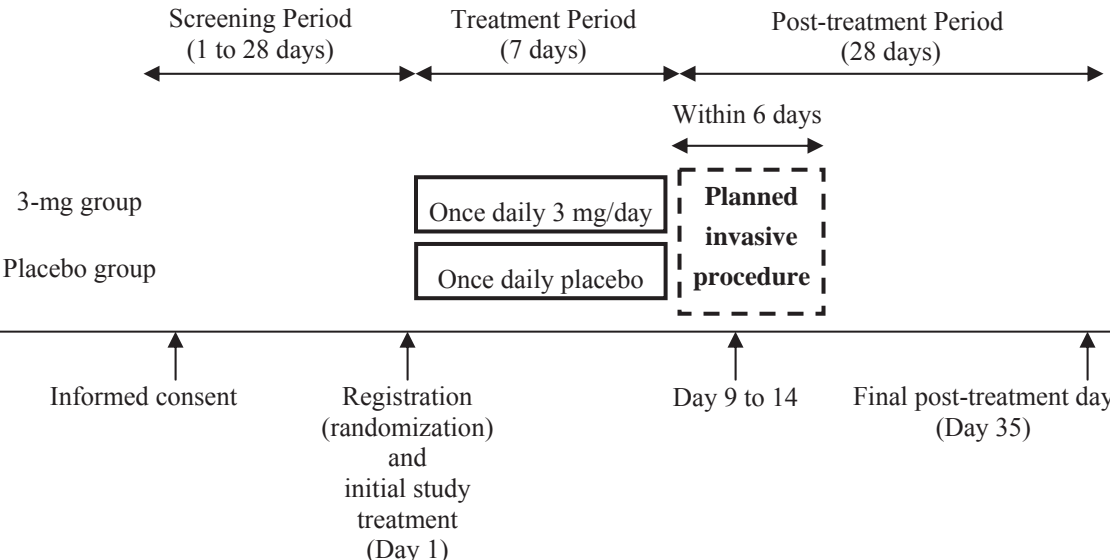## 2. SYNOPSIS

English Translation (The original report was written in Japanese)

Name of Sponsor: Shionogi & Co., Ltd.	Individual Study Table Referring to Part of the Dossier Volume:	(For National Authority Use Only)
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Title of Study: A phase 3 study of S-888711 in thrombocytopenic patients with chronic liver disease

Investigators: ███████████████████ ███████████████ and other investigators (81 investigators in total)

Study Centers: ███████████████████ ████, and other medical institutions (81 medical institutions in total)

Publication: None

Study Period: 8 months
- Date of the first administration of the study drug to the first patient: October ██, 2013
- Date of the final observation for the last patient: May ██, 2014

Phase of Development: 3

Study Objectives:

Primary Objective:

To evaluate the superiority of S-888711 over placebo in efficacy in thrombocytopenic patients with chronic liver disease receiving 3 mg of S-888711 as a pretreatment of invasive procedures based on the proportion of patients who required no platelet transfusion prior to invasive procedures.

Secondary Objectives:

To compare the efficacy, safety, and pharmacokinetics of S-888711 with those of placebo in thrombocytopenic patients with chronic liver disease receiving 3 mg of S-888711 as a pretreatment of invasive procedures based on the following variables:
- Proportion of patients who required no platelet transfusion during the study
- Proportion of patients who had a platelet count of $\geq 50,000/\mu L$ with an increase of $\geq 20,000/\mu L$ from baseline
- Duration of increase in platelet count (the number of days during which increased platelet count was maintained as $\geq 50,000/\mu L$, $\geq 70,000/\mu L$, or $\geq 50,000/\mu L$ with an increase of $\geq 20,000/\mu L$ from baseline)
- Time course of platelet count
- Adverse events (AEs) and adverse drug reactions (ADRs)
- Bleeding-related AEs

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- Thrombosis-related AEs
- Assessment of portal vein thrombosis and portal blood flow
- Laboratory test, vital sign, and electrocardiogram
- Plasma S-888711 concentration

Methodology:

The multicenter, randomized, double-blind, parallel-group, placebo-controlled study was conducted in 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 provided written informed consent were screened to assess the eligibility in the Screening Period. Eligible patients were enrolled in the study and randomized to either of the treatment groups (registration day): 3 mg of S-888711 (the 3-mg group) or placebo (the placebo group). The randomization was performed in a ratio of 1:1 with stochastic minimization method. Patients started receiving the assigned study drug once daily on 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). The planned invasive procedure was performed between Days 9 and 14. Determination of need for platelet transfusion was performed after Day 8 and immediately before performing the invasive procedure (ie, within 2 days before the day of the invasive procedure).

Number of Patients:

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Planned target sample size: 90 patients (45 per group)

Enrolled patients: 97 patients

Analysis population is as follows: 96 patients (48 in the 3-mg group and 48 in the placebo group)

- Efficacy analysis population: full analysis set (FAS), 96 patients (48 in the 3-mg group and 48 in the placebo group); per protocol set (PPS), 90 patients (46 in the 3-mg group and 44 in the placebo group)
- Safety analysis population: 96 patients (48 in the 3-mg group and 48 in the placebo group)

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 who were undergoing invasive procedures fulfilling the following criteria:
   - procedures were to be completed between 9 and 14 days after the initiation of the study treatment
   - procedures which were not involving any of the following situations: laparotomy, thoracotomy, craniotomy, open-heart surgery, organ resection, or partial organ resection (except for procedures comparable to tissue resection)

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 the day before the invasive procedure and the 14th day after the initiation of the study treatment

8. Only for male patients, 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

9. Only for female patients, 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 the post-treatment assessment, except for female patients who were postmenopausal or who were

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surgically sterile

Exclusion Criteria:

1. 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

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 past or present thrombosis (eg, cerebral infarction, myocardial infarction, angina pectoris, pulmonary thromboembolism, deep vein thrombosis, disseminated intravascular coagulation syndrome)

8. Patients with a complication 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

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9. Patients with portal vein thrombosis based on imaging evaluation within 28 days prior to enrollment or with a history of portal vein thrombosis

10. Patients for whom no hepatopetal portal blood flow was demonstrated by Doppler ultrasonography within 28 days prior to enrollment

11. Patients who required antithrombotic drugs within 14 days prior to enrollment and thereafter

12. Patients with untreated gastroesophageal varices which were bleeding or found to require treatment based on upper gastrointestinal endoscopy within 180 days prior to enrollment (except for patients in whom the primary invasive procedure were for the treatment of gastroesophageal varices)

13. Patients with a complication or with a history of 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 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

16. 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

17. Patients who had received any invasive procedures (except for the treatment of gastroesophageal varices) within 14 days prior to enrollment

18. Patients who had received blood transfusions (except for red blood cell preparations and albumin preparations) within 14 days prior to enrollment

19. Patients who previously received thrombopoietin (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

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subinvestigator for any other reasons

Test Drug, Dose and Mode of Administration, Lot Number:
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, ▮▮▮▮▮▮▮▮
Duration of Administration: Seven days.

Control Drug, Dose and Mode of Administration, Lot Number:
Control Drug:
S-888711 placebo tablet
Dose:
For the placebo group, 1 placebo tablet
Method of Administration:
Once-daily oral dose
Lot Number (Manufacturing Number):
S-888711 placebo tablet, ▮▮▮▮▮▮▮▮
Criteria for Evaluation:
Efficacy Assessment:

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

Primary endpoint:

- Proportion of patients who required no platelet transfusion prior to the primary invasive procedure

Secondary endpoints:

- Proportion of patients who required no platelet transfusion during the study, the frequency of platelets transfusion, and the dose (unit) transfused during the study
- Responder rate (defined as the proportion of patients for whom the platelet count reached $\geq 50,000/\mu L$ with an increase of $\geq 20,000/\mu L$ from baseline)
- Duration of the maintenance of the increase in platelet count, which is defined

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as follows:

- The number of days during which platelet count was maintained as $\geq$ 50,000/μL
- The number of days during which platelet count was maintained as $\geq$ 70,000/μL
- The number of days during which platelet count was maintained as $\geq$ 50,000/μL with an increase of $\geq$ 20,000/μL from baseline
- Time course of platelet count

Pharmacokinetic Assessment:

Plasma concentration of S-888711

Safety Assessment:

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

Statistical Methods:

Efficacy Analyses:

The FAS was the primary population for efficacy analyses. The PPS was used for sensitivity analyses of the primary endpoint.

Primary Efficacy Endpoint:

- As a primary analysis, the proportion of patients who required no platelet transfusion prior to invasive procedure was calculated in each treatment group and was compared between the 3-mg group and the placebo group with Cochran-Mantel-Haenszel test with consideration of stratification factors.
- As a secondary analysis, the proportion of patients who required no platelet transfusion prior to invasive procedure was calculated by each stratification factor, ie, platelet count at screening and planned primary invasive procedure in each treatment group. Also, the proportion of patients who required no platelet transfusion prior to invasive procedure was calculated by performed invasive primary invasive procedure, platelet count at baseline, and severity of liver

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disorder in each treatment group, and each relative risk of the 3-mg group compared with the placebo group and its 95% confidence interval were calculated. The interaction between each subgroup and the treatment group was tested with Breslow-Day test.

Secondary Efficacy Endpoints

1. Proportion of patients who required no platelet transfusion, the frequency of platelet transfusion, and the dose (unit) transfused during the study

   ● The proportion was calculated in each treatment group, and was compared between the 3-mg group and the placebo group with the Cochran-Mantel-Haenszel test with consideration of stratification factors.

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

2. Responder rate

   ● 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 the 3-mg group and the placebo group with Cochran-Mantel-Haenszel test with consideration of stratification factors. The number and proportions of responders except after platelet transfusion were calculated at each scheduled time point.

   ● The number and proportion of patients who met the criteria for the responder at least once during the study including data after platelet transfusion, was calculated in each treatment group. In the calculation, the patient was defined as non-responder if their platelet count met the responder criteria only after platelet transfusion. The responder rate was compared between the 3-mg group and the placebo group with Cochran-Mantel-Haenszel test with consideration of stratification factors. The number and proportions of responders except after platelet transfusion were calculated at each scheduled time point.

3. Duration of the maintenance of the increase in platelet count

   ● Summary statistics of the number of days during which increased platelet count was maintained as $\geq 50,000/\mu L$, $\geq 70,000/\mu L$, or $\geq 50,000/\mu L$ with an increase of $\geq 20,000/\mu L$ from baseline were calculated in each treatment group with or without platelet transfusion. The days were compared by using analysis of covariance between the 3-mg group and the placebo group without platelet transfusion and between the 3-mg group without platelet transfusion and the placebo group with platelet transfusion. The analysis of covariance model included the group consisting of combination of treatment and platelet transfusion as fixed effect, and planned invasive procedure, platelet count at

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baseline, and observation period of platelet count as covariates.

4. Time course of platelet count

- Summary statistics of platelet count and the change in platelet count from baseline were calculated at each scheduled time point in each treatment group. For patients who received platelet transfusion, summary statistics of the change in platelet count from baseline (defined as the value measured just before the first platelet transfusion) were calculated for measurements on the day of the first platelet transfusion, the next day of the first platelet transfusion, and the day after the next day of the first platelet transfusion. The time course of median platelet count with interquartile range (25th to 75th percentiles) and the mean change from baseline were depicted. Summary statistics of the maximum platelet count and the maximum change in the platelet count were calculated for each subject in each treatment group. For patients who required no platelet transfusion, the time point at which each patient showed the maximum platelet count was summarized in each treatment group.

Pharmacokinetic Analyses

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. Time profiles for individual and mean plasma concentrations were graphically presented.

Safety Analyses:

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. Adverse events reported after the initial dosing of study drug were considered treatment-emergent adverse events (TEAEs). TEAEs were used for safety analysis.

1. Incidence of TEAEs and ADRs

- 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 and outcome) was also summarized to calculate the incidence by system organ class and by preferred term. The number of events was also calculated in each category by severity. ADRs were summarized in a similar manner.

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- For patients who underwent invasive procedure, the number of patients experiencing TEAEs and the incidence was summarized by timing of the primary invasive procedure. The number of patients experiencing TEAEs 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 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 Common Terminology Criteria for Adverse Events (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, were calculated.

3. Electrocardiogram

- The number and proportion of patients who were considered abnormal for ECG finding were calculated at each scheduled time point.

4. Portal vein thrombosis and portal vein blood flow

- For patients who had results of imaging diagnosis to assess portal vein thrombosis, the number and proportion of patients experiencing portal vein thrombosis confirmed in diagnostic imaging were calculated for each time point.
- For patients who had results of Doppler ultrasonography, 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) was calculated for each time point.

Summary - Conclusions

Efficacy Results:

- In the FAS, the proportion of patients who required no platelet transfusion prior to the primary invasive procedure (hereafter referred to as the proportion of patients who required no preoperative platelet transfusion) was 79.2% (38/48 patients) in the 3-mg group and 12.5% (6/48 patients) in the placebo group; the proportion in the 3-mg group was significantly greater than that in the placebo group (P <0.0001).
- The proportion of patients who received no platelet transfusion during the study was 79.2% (38/48 patients) in the 3-mg group and 12.5% (6/48 patients) in the placebo group; the proportion in the 3-mg group was significantly greater than

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that in the placebo group (P <0.0001).

- The proportion of responders was 77.1% (37/48 patients) in the 3-mg group and 6.3% (3/48 patients) in the placebo group; the proportion in the 3-mg group was significantly greater than that in the placebo group (P <0.0001). The proportion of responders exceeded 50% on Day 10 to 17 in the 3-mg group, and reached the highest on Day 14. There was no time point when the proportion of responders exceeded 50% in the placebo group. The proportion of responders in the 3-mg group was significantly greater than that in the placebo group from Day 7 to 21.

- The days (adjusted mean) with the platelet count $\geq 50,000/\mu L$ were significantly longer in the 3-mg group without platelet transfusion (21.09 days) than in the placebo group with platelet transfusion (6.05 days) (P<0.0001). The days (adjusted mean) with the platelet count $\geq 70,000/\mu L$ were significantly longer in the 3-mg group without platelet transfusion (8.17 days) than in the placebo group with platelet transfusion (0.56 days) (P<0.0001). The days (adjusted mean) with the platelet count meeting the criteria for responder were significantly longer in the 3-mg group without platelet transfusion (12.39 days) than in the placebo group with platelet transfusion (0.74 days) (P<0.0001).

- The mean (range) maximum platelet count in patients without platelet transfusion was 9.02 (5.9 to 14.5) $\times 10^4/\mu L$ in the 3-mg group. The mean (range) time to reach the maximum platelet count was 13.4 days (6 to 28 days) in the 3-mg group. The mean maximum platelet count in patients with platelet transfusion was 6.85 $\times 10^4/\mu L$ in the 3-mg group and 5.28 $\times 10^4/\mu L$ in the placebo group.

- The maximum platelet count in the withdrawals from study treatment who met the criteria for increased platelet count (ie, platelet count $\geq 50,000/\mu L$ with an increase of $\geq 20,000/\mu L$ from baseline) was 14.0$\times 10^4/\mu L$ in 8 patients in the 3-mg group, indicating no excessive increase in platelet count.

- The subgroup analysis was performed for the primary endpoint. The proportion of patients who required no preoperative platelet transfusion tended to be lower in the subgroup with lower baseline platelet count. However, this tendency was found in both the 3-mg group and the placebo group, and the proportion of patients who required no preoperative platelet transfusion was 57.1% of patients (4/7 patients) with a platelet count of < 35,000/μL at screening in the 3-mg group; more than half of patients with a platelet count of < 35,000/μL at screening showed the efficacy in the 3-mg group. No meaningful differences were apparent for subgroup analyses by performed invasive procedure and by severity of liver disorder.

Safety Results:

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- A total of 436 TEAEs occurred in 93 of 96 patients (96.9%) in the safety analysis population: 203 TEAEs in 45 of 48 patients (93.8%) in the 3-mg group and 233 TEAEs in 48 of 48 patients (100.0%) in the placebo group.

- No deaths occurred. Serious TEAEs were reported in 1 patient (portal vein thrombosis) in the 3-mg group and 4 patients (1 event of urticaria, 1 event of asthma, 1 event of oesophageal varices hemorrhage, and 1 event each [in the same patient] of postoperative fever and pleural effusion) in the placebo group. Except for the portal vein thrombosis in the 3-mg group, all SAEs were considered not related to the study drug by the investigator or subinvestigator. The portal vein thrombosis was identified based on diagnostic imaging studies (computed tomography [CT] or magnetic resonance imaging [MRI]) after the primary invasive procedure, was considered not life-threatening by the investigator or subinvestigator, and was resolved by the anticoagulation therapy alone. No excessive increase in platelet count was observed in the patient with the portal vein thrombosis.

- No AEs leading to withdrawal from the study treatment occurred.

- Significant TEAEs (defined as any TEAE that led to withdrawal of study treatment or was severe other than SAE) occurred in 20 of 48 patients (41.7%) both in the 3-mg group and the placebo group. Among the significant TEAEs, the incidence of alanine aminotransferase (ALT) increased in the 3-mg group (3/48 subjects) was higher than that in the placebo group (0/48 subjects). All the events of ALT increased were considered due to the invasive procedure and not related to the study drug by the investigator or subinvestigator.

- TEAEs occurring at an incidence of 10% or more in the 3-mg group were postoperative fever, procedural pain, procedural hypertension, aspartate aminotransferase (AST) increased, ALT increased, procedural nausea, and procedural vomiting. There was no TEAE occurring at least 10% more frequently in the 3-mg group than in the placebo group.

- Thrombus-related TEAEs were reported in 1 of 48 patients (2.1%) in both the 3-mg group and the placebo group. The TEAEs included portal vein thrombosis in the 3-mg group and mesenteric vein thrombosis in the placebo group. These events were found in diagnostic images (CT or MRI) between 3 and 10 days after invasive procedure to examine the potential for the development of portal vein thrombosis. The portal vein thrombosis in the 3-mg group was severe and serious, and was considered by the investigator to be probably related to the study drug. In this patient, the maximum platelet count was $7.9 \times 10^4/\mu L$ and the most recent platelet count prior to the onset of event was $7.7 \times 10^4/\mu L$, indicating no excessive increase in platelet count was observed.

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- Bleeding-related TEAEs were reported in 7 of 48 patients (14.6%) in the 3-mg group and 13 of 48 patients (27.1%) in the placebo group. The incidence of bleeding-related TEAEs in the 3-mg group was lower than that in the placebo group.

- Seven ADRs were reported in 5 of 96 patients (5.2%) during the study: 6 ADRs in 4 of 48 patients (8.3%) in the 3-mg group and 1 ADR in 1 of 48 patients (2.1%) in the placebo group. Nausea occurred in 2 patients (4.2%) and the other events occurred in 1 patient each (pyrexia in 1 patient, headache in 1 patient, pain in 1 patient, and portal vein thrombosis in 1 patient) in the 3-mg group, and hypothermia in 1 patient in the placebo group.

- Of TEAEs which were found by laboratory tests, no TEAEs occurring at an incidence of at least 10% higher in the 3-mg group than that in the placebo group were found. Of severe TEAEs which were found by laboratory tests in the 3-mg group, only ALT increased was reported as a TEAE occurring in at least 2 patients with a higher incidence relative to placebo.

- No clinically significant findings were noted for vital signs or electrocardiogram.

Conclusions:

- The proportion of patients who required no preoperative platelet transfusion was significantly greater in the 3-mg group than in the placebo group with oral administration of 3 mg of S-888711 or placebo once daily for up to 7 days for the pretreatment of invasive procedure in thrombocytopenic patients with chronic liver disease.

- Oral administration of 3 mg of S-888711 had no significant safety concerns compared with placebo in thrombocytopenic patients with chronic liver disease.

- Oral administration of 3 mg of S-888711 was sufficient for replenishing platelet as an alternative therapy of preoperative platelet transfusion in thrombocytopenic patients with chronic liver disease undergoing invasive procedures, ensuring the safety of patients.

Date of the Report: 29 October 2014

Date of the Amendment 1: 16 Nov 2017