: none"> <li>– Child-Pugh class C liver disorder</li> <li>– uncontrollable hepatic encephalopathy with drugs</li> <li>– uncontrollable ascites with drugs</li> </ul> </li> <li>6. Patients with malignant tumor other than primary hepatic cancer or with a history of malignant tumor other than primary hepatic cancer within 5 years</li> <li>7. Patients with extrahepatic lesions of primary hepatic cancer</li> <li>8. Patients with past or existing thrombosis (eg, cerebral infarction, myocardial infarction, angina pectoris, pulmonary thromboembolism, deep vein thrombosis, disseminated intravascular coagulation syndrome)</li> <li>9. Patients with portal vein thrombosis based on imaging evaluation within 28 days prior to enrollment or with a history of portal vein thrombosis</li> <li>10. Patients complicated by or with a history of any of the following diseases:                             <ul style="list-style-type: none"> <li>– congenital thrombotic disease (eg, antithrombin deficiency, protein C deficiency, protein S deficiency, coagulation factor [Factor V Leiden] mutation)</li> <li>– acquired thrombotic disease (eg, antiphospholipid antibody syndrome, paroxysmal nocturnal hemoglobinuria, hyperhomocysteinemia, increased factor VIII)</li> <li>– Budd-Chiari syndrome</li> </ul> </li> <li>11. Patients for whom no hepatopetal portal blood flow was demonstrated by Doppler ultrasonography within 28 days prior to enrollment</li> <li>12. Patients who required antithrombotic drugs within 7 days prior to enrollment and thereafter</li> <li>13. Patients with untreated gastroesophageal varices from which are bleeding or which are found to require treatment based on upper gastrointestinal endoscopy within 6 months prior to enrollment</li> <li>14. Patients with past or existing disease associated with a risk of bleeding (eg, coagulation factor deficiency, von Willebrand factor deficiency)</li> <li>15. Patients with Grade 2 or more severe bleeding at the screening according to the World Health Organization (WHO) Bleeding scale</li> <li>16. Patients who received any of the following drugs or therapies within 90 days prior to enrollment:                             <ul style="list-style-type: none"> <li>– anticancer drugs except for transcatheter arterial chemoembolization (TACE) and lipiodolization</li> <li>– interferon preparations</li> <li>– radiation therapy</li> <li>– thoracotomy</li> <li>– laparotomy</li> <li>– partial splenic embolization</li> <li>– hepatectomy</li> <li>– transcatheter arterial infusion chemotherapy (TAI) except for lipiodolization</li> </ul> </li> </ol>		

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17. Patients who received any of the following drugs or therapies for treatment of hepatic cancer within 14 days prior to enrollment: <ul style="list-style-type: none"> <li>– percutaneous liver ablation</li> <li>– percutaneous ethanol injection therapy</li> <li>– TACE</li> <li>– lipiodolization with anticancer drugs (ie, Lip-TAI)</li> <li>– transcatheter arterial embolization (TAE) excluding Lipiodol infusion for marking</li> </ul> 18. Patients who received blood transfusions (except for red blood cell products and albumin preparations) within 14 days prior to enrollment 19. Patients receiving TPO receptor agonists 20. Female patients who were pregnant, possibly pregnant, or lactating 21. Patients who received other investigational products within 90 days prior to enrollment 22. Patients who were considered ineligible for the study by the investigator or subinvestigator for any other reasons		
<b>Test Drug, Dose and Mode of Administration, Lot Number:</b> <b>Test Drug (S-888711):</b> S-888711 1-mg tablet  <b>Dose:</b> <ul style="list-style-type: none"> <li>● For the 2-mg group, two 1-mg tablets of S-888711 and two placebo tablets</li> <li>● For the 3-mg group, three 1-mg tablets of S-888711 and one placebo tablet</li> <li>● For the 4-mg group, four 1-mg tablets of S-888711</li> </ul> <b>Method of Administration:</b> Once-daily oral dose of S-888711 1-mg tablets and placebo tablet(s)  <b>Lot Number (Manufacturing Number):</b> S-888711 1-mg tablet, ██████████		
<b>Duration of Administration:</b> Seven days.		
<b>Control Drug, Dose and Mode of Administration, Lot Number:</b> <b>Control Drug:</b> S-888711 placebo tablet  <b>Dose:</b> For the placebo group, four placebo tablets  <b>Method of Administration:</b> Once-daily oral dose of placebo tablets		

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<b>Lot Number (Manufacturing Number):</b> S-888711 placebo tablet, [REDACTED]		
<b>Criteria for Evaluation:</b> <b>Efficacy Assessment:</b> The following efficacy assessments were performed based on the results on measurements of platelet count and platelet transfusion: Primary endpoint: <ul style="list-style-type: none"> <li>● Proportion of patients who required no platelet transfusion prior to percutaneous liver ablation</li> </ul> Secondary endpoints: <ul style="list-style-type: none"> <li>● Proportion of patients who required no platelet transfusion, frequency of platelet transfusion, and dose (units) of platelets transfused during the study</li> <li>● Proportion of responders (ie, platelet count of <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 maintenance of the increase in platelet count</li> <li>● Time course of platelet count</li> </ul> <b>Pharmacokinetic Assessment:</b> Plasma concentration and pharmacokinetic parameters of S-888711  <b>Safety Assessment:</b> AEs reported during 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: <ol style="list-style-type: none"> <li>1. Incidence of AEs and ADRs</li> <li>2. Incidence of bleeding-related AEs</li> <li>3. Incidence of thrombus-related AEs</li> </ol>		
<b>Statistical Methods:</b> <b>Efficacy Analyses:</b> The FAS was the primary population for efficacy analyses. The PPS was used for sensitivity analyses of the primary endpoint.  <b>Primary Efficacy Endpoint:</b> <ul style="list-style-type: none"> <li>● The proportion of patients who required no platelet transfusion prior to percutaneous liver ablation was defined by the proportion of patients who received no platelet transfusion prior to the initial percutaneous liver ablation in respective analysis population, and calculated in each treatment group and compared between each of the</li> </ul>		

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S-888711 and placebo groups with the Cochran-Mantel-Haenszel test with consideration of stratification factors.		
<b>Secondary Efficacy Endpoints</b>		
<ol style="list-style-type: none"> <li>1. The proportion of patients who required no platelet transfusion, the frequency of platelet transfusion, and the dose (unit) transfused during the study                     <ul style="list-style-type: none"> <li>● The proportion was calculated in each treatment group, and was compared between each of the S-888711 dose and placebo groups with the Cochran-Mantel-Haenszel test with consideration of stratification factors.</li> <li>● Summary statistics of the number and dose (unit) of platelet transfusion during the study were calculated for patients who received platelet transfusion.</li> </ul> </li> <li>2. Responder rate                     <ul style="list-style-type: none"> <li>● The number and proportion of patients who met the criteria for the responder at least once during the study except after platelet transfusion was calculated in each treatment group. The responder rate was compared between each of the S-888711 dose and placebo groups with Cochran-Mantel-Haenszel test with consideration of stratification factors.</li> <li>● The number and proportions of responders except after platelet transfusion were calculated at each scheduled time point.</li> </ul> </li> <li>3. Duration of the maintenance of the increase in platelet count                     <ul style="list-style-type: none"> <li>● Summary statistics of the number of days during which increased platelet count was maintained were calculated in each treatment group with or without platelet transfusion. The days were compared between each of the S-888711 dose and placebo groups with analysis of covariance. Child-Pugh class, platelet count from baseline, and observation period of platelet count were included as covariates.</li> </ul> </li> <li>4. Time course of platelet count                     <ul style="list-style-type: none"> <li>● Summary statistics of platelet count and the change in platelet count from baseline were calculated at each scheduled time point in each treatment group. Summary statistics of the maximum platelet count and the maximum change in the platelet count were calculated for each subject in each treatment group.</li> </ul> </li> </ol>		
<b>Pharmacokinetic Analyses</b>		
For the plasma concentration of S-888711, arithmetic mean, standard deviation, coefficient of variation (CV%), geometric mean, coefficient of variation of geometric mean (GeoCV%), minimum, median and maximum were calculated at each time point for each dose group. Terminal elimination half-life ( $t_{1/2,z}$ [hr]) was calculated using a non-compartmental method.		
<b>Safety Analyses:</b>		
Reported AEs were coded using the Medical Dictionary for Regulatory Activities		

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(MedDRA, ver. 15.1) terms, and tabulated by system organ class and by preferred term. Treatment-emergent adverse events (TEAEs), which were AEs reported after the initial dosing of randomized study drug were , used for safety analyses.		
<p>1. Incidence of TEAEs and ADRs</p> <ul style="list-style-type: none"> <li>● 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.</li> <li>● 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, outcome, time of onset, and causal relationship with the test drug) was also summarized to calculate the incidence by system organ class and by preferred term. ADRs were summarized in a similar manner (excluding causal relationship with the study drug). The number of events was also calculated in each category by severity.</li> <li>● Bleeding-related or thrombus-related TEAEs were summarized to calculate the incidence by system organ class and by preferred term.</li> </ul> <p>2. Laboratory tests and vital signs (blood pressure, pulse rate)</p> <ul style="list-style-type: none"> <li>● Summary statistics were calculated for each time point. The change from the baseline was calculated and analyzed in a similar manner. Regarding the laboratory values included in CTCAE Term (Version 4.0), the proportions of patients with Grade 2 or more in laboratory test by time point, and at least once during the study, was calculated.</li> </ul> <p>3. Electrocardiogram</p> <ul style="list-style-type: none"> <li>● The frequency and percentage of abnormal findings in electrocardiogram (12-lead electrocardiography) were calculated by time point.</li> </ul> <p>4. Portal vein thrombosis and portal vein blood flow</p> <ul style="list-style-type: none"> <li>● The number and proportion of patients experiencing portal vein thrombosis after the first percutaneous liver ablation confirmed in diagnostic imaging were calculated.</li> <li>● The frequency of patients assessed by Doppler ultrasonography and classified in each category for direction of portal vein blood flow (hepatofugal, hepatopetal, portal blood stasis) after percutaneous liver ablation was calculated.</li> </ul>		
<p><b>Summary - Conclusions</b></p> <p><b>Efficacy Results:</b></p> <ul style="list-style-type: none"> <li>● In the FAS, the proportion of patients who required no platelet transfusion prior to percutaneous liver ablation was significantly higher in the S-888711 treatment groups than in placebo group (2-mg group P=0.0006, 3-mg group P=0.0014, 4-mg group P=0.0002): 80.0% (12/15) in the 2-mg group, 81.3% (13/16) in the 3-mg group, 93.3%</li> </ul>		



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<p>(14/15) in the 4-mg group, and 20.0% (3/15) in the placebo group. The proportion increased with increasing dose of S-888711, but no significant difference was found between S-888711 groups.</p> <ul style="list-style-type: none"> <li>• The proportion of patients who received no platelet transfusion during study was significantly higher in the S-888711 treatment groups than in the placebo group (2-mg group P=0.0006, 3-mg group P=0.0014, 4-mg group P=0.0064): 80.0% (12/15) in the 2-mg group, 81.3% (13/16) in the 3-mg group, 73.3% (11/15) in the 4-mg group, and 20.0% (3/15) in the placebo group.</li> <li>• The proportion of responders was greater in the S-888711 groups than in the placebo group during the study. The 4-mg group showed a higher proportion of the responders relative to 2- or 3-mg group, but not significant.: 66.7% (10/15) in the 2-mg group, 68.8% (11/16) in the 3-mg group, 80.0% (12/15) in the 4-mg group, and 6.7% (1/15) in the placebo group. The proportion of responders exceeded 50% on Day 12 and Day 14 in the 2-mg group, Day 10 to Day 21 in the 3-mg group, Day 8 to Day 21 in the 4-mg group. The duration of the proportion of responders exceeding 50% was longer with increasing dose of S-888711. There was no time point when the proportion of responders exceeded 50% in the placebo group.</li> <li>• The number of days (adjusted mean) with the platelet count <math>\geq 50,000/\mu\text{L}</math> was significantly larger in S-888711 groups without platelet transfusion (21.22-24.23 days) than in the placebo group with platelet transfusion (4.33 days)(P&lt;0.0001). The days (adjusted mean) with the platelet count <math>\geq 70,000/\mu\text{L}</math> were significantly larger in the 3-mg group and the 4-mg group without platelet transfusion than in the placebo group with platelet transfusion (2-mg group P=0.1175, 3-mg group P=0.0043, 4-mg group P&lt;0.0001): 4.28 days in the 2-mg group, 7.74 days in the 3-mg group, 11.45 days in the 4-mg group, and 0.69 days in the placebo group. The days (adjusted mean) with the platelet count meeting the criteria for responder were significantly larger in the S-888711 groups without platelet transfusion than in the placebo group with platelet transfusion (2-mg group P=0.0031, 3-mg group P=0.0001, 4-mg group P&lt;0.0001): 8.36 days in the 2-mg group, 11.59 days in the 3-mg group, 13.88 days in the 4-mg group, and 0.63 days in the placebo group.</li> <li>• The mean maximum platelet count in patients without platelet transfusion increased with increasing dose of S-888711: <math>7.38 \times 10^4/\mu\text{L}</math> in the 2-mg group, <math>9.48 \times 10^4/\mu\text{L}</math> in the 3-mg group, <math>10.38 \times 10^4/\mu\text{L}</math> in the 4-mg group, and <math>5.90 \times 10^4/\mu\text{L}</math> in the placebo group. The maximum increase in platelet count also increased with increasing dose of S-888711. The maximum platelet count was <math>19.5 \times 10^4/\mu\text{L}</math> in 1 patient in the 3-mg group, and none of the patients achieved platelet counts exceeding <math>20 \times 10^4/\mu\text{L}</math>. The mean (minimum-maximum) time to reach the maximum platelet count ranged from 13.2 to 13.5 days (8 to 21 days) with no significant difference between dose groups of S-888711.</li> <li>• The mean maximum platelet count in patients with platelet transfusion in each group</li> </ul>		

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<p>was similar with in the placebo group without platelet transfusion (<math>5.90 \times 10^4/\mu\text{L}</math>): <math>5.73 \times 10^4/\mu\text{L}</math> in the 2-mg group, <math>6.10 \times 10^4/\mu\text{L}</math> in the 3-mg group, <math>6.23 \times 10^4/\mu\text{L}</math> in the 4-mg group, and <math>5.64 \times 10^4/\mu\text{L}</math> in the placebo group.</p> <ul style="list-style-type: none"> <li>• The maximum platelet count in the withdrawals from study treatment who met the criteria for increased platelet count (ie, platelet count <math>\geq 50,000/\mu\text{L}</math> with an increase of <math>\geq 20,000/\mu\text{L}</math> from baseline) was <math>9.3 \times 10^4/\mu\text{L}</math> in the 2-mg group, <math>12.7 \times 10^4/\mu\text{L}</math> in the 3-mg group, and <math>13.4 \times 10^4/\mu\text{L}</math> in the 4-mg group, indicating no excessive increase in platelet count.</li> <li>• The plasma concentration of S-888711 increased in a dose-dependent manner. The elimination half-life (<math>t_{1/2,z}</math>) was relatively constant regardless of dose.</li> </ul>		
<p><b>Safety Results:</b></p> <ul style="list-style-type: none"> <li>• A total of 469 TEAEs occurred in 60 of 61 patients (98.4%) in the safety analysis population: 122 TEAEs in 15 of 15 patients (100%) in the 2-mg group, 115 TEAEs in 16 of 16 patients (100%) in the 3-mg group, 105 TEAEs in 14 of 15 patients (93.3%) in the 4-mg group, and 127 TEAEs in 15 of 15 patients (100%) in the placebo group.</li> <li>• Serious TEAEs (SAEs) were reported in 3 patients (malignant hepatic neoplasm/upper gastrointestinal hemorrhage, malignant hepatic neoplasm, hemorrhagic erosive gastritis) in the 2-mg group, 1 patient (sick sinus syndrome/incision site hemorrhage) in the 3-mg group, and 1 patient (patella fracture) in the placebo group. The patient (patient ID: ██████████) with upper gastrointestinal hemorrhage in the 2-mg group died. All SAEs were considered not related to the study drug by the investigator. No TEAEs leading to withdrawal from the study treatment occurred.</li> <li>• Significant TEAEs occurred in 9 of 15 patients (60.0%) in the 2-mg group, 10 of 16 patients (62.5%) in the 3-mg group, 7 of 15 patients (46.7%) in the 4-mg group, and 10 of 15 patients (66.7%) in the placebo group. None of the significant TEAEs indicated dose-related increase in the incidence.</li> <li>• TEAEs occurring at least 20% more frequently than placebo in any of the S-888711 groups were postoperative fever, AST increased, ALT increased, and blood bilirubin increased. No incidence of the AEs increased with increasing dose of S-888711.</li> <li>• Thrombus-related TEAEs were reported in 1 of 15 patients (6.7%) in the 2-mg group, 2 of 15 patients (13.3%) in the 4-mg group, 1 of 15 patients (6.7%) in the placebo group and no incidence of the TEAEs increased with increasing dose of S-888711. The TEAEs included 2 events of mesenteric vein thrombosis in 2 patients (1 patient each in the 4-mg group and the placebo group), 2 events of portal vein thrombosis in 2 patients (1 patient each in the 2-mg group and the 4-mg group), and 1 event of hepatic infarction in 1 patient (2-mg group). These events were found in diagnostic images (CT or MRI) between 3 and 10 days after percutaneous liver ablation to examine the potential for the development of portal vein thrombosis. These events were moderate or severe, but not serious.</li> <li>• Bleeding-related TEAEs were reported in 3 of 15 patients (20.0%) in the 2-mg group, 5</li> </ul>		

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<p>of 16 patients (31.3%) in the 3-mg group, 4 of 15 patients (26.7%) in the 4-mg group, and 8 of 15 patients (53.3%) in the placebo group. No incidence of the AEs increased with increasing dose of S-888711.</p> <ul style="list-style-type: none"> <li>● Sixteen treatment related-events were reported in 11 of 61 patients (18.0%) during the study: 10 events in 5 of 15 patients (33.3%) in the 2-mg group, 3 events in 3 of 16 patients (18.8%) in the 3-mg group, and 3 events in 3 of 15 patients (20.0%) in the 4-mg group. All events occurred only once and no incidence of the ADRs increased with increasing dose of S-888711.</li> <li>● Frequent AEs found in laboratory tests were AST increased, ALT increased, and blood bilirubin increased. Most of the changes of AST/ALT increased were within three times the upper limit of reference range. Blood bilirubin increased was not found in the patients with AST/ALT increased were beyond three times the upper limit of reference range.</li> <li>● No clinically significant findings were noted for vital signs or electrocardiogram.</li> </ul>		
<p><b>Conclusions:</b></p> <ul style="list-style-type: none"> <li>● Efficacy of S-888711 as a pretreatment for percutaneous liver ablation was found with oral administration at 2, 3 or 4 mg once daily for up to 7 days in thrombocytopenic patients with chronic liver disease. Proportion of patients who required no platelet transfusion was higher in S-888711 treatment groups than in the placebo group. Dose-related increase in the maximum platelet count and duration of the maintenance of the increase in platelet count was noted.</li> <li>● No trend of dose-related increase was noted for the incidence of TEAEs 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.</li> <li>● Oral administration of S-888711 at 3 mg once daily was considered optimal as a pretreatment for percutaneous liver ablation in thrombocytopenic patients with chronic liver disease, showing sufficient increase in platelet count and safety in patients as a medication alternative to platelet transfusion.</li> </ul>		
<p><b>Date of the Report:</b> 11 November 2013</p>		
<p><b>Date of Amendment 1:</b> 29 October 2014</p>		
<p><b>Date of Amendment 2:</b> 16 Nov 2017</p>		