Shionogi study title	A Phase 3 Randomised, Double-blind, Placebo-controlled Study to Assess the Safety and Efficacy of S-888711 (Lusutrombopag) for the Treatment of Thrombocytopenia in Patients with Chronic Liver Disease Undergoing Elective Invasive Procedures (L-PLUS 2)
Shionogi study no.	1423M0634
ClinicalTrials.gov registration no.	NCT02389621
Study document	Protocol (Edition 2 dated 03 Feb 2015)

The study was conducted in its entirety under Protocol Edition 2.

Clinical Study Protocol

Study Title:	A Phase 3 Randomised, Double-blind, Placebo-controlled Study to Assess the Safety and Efficacy of S-888711 (Lusutrombopag) for the Treatment of Thrombocytopenia in Patients with Chronic Liver Disease Undergoing Elective Invasive Procedures (L-PLUS 2)
Study Number:	1423M0634
EudraCT Number:	2014-004942-91
IND Number:	104047
Study Phase:	3
Product Name:	S-888711 (Lusutrombopag)
Sponsor:	Shionogi & Co., Ltd. (Head Office) 3-1-8 Doshomachi, Chuo-ku, Osaka 541-0045, Japan Shionogi Inc. 300 Campus Drive Florham Park, NJ 07932, United States Shionogi Ltd. 33 Kingsway London, WC2B 6UF, United Kingdom The study sponsor may be one or more of the above Shionogi companies. Throughout the protocol, the term "sponsor" represents the various legal entities identified in the "Sponsor List and Contact Information" in the protocol.

Amendment History	**Issue Date**
Edition 1 (original)	24 December 2014
Edition 2	3 February 2015

SYNOPSIS

Study Title:

A Phase 3 Randomised, Double-blind, Placebo-controlled Study to Assess the Safety and Efficacy of S-888711 (Lusutrombopag) for the Treatment of Thrombocytopenia in Patients with Chronic Liver Disease (CLD) Undergoing Elective Invasive Procedures (L-PLUS 2)

Study Number:

1423M0634

Study Phase: 3

Primary Objective:

- To compare the efficacy of S-888711 with placebo for the treatment of thrombocytopenia in patients with CLD who are undergoing elective invasive procedures

Secondary Objectives:

- To assess the safety and tolerability of S-888711 treatment compared with placebo
- To assess the platelet response following treatment with S-888711 compared with placebo
- To assess the pharmacodynamics (PD) and pharmacokinetics (PK) of S-888711

Study Design:

This is a phase 3, multinational, randomised, double-blind, placebo-controlled study to assess the safety and efficacy of S-888711 for the treatment of thrombocytopenia in patients with CLD undergoing elective invasive procedures. The study consists of 3 periods:

- Screening period: up to 28 days prior to randomisation
- Treatment period: 7 days (Days 1 to 7)
- Post-treatment period: through 28 days post-treatment

The maximum study duration for each patient will be 63 days. Potential patients who provide written informed consent will be screened for eligibility, and eligible patients will be randomised in a 1:1 ratio to either S-888711 3 mg once daily for up to 7 days or matched placebo control. The randomisation will be stratified by primary invasive procedure (liver ablation/coagulation or other invasive procedures) and baseline platelet count ($< 35 \times 10^9$/L or $\geq 35 \times 10^9$/L).

Patients will begin once daily treatment with assigned study medication on Day 1 after randomisation and will receive study medication for up to 7 days. A platelet count will be performed on Days 5, 6, and 7 prior to administration of study medication. After the final dose of study medication, patients will continue the protocol-specified assessments and procedures in the Post-treatment period.

The planned invasive procedure will be performed in the Post-treatment period between Days 9 and 14. A platelet count will be performed on or after Day 8, but no more than 2 days prior to the elective invasive procedure, in order to assess the need for a platelet

transfusion before the elective invasive procedure. A pre-operative platelet transfusion must be performed if the platelet count is $< 50 \times 10^9$/L.

The need for the invasive procedure will be reassessed in the event of any of the following:

- Platelet count $\geq 200 \times 10^9$/L
- Administration of an antithrombotic drug
- In the opinion of the investigator, the procedure is no longer in the patient's best interest because of an adverse event (AE) or other concern
- The patient requests cancellation of the elective procedure after randomisation

If any of the above criteria are met and the elective procedure cannot be performed between Days 9 and 14, it may be performed up to Day 35 of the study. If a patient does not undergo the procedure, all the relevant follow-up assessments should be performed and data should be collected up to Day 35. In case the invasive procedure performed between Days 9 and 14 needs to be repeated, the same procedure may be performed after Day 15 according to the discretion of the investigator.

Study Population:

A total of 200 adult patients with CLD and thrombocytopenia (defined as a platelet count $< 50 \times 10^9$/L) will be randomised into the study.

Inclusion Criteria:

Patients who fulfil the following criteria will be eligible for inclusion in the study:

1. Able to understand the study and comply with all the study procedures.
2. Willing to provide written informed consent prior to Screening.
3. Male or female.
4. 18 years of age or older at the time of signing informed consent.
5. CLD limited to Child-Pugh Class A and Class B disease (see Appendix 3).
6. Platelet count $< 50 \times 10^9$/L at baseline on Day 1 prior to randomisation.
7. Undergoing an elective invasive procedure that:
    - is likely to require administration of platelets
    - is expected to be performed between Days 9 and 14
    - does not include laparotomy, thoracotomy, craniotomy, open-heart surgery, organ resection, or
    - does not include partial organ resection (however, biopsy and other types of tissue removal will be allowed if risk of bleeding and invasiveness is considered comparable or lower than those procedures in the list of example procedures; see Appendix 4).
8. Eastern Cooperative Oncology Group (ECOG) performance status (PS) grade of 0 or 1 (see Appendix 5).
9. In the opinion of the investigator, able to meet the requirements of the study.
10. Male patients who are sterile or who agree to use an appropriate method of

contraception (including use of a condom with spermicide) from Screening to completion of the Post-treatment period.

11. Female patients who are not postmenopausal or surgically sterile need to agree to use a highly effective contraception (including contraceptive implant, injectable contraceptive, combination hormonal contraceptive [including vaginal rings], intrauterine contraceptive device or vasectomised partner) from Screening to completion of the Post-treatment period. Barrier method with or without spermicide, double barrier contraception and oral contraceptive pill are insufficient methods on their own.

Exclusion Criteria:

Patients who fulfil any of the following criteria will be excluded from the study:

1. Any of the following diseases:
   - haematopoietic tumour
   - aplastic anaemia
   - myelodysplastic syndrome
   - myelofibrosis
   - congenital thrombocytopenia
   - drug-induced thrombocytopenia
   - generalised infection requiring treatment except for viral liver disease
   - immune thrombocytopenia.
2. Any solid malignant tumour if:
   - the patient requires systemic chemotherapy or radiotherapy for that malignant tumour during the study
   - the malignant tumour is associated with nodal metastasis, distant metastasis, or invasion of the surrounding organs
   - The exceptions are:
     - a malignant tumour that is the treatment target of the primary invasive procedure
     - non-melanoma skin cancer, intramucosal cancer, or carcinoma in situ not requiring any treatment during the study.
3. History of splenectomy.
4. History of liver transplantation.
5. Any of the following at Screening:
   - hepatic encephalopathy uncontrolled by drugs
   - ascites uncontrolled by drugs.
6. Portal vein tumour embolism.
7. Known to be positive for the human immunodeficiency virus.
8. Past or present thrombosis or prothrombotic condition (eg, cerebral infarction,

myocardial infarction, angina pectoris, coronary artery stent placement, angioplasty, coronary artery bypass grafting, congestive heart failure [New York Heart Association {NYHA} Grade III/IV], arrhythmia known to increase the risk of thromboembolic events [eg, atrial fibrillation], pulmonary thromboembolism, deep vein thrombosis, or disseminated intravascular coagulation syndrome).

9. History or evidence of any of the following diseases:
    - congenital thrombotic disease (eg, antithrombin deficiency, protein C deficiency, protein S deficiency, or coagulation factor [Factor V Leiden] mutation)
    - acquired thrombotic disease (eg, antiphospholipid antibody syndrome, paroxysmal nocturnal haemoglobinuria, hyperhomocysteinaemia, or increased factor VIII)
    - Budd-Chiari syndrome.
10. Portal vein thrombosis based on ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) within 28 days prior to randomisation or a history of portal vein thrombosis.
11. Absence of hepatopetal blood flow in the main trunk of the portal vein as demonstrated by Doppler ultrasonography within 28 days prior to randomisation.
12. Untreated gastro-oesophageal varices that are bleeding or require treatment based on upper gastrointestinal endoscopy within 180 days prior to randomisation (except for patients in whom the primary invasive procedure is for the treatment of gastro-oesophageal varices).
13. History or evidence of disease associated with a risk of bleeding (eg, coagulation factor deficiency or von Willebrand factor deficiency).
14. Bleeding score at randomisation $\geq$ Grade 2 according to the World Health Organization (WHO) Bleeding Scale (see Appendix 7).
15. Any of the following drugs or therapies within 90 days prior to randomisation:
    - anticancer drugs except for transcatheter arterial chemoembolisation (TACE) and lipiodolisation
    - interferon preparations
    - radiation therapy
    - exsanguination
    - other TPO receptor agonist
    - any investigational agent.
16. Any of the following invasive procedures within 90 days prior to randomisation:
    - laparotomy, thoracotomy, craniotomy, or open-heart surgery
    - procedures involving any organ resection or any partial organ resection (tissue resection associated with an endoscopic examination is permitted)
    - partial splenic embolisation.
17. Any invasive procedure (except for the treatment of gastro-oesophageal varices) within 14 days prior to randomisation.

18. Blood transfusion (except for red blood cell products and albumin preparations) within 14 days prior to randomisation.
19. Patients who have received S-888711 before.
20. Pregnant or lactating female.
21. Patients with known or suspected ongoing, active alcohol or substance abuse. Patients with a recent history who the investigator feels are able to comply with the study procedures and medications will be allowed to participate.
22. Considered ineligible by the investigator for any other reason.

Test Drug, Dose, and Mode of Administration:

Once daily oral dose of a 3 mg tablet of S-888711

Control Drug, Dose, and Mode of Administration:

Once daily oral dose of a matching placebo tablet

Duration of Treatment:

Study drug will be administered for up to 7 days. On Days 5 to 7, the platelet count must be measured before administration of study drug. If a patient meets the administration stopping criterion (ie, platelet count $\geq 50 \times 10^9$/L with an increase of $\geq 20 \times 10^9$/L from baseline), no additional dose of study drug will be administered.

Study Endpoints:

Primary endpoint:

- Proportion of patients who require no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomisation through 7 days after the primary elective procedure.

Secondary endpoints:

- Proportion of patients who require no platelet transfusion during the study
- Proportion of responders: patients who achieve a platelet count of $\geq 50 \times 10^9$/L with an increase of $\geq 20 \times 10^9$/L from baseline at any time during the study
- Duration of the platelet count defined as the number of days during which the platelet count was maintained as $\geq 50 \times 10^9$/L
- Proportion of patients who require rescue therapy for bleeding at any time during the study
- Frequency of platelet transfusions
- The change from baseline in platelet count over time (time course of platelet count)
- Safety and tolerability
- Assessment of plasma concentrations of S-888711

Efficacy Assessments:

Platelet transfusions, use of rescue therapy for bleeding, and platelet counts

Safety Assessments:

Physical examination, vital signs, electrocardiograms, laboratory tests (haematology, blood chemistry, and blood coagulation/fibrinolysis assays), imaging studies (ultrasound, CT, or MRI and Doppler ultrasonography), bleeding events as graded on the WHO Bleeding Scale, adverse events, adverse drug reactions, and adverse events of special interest (ie, thrombosis-related AEs).

Pharmacokinetic Assessments:

Blood samples to determine S-888711 plasma concentrations and PK; intensive blood sampling in a cohort of 20 patients and sparse blood sampling in the remainder of patients.

Statistical Methods:

Two hundred patients with CLD and thrombocytopenia who are scheduled to undergo elective invasive procedures will be randomised into either of two treatment groups (100 patients per group). Assuming that the proportion of patients who meet the primary endpoint is 20% in the placebo group and 70% in the S-888711 treatment group, 100 patients per arm will provide 99% power to detect a difference of 50% between S-888711 and placebo groups at a two-sided significance level of 0.05.

For the analysis of the primary endpoint, the number and proportion of patients who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomisation through 7 days after the primary elective procedure will be calculated by treatment group. The proportion of patients who required no platelet transfusion in the S-888711 group will be compared with that in the placebo group using the Cochran-Mantel-Haenszel test adjusted by stratification factors.

The secondary efficacy endpoints will be summarised by treatment group, with data in the S-888711 group and the placebo group compared for statistical significance.

A gatekeeping strategy will be employed for sequentially testing the important secondary hypotheses. If the primary hypothesis is statistically significant, the secondary hypotheses will be tested in sequence. Sequential testing for the secondary endpoints will be conducted in the following order:

- Proportion of patients who require no platelet transfusion during the study
- Proportion of responders: patients who achieve a platelet count of $\geq 50 \times 10^9$/L, with an increase of $\geq 20 \times 10^9$/L from baseline at any time during the study
- Duration of the platelet count $\geq 50 \times 10^9$/L

Treatment-emergent AEs (TEAEs) will be summarised by treatment group for the analyses of safety.

Study Duration:

The study duration for each patient is up to 63 days (Screening period, up to 28 days; Treatment period, 7 days; Post-treatment period, 28 days).

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADR(s)	adverse drug reaction(s)
AE(s)	adverse event(s)
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$AUC_{0-\tau}$	AUC over the dosing interval τ (ie, 24 hours)
BCRP	breast cancer resistance protein
CI	confidence interval
CLD	chronic liver disease
C_{max}	maximum plasma concentration
CRF	case report form
CRO	Contract Research Organisation
CT	computed tomography
CV%	coefficient of variation
ECG	electrocardiography
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EIS	endoscopic injection sclerotherapy
EMR	endoscopic mucosal resection
EMS	endoscopic metallic stenting
EPBD	endoscopic papillary balloon dilatation
ESD	endoscopic submucosal dissection
EST	endoscopic sphincteropapillotomy
EUS-FNA	endoscopic ultrasound-guided fine needle aspiration
EVL	endoscopic variceal ligation
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IgG	immunoglobulin G
IRB	institutional review board
ITT	intention-to-treat
IVRS/IWRS	interactive voice or web response system
Lip-TAI	lipiodolisation with anticancer drugs
LMC	laparoscopic microwave coagulation
ln	natural logarithm
LRA	laparoscopic radiofrequency ablation
M-CSF	macrophage colony-stimulating factor
MCT	microwave coagulation therapy

MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
N	number of non-missing observations
NYHA	New York Heart Association
PD	pharmacodynamics
PEG	percutaneous endoscopic gastrostomy
PEIT	percutaneous ethanol injection therapy
P-gp	P-glycoprotein
PK	pharmacokinetics
PMCT	percutaneous microwave coagulation therapy
PP	per protocol
PS	performance status
PT-INR	prothrombin time-international normalised ratio
RFA	radiofrequency ablation
SAE(s)	serious adverse event(s)
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	standard deviation
SMQ	Standard MedDRA query
SUSAR	suspected unexpected serious adverse reaction
TACE	transcatheter arterial chemoembolisation
TAE	transcatheter arterial embolisation
TAI	transhepatic arterial infusion
TEAE(s)	treatment-emergent adverse event(s)
TPO	thrombopoietin
TUL	transurethral ureterolithotripsy
TURBT	transurethral resection of the bladder tumour
ULN	upper limit of normal
US	United States
WHO	World Health Organization

1. INTRODUCTION

1.1 Thrombocytopenia in Chronic Liver Disease Undergoing Elective Invasive Procedures

Chronic liver disease (CLD) comprises a number of types of disease, including chronic viral hepatitis B and C, cirrhosis, hepatocellular carcinoma, alcohol-related liver disease, and nonalcoholic-related fatty liver disease, as well as many others. In Europe, an estimated 29 million people suffer from CLD.[1] In the United States (US), an estimated 25.8 million ambulatory care visits were related to CLD in the 2006 to 2010 period,[1] and an estimated 31,903 deaths were attributed to CLD in 2010.[2] Overall, CLD is recognised as a major public health problem and an important cause of morbidity and mortality in both Europe and the US,[1,3,4] and its prevalence is increasing.[4]

Thrombocytopenia is a common complication in patients with CLD and has been reported in up to 76% of patients with this condition[5]. Furthermore, severe thrombocytopenia in liver disease can be associated with significant morbidity.[6] Thrombocytopenia is associated with an increased risk of clinically significant bleeding, such as cerebral or other internal haemorrhage, as well as petechiae, purpura, and mucosal bleeding. Moderate liver disease-related thrombocytopenia is defined as a platelet count $< 100 \times 10^9$/L, with severe thrombocytopenia defined by a platelet count of $< 50 \times 10^9$/L.[6] Clinically significant spontaneous bleeding does not typically occur until platelet counts are $< 10\text{-}20 \times 10^9$/L[6]; however, patients with CLD may undergo invasive treatments, such as percutaneous therapies, trans-catheter arterial embolization, and trans-hepatic arterial infusion chemotherapy for CLD-related pathologies. As all invasive procedures are associated with some degree of bleeding, patients with CLD are at an increased risk of potentially serious bleeding events if their platelet count is $< 50 \times 10^9$/L.

Thrombocytopenia in patients with CLD is multifactorial in origin. Possible causes include decreased production and/or decreased activity of the haematopoietic growth factor thrombopoietin (TPO), suppression of platelet production in the bone marrow due to the underlying liver disease (eg, chronic hepatitis C infection), or use of anti-cancer agents, use of interferon-based therapy as an antiviral treatment, and the splenic sequestration of platelets. Of these, platelet sequestration in the spleen and decreased TPO production in the liver are the major mechanisms for thrombocytopenia in patients with liver cirrhosis.[6] As platelets are essential to haemostasis, the risk of clinically significant bleeding is increased in patients with CLD.

1.2 Current Treatment Options

Treatment options for thrombocytopenia in CLD may be directed at the disease underlying the thrombocytopenia or at the thrombocytopenia itself. Patients with platelet counts below 50×10^9/L may benefit from prophylactic platelet transfusions prior to any invasive procedures; however, no specific guidelines on the use of prophylactic platelet transfusions in patients with CLD are available and currently there is no consensus on the appropriate threshold for administering such transfusions.[6] Thus, clinicians may rely on currently available general guidelines, which recommend prophylactic administration of platelets to maintain a platelet count of $>50 \times 10^9$/L in patients undergoing many invasive procedures.[7] Furthermore, several complications are associated with this intervention,

including febrile non-haemolytic and allergic reactions, the need for hospitalisation, iron overload with chronic transfusions and the risk of infections.[8] In addition, platelet transfusions do not ensure a haemostatic platelet level may be a limitation.[9,10]

Thus, alternative therapeutic options to platelet transfusions would be desirable for patients with thrombocytopenia and CLD. TPO is a cytokine that stimulates proliferation and differentiation of megakaryocytic progenitor cells from haematopoietic stem cells, stimulates megakaryocyte maturation and regulates platelet production. It plays a central role in regulating thrombopoiesis, and decreases in TPO production or activity in patients with CLD suggest that TPO mimetics may stimulate platelet production.[11,12] Thus, TPO serves as a rational therapeutic target to stimulate platelet production and provides an alternative to platelet transfusion in patients with CLD.

Currently, two TPO mimetics have been approved in the US and European Union (EU), romiplostim and eltrombopag for the treatment of immune thrombocytopenia. These have both been shown to increase platelet counts in healthy subjects and in patients with immune thrombocytopenia. Additionally, eltrombopag has been approved for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. Eltrombopag was shown to increase platelet counts in ≥75% of patients with hepatitis C-associated thrombocytopenia and compensated liver disease after 4 weeks of treatment, with significantly more patients than placebo-treated patients completing 12 weeks of antiviral therapy.[13]

An orally administered agent that reduces the need for platelet transfusions and has an acceptable safety profile would provide clinical benefit for patients with CLD who are undergoing elective invasive procedures. Shionogi has developed S-888711 to fulfil this unmet clinical need.

1.3 Clinical Studies with of Lusutrombopag (S-888711)

S-888711 is an orally active, small-molecule TPO receptor agonist that acts on the transmembrane domain of human TPO receptors, activates the signal transduction pathway in the same manner as endogenous TPO, and leads to an upregulation of platelet production.

Following single (0.1 to 50 mg) and multiple (once daily for 14 days; 0.25 to 2 mg) dosing, S-888711 increased platelet production in a plasma-exposure dependent manner. Furthermore, S-888711, at the doses and regimens investigated, was safe and well tolerated. The maximum plasma concentration (C_{max}) and the area under the plasma concentration-time curve (AUC) for S-888711 increased dose-proportionally, with plasma S-888711 concentrations reaching steady state within 7 days of the initial dose. Further studies showed that the pharmacokinetics (PK) of S-888711 were unlikely to be affected by food, race, most concomitant drugs, or hepatic function.

Two open-label, phase 2 studies (Studies 1017M0623 and 1112M0625) conducted in Japan were designed to investigate the optimal dose of S-888711, administered once daily for 7 days, in thrombocytopenic patients with CLD who were scheduled to undergo percutaneous liver ablation (including liver coagulation). The efficacy, safety, and PK of S-888711 as a pre-treatment for percutaneous liver ablation were assessed at doses of 0.25, 0.5, 1, 1.5, and 2 mg/day (Study 1017M0623) or 2.5, 3, and 4 mg/day (Study 1112M0625). The data demonstrated that doses of ≥ 2 mg/day were required to increase platelet counts in thrombocytopenic patients to levels above 50×10^9/L to perform percutaneous liver ablation.

Consequently, a double-blind, phase 2b, dose-finding study (Study 1208M0626) conducted in Japan evaluated 3 doses of S-888711 (2, 3, and 4 mg) to determine the optimal dose for future studies. The data showed that 80.0% (12/15), 81.3% (13/16), and 93.3% (14/15) of patients in the 2, 3, and 4 mg groups, respectively, received no platelet transfusion prior to percutaneous liver ablation compared to 20.0% (3/15) of placebo-treated patients. In patients who received no platelet transfusion, mean maximum platelet counts were 59×10^9/L, 73.8×10^9/L, 94.8×10^9/L, and 103.8×10^9/L in the placebo, and 2, 3, and 4 mg S-888711 groups, respectively. These data suggest that platelet counts increased with increasing doses of S-888711. For patients with a platelet count $\geq 50 \times 10^9$/L, the increased platelet count duration without a platelet transfusion was 20 days or more for all S-888711 treatment groups. All patients, with the exception of one in the 4 mg group, experienced adverse events (AEs) during the study. There was no increased incidence of thrombus-related AEs with increasing dose of S-888711 (6.7% [1/15], 6.7% [1/15], 0% [0/16], and 13.3% [2/15] in the placebo, and 2, 3, and 4 mg S-888711 groups, respectively).

A randomised, double-blind, phase 3 study (Study 1304M0631) conducted in Japan compared 3 mg of S-888711 to placebo as a treatment for thrombocytopenia in patients with CLD undergoing elective invasive procedures. The list of allowed invasive procedures in this study was broadened from the phase 2 study to allow inclusion of many other procedures. The primary endpoint was the proportion of patients who received no platelet transfusion prior to the primary invasive procedure. A statistically significantly greater proportion of patients in the S-888711 3 mg group than in the placebo group (79.2% [38/48] versus 12.5% [6/48]; $P < 0.0001$) received no platelet transfusion prior to the invasive procedure. In patients who received no platelet transfusion, mean maximum platelet counts were 90.2×10^9/L and 66.7×10^9/L in the S-888711 3 mg and placebo groups, respectively. A 'responder' was defined as a patient with a platelet count of $\geq 50 \times 10^9$/L with an increase of $\geq 20 \times 10^9$/L from baseline. The adjusted mean number of days on which the responder criterion was met in patients without platelet transfusion was significantly greater in the S-888711 3 mg group than in the placebo group (12.39 versus 0.74 days; $P < 0.0001$). Overall, AEs were reported at a comparable incidence in both treatment groups (93.8% [45/48] and 100% [48/48] in the S-888711 and placebo groups, respectively). Importantly, thrombotic events were reported for 1 (2.1%) patient in each treatment group.

In summary, the data indicate that C_{max} and AUC values increased in a dose proportional manner across the dose range 0.25 to 4 mg. Furthermore, no significant safety concerns were raised.

1.4 Rationale for the Current Study

This phase 3, multinational, randomised, double-blind, placebo-controlled study is designed to assess the efficacy and safety of S-888711 3 mg for the treatment of thrombocytopenia in patients with CLD prior to undergoing an elective invasive procedure. The study will be conducted to test the hypothesis that in patients with thrombocytopenia and CLD, relative to placebo, treatment with S-888711 3 mg once daily for up to 7 days prior to an elective invasive procedure is associated with a higher proportion of patients who do not require platelet transfusion prior to the procedure nor rescue therapy for bleeding from randomisation through 7 days after the procedure.

1.5 Appropriateness of Conduct of the Study

The 3 mg dose of S-888711 selected was based on data from the Japanese studies (see Section 3.2) with a requirement to avoid pre-operative platelet transfusions while ensuring patient safety. Study design features necessary for ensuring individual patient safety have been incorporated. Inclusion of patients who are at high risk of spontaneous bleeding or thrombosis is not permitted and measures included minimising the numbers of patients being dosed who have rapid rises in platelet counts. In addition, patients will have their hepatic circulation imaged pre-dosing/pre-procedure and will be excluded if there is any evidence of portal vein thrombosis.

Further details on the rationale for the study design, including selection of the 3 mg dose and choice of control group are provided in Section 3.2.

An Independent Safety Committee will periodically review elements of the study data (see Section 9.8.2).

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is:

- To compare the efficacy of S-888711 with placebo for the treatment of thrombocytopenia in patients with CLD who are undergoing elective invasive procedures.

2.2 Secondary Objectives

The secondary objectives of the study are:

- To assess the safety and tolerability of S-888711 treatment compared with placebo.
- To assess the platelet response following treatment with S-888711 compared with placebo.
- To assess the pharmacodynamics (PD) and PK of S-888711.

3. INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a phase 3, multinational, randomised, double-blind, placebo-controlled study to assess the safety and efficacy of S-888711 for the treatment of thrombocytopenia in patients with CLD undergoing elective invasive procedures. A schematic of the study design is provided in Figure 2-1.

The study consists of 3 periods:

- Screening period: up to 28 days prior to randomisation
- Treatment period: 7 days (Days 1 to 7)
- Post-treatment period: through 28 days post-treatment

The maximum study duration for each patient will be 63 days. Potential patients who provide written informed consent will be screened for eligibility, and eligible patients will be randomised in a 1:1 ratio to either S-888711 3 mg once daily for up to 7 days or

matched placebo control. The randomisation will be stratified by primary invasive procedure (liver ablation/coagulation or other invasive procedures) and baseline platelet count ($< 35 \times 10^9$/L or $\geq 35 \times 10^9$/L).

Patients will begin once daily treatment with assigned study medication on Day 1 after randomisation and will receive study medication for up to 7 days. A platelet count will be performed on Days 5, 6, and 7 prior to administration of study medication. After the final dose of study medication, patients will continue the protocol-specified assessments and procedures in the Post-treatment period.

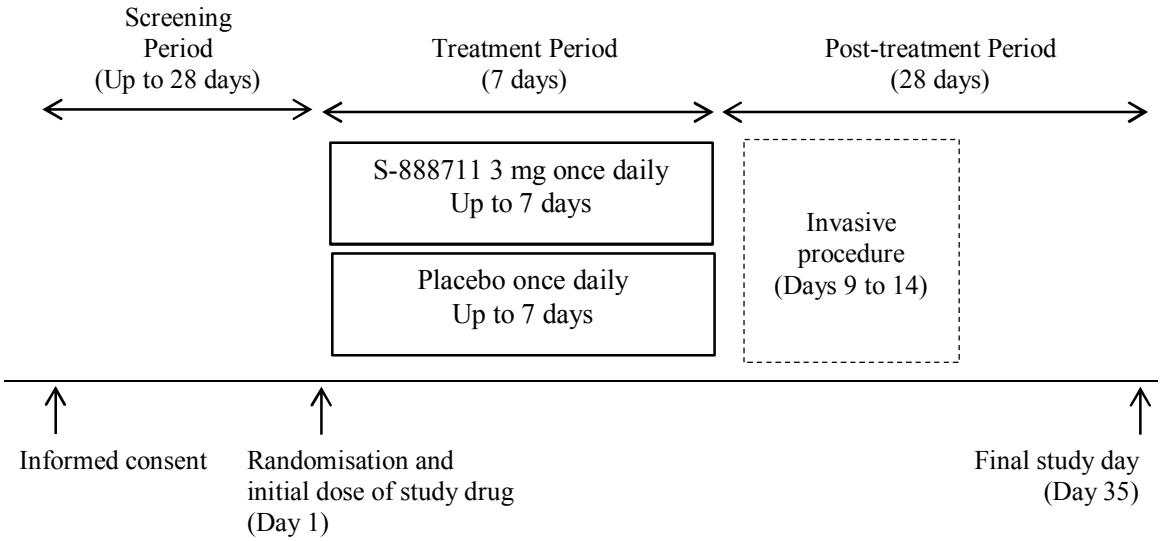
The planned invasive procedure will be performed in the Post-treatment period between Days 9 and 14. A platelet count will be performed on or after Day 8, but no more than 2 days prior to the elective invasive procedure in order to assess the need for a platelet transfusion before the planned elective procedure. A pre-operative platelet transfusion must be performed if the platelet count is $< 50 \times 10^9$/L. Patients may be admitted to the study centre for the elective invasive procedure if required.

The need for the invasive procedure will be reassessed in the event of any of the following:

- Platelet count $\geq 200 \times 10^9$/L
- Administration of an antithrombotic drug
- In the opinion of the investigator, the procedure is no longer in the patient's best interest because of an AE or other concern
- The patient requests cancellation of the elective procedure after randomisation

If any of the above criteria are met and the elective procedure cannot be performed between Days 9 and 14, it may be performed up to Day 35 of the study. If a patient does not undergo the procedure, all the relevant follow-up assessments should be performed and data should be collected up to Day 35. In case the invasive procedure performed between Days 9 and 14 needs to be repeated, the same procedure may be performed after Day 15 according to the discretion of the investigator. The overall schedule of events for the study is provided in Appendix 1.

Figure 2-1 Study Schematic



3.2 Rationale for Study Design and Control Group

This study will be conducted to test the hypothesis that in patients with thrombocytopenia and CLD, relative to placebo, treatment with S-888711 3 mg once daily for up to 7 days prior to an elective invasive procedure is associated with a higher proportion of patients who do not require platelet transfusion prior to the procedure nor rescue therapy for bleeding from randomisation through 7 days after the procedure.

The list of potential invasive procedures included in this study were selected based on the phase 3 study completed in Japan (Study 1304M0631). In that study, a number of invasive procedures were permitted, unless they were associated with a high degree of invasiveness and high risk of bleeding, such as laparotomy, thoracotomy, craniotomy, open-heart surgery, and organ resection.

The dose of S-888711 selected for this phase 3 study is 3 mg based upon results from the phase 2b and phase 3 studies conducted in Japan. In the phase 2b study S-888711 doses of 2 mg, 3 mg, and 4 mg were evaluated. All three doses were effective. The 2 mg dose was eliminated from further study as the number of days on which the criterion for responder was met (least squares mean ± standard error) with the 2 mg dose was less (8.36 ± 1.73 days) than that observed with the 3 mg and 4 mg doses (11.59 ± 1.84 days and 13.88 ± 1.85 days, respectively) and thus would afford the clinician less flexibility if a patient's condition or schedule necessitated delay of the elective procedure. The 4 mg dose was eliminated from further study due to concern that increases in platelet counts might exceed 200×10^9/L, as the platelet count had increased to 195×10^9/L in one patient in the 3 mg group who had a platelet count of 45×10^9/L at screening and 65×10^9/L at baseline. In the phase 3 study, the proportion of patients who required no platelet transfusion prior to the planned invasive procedure was significantly greater in the S-888711 3 mg group than in the placebo group: 79.2% (38/48 patients) in the 3 mg group and 12.5% (6/48 patients) in the placebo group ($P < 0.0001$). The incidence of thrombotic events was the same in the S-888711 3 mg and placebo groups: 2.1%. No PK or PD differences were observed between white and Japanese subjects in phase 1 studies that would suggest a different S-888711 dose is required in these populations. PK modelling and PK/PD modelling based on data in white and Japanese subjects (including Japanese patients with thrombocytopenia and CLD who were undergoing elective invasive procedures) were performed, and platelet count profiles were simulated by using the PK/PD model. Results support an S-888711 dose of 3 mg as the optimal daily dose regardless of ethnicity.

As per the previous phase 2 and 3 studies, the dosage of S-888711 will be once daily administration for up to 7 days. The study duration (excluding Screening) will be 35 days (7 days for the Treatment period followed by a 28-day Post-treatment period). This was based on the assessment of the post-treatment change in platelet counts. The planned invasive procedure will be performed between Days 9 and 14 because an adequate increase in platelet counts is assumed in this period based on the results of Studies 1208M0626 and 1304M0631, which indicate that mean platelet count increases extend out to around 20 days.

3.3 Study Duration

3.3.1 Study Duration for Individual Patients

The study duration for each patient is up to 63 days (Screening period, up to 28 days; Treatment period, 7 days; Post-treatment period, through 28 days).

4. STUDY POPULATION SELECTION

4.1 Study Population

A total of 200 adult patients with CLD and thrombocytopenia (defined as a platelet count $< 50 \times 10^9$/L) will be randomised into the study provided they fulfil all of the eligibility criteria.

4.2 Inclusion Criteria

Patients who fulfil the following criteria will be eligible for inclusion into the study:

1. Able to understand the study and comply with all the study procedures.
2. Willing to provide written informed consent prior to Screening.
3. Male or female.
4. 18 years of age or older at the time of signing informed consent.
5. CLD limited to Child-Pugh Class A and Class B disease (see Appendix 3).
6. Platelet count $< 50 \times 10^9$/L at baseline on Day 1 prior to randomisation.
7. Undergoing an elective invasive procedure that:
    - is likely to require administration of platelets
    - is expected to be performed between Days 9 and 14
    - does not include laparotomy, thoracotomy, craniotomy, open-heart surgery, organ resection, or
    - does not include partial organ resection (however, biopsy and other types of tissue removal will be allowed if risk of bleeding and invasiveness is considered comparable or lower than those procedures in the list of example procedures; see Appendix 4).
8. Eastern Cooperative Oncology Group (ECOG) performance status (PS) grade of 0 or 1 (see Appendix 5).
9. In the opinion of the investigator, able to meet the requirements of the study.
10. Male patients who are sterile or who agree to use an appropriate method of contraception (including use of a condom with spermicide) from Screening to completion of the Post-treatment period.
11. Female patients who are not postmenopausal or surgically sterile need to agree to use a highly effective contraception (including contraceptive implant, injectable contraceptive, combination hormonal contraceptive [including vaginal rings], intrauterine contraceptive device, or vasectomised partner) from Screening to

completion of the Post-treatment period. Barrier method with or without spermicide, double barrier contraception and oral contraceptive pill are insufficient methods on their own.

4.3 Exclusion Criteria

Patients who fulfil any of the following criteria will be excluded from the study:

1. Any of the following diseases:
   - haematopoietic tumour
   - aplastic anaemia
   - myelodysplastic syndrome
   - myelofibrosis
   - congenital thrombocytopenia
   - drug-induced thrombocytopenia
   - generalised infection requiring treatment except for viral liver disease
   - immune thrombocytopenia.
2. Any solid malignant tumour if:
   - the patient requires systemic chemotherapy or radiotherapy for that malignant tumour during the study
   - the malignant tumour is associated with nodal metastasis, distant metastasis, or invasion of the surrounding organs
   - The exceptions are:
     - a malignant tumour that is the treatment target of the primary invasive procedure
     - non-melanoma skin cancer, intramucosal cancer, or carcinoma in situ not requiring any treatment during the study.
3. History of splenectomy.
4. History of liver transplantation.
5. Any of the following at Screening:
   - hepatic encephalopathy uncontrolled by drugs
   - ascites uncontrolled by drugs.
6. Portal vein tumour embolism.
7. Known to be positive for the human immunodeficiency virus.
8. Past or present thrombosis or prothrombotic condition (eg, cerebral infarction, myocardial infarction, angina pectoris, coronary artery stent placement, angioplasty, coronary artery bypass grafting, congestive heart failure [New York Heart Association {NYHA} Grade III/IV], arrhythmia known to increase the risk of thromboembolic events [eg, atrial fibrillation], pulmonary thromboembolism, deep vein thrombosis, or disseminated intravascular coagulation syndrome).

9. History or presence of any of the following diseases:
    - congenital thrombotic disease (eg, antithrombin deficiency, protein C deficiency, protein S deficiency, or coagulation factor [Factor V Leiden] mutation)
    - acquired thrombotic disease (eg, antiphospholipid antibody syndrome, paroxysmal nocturnal haemoglobinuria, hyperhomocysteinaemia, or increased factor VIII)
    - Budd-Chiari syndrome.
10. Portal vein thrombosis based on ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) within 28 days prior to randomisation or a history of portal vein thrombosis.
11. Absence of hepatopetal blood flow in the main trunk of the portal vein as demonstrated by Doppler ultrasonography within 28 days prior to randomisation.
12. Untreated gastro-oesophageal varices that are bleeding or require treatment based on upper gastrointestinal endoscopy within 180 days prior to randomisation (except for patients in whom the primary invasive procedure is for the treatment of gastro-oesophageal varices).
13. History or presence of disease associated with a risk of bleeding (eg, coagulation factor deficiency or von Willebrand factor deficiency).
14. Bleeding score at randomisation $\geq$ Grade 2 according to the World Health Organization (WHO) Bleeding Scale (see Appendix 7).
15. Any of the following drugs or therapies within 90 days prior to randomisation:
    - anticancer drugs except for transcatheter arterial chemoembolisation (TACE) and lipiodolisation
    - interferon preparations
    - radiation therapy
    - exsanguination
    - other TPO receptor agonist
    - any investigational agent.
16. Any of the following invasive procedures within 90 days prior to randomisation:
    - laparotomy, thoracotomy, craniotomy, or open-heart surgery
    - procedures involving any organ resection or any partial organ resection (tissue resection associated with an endoscopic examination is permitted)
    - partial splenic embolization.
17. Any invasive procedure (except for the treatment of gastro-oesophageal varices) within 14 days prior to randomisation.
18. Blood transfusion (except for red blood cell products and albumin preparations) within 14 days prior to randomisation.
19. Patients who have received S-888711 before.
20. Pregnant or lactating female.

21. Patients with known or suspected ongoing, active alcohol or substance abuse. Patients with a recent history who the investigator feels are able to comply with the study procedures and medications will be allowed to participate.
22. Considered ineligible by the investigator for any other reason.

5. STUDY MEDICATION(S)

5.1 Description of Study Medication(s)

5.1.1 Test Drug

Laboratory code:	S-888711
USAN, INN:	Lusutrombopag
Chemical name:	(2*E*)-3-{2,6-dichloro-4-[(4-{3-[(1*S*)-1-(hexyloxy)ethyl]-2-methoxyphenyl}-1,3-thiazol-2-yl)carbamoyl]-phenyl}-2-methylprop-2-enoic acid
Constituent ingredients, content, and dosage form:	Slight red to light red, round shaped film-coated tablet containing 3 mg of S-888711 per tablet, [redacted]

5.1.2 Placebo or Control Drug

Name of test drug:	Placebo
Constituent ingredients, content, and dosage form:	Tablet matching the S-888711 tablet but lacking the active ingredient, [redacted]

5.2 Treatments to be Administered

One S-888711 3 mg tablet or matching placebo tablet will be taken once daily. Study drug will be administered for up to 7 days. On Days 5 to 7, the platelet count must be measured before administration of study drug. If a patient meets the administration stopping criterion (ie, platelet count $\geq 50 \times 10^9$/L with an increase of $\geq 20 \times 10^9$/L from baseline), no additional dose of study drug will be administered.

5.3 Selection and Timing of Dose for Each Patient

Patients will be randomly assigned to either of the two treatment groups and the treatment group assigned will not be changed during the Treatment period. Administration of the study drug on Day 2 will be performed at 12 hours or longer after administration on Day 1. The study drugs will be administered at the same time of the days between Days 2 and 7 to the extent possible.

5.4 Method of Assigning Patients to Treatment Groups

The treatments will be randomized to subject identification numbers by the interactive voice or web response system (IVRS/IWRS) provider in a 1:1 fashion to either of the two treatment groups (S-888711 3 mg/day for up to 7 days or placebo for up to 7 days). Randomisation will be stratified by the primary invasive procedure and the platelet count at baseline as follows:

- Primary invasive procedure: liver ablation/coagulation or other invasive procedures
- Platelet counts at baseline: $< 35 \times 10^9$/L or $\geq 35 \times 10^9$/L

The study drug assigned from the interactive voice or web response system (IVRS/IWRS) on the day of randomisation is the study drug to be dosed between Days 1 and 4. Before dosing on Days 5 to 7, the investigator will submit to IVRS/IWRS a platelet count. Study drug on Days 5 to 7 will then be assigned on each day from IVRS/IWRS. Once the study medication is stopped, no submission of data on platelet counts to the IVRS/IWRS system is necessary. However platelet counts should still be collected on the CRF.

5.5 Blinding

The study will be conducted in a double-blind manner using a placebo matching the active drug in appearance, labelling, and packaging. An IVRS/IWRS will be used for central patient randomisation and study drug assignment. IVRS/IWRS will assign drug identifiers according to a randomisation schedule. Only an unblinded Contract Research Organisation (CRO) or designee will have the authority to assign the drug identifiers. All patients, the investigator, all study personnel, and data analysts will be blinded to the treatment assigned at randomisation until database lock. The randomisation schedule will be kept confidential and will not be accessible to anyone until unblinding, except for Drug Supply Management staff, IVRS/IWRS Clinical Coordinator(s), IVRS/IWRS vendor staff, unblinded statistician on the Independent Safety Committee, and for reporting suspected unexpected serious adverse reaction (SUSAR) as required by local regulation.

Unblinding, at the investigator's request, should occur only in the event of an emergency or an AE where details of the treatment assigned are required to determine an appropriate course of therapy. In such cases, the investigator or qualified designee is to contact the IVRS/IWRS. Prior to unblinding, and if the situation allows it, the investigator should try to contact the sponsor in order to obtain additional information about the investigational product. If this is impractical, the investigator must notify the sponsor as soon as possible, without revealing the treatment assignment of the unblinded patient. The investigator must document the patient identification and the date and time for breaking the blind, as well as clearly explaining the reasons for breaking the code.

Treatment assignment may be determined from plasma drug concentrations; therefore, these data will be reported to the sponsor after the database is locked.

If the Independent Safety Committee (see Section 9.8.2) requires emergency codes due to a medical emergency or for any other issues arising during the study, the required information will be reported to them according to the procedures outlined in a separate document.

5.6 Packaging and Labelling

Study drug will be supplied in a Patient Medication Box containing 1 Tablet Card. The Tablet Card for Days 1 to 4 will contain 4 tablets. Separate Tablet Cards for Days 5, 6, and 7 will contain 1 tablet each and will be assigned by the IVRS/IWRS for each day. The treatment label will include a study reference code, drug identifier, quantity of dosage units, and lot number at a minimum, as well as other pertinent information according to local regulations. The expiry or use-by date will be shown on the label and stored in the IVRS/IWRS, and printable blinded assignment reports are available to site personnel. S-888711 should not be used after the expiry or use-by date.

All packaged and labelled supplies will be formally released in accordance with both Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) guidelines.

5.7 Storage and Accountability

S-888711 and matching placebo tablets should be stored in their original package at room temperature (15°C to 30°C [59°F to 86°F]), with daily minimum and maximum temperature logs maintained at the study sites.

Study medication accountability is the responsibility of the investigator who should ensure that all study drugs are stored and dispensed according to local regulations. All drug supplies must be kept in a secure, locked area, with access limited to those authorised by the investigator.

The investigator, pharmacist, or designee will maintain accurate records for the receipt of and condition of all study drugs, date of receipt, when and how much study drug is dispensed and used by each patient in the study, and any reasons for departure from the protocol-dispensing regimen. All patients are required to bring used and unused Tablet Cards to each study visit for compliance assessments.

Unless otherwise notified, all study drug supplies (both used and unused Tablet Cards) must be saved for study medication accountability. Drug accountability records will be available at each monitoring visit for verification by the sponsor's monitor. At study completion, a final reconciliation of all study drugs will be performed. Study drug must not be used for any purpose other than in the current study.

5.8 Investigational Product Retention at Study Site

At the end of the study, all unused study drug and used (empty) Tablet Cards will be returned or disposed of as instructed by the sponsor. Transmittal forms will be provided and must be included with all returns. If any S-888711 supplies are to be destroyed at the investigational site, the institution/investigator(s) must obtain prior approval by Shionogi and final reconciliation must be completed by the unblinded monitor prior to destruction. After such destruction, the institution/investigator(s) must notify Shionogi, in writing, of the method, date, and location of destruction.

5.9 Treatment Compliance

The investigator or designee will instruct each patient to record daily drug compliance and the time they took study medication in their study drug booklet. These data will be checked and recorded on the case report form (CRF). In addition, the drug identifier, the date, and the number of tablets actually taken will be recorded on the CRF. Patients will bring all used and unused Tablet Cards to each study visit to check compliance and for the purpose of drug accountability. Based on compliance checks, if any study drug has not been taken by a patient, they will be counselled about the importance of taking study drug.

In the event that a subject is withdrawn for compliance reasons (e.g. missed doses or visits), the investigator will promptly notify the sponsor or designee and will make every effort to complete the early termination assessments. The investigator must register all subject discontinuations in the IVRS/IWRS system.

6. PATIENT RESTRICTIONS

6.1 Prior Therapy

Prior therapies are defined as therapies taken prior to randomisation into the study.

Restrictions regarding the prior therapy are specified in the exclusion criteria (see Section 4.3) and summarised below.

- Any of the following drugs or therapies within 90 days prior to randomisation:
  - anticancer drugs except for TACE and lipiodolisation
  - interferon preparations
  - radiation therapy
  - exsanguination
  - other TPO receptor agonist
  - any investigational agent
- Any of the following invasive procedures within 90 days prior to randomisation:
  - laparotomy, thoracotomy, craniotomy, or open-heart surgery
  - procedures involving any organ resection or any partial organ resection (tissue resection associated with an endoscopic examination is permitted)
  - partial splenic embolisation
- Any invasive procedure (except for the treatment of gastro-oesophageal varices) within 14 days prior to randomisation
- Blood transfusion (except for red blood cell products and albumin preparations) within 14 days prior to randomisation
- S-888711

6.2 Concomitant Therapy During the Study

6.2.1 Concomitant Therapy

Concomitant therapies are defined as any drug or substance administered between randomisation and the end of study or withdrawal from the study. Restricted and prohibited concomitant therapies are specified in the exclusion criteria and in Sections 6.2.1.1 and 6.2.1.2.

The following information on all therapies (including prescription drugs, over-the-counter drugs, and procedures) from randomisation until completion of the Post-treatment period (or early termination) will be recorded on the CRF by the investigator or designee:

- Name of used drug or procedure
- Route of administration (if a drug is administered)
- Duration of treatment
- Reason for use

6.2.1.1 Restricted Therapy

Use of vitamin K from Screening to completion of the Post-treatment period is permitted for patients who have received vitamin K for at least 28 days prior to randomisation; however, a change in vitamin K dose is not permitted during the study.

If taking P-glycoprotein (P-gp) inhibitors or breast cancer resistance protein (BCRP) inhibitors (see Appendix 6), the dose must be stable for 7 days prior to randomisation and during the Treatment period and extra vigilance should be given to patients whose platelet counts increase $\geq 50 \times 10^9$/L with an increase of $\geq 20 \times 10^9$/L.

6.2.1.2 Prohibited Therapy

Use of the following therapies is not permitted from the day of Screening until completion of the Post-treatment period:

- Platelet preparations (except for use prior to the invasive procedure and as rescue therapy). Note that patients who receive a platelet transfusion prior to the invasive procedure (based on the determination of platelet count pre-operatively) may receive subsequent platelet transfusions.
- Blood preparations and alternatives to blood, except for platelet preparations, red blood cell preparations, and albumin preparations (eg, whole blood cell preparations; human immunoglobulin preparations other than those targeting specific infections, such as antitetanic globulin and hepatitis B immune globulin; coagulation factor products; fibrinogen other than fibrinogen for tissue adhesion; antithrombin III; fresh frozen plasma; and recombinant coagulation factor product) unless needed as rescue therapy for bleeding
- Anticancer drugs, except for those used in patients in whom the primary invasive procedure is TACE or lipiodolisation, and patients in whom the primary invasive procedure is liver ablation/coagulation with TACE or lipiodolisation planned after completion of study assessments on Day 8
- Interferon products
- Macrophage colony-stimulating factor (M-CSF) products
- Granulocyte CSF (G-CSF) products
- Erythropoietin
- TPO receptor agonists other than the study drug
- Antithrombotic agents (heparin, aspirin, dipyridamole, ticlopidine, urokinase, etc.) except for use as rescue therapy
- Desmopressin products
- Monoethanolamine oleate
- Other investigational products
- Radiotherapy
- Exsanguination
- Any invasive procedures except for the primary invasive procedure in the study

  The following therapies can be concomitantly used after assessment on Day 8 provided

that the primary invasive procedure is liver ablation/coagulation:

- TACE
- Lipiodolisation with anticancer drugs (ie, Lip-TAI)
- transcatheter arterial embolisation (TAE) excluding Lipiodol infusion for marking

6.2.1.3 Rescue Therapy

Use of the following therapies is permitted as rescue therapy for bleeding events, independent of platelet count:

- Platelet preparations
- Other blood preparations, including red blood cells and plasma
- Volume expanders

Antithrombotic drugs may be administered as rescue therapy for thrombotic events when the platelet count is $\geq 200 \times 10^9$/L or when, in the opinion of the investigator, formation of a thrombus is highly suspected.

7. STUDY PROCEDURES AND METHODS OF ASSESSMENTS

7.1 Informed Consent

The nature of the study will be fully explained to each patient by the investigator or designee using the institutional review board (IRB)-approved informed consent form. Patients who agree to participate in the study must voluntarily sign the informed consent form prior to the initiation of any study-related procedures. Informed consent will be obtained from all patients and they cannot be entered into the study until they have signed and dated the informed consent form. A copy of the signed and dated informed consent form will be given to the patient, and the investigator should retain the original document.

The investigator or designee is responsible for ensuring that patients understand the risks and benefits of participation in the study, and should be available to answer any questions patients may have throughout the study. In addition, they should share with patients, in a timely manner, any new information that may affect patient willingness to continue in the study.

7.2 Baseline Characteristics and Eligibility Assessment

The following information will be collected during the Screening period. In addition, safety assessments conducted at Screening, as well as at specified time points throughout the study, are detailed in Section 7.7.

7.2.1 Baseline Characteristics

The following baseline characteristics will be recorded on the CRF: date of birth, sex, race, ethnicity, patient identification number, date informed consent signed, height, weight, and whether pregnant/lactating (for females only).

7.2.2 Medical History

Any concomitant disease (including the type of medical history of CLD) at Screening will be recorded on the CRF.

For medical history, any of the followings will be recorded on the CRF:

- any diseases controlled by drugs irrespective of symptoms
- hepatic encephalopathy, jaundice, or other signs along with CLD (Note: splenomegaly, ascites, and gastro-oesophageal varices will be recorded on the CRF separately. See the Section 7.2.8 to 7.2.10)
- history of hepatectomy, drug allergy, food allergy, pollinosis.

7.2.3 History of Transfusion

Details of transfusion history (eg, whole blood, red blood cell, platelet, other transfusions, or unknown) will be recorded on the CRF.

7.2.4 Performance Status

Performance status will be assessed according to the ECOG PS (see Appendix 5), and the date of assessment and grade will be recorded on the CRF.

7.2.5 Type of Chronic Liver Disease

The type of medical history of CLD (hepatitis C, hepatitis B, alcoholic hepatitis, non-alcoholic hepatitis, autoimmune hepatitis, other hepatitis) will be recorded on the CRF.

7.2.6 Severity of Liver Disorder

Severity of liver disorder will be assessed according to the Child-Pugh class, and the date of assessment and assessment of each item will be recorded on the CRF.

7.2.7 Planned Invasive Procedure

The planned invasive procedure will be recorded on the CRF.

If the planned invasive procedure is not included in the list of invasive procedures (see Appendix 4), the investigator or designee should contact the Medical Monitor (see Section 9.1) to discuss the enrolment of such a patient based upon invasiveness and bleeding risk of the procedure and which is comparable to the permitted surgeries on the provided list (see Appendix 4).

7.2.8 Gastro-oesophageal Varices

During the Screening period, should an upper gastrointestinal endoscopy be performed to assess any gastro-oesophageal varices, the date of endoscopy and the presence or absence of gastro-oesophageal varices will be recorded on the CRF. If gastro-oesophageal varices are present, details on whether the planned invasive procedure is for the treatment of these will be recorded on the CRF. If the planned invasive procedure is not for the treatment of gastro-oesophageal varices, bleeding status or the requirement of treatment will be recorded on the CRF. If an endoscopy has been performed within 180 days of

randomisation, results from that assessment can be used.

7.2.9 Splenomegaly

During the Screening period, diagnostic imaging (ultrasonography, CT, or MRI) will be performed to assess the presence or absence of splenomegaly. The test date and method, and the presence or absence of splenomegaly will be recorded on the CRF. If ultrasonography, CT, or MRI has been performed within 28 days of randomisation, that image can be used for the assessment of splenomegaly.

7.2.10 Presence of Ascites

During the Screening period, diagnostic imaging (ultrasonography, CT, or MRI) will also be used to assess the presence of ascites. The test date and method, and the presence or absence of ascites will be recorded on the CRF.

7.2.11 Pregnancy Test

For women of childbearing potential, a urine pregnancy test will be performed during the Screening period before dosing at Day 1 and at the end of the study at Day 35 (or early termination of assessment, if applicable) for the investigator or designee to assess pregnancy status at the beginning and the end of the trial. For women of childbearing potential who withdraw from the study, a pregnancy test will also be performed. The test will not be required for women of non-childbearing potential, ie, those who meet any of the following criteria:

- Postmenopausal women (ie, those in whom at least 1 year has elapsed since their last regular menstrual period)
- Women who have undergone hysterectomy, bilateral oophorectomy, or sterilisation.

7.2.12 Laboratory Test (Immunological Test and Blood Thrombopoietin Concentration)

Laboratory tests, including immunological tests and blood TPO concentration measurements, will be performed during the Screening period (see Table 7-1). Full details of all laboratory tests are provided in Appendix 2.

Blood samples will be collected by the investigator or designee at the pre-specified time points. All samples will be sent to the central laboratory for processing. Full details of the sample collection, handling, labelling, storage, and shipping procedures will be specified in a separate manual.

Table 7-1: Immunological Test and Blood Thrombopoietin Concentration

Test	Items Evaluated
Immunological	platelet-associated IgG, antiplatelet antibody, *Helicobacter pylori* antibody IgG
Other	TPO

Abbreviation: immunoglobulin G (IgG).

7.3 Enrolment in the Study and Dispensing Study Drug

Upon obtaining the informed consent, the investigator or designee will contact the

IVRS/IWRS and provide the requested identifying information for the subject to register them into the IVRS/IWRS. Once assigned to a patient, the randomisation number will not be reused. If the patient's enrolment is accepted, the patient will be start Screening procedures but must not begin the study medication before randomisation. If the patient fails to be randomised for any reason, the IVRS/IWRS must be notified that the subject was not randomised. The investigator or designee will input the reason for not being randomised into the IVRS/IWRS. Once a patient is randomised the investigator, designee, or site pharmacist will dispense study drug as specified in Section 5. Full details of the randomisation processes are provided in a separate manual. The date of randomisation and the assigned patient identification number will be entered on the CRF.

7.4 Invasive Procedures

The planned invasive procedure will be performed in the Post-treatment period between Days 9 and 14. The need for the invasive procedure will be reassessed in the event of the following:

- Platelet count $\geq 200 \times 10^9$/L
- Administration of an antithrombotic drug
- In the opinion of the investigator, the procedure is no longer in the patient's best because of an AE or other concern
- The patient requests cancellation of elective procedure after randomisaton

If any of the above criteria are met and the elective procedure cannot be performed between Days 9 and 14, it may be performed up to Day 35 of the study. If a patient does not undergo a procedure, all relevant follow-up assessments should be performed and data should be collected up to Day 35. In case the invasive procedure performed between Days 9 and 14 needs to be repeated, the same procedure may be performed after Day 15 according to the discretion of the investigator.

Information on whether to perform the planned invasive procedure, details of the procedure performed (eg, percutaneous radiofrequency ablation [RFA]/microwave coagulation therapy [MCT], laparoscopic RFA/MCT, endoscopic variceal ligation [EVL], endoscopic injection sclerotherapy [EIS], TACE, TAE, or other), the date performed, the initiation time of the procedure, and whether the procedure was performed within the specified period will be recorded on the CRF. If the planned invasive procedure is not performed within the specified period or is not performed at all, the reason will be recorded on the CRF.

7.5 Efficacy Assessments

7.5.1 Determination of the Need for Pre-operative and Platelet Transfusion Post-procedural Rescue Therapy

A platelet count will be performed on or after Day 8, but no more than 2 days prior to the elective invasive procedure, in order to assess the need for a pre-operative platelet transfusion before the planned elective procedure.

The date of this platelet count, the time of measurement, the measured value, and, if applicable, the date and the initiation time of the platelet transfusion, the dose (units) transfused, and the reason for the transfusion will be recorded on the CRF.

7.5.2 Laboratory Tests (Platelet Count)

A blood sample for a platelet count will be collected at Screening, and this will be used to determine whether the patient is considered eligible to enter the study and proceed to randomisation. Blood samples for the platelet count will be collected and analysed locally on Days 1 (ie, before randomisation to confirm eligibility into the study), 5 to 8, 10, 12, 14, 17, 21, 28, and 35 (or at drug withdrawal and/or early termination of assessment, if applicable) using standard methods at each participating site. Full details of all laboratory tests are provided in Appendix 2.

The date of platelet count performed, the time of each measurement, and the measured value will be recorded on the CRF.

Platelet counts are measured for the assessment of efficacy. However, the investigator or designee will assess whether any abnormal changes from baseline (Day 1) are considered to be clinically significant (see Section 7.8.9), and any clinically significant results should be recorded as AEs by the investigator or designee. The reference ranges provided by each participating site will be used to assess whether values are normal (ie, within the reference range) or abnormal (ie, outside the reference range).

If the platelet count has not returned to baseline level at the final post-treatment assessment on Day 35, appropriate follow-up review will be performed until the platelet count returns to baseline levels or the investigator or designee considers that no further review is warranted.

7.6 Pharmacokinetic Assessment

7.6.1 Drug Concentration Measurement

All patients will undergo blood sampling for the PK assessment of S-888711. At least 20 patients will undergo intensive blood sampling (Table 7-2) and the remaining patients will undergo sparse blood sampling (Table 7-3). The actual time and date of all blood collections will be recorded on the CRF.

Table 7-2: Intensive Blood Sampling

Study Day	Blood Sampling Time	Allowance
Day 5	• Pre-dose	• Within 60 minutes before administration
	• 2 hours after dose • 4 hours after dose • 6 hours after dose • 8 hours after dose	• ± 15 minutes after dose
Day 6	• 24 hours after Day 5-dose	• ± 60 minutes after Day 5-dose, but before Day 6-dose
Day 7	• 48 hours after Day 5-dose	• Simultaneous sampling with platelet count determination

Table 7-3: Sparse Blood Sampling

Study Day	Blood Sampling Time	Allowance
Day 5	• Pre-dose	• Within 60 minutes before administration
	• 2 to 4 hours after dose	• Within the specified time window (ie, 2 to 4 hours after dose)
Day 6	• 24 hours after Day 5-dose	• Simultaneous sampling with platelet count determination
Day 7	• 48 hours after Day 5-dose	• Simultaneous sampling with platelet count determination

Blood samples for the PK assessment will be collected by the investigator or designee at the pre-specified time points. All samples will be sent to the central laboratory for processing. Full details of the sample collection, handling, labelling, storage, and shipping procedures will be specified in a separate manual.

7.7 Safety Assessment

7.7.1 Physical Examination

The investigator or designee will perform a physical examination during the Screening period, on Days 1 (before the initial administration), 5 to 8, 10, 12, 14, 21, 28, and 35 (or at drug withdrawal and/or early termination of assessment, if applicable). Clinically significant findings on physical examination will be recorded as an AE on the CRF.

7.7.2 Portal Vein Thrombosis

Portal vein thrombosis will be assessed by the investigator or designee using diagnostic imaging (ultrasonography, CT, or MRI) during the Screening period, and between 3 and 10 days after the planned invasive procedure* in the Post-treatment period (Days 12 to 21). For assessment in the Screening period, the investigation should be arranged as close to randomisation as possible. However, for patients in whom gastro-oesophageal varices are treated, portal vein thrombosis will be confirmed using imaging performed after the treatment.

The imaging date and method, and the presence or absence of portal vein thrombosis will be recorded on the CRF. The independent safety committee will assess portal vein thrombosis (see Section 9.8.2).

* Even if the planned invasive procedure is postponed. In addition, if any additional invasive procedures are performed, diagnostic imaging should also be performed before and after the additional procedure for post-assessment of the initial and additional procedures.

7.7.3 Portal Blood Flow

The direction of portal blood flow (hepatofugal, hepatopetal, stasis) will be assessed by the investigator or designee using Doppler ultrasonography during the Screening period, and between 3 and 10 days after the planned invasive procedure* in the Post-treatment period (Days 12 to 21). The test date and the results will be recorded on the CRF.

* Even if the planned invasive procedure is postponed. In addition, if any additional invasive procedures are performed, diagnostic imaging should also be performed before and after the additional procedure for post-assessment of the initial and additional procedures.

7.7.4 WHO Bleeding Scale

The severity of bleeding will be assessed according to the WHO Bleeding Scale (see Appendix 7)[15] during the Screening period, on Days 1 and 8, between 3 and 10 days after the invasive procedure (Days 12 to 21), and on Day 35 (or early termination of assessment, if applicable). The date of the assessment and the grade will be recorded on the CRF.

7.7.5 Blood Pressure and Pulse Rate

Resting blood pressure (systolic blood pressure and diastolic blood pressure in supine position) and pulse rate will be measured during the Screening period, and on Days 1 (ie, immediately before S-888711 administration), 5, 8, 10, 12, 14, 21, 28, and 35 (or at drug withdrawal and/or early termination of assessment, if applicable).

The test date and the results will be recorded on the CRF.

The investigator or designee will assess whether any abnormal changes from baseline (Day 1) are considered to be clinically significant (see Section 7.8.9), and any clinically significant results should be recorded as AEs by the investigator or designee.

7.7.6 Electrocardiography

Electrocardiography (ECG) will be performed during the Screening period and on Day 35 (or at drug withdrawal and/or early termination of assessment, if applicable).

All ECG traces will be evaluated by the investigator or designee and categorised as normal or abnormal. The date of the ECG and any abnormality observed should be recorded on the CRF. Any abnormal traces will be reviewed by the investigator or designee for clinical significance (see also Section 7.8.9), with any clinically significant findings recorded as an AE on the CRF.

7.7.7 Laboratory Tests (Except for Platelet Count)

A list of clinical laboratory tests is shown in Table 7-4. Full details of all laboratory tests are provided in Appendix 2. Central Laboratory tests (except for platelet count) will be performed during the Screening period, and on Days 1 (ie, immediately before the first dose of study drug), 8*, 14, and 35 (or at drug withdrawal and/or early termination of assessment, if applicable).

Blood samples will be collected by the investigator or designee at the pre-specified time points. All samples will be sent to the central laboratory for processing. Full details of the sample collection, handling, labelling, storage, and shipping procedures will be specified in a separate manual.

The reference ranges provided by the central laboratory will be used to assess whether values are normal (ie, within the reference range) or abnormal (ie, outside the reference range).

Any abnormal changes from baseline (Day 1) will be assessed by the investigator or designee for clinical significance (see Section 7.8.9), with any clinically significant

findings recorded as an AE on the CRF.

* If laboratory tests are measured at drug withdrawal, laboratory tests on Day 8 are not necessary.

Table 7-4: Routine Laboratory Tests (Except for Immunological Test, Blood Thrombopoietin Concentration, and Platelet Count)

Test	Items Evaluated
Haematology (except for platelet count)	Red blood cell count, white blood cell count, haemoglobin, and haematocrit
Blood chemistry	aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase, gamma glutamyl transferase, alkaline phosphatase, total bilirubin, bilirubin direct, indirect bilirubin, total protein, albumin, blood urea nitrogen, serum creatinine, sodium, potassium, chloride, and calcium
Blood coagulation/ fibrinolysis assay	Prothrombin time (international normalised ratio value), activated partial thromboplastin time, antithrombin III activity[a], fibrinogen[a], fibrin degradation products[a], D-dimer[a], protein C activity[a], free protein S antigen[a] and von Willebrand factor activity[a]

[a] Only at Screening.

7.8 Adverse Events Assessments

7.8.1 Adverse Events Definitions

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, including an investigational drug and which does not necessarily have to have a causal relationship with this treatment. The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the investigational medicinal product.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with use of an investigational product, regardless of whether it is considered related to the investigational product.

AEs include events spontaneously reported by the patient and events elicited from non-leading questions, as well as abnormal findings on physical examination, vital signs, ECG, or laboratory tests at each visit during the study. AEs include any new occurrences of an event or events that have increased in severity or frequency from Screening, as well as abnormal results from any diagnostic procedures, including any laboratory test abnormalities. Treatment-emergent AEs (TEAEs) are defined in Section 7.8.2. Any medical history reported as ongoing at the time of informed consent will be considered an AE if it worsens during the course of the study.

A serious adverse event (SAE) is defined by regulations as any AE occurring at any dose that results in any of the following outcomes:

- death
- is life-threatening condition
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity

- consists of a congenital anomaly/birth defect
- is a medically important event

Important medical events that do not result in death, are not life threatening, or do not require hospitalisation may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardise the patient and may require medical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalisation, or the development of drug dependency or drug abuse. The investigator or designee will determine the seriousness of all AEs.

7.8.2 **Timing**

AEs (both serious and non-serious) will be collected throughout the study from the time of informed consent until the patient's final follow-up visit or 28 days after the last dose of study medication, whichever is the later (or at drug withdrawal and/or early termination of assessment, if applicable).

The investigator or designee is responsible for assessing AEs. AEs should be fully investigated, and details of the onset and outcome dates, severity, seriousness, relationship to study drug, action taken with regards to study drug, concomitant drugs or therapies taken as a result of the AE, and outcome will be recorded on the CRF. The onset of the AEs will be recorded on the CRF as before or after the initiation of the primary invasive procedure.

Reported AEs (both serious and non-serious) will be followed up until recovery, or until the patient's final follow-up visit or 28 days after the last dose of study medication, whichever is the later (or at drug withdrawal and/or early termination of assessment, if applicable). Any AEs reported after the first dose of S-888711 or placebo will be considered as TEAEs.

Any SAE assessed as causally related to the study drug and is ongoing 28 days after the last dose of study medication will be followed until resolution, stabilisation, the condition becomes chronic, or the patient is lost to follow-up.

After the follow-up assessment, the necessary information will be recorded on the CRF. If a patient ceases to visit the hospital during the study, a follow-up interview will be performed by telephone or other appropriate method. The reason for discontinuation and the results of the follow-up assessment will be recorded on the CRF.

Further details of the follow-up of platelet counts are provided in Section 7.5.2.

7.8.3 **Severity**

The severity of an AE will be graded by the investigator or designee according to the following definitions:

- **Mild:** A finding or symptom is minor and does not interfere with usual daily activities.
- **Moderate:** The event is discomfort and causes interference with usual daily activity or affects clinical status.
- **Severe:** The event causes interruption of the patient's usual daily activities or has a

clinically significant effect.

7.8.4 **Relationship**

The relationship of an AE to study drug should be determined by the investigator or designee according to the following criteria. Causal relationship assessment to drug treatments is required for purposes of reporting AEs. To promote consistency, the following guidelines should be taken into considerations along with good clinical and scientific judgment when determining the relationship of drug treatments to an AE:

Related: An AE which can be reasonably explained that the study drug caused the AE. For example, the occurrence of the AE cannot be explained by other causative factors, can be explained by pharmacological effect of the study drug such as similar event had been reported previously, or increase/decrease of the dose effect the occurrence or seriousness of the AE.

Not Related: An AE which cannot be reasonably explained that the study drug caused the AE.

7.8.5 **Expectedness**

An expected treatment-related TEAE is any adverse drug reaction (ADR) consistent with the current Investigator's Brochure (IB) for S-888711.

An adverse reaction is ‘unexpected’ if its nature and severity are not consistent with the information about the medicinal product in question set out in the IB.

7.8.6 **Outcome**

Outcome will be defined as:

- Recovered/resolved;
- Recovering/resolving;
- Not recovered/not resolved;
- Recovered/resolved with sequelae;
- Fatal;
- Unknown.

If the outcome was recovered, recovered with sequelae, or fatal, the date on which that outcome occurred will be recorded in the patient's CRF as the AE stop date.

AEs should be followed until recovery, or until the patient’s final follow-up visit or 30 days after the last dose of study medication, whichever is the later. If the outcome was recovering**,** not recovered, or unknown at this time, the date on which the investigator or designee confirmed that follow-up investigations were finished will be recorded in the patient’s CRF as the date of last assessment, and the reason for completion of follow-up of the AE will be entered in the comment box.

7.8.7 Action Taken

Action taken will be defined as:

- Drug withdrawn;
- Dose not changed;
- Not applicable.

7.8.8 Adverse Events of Special Interest

7.8.8.1 Thrombotic/Thromboembolic Complications

The investigator or designee will assess all thrombotic/thromboembolic events, with particular attention given to, but not limited to, the following AEs:

- Portal vein thrombosis
- Mesenteric vein thrombosis

The investigator or designee should carefully monitor patients with thrombotic/thromboembolic events, as defined above, as well as those who experience AEs that have the potential to be classified as above.

7.8.9 Clinical Laboratory Adverse Events

For any abnormal laboratory test results (haematology, blood chemistry, or urinalysis, blood coagulation/fibrinolysis assay) or other safety assessments (eg, physical examination and vital signs) that worsen from baseline, the investigator or designee will assess whether the changes are considered clinically significant. Abnormal laboratory test results are defined as those that are outside of the reference range. Test results that are abnormal at baseline and worsen during the study will also be assessed by the investigator or designee must for clinically significant changes. Any test results considered clinically significant by the investigator or designee should be recorded as AEs. If an abnormal laboratory finding is associated with a disease or organ toxicity, the investigator or designee will report only the disease or organ toxicity as an AE.

The following laboratory test results will be considered as clinically significant by the investigator or designee:

- Those leading to any of the outcomes included in the definition of an SAE.
- Those requiring withdrawal of study drug.
- Those leading to initiation of concomitant drug treatment or other therapy.
- Those requiring additional diagnostic testing or other medical or surgical intervention.

In all other circumstances, the investigator or designee will use their discretion in assessing clinical significance. The investigator or designee should not consider withdrawal from study drug due to an increase in platelets as clinically significant.

7.8.10 Serious Adverse Events

7.8.10.1 Reporting Serious Adverse Events

All AEs must be fully recorded in the patient notes throughout the study from the time of informed consent until the patient's final follow-up visit and the data after randomisation will be transcribed into the patients' CRF. AEs resulting from concurrent illnesses, concomitant medications, or progression of disease must also be collected and reported to the sponsor or designee. AEs would not include information recorded as medical history at screening, for pre-planned procedures for which the underlying condition was known and no worsening occurred.

Quintiles Drug Safety Department will be responsible for collection of all safety information on behalf of the sponsor.

All SAEs with date of onset after the end of trial visit or 28 days after the last dose, whichever is later, must be reported to Quintiles Drug Safety Department in detail on the SAE form within 24 hours of the investigator first becoming aware of the event. The investigator will be requested to complete a separate paper SAE reporting form in addition to the information on the CRF. The investigator site must fax the SAE report to Quintiles Drug Safety according to the instructions on the SAE form; a dedicated phone number is available for any queries on completing the SAE form, and country specific SAE reporting phone and fax numbers will be specified in a separate document. Quintiles Drug Safety will forward details of the SAE to the sponsor.

All SAEs must be reported regardless of causal relationship to study drug. Follow-up information on each SAE may be requested by the sponsor.

When reporting the SAEs, the investigator should record the diagnosis whenever possible. If no diagnosis is available at the time of reporting, individual signs and symptoms can be reported.

Contact Information on Reporting the Completed SAE Form
Medical Monitor: [redacted]
24 hour emergency number if the Medical Monitor cannot be reached within 2 hours:
➔ 24 hour Urgent Medical Contact (Contact directly, on mobile/office phone, for urgent issues: Tel: [redacted]
Quintiles Emergency SAE Fax Number: [redacted]

If the sponsor requires follow-up information, the investigator should provide new information to them using the SAE form and fax it to the number provided above. Discharge summaries, consultant reports, autopsy reports, or other relevant documents must be evaluated by the investigator, with all relevant information included on the follow-up SAE form. Copies of these reports may also be requested by the sponsor.

Appropriate remedial measures should be taken by the investigator using their best medical judgment to treat the SAE. These measures and the patient's response should be recorded. Clinical, laboratory, and diagnostic measures should be used by the investigator, as needed, to adequately determine the aetiology of the SAE.

Any SAEs occurring after the AE assessment period (see Section 7.8.2) that the investigator considers related to study drug must be reported to the sponsor.

The investigator will be responsible for reporting all SAEs to the IRB, as well as to the sponsor. The sponsor will be responsible for reporting all SAEs to the regulatory authorities as required by the applicable regulatory requirements.

7.8.11 Liver Function Abnormalities

When liver function abnormalities meet any of the following criteria (Hy's law) the investigator or designee must report these abnormalities to the sponsor using the specified form within 24 hours.

- AST or ALT > 3 × upper limit of normal (ULN) and total bilirubin > 2 × ULN
- AST or ALT > 3 × ULN and prothrombin time-international normalised ratio (PT-INR) > 1.5

7.8.12 Special Situations-Abuse, Misuse, Overdose, and Medication Error

The investigator must report all cases of abuse, misuse, overdose and medication error (as defined below) to the sponsor's medical monitor via fax using a Special Situations Report Form as soon as possible. If there are any associated SAEs, the investigator will also complete an SAE Form.

- **Abuse:** persistent or sporadic, intentional excessive use of an investigational product(s), which is accompanied by harmful physical or psychological effects.
- **Misuse:** Intentional and inappropriate use of an investigational product(s) other than as directed or indicated at any dose.
- **Overdose:** intentional or unintentional intake of a dose of investigational product(s) higher than the assigned dose in the protocol.
- **Medication Error:** any unintended error in the prescribing, dispensing, or administration of an investigational product(s). Cases of patients missing doses of investigational product(s) do not need to be reported as a medication error.

7.8.13 Pregnancy

All patients (males and females) who are participating in the study must agree to use an appropriate method of contraception (see Section 4.2), from Screening to completion of the Post-treatment period, excluding male patients who have been surgically sterilised or female patients who are postmenopausal or have undergone hysterectomy, bilateral oophorectomy, or sterilisation.

If a female patient becomes pregnant during the study, she must be instructed to discontinue study drug and inform the investigator immediately. All pregnancies occurring between the time of patient consent through to study completion must be reported by the investigator to the sponsor within 24 hours by faxing the Pregnancy Form. Any pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE, as appropriate. Spontaneous abortions must be reported as an SAE. The outcome of the pregnancy should be followed by the study site and it must be reported to the sponsor by faxing the Pregnancy Form. All pregnancies confirmed after the Post-treatment period but within 3 months of the last dose of study drug should be reported to the sponsor or designee and followed to completion. At the end of the pregnancy (ie, birth, miscarriage, abortion), the outcome should be reported to the

sponsor.

In addition, the investigator (or designee) must attempt to collect pregnancy information on any female partners of male patients who become pregnant during the study. Pregnancy information must be reported to the sponsor as described above.

7.9 Withdrawal of Patients from the Study Drug or Study

7.9.1 Withdrawal of Patients from the Study Drug (ie, Study Medication)

The investigator or designee will withdraw a patient from study medication for any of the following reasons:

- Platelet count $\geq 50 \times 10^9$/L, with an increase of $\geq 20 \times 10^9$/L from baseline (ie, the administration stopping criterion).
- Occurrence of a thrombosis-related AE.
- If a serious or intolerable AE occurs and the investigator believes the patient should be withdrawn from the study medication because of that AE.
- The patient requests to be withdrawn from the study medication.
- The patient is proved to be ineligible for the study after participation in the study has begun.
- The investigator determines that the patient should be withdrawn from the study medication due to other reasons.

Even after withdrawal from study medication, study assessments in the Treatment period (Days 1 to 7) and the Post-treatment period (Days 8 to 35) will be performed on schedule, as specified in the study protocol.

7.9.2 Withdrawal of Patients from the Study (ie, Study Assessment)

The investigator or designee will withdraw a patient from study assessment for any of the following reasons:

- The patient requests to be withdrawn from the study.
- The patient is lost to follow-up.
- The investigator determines that the patient should be withdrawn from the study due to other reasons.

In the event of withdrawal from study medication or termination of the study assessments, the investigator or designee will promptly notify the sponsor or designee, and will make every effort to determine the reason for withdrawal and to complete the assessments required at drug withdrawal/early termination of the study. The reason for withdrawal/termination and the date of withdrawal/termination will be recorded on the CRF. However, assessments at early termination of the study are not mandatory for patients who are withdrawn from the study without study drug administration. Follow-up of AEs will be performed in accordance with the specifications in Section 7.8.2. For patients withdrawn due to an AE, information related to the AE will also be followed.

7.10 Appropriateness of Measurements

The primary endpoint in the study will be the proportion of patients who did not require a platelet transfusion prior to the primary invasive procedure and who did not receive rescue therapy for bleeding from randomisation through 7 days after the primary elective procedure. This is considered to be an appropriate primary endpoint because the desired effect of S-888711 is to increase the patient's platelet count and thereby avoid the need for a platelet transfusion for the prevention of bleeding prior to the scheduled invasive procedures. The criteria for assessing whether a patient needs a platelet transfusion are not consistent with actual clinical practice. In this study, a platelet count of $< 50 \times 10^9$/L will be used as the criterion to determine whether a pre-operative platelet transfusion is needed. This will allow the efficacy of S-888711 to be evaluated appropriately, by referencing the Guideline for Use of Blood Preparations.[12] As a secondary variable, the time course of the platelet count will be assessed to provide comprehensive efficacy data.

Safety assessments will consist of those typical in clinical trials. In addition, in order to assess the effect of S-888711 on bleeding, the incidence of bleeding-related AEs will be calculated. The risk of thrombus formation due to an increase in platelet count due to S-888711 will also be assessed by monitoring the incidence of thrombosis-related AEs.

PK assessments will consist of measurements of the plasma concentration of S-888711 in order to assess the time profile of plasma drug concentrations.

7.11 Allowable Time Window

All measurements and assessments will be performed according to the schedule provided in Appendix 1. If, for unavoidable reasons, study measurements and assessments are not possible at the specified time points, they should be performed within an allowable time window (see Table 7-5). Data collected outside of the allowable time window will be handled as missing data for that study visit.

Table 7-5: Allowable Time Window

Timing	Study Day	Allowance
Screening	After obtaining consent and before randomisation	After obtaining consent and within 28 days prior to randomisation[a]
Randomisation	Before initiation of study medication	Within 7 days before initiation of study medication
Before initiation of study medication	Day 1	Within 7 days before initiation of study medication[b]
Treatment period	Days 1-7	±0 day
Post-treatment period	Day 8	±0 day
	Day 10	±1 day
	Days 12 and 14	+1 day
	Days 17 and 21	−1 day to +2 days
	Day 28	±2 days
	Day 35	−2 day to +7 days
At drug withdrawal	-	Within 2 days after the next day of final administration
At early termination of study assessment	-	Within 7 days after the day of early termination of study assessment

a The result of the upper gastrointestinal endoscopy for the assessment of gastro-oesophageal varices can be used if the test is performed within 180 days before randomisation. The diagnostic imaging

(ultrasonography, CT, or MRI) for the assessment of splenomegaly can be used if the diagnostic imaging is performed within 28 days before randomisation. The diagnostic imaging (ultrasonography, CT, or MRI) for the assessment of portal vein thrombosis should be arranged as close to randomisation as possible; however, if gastro-oesophageal varices are treated, confirmation should be made after the treatment.

b Data obtained within 7 days before initiation of study medication can be used as baseline data (Day 1).

8. STATISTICAL ANALYSIS

8.1 Statistical Analysis Methods

Statistical and PK analyses will be performed by the sponsor (Shionogi & Co., Ltd.). Full details of the statistical analyses will be specified in the Statistical Analysis Plan (SAP), which will be finalised before unblinding of the study data.

In principle, summary statistics, including the number of patients, arithmetic mean, standard deviation (SD), median, and minimum and maximum values will be calculated for continuous variables. The number and proportion of patients in each category will be calculated for categorical variables.

Unless otherwise noted, all statistical tests will be performed at a 0.05 (two-sided) significance level.

In general, all tabulations will be presented by treatment group. Individual patient data, PK data, and any derived data will be summarised by treatment group and listed by patient. All the analyses and listings will be performed using Statistical Analysis Software (SAS) (Version 9.2 or higher) and/or WinNonlin (Version 6.2.1 or higher).

8.2 Rationale for Target Sample Size and Stratification Factors

Two hundred patients with CLD and thrombocytopenia who are scheduled to undergo elective invasive procedures will be randomised into either of two treatment groups (100 patients per group).

In the phase 3 study (Study 1304M0631) conducted in Japan, the proportion of patients who required no platelet transfusion prior to the primary invasive procedure was 79.2% in S-888711 3 mg group for up to 7 days and 12.5% in the placebo group. The difference of proportion of patients was 66.7% and its 95% confidence interval (CI) was [51.9%, 81.5%]. Based on the results, it was assumed that the difference in the primary endpoint to be obtained in this study is 50% between S-888711 and placebo groups. Assuming that the proportion of patients who meet the primary endpoint is 20% in the placebo group and 70% in the S-888711 group, 100 patients per arm will provide 99% power to detect a difference of 50% between S-888711 and placebo groups at a two-sided significance level of 0.05.

With 100 patients per arm, from the safety point of view, the sample size will assure at least 95% probability to detect an AE with an incidence of 3% or more.

Since the risk of bleeding is different for each elective procedure, primary invasive procedure has been selected as a stratification factor as per the phase 3 Japanese study (Study 1304M0631). Furthermore, in the Japanese study, the proportion of patients in the 3 mg group who received no platelet transfusion prior to the primary invasive procedure was relatively low in the group whose platelet count at baseline was $< 35 \times 10^9$/L (57.1%, 4/7 patients) compared to the group whose platelet count at baseline was $\geq 35 \times 10^9$/L

(82.9%, 34/41 patients). Thus, for the current study, platelet count at baseline has been selected as an additional stratification factor

8.3 Analysis Populations

The following analysis populations are defined:

Intention-to-Treat (ITT) Population will include all randomised patients. Any mis-randomised patients will be analysed according to the treatment randomised to. This population is the primary population for the analysis of efficacy.

Safety Analysis Population will include all randomised patients who actually receive at least 1 dose of the study drug. This population will be analysed according to the treatment that patients actually received, rather than the treatment to which they were randomised. This population is the primary population for the analysis of safety.

Per Protocol (PP) Population will include all randomised patients who have no major protocol deviations pertaining to the efficacy evaluation. This population will be used in a sensitivity analysis.

Pharmacokinetic Concentration Population will include all patients who undergo plasma PK sampling and who have at least one evaluable PK assay result for S-888711. This population will be used for the concentration listing, as well as for plotting the concentration-time data.

Pharmacokinetic Parameter Population will include all patients with at least one PK parameter estimated in the intensive PK sampling group. This population will be used for PK parameter listing and summary.

8.4 Handling of Missing Data

Unless otherwise noted, missing data will not be imputed. All analyses will be performed using actual observations.

8.5 Patient Disposition

The number and proportion of patients who completed and prematurely discontinued the study will be calculated by treatment group for all randomised patients. In addition, reasons leading to discontinuation will be summarised by treatment group. The number and proportion of patients included in each analysis population will also be calculated for all randomised patients.

8.6 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be tabulated using summary statistics for the ITT population.

8.7 Treatment and Treatment Compliance

The number of days of study drug dosing will be tabulated using summary statistics in each treatment group for the safety analysis population.

8.8 Concomitant Therapies

Concomitant drugs will be coded using the WHO Drug Dictionary.

8.9 Endpoints

8.9.1 Primary Endpoint

The primary endpoint is the proportion of patients who require no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomisation through 7 days after the primary elective procedure. The following patients will also be considered as failures for the primary endpoint:

- Patients who withdrew from the study before receiving the primary invasive procedure
- Patients who did not receive the invasive procedure

8.9.2 Secondary Endpoints

The secondary efficacy endpoints are as follows:

- Proportion of patients who require no platelet transfusion during the study
- Proportion of responders: patients who achieve a platelet count of $\geq 50 \times 10^9$/L with an increase of $\geq 20 \times 10^9$/L from baseline at any time during the study
- Duration of the platelet count defined as the number of days during which the platelet count was maintained as $\geq 50 \times 10^9$/L
- Proportion of patients who require rescue therapy for bleeding at any time during the study
- Frequency of platelet transfusions
- The change from baseline in platelet count over time (time course of platelet count)
- Safety and tolerability
- Assessment of plasma concentrations of S-888711

8.10 Efficacy Analyses

The ITT population is the primary population for the analyses of efficacy. The PP population will be used for sensitivity analyses of the primary endpoint.

8.10.1 Analyses of Efficacy Endpoints

8.10.1.1 Primary Endpoint Analysis

The number and proportion of patients who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomisation through 7 days after the primary elective procedure will be calculated by treatment group. The proportion of patients who required no platelet transfusion in the S-888711 group will be compared with that in the placebo group using the Cochran-Mantel-Haenszel test adjusted by the stratification factors.

8.10.1.2 Secondary Endpoint Analysis

A gatekeeping strategy will be employed for sequentially testing the important secondary hypotheses. If the primary hypothesis is statistically significant, the secondary hypotheses will be tested in sequence at a level of 0.05 (two-sided). Sequential testing for the secondary endpoints will be conducted in the following order:

- The comparison between S-888711 and placebo on the proportion of patients who require no platelet transfusion during the study
- The comparison between S-888711 and placebo on the proportion of responders: patients who achieve a platelet count of $\geq 50 \times 10^9$/L, with an increase of $\geq 20 \times 10^9$/L from baseline at any time during the study
- The comparison between S-888711 and placebo for the duration of platelet count $\geq 50 \times 10^9$/L

8.10.1.2.1 Proportion of Patients Requiring no Platelet Transfusion During the Study

The number and proportion of patients who required no platelet transfusion during the study will be calculated by treatment group. The proportion of patients who required no platelet transfusion in the S-888711 group will be compared with that in the placebo group using the Cochran-Mantel-Haenszel test adjusted by the stratification factors.

8.10.1.2.2 Proportion of Responder Rate

The number and proportion of patients who meet the criteria for a responder at least once during the study (ie, 'Responders') will be calculated for each treatment group. The responder rate in the S-888711 group will be compared with that in the placebo group using the Cochran-Mantel-Haenszel test, with consideration of stratification factors.

The number and proportion of 'Responders' will be calculated at each scheduled time point.

8.10.1.2.3 Duration of the Increase in Platelet Count

Median and quartiles for the duration of increased platelet count will be calculated in each treatment group with or without platelet transfusions. The duration will be compared between the S-888711 group and placebo group using Wilcoxon rank sum test.

8.10.1.2.4 Proportion of Patients who Required Rescue Therapy

The number and proportion of patients who required rescue therapy will be calculated for each treatment group.

8.10.1.2.5 Frequency of Platelet Transfusion and Dose (Unit) Transfused During the Study

Summary statistics for the number and dose (unit) of platelet transfusions during the study will be calculated for patients who received a platelet transfusion.

8.10.1.2.6 Time Course of Platelet Count

Summary statistics for platelet count will be calculated at each scheduled time point in each treatment group. Summary statistics for the change in platelet count from baseline will also be calculated.

Summary statistics for the maximum platelet count and the maximum change in platelet count of each patient will be calculated by treatment group.

8.11 Safety Analyses

Safety analyses will be performed for the safety population.

8.11.1 Adverse Events

AEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) Version 18.0 or higher. Of the AEs reported on the CRF, TEAEs will be used for the analyses of safety. The definition of a TEAE is provided in Section 7.8.2.

The number of patients who experience at least 1 TEAE, death, other treatment-emergent SAEs, significant TEAEs, and TEAEs leading to withdrawal will be counted for each treatment group. The number of TEAEs, counted by cases reported, will also be presented. Treatment-related TEAEs will be summarised in the same manner as the overall summary of TEAEs.

A summary of TEAE by MedDRA system organ class and preferred term will be presented for each treatment group, including the percentage of patients. The summary of TEAEs by severity will also be presented by system organ class and preferred term.

The number and proportion of patients who experience bleeding-related TEAEs will be calculated by treatment group. Bleeding-related TEAEs are defined as TEAEs which were classified as "haemorrhage terms (except laboratory terms)" using Standard MedDRA Queries (SMQ).

8.11.2 Adverse Events of Special Interest

- Thrombotic/thromboembolic complications

The number and percentage of patients who have a thrombotic/thromboembolic AE or that may have the potential to be classified as a thrombotic/thromboembolic AE will be summarised by treatment group. Thrombotic/thromboembolic AEs include, but are not limited to, portal vein thrombosis and mesenteric vein thrombosis. The definition of thrombotic/thromboembolic AEs is described as AEs which are classified as follows using the SMQ: "embolic and thrombotic events, arterial", "embolic and thrombotic events, venous", or "embolic and thrombotic events, vessel type unspecified and mixed arterial and venous".

8.11.3 Vital Signs

Summary statistics for vital signs, measured after randomisation, and their changes from baseline will be calculated at each scheduled time point by treatment group. Baseline will be the value obtained on Day 1 (before initiation of study medication). If the value on Day 1 is missing and the value obtained before randomisation was obtained within 7 days of initiation of study medication, that value can be used as a baseline measurement.

8.11.4 Laboratory Tests

Summary statistics for laboratory tests, measured after randomisation, and their changes

from baseline will be calculated at each scheduled time point by treatment group. Baseline will be the value obtained on Day 1 (before initiation of study medication). If the value on Day 1 is missing and the value obtained before randomisation was obtained within 7 days of initiation of study medication, that value can be used as a baseline measurement.

8.11.5 **Electrocardiogram**

The number and proportion of patients with an abnormal ECG finding will be calculated at each scheduled time point.

8.11.6 **Portal Vein Thrombosis**

The number and proportion of patients who experienced portal vein thrombosis will be counted.

8.11.7 **Portal Blood Flow**

Summary statistics by category for the direction of portal blood flow (ie, hepatofugal, hepatopetal, stasis) will be counted for patients who underwent Doppler ultrasonography at each scheduled time point.

8.12 Pharmacokinetic Analysis

Plasma S-888711 concentrations will be listed by nominal sampling time and sampling design group (intensive PK sampling or sparse PK sampling). Plasma S-888711 concentrations for patients who completed at least 5 days of study drug administration will be summarised by nominal sampling time and sampling design group. Summary statistics will include the number of non-missing observations (N), arithmetic mean (Mean), SD, and 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 will be calculated according to a formula CV% Geometric Mean = $[\exp(sd^2)-1]^{1/2} \times 100$, where sd is the standard deviation for natural logarithm (ln)-transformed data. Time course profiles for plasma concentration data will be presented graphically. Based on plasma concentration data on Days 5 and 6 and using non-compartmental methods, the following PK parameters will be calculated, whenever possible, for each patient who completed at least 5 days of study drug administration in the intensive PK sampling group:

C_{max} (ng/mL): Maximum plasma concentration

T_{max} (hr): Time to C_{max}

$AUC_{0-\tau}$ (ng·hr/mL): AUC over the dosing interval τ (ie, 24 hours), calculated by the trapezoidal method (Linear Up/Log Down Trapezoidal Method)

CL/F (L/hr): Apparent total clearance estimated according to: $CL/F=Dose/AUC_{0-\tau}$

The estimated PK parameters will be summarised with N, Mean, SD, CV%, geometric mean, CV% Geometric Mean, median, minimum, and maximum values. The T_{max} will be summarised with N, Mean, SD, CV%, median, minimum, and maximum values.

Specification of the PK parameters for analysis and the level of statistical significance, together with procedures for accounting for missing, unused or spurious data, procedures for reporting deviations from the original statistical plan, and the selection of patients to be included in the analyses population(s) will be presented in the report and/or the PK analysis plan, as appropriate.

PK parameters to be reported will be detailed in the PK analysis plan. Other parameters may be added if appropriate.

Non-compartmental PK calculations will be performed by using WinNonlin Version 6.2.1 or higher.

Population PK and PK/PD analyses will be planned and reported separately.

8.13 Interim Analysis

No interim analyses are planned for this study.

9. ADMINISTRATIVE CONSIDERATIONS

9.1 Investigators and Study Administrative Structure

Sponsor list and contact information	In Eastern and Western Europe, and Australia: Shionogi Ltd. 33 Kingsway, London, WC2B 6UF, United Kingdom Tel: [redacted] In North and South America, and Asia: Shionogi Inc. 300 Campus Drive Florham Park, NJ 07932, USA Tel: [redacted]
Sponsor's Representative:	[redacted] 33 Kingsway, London, WC2B 6UF, United Kingdom Tel: [redacted]
Sponsor's Study Manager:	[redacted] 33 Kingsway, London, WC2B 6UF, United Kingdom Tel: [redacted]
Medical Officer:	[redacted] 33 Kingsway, London, WC2B 6UF, United Kingdom Tel: [redacted]
Sponsor's Chief Medical Officer:	[redacted] Shionogi & Co., Ltd.

	[redacted] 12F, Hankyu Terminal Bldg., 1-4, Sh ba a 1-chome, Kita-ku, Osaka 530-0012, Japan Tel: [redacted]
Sponsor's Global Project Leader:	[redacted] Shionogi & Co., Ltd. [redacted] 12F, Hankyu Terminal Bldg., 1-4, Sh ata 1-chome, Kita-ku, Osaka 530-0012, Japan Tel: [redacted]
Investigator and Study Centre:	Multicentre global study
Medical Monitor:	[redacted] Tel: [redacted]
IVRS/IWRS:	Cenduit Europe Binningerstrasse 95, CH-4123 Allschwil, Switzerland Tel: [redacted]
Central Laboratory:	Quintiles Laboratories Europe Robert Stewart, Alba Campus, Rosebank, Livingston, West Lothian, Scotland, EH54 7EG, UK
Bioanalytical Laboratory:	inVentiv Health Clinical Lab 301D College Road East Princeton, NJ 08540, USA Tel: [redacted]
CRO (for study monitoring and its quality control):	Quintiles [redacted] Quintiles Hungary Ltd. H-1117 Budapest, Budfoki ut 91-93, Hungary Tel: [redacted] Email: [redacted] [redacted] Quintiles Italy LTd. Via Roma, 108 – Edificio F – Scala 2 Cassina De' Pecchi 20060, Italy Tel: [redacted] Email: [redacted]
Emergency Contact:	Medical Monitor: [redacted] The following additional number is also available for

	urgent contact: Tel: [redacted]

9.2 Institutional Review Board Approval

The IRB will safeguard the rights, safety, and well-being of patients in the study by reviewing the following study documentation: protocol, informed consent form, written information on patient recruitment procedures (if applicable), other written information given to patients, IB, safety updates, annual progress reports (if applicable), and any significant revisions to these documents. These documents will be provided to the IRB by the investigator or the sponsor. The IRB will be appropriately constituted in accordance with International Conference on Harmonisation (ICH) GCP, and local requirements, as applicable. The study will commence only after the IRB has given full approval and the investigator has received the document being approved.

Amendments to the protocol will be subject to the same requirements as the initial review. The investigator will submit periodic reports and updates to the IRB, as required, and will inform the IRB of any reportable AEs.

9.3 Ethical Conduct of the Study

The study will be conducted in accordance with all appropriate regulatory requirements and under the IRB-approved protocol. The study will be conducted in accordance with current ICH GCP, all appropriate patient privacy requirements, and the ethical principles outlined in the Declaration of Helsinki.

9.4 Patient Information and Consent

The investigator will generate an informed consent form for the study. The sponsor will provide the investigators with a proposed informed consent form that complies with ICH GCP guidelines and applicable regulatory requirements. The informed consent form will include all the elements required by ICH GCP plus any additional elements required due to local regulations. The informed consent form will be reviewed and approved by the appropriate IRB before use. The sponsor must agree to any changes to the proposed informed consent form suggested by the investigator prior to submission to the IRB, and the IRB-approved version must be provided to the site monitor following IRB approval.

Prior to each patient entering the study, the investigator or designee will explain the nature, purpose and methods, reasonably anticipated benefits and potential hazards of the study to them in simple terms using the IRB-approved informed consent form. The method of obtaining and documenting informed consent will comply with ICH GCP and all applicable regulatory requirement(s).

9.5 Patient Confidentiality

Patient privacy must adhere to all applicable data privacy laws and regulations. In order to maintain patient privacy, all CRFs, study drug accountability records, study reports, and communications will identify the patient by their patient number. The investigator will grant site monitor(s) and auditor(s) of the sponsor or designee, as well as regulatory authority(ies), access to all source documents for verification of data collected on the CRFs and for verification of the data collection process. The patient's confidentiality will

be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations. Appropriate consent and authorisations for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

Patient data collected on the CRF during the study will be documented in an anonymous manner and patients will only be identified by a patient identification number. In the event that it is necessary to identify a patient for safety or regulatory reasons, the sponsor and investigator are required to keep this information confidential.

9.6 Study Monitoring

The sponsor and designated study monitors will monitor the study to ensure that it is conducted in accordance with ICH GCP requirements and the IRB-approved protocol. Study monitoring will be performed by a representative of the sponsor (site monitor) through on-site monitoring visits as frequently as necessary and through frequent communications (e-mail, letter, telephone, and fax). The site monitor will review data recorded on the CRFs, verify the CRF entries directly against the source documents, collect any safety/efficacy information on patients, verify that amounts of unused study drug are accurate, and check retention of source documents and essential documents.

9.7 Case Report Forms and Source Documents

9.7.1 Case Report Forms

The term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study. The sponsor or designee will supply CRFs for each randomised patient. Historical information and study data, specified in the protocol, will be recorded on the CRFs by the investigator or designee. All patient data from each study visit must be collected on source documents and must be promptly entered on the CRFs in accordance with the specific instructions given. CRF entries will be performed by an investigator or designee, and the study coordinator who are authorised to complete such documentation. It is the investigator's responsibility to ensure completion and to review and approve all CRFs. CRFs must be signed by the investigator. These signatures serve to attest that the information contained on the CRFs is true. At all times, the investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered onto the CRFs. Patient source documents are the physician's patient records maintained at the trial site. In most cases, the source documents will be the hospital's or the physician's chart and information collected on the CRFs must match those charts.

In some cases, the CRF may also serve as the source document. In these cases, Shionogi and the investigator must prospectively document which items will be recorded in the source documents and for which items the CRF will stand as the source document.

If queries are generated by the sponsor or designee to the participating medical institutions for resolution, the CRF data will be changed or a response will be recorded in accordance with the specific instructions given.

A list of reference ranges for all laboratory tests to be undertaken will be part of the documentation collected prior to study initiation. These should be updated if they are changed during the study. If a central laboratory has been used to perform any or all of the tests, it is essential that all reference ranges for the laboratory tests analysed at that

laboratory should be collected.

9.7.2 **Source Documents**

Source documentation supporting the CRF data should indicate the patient's participation in the study, and should document the dates and details of all study procedures, AEs, and patient status. However, the following data can be directly recorded on the CRF:

- severity, seriousness, outcome, causal relationship to the study drug of AEs
- reason for withdrawal
- reason for use of concomitant therapy
- any comments inserted into CRF

The items listed below are only recorded on the CRF (ie, items automatically-calculated by the electronic data capture [EDC] system):

- age at informed consent
- total score and class of Child-Pugh
- body mass index

The investigator must maintain source documents, such as laboratory reports, complete medical history, and physical examination reports. All source documents should be accessible for verification by the site monitor, auditor, the IRB, or for inspections by the regulatory authorities. Direct access to these documents must be guaranteed by the investigator or designee, or the study coordinator, who must provide support at all times for these activities. The nature and location of all sources of original data required to complete the CRF will be identified by the sponsor and the site staff. If electronic records are maintained at the medical institution, the method of verification must be specified in documents within that medical institution.

9.7.3 **External Data**

The following data will not be included in the CRF. Those will be separately reported.

- laboratory data (expect for platelet count)
- plasma S-888711 concentrations

9.8 Committees

9.8.1 **Case Review Committee**

Prior to database lock, the sponsor, together with the medical officer, will review all data reported on the CRFs for all patients under blind conditions. At the case review committee meeting, the sponsor will decide which patients will be included in the analysis populations based on the definition of each population (see Section 8.3) and each patient's results. The case review committee will also evaluate whether medical decisions made by the investigators were appropriate for important data affecting the safety and efficacy endpoints.

9.8.2 Independent Safety Committee

An Independent Safety Committee will review results of thrombotic/thromboembolic events and report back to the sponsor. The procedures for review, including maintaining the blind, and for management of the committee will be specified in a separate document.

9.8.3 Coordinating Committee

Not applicable to this study.

9.9 Termination or Suspension of the Study

9.9.1 Termination or Suspension of the Entire Study

The sponsor may prematurely terminate or suspend the study at any time for the following reasons:

- Ensuring the safety of the patients is difficult due to safety concerns (eg, occurrence of many serious ADRs)
- Achieving the purpose of the study is considered impossible (eg, inadequate recruitment of patients)

If the study is prematurely terminated or suspended, the sponsor should promptly inform the investigators. The investigator or designee should promptly inform the participating patients and change the study medication to other appropriate therapy(ies).

For withdrawal criteria for individual patients, see Section 7.9.

9.9.2 Termination or Suspension of the Study by Medical Institution

The investigator may prematurely terminate or suspend the study at their medical institution with the agreement of the sponsor. This may be done at any time during the study if they consider that ensuring patient safety during the study is difficult due to safety concerns (eg, occurrence of many SAEs).

The sponsor may request that the investigator prematurely terminates or suspends the study at their medical institution at any time during the study if major violations/deviations of the protocol, other procedures, or ICH GCP have not been improved.

If the study is prematurely terminated or suspended, the investigator or designee should promptly inform the corresponding IRB and any participating patients, and should change the study medication to other appropriate therapy(ies).

9.10 Protocol Deviations and Modifications

The investigator will conduct the study in compliance with the protocol provided by the sponsor, which has received approval/favourable opinion by the IRB and the regulatory authority(ies). Modifications to the protocol should not be performed without agreement of both the investigator and the sponsor. Changes to the protocol will require written IRB approval/favourable opinion prior to implementation, except when a modification is needed to eliminate an immediate hazard(s) to the patients.

The investigator or designee should document any deviation from the protocol, together

with the reason for such a deviation. If the investigator deviates from the protocol or a protocol amendment in order to eliminate an immediate hazard(s) to the patients, they should submit a record of the deviation to the sponsor, the medical institution, and the IRB immediately. The IRB will provide an expedited review and grant approval/favourable opinion if appropriate. After the investigator has obtained approval/favourable opinion from the IRB, they should obtain written agreement for the change from the sponsor.

When deviations from the protocol are required to eliminate an immediate hazard(s) to patients, the investigator will contact the sponsor, if circumstances permit, to discuss the planned course of action. Any deviations from the protocol must be fully documented on the source documentation.

9.11 Data Management

The sponsor (Shionogi & Co., Ltd.) will be responsible for data management and data analysis. These procedures are specified in a separate document.

9.12 Retention of Data

To enable evaluations and/or audits from regulatory authorities or Shionogi, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRF, hospital records), all original signed informed consent forms, source documents, and detailed records of treatment disposition. The study documents should be retained by the investigator according to ICH GCP, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The investigator and study centre should take measures to prevent accidental or premature destruction of these documents.

If the sponsor is granted manufacturing and marketing approval for the drug, they will promptly notify the head of the study centre and the investigator.

Records will be retained for one of the following periods of time (whichever is longest):

- at least 2 years after the last marketing application approval
- 2 years after formal discontinuation of the clinical development of the investigational product

If the investigator relocates, retires, or for any reason withdraws from the study, Shionogi should be prospectively notified. The study documents must be transferred to an acceptable designee, such as another investigator, another institution, or to Shionogi. The investigator must obtain Shionogi's written permission before disposing of any records, even if the retention requirements have been met.

9.13 Quality Control and Assurance

The sponsor will implement and maintain quality control and quality assurance procedures with written standard operating procedures to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, ICH GCP, and all applicable regulatory requirements. This study will be conducted in accordance with the provisions of the Declaration of Helsinki and all revisions thereof, in accordance with ICH GCP, and as required by applicable regulatory requirements.

Necessary training for the study will be provided to investigators and any other required study centre personnel by the sponsor or appropriate designee prior to study initiation.

9.14 Publication and Disclosure Policy

All information on S-888711 supplied by the sponsor to the investigator is privileged and confidential. The investigator agrees to use this information to perform the study and will not use it for any other purposes without consent from the sponsor. It is understood that there is an obligation to provide the sponsor with complete data obtained during the course of the study. Information obtained from the clinical trial will be used for the development of S-888711 and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

The sponsor will retain ownership of all data. All proposed publications based on the study will be subject to the sponsor's approval requirements which will be detailed in the Clinical Study Agreement

The key design elements of this protocol will be posted in a publicly accessible database.

10. REFERENCE LIST

10.1 Reference Materials

S-888711 Investigator's Brochure Version 8

10.2 Publications

1. Roberts HW, Utuama OA, Klevens M, Teshale E, Hughes E, Jiles R. The contribution of viral hepatitis to the burden of chronic liver disease in the United States. Am J Gastroenterol. 2014;109(3):387-93.
2. Murphy SL, Xu J, Kochanek KD. Deaths: Final data for 2010. National Vital Statistics Reports. 2013;61(4). www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_04.pdf Accessed on 20 Jun 2014.
3. Blachier M, Leleu H, Peck-Radosavljevic M, Valla D-C, Roudot-Thoraval F. The burden of liver disease in Europe: a review of available epidemiological data. J Hepatol. 2013;58(3):593-608.
4. Rahimi RS, Rockey DC. Complications and outcomes in chronic liver disease. Curr Opin Gastroenterol. 2011;27(3):204-9.
5. Afdhal N, McHutchison J, Brown R, et al. Thrombocytopenia associated with chronic liver disease. J Hepatol. 2008;48(6):1000–7.
6. Hayashi H, Beppu T, Shirabe K, Maehara Y, Baba H. Management of thrombocytopenia due to liver cirrhosis: a review. World J Gastroenterol. 2014;20(10):2595-605.
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8. Blumberg N, Heal JM, Phillips GL. Platelet transfusions: trigger, dose, benefits, and risks. F1000 Med Rep. 2010;2:5. Published online Jan 27, 2010. doi: 10.3410/M2-5.
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10. Legler TJ, Fischer I, Dittmann J, Simson G, Lynen R, Humpe A, et al. Frequency and causes of refractoriness in multiply transfused patients. Ann Hematol. 1997;74:185-9.
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13. McHutchison GJ, Dusheiko G, Shiffman LM, et al. Eltrombopag for Thrombocytopenia in Patients with Cirrhosis Associated with Hepatitis C. N Engl J Med. 2007;357(22):716-24.

14. Afdhal NH, Giannini EG, Tayyab G, et al. Eltrombopag before procedures in patients with cirrhosis and thrombocytopenia. N Engl J Med. 2012;367(8):716-24.

15. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer. 1981;47(1):207-14.

16. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60(8):646-9.

17. The Eastern Cooperative Oncology Group. http://www.ecog.org/general/perf_stat.html. Accessed on 20 Jun 2014.

18. FDA draft guidance. Drug Interaction Studies Study Design, Data Analysis, Implications for Dosing, and Labelling Recommendations. February 2012.

Appendix 1: Time and Events Schedule

	Screening		Treatment Period							Post-treatment Period (Invasive Procedure, Days 9 to 14)											With-drawal[a]	Unsche duled[b]
Study Day	From Day −28	Day 1		Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 17	Day 21	Day 28	Day 35		
		Pre-dosing	Post-dosing																			
Informed consent	X																					
Inclusion/exclusion criteria	X																					
Demography (including body weight and height)	X																					
Medical history	X																					
Enrolment (IVRS/IWRS)	X																					
Randomisation (IVRS/IWRS)		X																				
Drug assignment (IVRS/IWRS)							X[c]	(X)[c]	(X)[c]													
Concomitant medication	◄	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─	─►		
ECOG performance status	X																					
Type of CLD and severity of liver disorder (Child-Pugh)	X																					
Gastro-oesophageal varices[d]	X																					
Splenomegaly and severity of ascites[e]	X																					
Pregnancy test (urine)	X																			X	X	
Physical examination	X	X					X	X	X	X		X		X		X		X	X	X	X	X[b]
Portal vein thrombosis assessment [f]	X													◄	─	X[g]	─	─►			X	X[b]
Portal blood flow (direction) [h]	X													◄	─	X[g]	─	─►			X	X[b]
WHO Bleeding Scale	X	X								X				◄	─	X[g]	─	─►		X	X	
Blood pressure, pulse rate	X	X					X			X		X		X		X		X	X	X	X	X[b]
Electrocardiography	X																			X	X	X[b]
Platelet count (local laboratory)	X	X					X[i]	X[i]	X[i]	X		X		X		X	X	X	X	X	X	X[b]
Haematology except for platelet count (central laboratory)	X	X								X						X				X	X	X[b]
Blood chemistry	X	X								X						X				X	X	X[b]

	Screening		Treatment Period							Post-treatment Period (Invasive Procedure, Days 9 to 14)											With-drawal[a]	Unsche duled[b]
Study Day	From Day −28	Day 1 Pre-dosing	Day 1 Post-dosing	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 17	Day 21	Day 28	Day 35		
Blood coagulation/fibrinolysis assay[j]	X	X								X						X				X	X	X[b]
Immunological tests/other tests	X																					
Adverse events	◄	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	►
Administration of study medication			X	X	X	X	X[c,k]	X[c,k]	X[c,k]													
Invasive procedure											◄	—	X[l]	—	—	►						
Sampling for plasma drug concentration (Sparse PK)[m]							X	X	X													
Sampling for plasma drug concentration (Intensive PK)[n]							X	X	X													

a Applied to both study medication withdrawn and study assessment withdrawn, except for a patient with drug withdrawn because of the administration stopping criterion (ie, platelet count $\geq 50 \times 10^9$/L with an increase of $\geq 20 \times 10^9$/L from baseline).
b Only necessary assessments will be performed.
c If platelet count on Day 5, 6 or Day 7 is $\geq 50 \times 10^9$/L with an increase of $\geq 20 \times 10^9$/L from baseline, a patient must stop taking study medication.
d Confirmed by upper gastrointestinal endoscopy. If data on upper gastrointestinal endoscopy are obtained within 180 days before randomisation, the data can be used.
e Confirmed by ultrasonography, CT, or MRI. If ultrasonography, CT, or MRI is performed within 28 days before randomisation, the image can be used for assessing the presence or absence of splenomegaly.
f Confirmed by ultrasonography, CT, or MRI in the Screening period and after the invasive procedure. The Screening investigation should be arranged as close to randomisation as possible. However, if gastro-oesophageal varices are treated, portal vein thrombosis will be confirmed with the image obtained after the treatment.
g Performed within 3 to 10 days after the invasive procedure. When any additional invasive procedure is performed, the assessment of bleeding events as graded on the WHO Bleeding Scale, portal vein thrombosis, and portal blood flow will be performed before and after the invasive procedure.
h Confirmed by Doppler ultrasonography (at Screening, the investigation should be as close to randomisation as possible).
i Blood samples will be collected before study medication.
j Antithrombin III activity, fibrinogen, fibrin degradation products, D-dimer, Protein C activity, free protein S antigen, von Willebrand factor activity will be performed only at Screening. Prothrombin time (international normalised ratio value) and activated partial thromboplastin time will be performed at Screening, Day 1, Day 8, Day 14, and Day 35.
k Administered after platelet count is confirmed and drug assignment.
l Performed between Days 9 and 14.
m All patients except for Intensive PK; pre-dose, 2 to 4 hours post-dose on Day 5, and pre-dose on Days 6 and 7.
n At least 20 patients; pre-dose, 2, 4, 6, 8 hours post-dose on Day 5, pre-dose on Days 6 and 7.

Appendix 2: List of Laboratory Tests

Test	Items Evaluated
Haematology	Platelet count
Haematology (except for platelet count)	Red blood cell count, white blood cell count, haemoglobin, and haematocrit
Blood chemistry	Aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, gamma glutamyl transferase, alkaline phosphatase, total bilirubin, bilirubin direct, indirect bilirubin, total protein, albumin, blood urea nitrogen, serum creatinine, sodium, potassium, chloride, and calcium
Blood coagulation/ fibrinolysis assay	Prothrombin time (international normalised ratio value), activated partial thromboplastin time, antithrombin III activity[a], fibrinogen[a], fibrin degradation products[a], D-dimer[a], protein C activity[a], free protein S antigen[a], and von Willebrand factor activity[a]
Immunological[a]	Platelet-associated IgG, antiplatelet antibody, Helicobacter pylori antibody IgG
Other[a]	Thrombopoietin

a Only at Screening.

Appendix 3: Child-Pugh Class

Child-Pugh Class[16]

Point / Measurement	1 point	2 points	3 points
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)
Ascites	None	Mild	Moderate to Severe
Serum bilirubin (μmol/L [mg/dL])	<34 (<2.0)	34 – 50 (2.0 - 3.0)	>50 (>3.0)
Serum albumin (g/L)	>35	28 - 35	<28
Prothrombin time-international normalised ratio value (PT-INR)	<1.71	1.71 - 2.30	>2.30

Points for each measurement are totalled and the total score is used for determination of classification: Class A, 5 to 6 points; Class B, 7 to 9 points; Class C, 10 to 15 points.

Appendix 4: List of Example Invasive Procedures

Region	Type of Surgery
Liver	• radiofrequency ablation (RFA) • percutaneous microwave coagulation therapy (PMCT) • percutaneous ethanol injection therapy (PEIT) • transcatheter arterial embolisation (TAE)/transhepatic arterial infusion (TAI)/transcatheter arterial chemoembolisation (TACE) • endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) • laparoscopic radiofrequency ablation (LRA) • laparoscopic microwave coagulation (LMC)
Biliary-pancreas	• endoscopic metallic stenting (EMS) • endoscopic sphincteropapillotomy (EST) • endoscopic papillary balloon dilatation (EPBD) • endoscopic ultrasound-guided fine needle aspiration (EUS-FNA)
Gastrointestinal tract	• endoscopic polypectomy • endoscopic submucosal dissection (ESD) • endoscopic mucosal resection (EMR) • percutaneous endoscopic gastrostomy (PEG) • endoscopic variceal ligation (EVL) • endoscopic injection sclerotherapy (EIS) • endoscopic ultrasound-guided fine needle aspiration (EUS-FNA)
Urinary system	• transurethral resection of the bladder tumour (TURBT) • transurethral ureterolithotripsy (TUL)
Other regions	• percutaneous needle biopsy • laparoscopy • arthroscopic surgery • endoscopy with possible biopsy • various paracenteses • tooth extraction

Appendix 5: ECOG Performance Status

ECOG Performance Status[17]

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix 6: List of P-gp and BCRP Inhibitors

List of P-gp and BCRP Inhibitors[18]

P-gp Inhibitor	BCRP Inhibitor
Amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, and ritonavir, quercetin, quinidine, ranolazine, ticagrelor, verapamil	Cyclosporine, elacridar (GF120918), eltrombopag, gefitinib

Appendix 7: WHO Bleeding Scale

WHO Bleeding Scale[15]

Grade	WHO Bleeding Scale
0	No bleeding
1	Petechial bleeding
2	Mild blood loss (clinically significant)
3	Gross blood loss, requiring transfusion (severe)
4	Debilitating blood loss, retinal or cerebral, associated with fatality

Appendix 8: Sponsor Signatures

SPONSOR SIGNATURE

Study Title: A Phase 3 Randomised, Double-blind, Placebo-controlled Study to Assess the Safety and Efficacy of S-888711 (Lusutrombopag) for the Treatment of Thrombocytopenia in Patients with Chronic Liver Disease Undergoing Elective Invasive Procedures (L-PLUS 2)

Study Number: 1423M0634

This clinical study protocol was subject to critical review and has been approved by the sponsor.

[redacted]

3 Feb 2015
Date

Shionogi & Co., Ltd.

SPONSOR SIGNATURE

Study Title: A Phase 3 Randomised, Double-blind, Placebo-controlled Study to Assess the Safety and Efficacy of S-888711 (Lusutrombopag) for the Treatment of Thrombocytopenia in Patients with Chronic Liver Disease Undergoing Elective Invasive Procedures (L-PLUS 2)

Study Number: 1423M0634

This clinical study protocol was subject to critical review and has been approved by the sponsor:

[redacted]

10-FEB-2015

Date

Shionogi Ltd.

Appendix 9: Investigator's Signature

INVESTIGATOR SIGNATURE

Study Title: A Phase 3 Randomised, Double-blind, Placebo-controlled Study to Assess the Safety and Efficacy of S-888711 (Lusutrombopag) for the Treatment of Thrombocytopenia in Patients with Chronic Liver Disease Undergoing Elective Invasive Procedures (L-PLUS 2)

Study Number: 1423M0634

I agree with the content of this protocol and the confidential nature of the documentation made as part of this study. I also acknowledge that the sponsor of the study has the right to discontinue the study at any time. I have read the protocol and understand it and will work according to it and according to the principles of GCP, applicable laws and regulations, and the Declaration of Helsinki.

Principal Investigator **Date**

Name and Qualifications:

Institution and Address: