16.1.1 Protocol and Protocol Amendments

The final study protocol is provided on the following pages.

Revisions to V6.0: 31 May 2016 (Amendment 03) Date: V7.0: 02 Dec 2016 (Amendment 04)		
Change	**Rationale**	**Affected Protocol Sections**
Sample size reduced from approximately 300 subjects to approximately 200 subjects	After consultation with the FDA, it was decided that the current study has reached adequate enrollment to demonstrate the safety and benefit of avatrombopag in reducing the need for platelet transfusion in subjects with thrombocytopenia and liver disease undergoing an elective procedure.	**Synopsis** – • Number of Subjects • Sample Size Rationale Section 9.3 Section 9.4.3 Section 9.7.2
The secondary endpoint, proportion of subjects with a World Health Organization (WHO) bleeding score ≥2 after randomization and up to 7 days following an elective procedure, will be an exploratory endpoint	Given the rare occurrence of bleeding events (less than expected), this endpoint is better suited as an exploratory endpoint.	**Synopsis** – • Secondary Objectives • Exploratory Objectives • Secondary Endpoints • Exploratory Endpoints • Secondary Efficacy Variable Analyses • Exploratory Efficacy Variables Section 8.2 Section 8.3 Section 9.7.1.1 Section 9.7.1.6

Revisions to V5.0: 22 June 2015 (Amendment 02) Date: V6.0: 31 May 2016 (Amendment 03)		
Change	**Rationale**	**Affected Protocol Sections**
Clarification to Inclusion Criteria #3: replace the word "change" with the word "increase	Per FDA request	**Synopsis** – • Inclusion Criteria Section 9.3.1

REVISION HISTORY

Revisions to V4.0: 12 Nov 2013 (Amendment 01) Date: V5.0: 22 June 2015 (Amendment 02)		
Change	**Rationale**	**Affected Protocol Sections**
Revised the risk of bleeding associated with procedures	Additional procedures included in the source article (Malloy et al., 2009) that originated the initial classification were added. Ongoing study observations, supported by key opinion leader (KOL) review and current literature review resulted in additional updates in the bleeding risk categories classification	**Synopsis** – • Study Design • Statistical Methods • Efficacy Analyses Section 9.1.2.3 • Table 1 Section 9.7.1.6
Clarification of Inclusion #3 that subjects scheduled to undergo a permitted elective procedure who will require a platelet transfusion **unless there is a clinically significant change to platelet count from baseline**	Clarification	**Synopsis** – • Inclusion Criteria Section 9.3.1
Revised the exclusion around hemoglobin changing the upper limit from 16 to 17 g/dL and removed the white blood cell count and serum sodium levels exclusion criteria. Subjects who screen failed previously will be permitted to rescreen due to removal of this criteria.	Based upon feedback received from the KOL that these criteria are in contradiction with the requirement for platelet count $<50 \times 10^9$/L (ie, subjects meeting such lab criteria would be relatively too healthy to present with such a low platelet count). Other existing criteria (eg, MELD score and BCLC) will ensure subjects are not too compromised. This also provides for a more diverse population by dropping these restrictions.	**Synopsis** – • Exclusion Criteria Section 9.1.1.1 Section 9.3.2
Addition of eltrombopag and romiplostim as prohibited	As eltrombopag and romiplostim are used off-label for this indication, both approved	**Synopsis** – • Prohibited Concomitant Therapy

Revisions to V4.0: 12 Nov 2013 (Amendment 01) Date: V5.0: 22 June 2015 (Amendment 02)		
Change	**Rationale**	**Affected Protocol Sections**
medication	thrombopoietin receptor agonists were added	Section 9.4.7.3
Added an evaluation for platelet aggregation to be measured at selected sites	Japan's Pharmaceuticals and Medical Devices Agency (PMDA) requires exploratory assessment of platelet aggregation as part of the platelet function study.	**Synopsis** – • Safety Assessments Section 9.5.1.5, • Table 4, Table 5 Section 11.3
Updated study director and medical monitor information	Change in Eisai staffing	Protocol Signature Page
Clarified in the appendix the fasting glucose laboratory result should only be considered a treatment-emergent significant abnormality if the result is within normal limits at baseline and has increased in severity to meet the sponsor's grading criteria for laboratory values of Grade 3 or above when fasting.	Clarification	Appendix 2

Revisions to previous V3.0, 29 Sep 2013 **Date: V4.0 (Amendment 01): 12 Nov 2013**		
Change	**Rationale**	**Affected Protocol Sections**
• Addition of tranexanic acid as a rescue procedure when used specifically for bleeding	Changes were made upon regulatory agency request during a Voluntary Harmonisation Procedure submitted to the following EU Member States: Austria, Belgium, France, Germany, Hungary, Italy, Spain, and United Kingdom.	● Synopsis, Study Design ● Section 9.1.2.3 ● Section 9.5.1.3
• Inclusion of specific examples of genetic prothrombotic syndromes (eg, Factor V Leiden; prothrombin G20210A; ATIII deficiency etc.)	For clarity	● Synopsis, Exclusion Criteria ● Section 9.3.2

Revisions to previous Version 2.0, 24 Jul 2013 **Date: V3.0, 29 Sep 2013**		
Change	**Rationale**	**Affected Protocol Sections**
• Removal of language indicating a training program will be implemented for the sonography operator	Administrative change – incorrect language used to describe sonography operation	• Appendix 3
• Medical monitor updated	Change in Eisai staffing	• Protocol Signature Page

Revisions to previous Version 1.0, 21 Mar 2013 **Date: V2.0, 24 Jul 2013**		
Change	**Rationale**	**Affected Protocol Sections**
• Sponsor information updated to title page	Japanese address required as 310 & 311 are global studies	• Title page
• The higher baseline platelet count cohort was changed from 40 to $\leq 50 \times 10^9$/L to 40 to $<50 \times 10^9$/L which resulted in endpoints changing accordingly.	Required due to the inclusion criterion and baseline platelet count cohort change from $\leq 50 \times 10^9$/L to $<50 \times 10^9$/L.	• Synopsis – Objectives • Synopsis – Study Design • Synopsis – Exploratory Endpoints • Section 7 • Section 8 • Section 9
• Added exploratory objective and endpoint to characterize platelet count changes from baseline, the extent of platelet transfusion use, and assess the severity of any bleeding events	Eisai agrees with CHMP that the BARC bleeding scale could be used in addition to the WHO bleeding score and therefore proposes it be included as an exploratory endpoint.	• Synopsis – Exploratory Objectives • Synopsis – Exploratory Endpoints • Section 8.3
• Inclusion criteria age changed to include those subjects ≥18 years of age for both US and rest of world	Brings protocol into line with current pediatric strategy	• Synopsis – Inclusion Criteria • Section 9.3.1
• Occurrence of bleeding as measured by World Health Organization (WHO) bleeding score and Bleeding Academic Research Consortium (BARC) bleeding scale	EMA requested that the BARC bleeding scale be used in addition to the WHO bleeding score. EMA agreed to Eisai proposal for BARC scale to be included as an exploratory endpoint.	• Synopsis – Efficacy Assessments • Section 9.2 • Section 9.5 • Section 9.7.1

Revisions to previous Version 1.0, 21 Mar 2013 **Date: V2.0, 24 Jul 2013**		
Change	**Rationale**	**Affected Protocol Sections**
• The hypothesis testing for the combined group (regardless of baseline platelet count cohort) was removed from the primary efficacy analysis and the first 2 secondary efficacy variable analyses. The primary efficacy variable analysis to clarify the null hypothesis will be tested separately within each baseline cohort.	Agreed with both FDA and EMA	• Synopsis – Primary Efficacy Variable Analysis • Section 9.7.1.6
• This study will be considered as positive if statistical significance is achieved for the primary efficacy endpoint for both baseline platelet count cohorts.	Statistical analysis changes requested by the FDA	• Synopsis – Primary Efficacy Variable Analysis • Section 9.7.1.6
• Clarification that the safety parameters the DSMB will review will include variables that are also being assessed in this study for efficacy	Requested as clarification during PRC review	• Synopsis, Interim Analysis • Section 9.7.3
• Sample size /power calculation was removed for the test on the combined group	Requested as clarification by the FDA	• Synopsis, Sample Size Rationale • Section 9.7.2

1 TITLE PAGE

CLINICAL STUDY PROTOCOL

Study Protocol Number:	E5501-G000-311
Study Protocol Title:	A Randomized, Global, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Once-daily Oral Avatrombopag for the Treatment of Adults with Thrombocytopenia Associated with Liver Disease Prior to an Elective Procedure
Sponsor:	Eisai Inc. 155 Tice Boulevard Woodcliff Lake New Jersey 07677 US Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112 8088 Japan
Investigational Product Name:	E5501/avatrombopag maleate
Indication:	Treatment of Thrombocytopenia in Patients with Chronic Liver Disease Undergoing an Elective Procedure
Phase:	3
Approval Date:	V3.0 29 Sep 2013 (original protocol) V4.0 12 Nov 2013 (Amendment 01) V5.0 22 Jun 2015 (Amendment 02) V6.0 31 May 2016 (Amendment 03) V7.0 02 Dec 2016 (Amendment 04)
IND Number:	76,680
EudraCT Number:	2013-000934-36
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.

Confidentiality Statement:

This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.
E5501

Name of Active Ingredient
Avatrombopag maleate

Study Protocol Title
A Randomized, Global, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Once-daily Oral Avatrombopag for the Treatment of Adults with Thrombocytopenia Associated with Liver Disease Prior to an Elective Procedure

Investigators
To be determined

Sites
Approximately 80 to 100 sites worldwide

Study Period and Phase of Development
Approximately 20 months
Phase 3

Objectives

Primary Objective

To confirm that avatrombopag (60 mg avatrombopag for subjects with platelet count $<40 \times 10^9$/L and 40 mg avatrombopag for subjects with platelet count from 40 to $<50 \times 10^9$/L) is superior to placebo in removing the need for platelet transfusions or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure in subjects with chronic liver disease who have thrombocytopenia.

Secondary Objectives (revised per Amendment 04)

- To confirm that avatrombopag is superior to placebo in achieving a platelet count of $\geq 50 \times 10^9$/L on Procedure Day in the proposed target population
- To confirm that avatrombopag is superior to placebo in elevating platelet counts from baseline on Procedure Day in the proposed target population
- To evaluate the safety of avatrombopag in the proposed target population

Exploratory Objectives

- To characterize the pharmacokinetics and the relationship between avatrombopag plasma concentrations and platelet count using the population approach
- To characterize platelet count changes from baseline, the extent of platelet transfusion use, evaluate the incidence of bleeding events, and assess the severity of any bleeding events (revised per Amendment 04)

- To assess the health economic impact associated with minimizing the need for platelet transfusions and any rescue procedure for bleeding associated with an elective procedure

Study Design

This is a global, multicenter, randomized, double-blind, placebo-controlled, parallel group study using avatrombopag to treat adults with thrombocytopenia associated with liver disease. Subjects will be enrolled into 2 cohorts according to mean baseline platelet count and, within each baseline platelet count cohort will be further stratified by risk of bleeding associated with the elective procedure (low, moderate, or high) and hepatocellular carcinoma (HCC) status (Yes or No). Neither baseline platelet count cohort will comprise greater than 55% of the total number of subjects enrolled into the study.

Within the **lower** baseline platelet count cohort ($<40 \times 10^9$/L) and each stratum, subjects will be randomized in a 2:1 ratio to receive avatrombopag or placebo as follows:

- 60 mg avatrombopag on Days 1 to 5 (Group A: avatrombopag, lower baseline platelet count)
- Matching placebo on Days 1 to 5 (Group B: placebo, lower baseline platelet count)

Within the **higher** baseline platelet count cohort (from 40 to $<50 \times 10^9$/L) and each stratum, subjects will be randomized in a 2:1 ratio to receive avatrombopag or placebo as follows:

- 40 mg avatrombopag on Days 1 to 5 (Group C: avatrombopag, higher baseline platelet count)
- Matching placebo on Days 1 to 5 (Group D: placebo, higher baseline platelet count)

Platelet counts must be measured on 2 separate occasions, during the Screening Period and at Baseline, and must be performed at least 1 day apart with neither platelet count $>60 \times 10^9$/L. The mean of these 2 platelet counts (mean baseline platelet count $<50 \times 10^9$/L) will be used for entry criteria.

This study will consist of 3 phases: Prerandomization, Randomization, and a Follow-up Phase. The Prerandomization Phase includes 1 Screening Visit that will take place from Day -14 through Day -1; the Randomization Phase includes the Baseline Period, Treatment Period, and Procedure Day Period (5 to 8 days after last dose of study drug [Study Day 10 to 13]). The Follow-up Phase comprises 2 visits: 7 days post Procedure Day and 30 days after receiving the last dose of study drug.

The elective procedure for those subjects whose preprocedural platelet count is $>200 \times 10^9$/L on Visit 4 (Procedure Day) may be delayed at the discretion of the investigator until platelet counts are below 200×10^9/L. All subjects whose platelet count exceeds 200×10^9/L will be required to have a Doppler assessment at Visit 5. For any subjects where the presence of a portal vein thrombosis (PVT) is suspected, confirmation of diagnosis via computerized tomography (CT) scan or magnetic resonance imaging (MRI) should be performed and treatment for PVT initiated per local guidelines.

Permitted procedures and the risk of bleeding associated with each procedure are listed in the following table. It is planned that no fewer than 10% of subjects will be enrolled into the high risk group and no more than 60% of subjects in the low risk group.

(table revised per Amendment 02)

Risk of Bleeding Associated with Procedure	Procedure
Low risk	Paracentesis
	Thoracentesis
	Gastrointestinal endoscopy with or without plans for biopsy, colonoscopy, polypectomy, or variceal banding
Moderate risk	Liver biopsy
	Bronchoscopy with or without plans for biopsy
	Ethanol ablation therapy or chemoembolization for HCC
High risk	Vascular catheterization (including right side procedures in subjects with pulmonary hypertension)
	Transjugular intrahepatic portosystemic shunt
	Dental procedures
	Renal biopsy
	Biliary interventions
	Nephrostomy tube placement
	Radiofrequency ablation
	Laparoscopic interventions

Level of risk based on key opinion leader (KOL) input and Malloy PC, Grassi CJ, Kundu S, Gervais DA, Miller DL, Osnis RB, et al. for the Standards of Practice Committee with Cardiovascular and Interventional Radiological Society of Europe (CIRSE) Endorsement. Consensus guidelines for periprocedural management of coagulation status and hemostasis risk in percutaneous image-guided interventions. J Vasc Interv Radiol 2009; 20:S240–9.

Subjects who have an International Normalization Ratio (INR) >1.6 should be treated with fresh frozen plasma (FFP) or other appropriate therapies, where indicated, as per local guidelines and practices.

The following are considered as rescue procedures when used specifically for bleeding:

- Platelet transfusion
- FFP
- Cryoprecipitate
- Vitamin K (phytonadione)
- Desmopressin
- Recombinant activated factor VII
- Aminocaproic acid
- Tranexanic acid (added per Amendment 01)
- Whole blood transfusion
- Packed red cell transfusion
- Surgical intervention or interventional radiology

The end of the study will be the date of the clinical database lock (ie, when all study data are collected and data validation is complete).

Number of Subjects

Approximately 200 subjects (revised per Amendment 04)

Inclusion Criteria

1. Subjects ≥18 years of age at Screening with chronic liver disease
2. Subjects who have a mean baseline platelet count of $<50 \times 10^9$/L. Platelet counts must be measured on 2 separate occasions, during the Screening Period and at Baseline, and must be performed at least 1 day apart with neither platelet count $>60 \times 10^9$/L. The mean of these 2 platelet counts (mean baseline platelet count) will be used for entry criteria and for assignment to the low or high baseline platelet count cohort.
3. Subjects scheduled to undergo a permitted elective procedure who, in the opinion of the investigator, will require a platelet transfusion to address a risk of bleeding associated with the procedure unless there is a clinically significant increase in platelet count from baseline (revised per Amendments 02 and 03)
4. Model For End-stage Liver Disease (MELD) score ≤24 at Screening
5. If taking inhibitors of P glycoprotein (P-gp), except for verapamil, dose must be stable for 7 days prior to Screening
6. Provide written informed consent
7. Willing and able to comply with all aspects of the protocol

Exclusion Criteria (revised per Amendment 02)

1. Any history of arterial or venous thrombosis, including partial or complete thrombosis
2. Evidence of thrombosis (partial or complete) in the main portal vein, portal vein branches, or any part of the splenic mesenteric system at Screening
3. Portal vein blood flow velocity rate <10 cm/second at Screening
4. Hepatic encephalopathy that cannot be effectively treated
5. Subjects with HCC with Barcelona Clinic Liver Cancer (BCLC) staging classification C or D
6. Platelet transfusion or receipt of blood products containing platelets within 7 days of Screening. However packed red blood cells are permitted.
7. Heparin, warfarin, nonsteroidal anti-inflammatory drugs (NSAID), aspirin, verapamil, and antiplatelet therapy with ticlopidine or glycoprotein IIb/IIIa antagonists (eg, tirofiban) within 7 days of Screening
8. Use of erythropoietin stimulating agents within 7 days of Screening
9. Interferon (IFN) use within 14 days of Screening
10. Estrogen-containing hormonal contraceptive or hormone replacement therapy use within 30 days of Screening
11. Active infection requiring systemic antibiotic therapy within 7 days of Screening. However, prophylactic use of antibiotics is permitted.
12. Alcohol abuse, alcohol dependence syndrome, drug abuse, or drug dependence within

6 months of the study start (unless participating in a controlled rehabilitation program) or acute alcoholic hepatitis (chronic alcoholic hepatitis is allowed) within 6 months of the study start

13. Elective procedure performed prior to Visit 4 (Procedure Day)
14. Known to be human immunodeficiency virus positive
15. Any clinically significant acute or active bleeding (eg, gastrointestinal, central nervous system)
16. Known history of any primary hematologic disorder (eg, immune thrombocytopenic purpura, myelodysplastic syndrome)
17. Known medical history of genetic prothrombotic syndromes (eg, Factor V Leiden; prothrombin G20210A; ATIII deficiency etc.) (revised per Amendment 01)
18. Subjects with a history of significant cardiovascular disease (eg, congestive heart failure New York Heart Association Grade III/IV, arrhythmia known to increase the risk of thromboembolic events [eg, atrial fibrillation], coronary artery stent placement, angioplasty, and coronary artery bypass grafting)
19. Females of childbearing potential who have had unprotected sexual intercourse within 30 days before study entry and who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a progesterone-only contraceptive implant/injection, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 30 days after study drug discontinuation. If currently abstinent, the subject must agree to use a double-barrier method as described above if she becomes sexually active during the study period or for 30 days after study drug discontinuation. All females will be considered to be of childbearing potential unless they are postmenopausal (at least 12 months consecutive amenorrhea in the appropriate age group and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, hysterectomy, or bilateral oophorectomy) at least 1 month before dosing.
20. Females who are lactating or pregnant at Screening or Baseline (as documented by a positive serum beta-human chorionic gonadotropin [β-hCG] test with a minimum sensitivity 25 IU/L or equivalent units of β-hCG). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
21. Post liver transplant subjects
22. Any subject who has previously received avatrombopag
23. Hypersensitivity to avatrombopag maleate or any of its excipients
24. Hemoglobin levels ≤8.0 or ≥18.0 g/dL for men and >15 for women at Screening, with hematocrit ≥54% for men and ≥45% for women
25. Current malignancy including solid tumors and hematologic malignancies (except HCC)
26. Any history of concomitant medical condition that, in the opinion of the investigator(s), would compromise the subject's ability to safely complete the study

27. Currently enrolled in another clinical trial with any investigational drug or device within 30 days of Screening

Study Treatments

Test drug

Subjects will be instructed to take avatrombopag 20-mg tablets or matching placebo orally, once daily, with a meal, as follows:

- Group A (avatrombopag, lower baseline platelet count): 60 mg avatrombopag (3 × 20-mg tablets) once daily on Days 1 through 5
- Group B (placebo, lower baseline platelet count): placebo (3 × 20-mg matching placebo tablets) once daily on Days 1 through 5
- Group C (avatrombopag, higher baseline platelet count): 40 mg avatrombopag (2 × 20-mg tablets) once daily on Days 1 through 5
- Group D (placebo, higher baseline platelet count): placebo (2 × 20-mg matching placebo tablets) once daily on Days 1 through 5

Duration of Treatment

Each subject will receive study drug for 5 days

Concomitant Drugs/Therapy

Permitted Concomitant Therapy

Subjects should be instructed to contact site personnel before starting any new medications or treatments. Medications or treatments not specified as prohibited (see below) are permitted during the study. Medications used by the subject during the month before Visit 1 (Screening) will be recorded in the subject's case report form.

All prescription drugs, herbal products, nutritional supplements (including vitamins), and over-the-counter medications are to be recorded, as well as any changes in concomitant medications, including dose, after Visit 1 and while the subject is in the study. Stable doses of inhibitors of P-gp (excluding verapamil) are permitted during the study. The dose of these medications should remain unchanged until the first postprocedure visit (Visit 5).

Subjects may receive therapy if clinically indicated as rescue therapy for bleeding.

Prohibited Concomitant Therapy

Erythropoietin stimulating agents are prohibited throughout the study. Interferon use is prohibited during the study; however, at the investigator's discretion, subjects may restart IFN therapy if clinically indicated during the Follow-up Phase.

Eltrombopag, romiplostim, heparin, warfarin, NSAIDs, aspirin, verapamil, estrogen, and antiplatelet therapy with ticlopidine or glycoprotein IIb/IIIa antagonists (eg, tirofiban) are prohibited. (revised per Amendment 02) Aspirin, for antiplatelet therapy, can be prescribed at the discretion of the investigator in subjects in which the platelet count rises and who are believed to have an increased risk of thrombosis. In subjects where use of aspirin is contraindicated, an alternate antiplatelet therapy such as a platelet adenosine diphosphate receptor inhibitor (eg, clopidogrel) can be prescribed. It should be noted that clopidogrel should

be used with due consideration in subjects with liver disease. Lack of activation due to liver disease could lead to a reduction in activation of the prodrug. In addition, as clopidogrel is activated by the cytochrome P450 (CYP) system, care is required when administering clopidogrel to liver patients and co-administering clopidogrel with agents that are substrates or inhibitors of CYP.

Assessments

Efficacy Assessments

- The number of transfusions administered and units given per transfusion
- Any rescue procedure for bleeding
- Platelet counts as measured by local laboratory will be measured at Screening (Days -14 to -1) and at Baseline (Day 1), then on the Procedure Day (Day 10), 7 days postprocedure and Day 35
- Occurrence of bleeding as measured by World Health Organization (WHO) bleeding score and Bleeding Academic Research Consortium (BARC) bleeding scale

Pharmacokinetic Assessments

The pharmacokinetics of avatrombopag and effects of covariates will be assessed using population modeling. A total of 3 blood samples for pharmacokinetic (PK) analysis will be collected. One sample will be collected on Day 1 between 2 to 6 hours postdose. Two samples will be collected on Day 4 (±1 day): a predose sample within 2 hours prior to dosing and a second sample between 2 to 6 hours postdose.

Pharmacodynamic Assessments

Platelet count will be measured by local laboratory in all subjects at least 1 day apart at Screening (Days -14 to -1) and Baseline (Day 1), then on the Procedure Day (Day 10), 7 days postprocedure, and Day 35.

Pharmacokinetic/Pharmacodynamic Assessments

The relationship between avatrombopag plasma concentrations and platelet count will be evaluated using population PK/pharmacodynamic (PD) modeling. Effects of covariates on the PD parameters will be evaluated.

Pharmacogenomic/Pharmacogenetic Assessments

Not applicable

Safety Assessments

Safety assessments will consist of monitoring and recording of all adverse events (AEs) and serious adverse events (SAEs), including platelet transfusion-related complications; routine laboratory evaluation for hematology, serum chemistry, and urine values; periodic measurement of vital signs and electrocardiograms (ECGs); the performance of physical examinations; and Doppler sonography. An independent Data Safety Monitoring Board (DSMB) will be established in order to ensure the safety of the subjects.

At selected sites, platelet function will also be measured using specified flow cytometric markers or platelet aggregometry. (revised per Amendment 02)

Health Economic Assessments

The health economic assessment consists of translating the primary efficacy variable, reduced need or reduction in the proportion of platelet transfusions in the avatrombopag study arm compared to the placebo arm. Specifically, the following health care resource utilization is assessed: (including any rescue treatment, procedure, and laboratory test for bleeding including the number of transfused platelet units, the supply from which the transfused platelet units were procured including whole blood platelets from a random donor pool (if known) with or without leukocyte depletion, as an apheresis product (as platelets alone) from a single donor and/or autologous blood donation, number of hospital days, number of intensive care bed-days, number of outpatient visits to the hospital's outpatient department, the clinic, the physician's office, home health care or other place of service, and health care resource utilization related to other transfusion-related complications during all scheduled and unscheduled visits will be collected during all scheduled and unscheduled visits.

Bioanalytical Methods

Plasma samples will be assayed for avatrombopag concentrations using a validated liquid chromatography-tandem mass spectrometry method. Lower limit of quantification is 1.00 ng/mL.

Statistical Methods

Study Endpoints

Primary Endpoint

Proportion of subjects who do not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure

Secondary Endpoints

- Proportion of subjects who achieve platelet counts of $\geq 50 \times 10^9$/L on Procedure Day (ie, prior to receiving a platelet transfusion or undergoing the elective procedure)
- Change from baseline in platelet count on Procedure Day (ie, prior to receiving a platelet transfusion or undergoing the elective procedure)

(revised per Amendment 04)

Exploratory Endpoints

- Platelet count and change from baseline in platelet count at each visit
- Proportion of subjects who achieve platelet count of $\geq 50 \times 10^9$/L, $\geq 75 \times 10^9$/L, or $\geq 200 \times 10^9$/L at each visit
- Number of platelet units used per platelet transfusion episode
- Severity of bleeding events assessed by WHO bleeding score and BARC bleeding scale
- Proportion of subjects with a WHO bleeding score ≥2 after randomization and up to 7 days following an elective procedure (revised per Amendment 04)

- Health economics assessed by resource use

Analysis Sets

Full Analysis Set (FAS): The FAS is the group of randomized subjects. The FAS will be analyzed "as randomized".

Per Protocol Set (PP): The PP Set is the group of all randomized subjects who receive protocol-assigned study drug and do not meet any of the following criteria:

- Subjects who have any major protocol violations (major inclusion/exclusion violations or other major protocol violations that impact the evaluation of efficacy)
- Subjects who use a prohibited concomitant medication that affects the assessment of study endpoints
- Subjects who are noncompliant in terms of study medication

A comprehensive list of subjects to be excluded from the PP will be agreed upon by the study team prior to database lock.

Safety Analysis Set: The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment. This set will be analyzed "as treated."

PK Analysis Set: The PK Analysis Set is the group of randomized subjects who receive at least 1 dose of avatrombopag and have at least 1 quantifiable avatrombopag concentration with a documented dosing history.

PK/PD Analysis Set: The PK/PD Analysis Set is the group of randomized subjects who receive at least 1 dose of avatrombopag, have at least 1 quantifiable avatrombopag concentration, and at least 1 platelet count, with a documented dosing history.

Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PP will be used as the supportive population. All analyses of platelet counts will be based on local laboratory results.

Primary Efficacy Variable Analysis

The null hypothesis is that the proportion of subjects not requiring a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure is the same between the avatrombopag and placebo treatment groups. The corresponding alternative hypothesis is that the proportion of subjects not requiring a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure is not the same between avatrombopag and placebo. This hypothesis will be tested separately within each baseline platelet cohort.

The proportion of subjects not requiring a platelet transfusion or any rescue procedure for bleeding will be tested between the individual avatrombopag treatment group (40 or 60 mg) and matching placebo within each baseline platelet count cohort ($<40 \times 10^9$/L or from 40 to $<50 \times 10^9$/L), each at a significance level of α=0.05, using the generalized Cochran Mantel Haenszel (CMH) test adjusting for risk of bleeding associated with the elective procedure (low,

moderate, or high based on Amendment 02 categorization).

- For subjects with platelet count <40 x 10^9/L at baseline, the treatment comparison will be carried out between the 60 mg avatrombopag treatment group versus matching placebo.
- For subjects with platelet count from 40 to <50 × 10^9/L at baseline, the treatment comparison will be carried out between the 40 mg avatrombopag treatment group versus matching placebo.

This study will be considered as positive if statistical significance is achieved for the primary efficacy endpoint for both baseline platelet count cohorts.

The 95% confidence interval (CI) for the proportion of subjects not requiring a platelet transfusion or any rescue procedure for bleeding will be calculated for each treatment group within each baseline platelet count cohort. In addition, the 95% CI for the difference between avatrombopag and matching placebo will be provided within each baseline platelet count cohort.

Since the HCC status is included in the randomization stratification for safety purposes only, not for efficacy consideration, HCC will not be included in the CMH model for the primary efficacy analysis.

Subjects with missing information about the primary efficacy outcome due to early withdrawal or other reasons will be considered as having received a transfusion for the primary analysis.

Subgroup analyses and additional sensitivity analyses will be performed, as appropriate.

Secondary Efficacy Variable Analyses

The analysis of the secondary efficacy variables as defined above will proceed following a sequential gatekeeping testing procedure with the multiplicity adjustment to control the Type I error rate at significance level α=0.05.

The proportion of subjects who achieve platelet counts of ≥50 × 10^9/L on the Procedure Day will be analyzed first. The proportion of subjects with platelet counts of ≥50 × 10^9/L on the Procedure Day will be tested between the individual avatrombopag treatment group (40 or 60 mg) and matching placebo separately within each baseline platelet count cohort (<40 × 10^9/L or from 40 to <50 × 10^9/L), each at a significance level of α=0.05, using the generalized CMH test adjusting for risk of bleeding associated with the elective procedure (low, moderate, or high based on Amendment 02 categorization).

The second secondary efficacy variable, change from baseline in platelet count on the Procedure Day, will be analyzed only if the test for the first secondary efficacy variable is statistically significant for both baseline platelet count cohorts. The change from baseline in platelet count will be analyzed using the Wilcoxon rank sum test separately within each baseline platelet count cohort (<40 × 10^9/L or from 40 to <50 × 10^9/L), each at a significance level of α=0.05. (revised per Amendment 04)

Exploratory Efficacy Variables

- Platelet count and change from baseline in platelet count at each visit
- Proportion of subjects who achieve platelet count of ≥50 × 10^9/L, ≥75 × 10^9/L, or ≥200 × 10^9/L at each visit

- Number of platelet units used per platelet transfusion episode
- Severity of bleeding events assessed by WHO bleeding score and BARC bleeding scale
- Proportion of subjects with a WHO bleeding score ≥2 after randomization and up to 7 days following an elective procedure (revised per Amendment 04)

Additional analyses may be performed as needed. Further details of the proposed statistical analyses will be included in the Statistical Analysis Plan.

Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic/Pharmacogenetic Analyses

Pharmacokinetic Analyses

Plasma concentration versus time data will be listed. The data will be analyzed using a population PK approach to estimate population PK parameters and the effect of covariates on the PK parameters will be evaluated.

Pharmacokinetic/Pharmacodynamic Analyses

The data will be analyzed using a population PK/PD approach to estimate population PD parameters.

The population PK and PK/PD analyses will be detailed in a separate analysis plan.

Pharmacogenomic/Pharmacogenetic Analyses

Not applicable

Safety Analyses

Evaluation of safety will be performed on the Safety Analysis Set. Safety assessments will be summarized for overall and within each baseline platelet count cohort as appropriate. Safety assessments including AEs, laboratory tests, vital signs, ECG, and Doppler sonography will be summarized by treatment groups using descriptive statistics (mean, standard deviation, median and range) or frequency count as appropriate. No hypothesis testing will be performed for safety assessment.

All AEs will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities. The incidence of AEs, SAEs, AEs leading to discontinuation of study drug, and AEs of special interest will be summarized by treatment group, as well as by severity and by relationship to study drug. Mean and mean change from baseline of laboratory tests, vital signs, and ECG parameters will also be summarized by treatment group.

Other Analyses

Details of the health economic analyses will be provided in a separate analysis plan.

Interim Analyses

An independent DSMB will be established to monitor the ongoing safety data. Some of the safety parameters that DSMB will review will include variables that are also being assessed in this study for efficacy (eg, platelet count to ensure there are not too many subjects with a platelet count that exceeds 200×10^9/L and bleeding). No interim efficacy analysis is planned, and therefore no adjustment of the *P*-value for the final efficacy analysis is needed.

Sample Size Rationale

The proposed sample size is based on comparisons of the primary efficacy variable, with the response rate defined as the proportion of subjects who do not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure. Based on clinical opinion and the published results of a similar compound in adults with thrombocytopenia associated with liver disease (ELtrombopag EValuated for its Ability to overcome Thrombocytopenia and Enable procedures [ELEVATE] study), the response rate in the placebo group is assumed to be 18%. With each baseline platelet count cohort, a sample size of 100 randomized subjects, 67 subjects for avatrombopag and 33 subjects for placebo, will have greater than 90% power to detect an absolute difference of 35% between the avatrombopag response rate and the placebo response rate assuming 18% response rate for placebo using Fisher's Exact tests with a 2-sided α=0.05. (revised per Amendment 04) The hypothesized treatment group difference is based on platelet count changes found in the Phase 2 study (E5501-G000-202) and dose-response modeling using data from that study and others in the project development. Based on the baseline data in the Phase 2 study and assuming these are projected to be similar for this study, it is anticipated that this study will enroll roughly half of the total number of subjects in each of the 2 baseline platelet count cohorts to make the total sample size of 200 randomized subjects, 133 subjects for avatrombopag and 67 subjects for placebo. (revised per Amendment 04)

3 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
β-hCG	beta-human chorionic gonadotropin
AE	adverse event
BARC	Bleeding Academic Research Consortium
BCLC	Barcelona Clinic Liver Cancer
CA	Competent Authority
CABG	coronary artery bypass graft
CI	confidence interval
CMH	Cochran Mantel Haenszel
CPK	creatinine phosphokinase
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Child-Turcotte-Pugh
CYP	cytochrome P450
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
ELEVATE	ELtrombopag EValuated for its Ability to overcome Thrombocytopenia and Enable procedures
EU	European Union
FAS	Full Analysis Set
FFP	fresh frozen plasma
GCP	Good Clinical Practice
HCC	hepatocellular carcinoma
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
INR	International Normalized Ratio
IRB	Institutional Review Board
ITP	Immune Thrombocytopenic Purpura
IxRS	interactive voice and web response system
KOL	key opinion leader
LNH	low/normal/high
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model For End-stage Liver Disease
MRI	magnetic resonance imaging
NOAEL	no-observed-adverse-effect-level

Abbreviation	Term
NSAID	nonsteroidal anti-inflammatory drug
PD	pharmacodynamic
P-gp	P-glycoprotein
PK	pharmacokinetic
POC	proof of concept
PP	Per Protocol Set
PT	preferred term
PVT	portal vein thrombosis
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory value
TPO	thrombopoietin
US	United States
WBC	white blood cell
WHO	World Health Organization

5 ETHICS

5.1 INSTITUTIONAL REVIEW BOARDS/INDEPENDENT ETHICS COMMITTEES

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation (ICH) E6 (Good Clinical Practice [GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate[s] [CRA], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority (CA) within 90 days. The end of the study will be the date of the clinical database lock (ie, when all study data are collected and data validation is complete). The sponsor should also provide the IRB/IEC with a summary of the study's outcome (within a year of the end of the study for the European Union [EU]).

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and CA within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 ETHICAL CONDUCT OF THE STUDY

This study will be conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki (2008)
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All suspected unexpected serious adverse reactions will be reported, as required, to the CAs of all involved EU member states.
- Other applicable regulatory authorities' requirements or directives

5.3 SUBJECT INFORMATION AND INFORMED CONSENT

As part of administering the informed consent document, the investigator must explain to each subject (or guardian/legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

The subject or the subject's legally authorized representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 80 to 100 investigational sites worldwide.

The names and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and the designated contract research organization (CRO) are listed in the Regulatory Binder provided to each site.

7 INTRODUCTION

7.1 INDICATION

Thrombocytopenia is the occurrence of low platelets in the blood and, in severe cases, can be associated with significant morbidity and mortality. Patients with chronic liver disease can develop thrombocytopenia from decreased production of thrombopoietin (TPO), as well as from increased destruction of platelets from auto-antibodies or platelet sequestration with splenomegaly. In addition, depending upon the etiology of the liver disease, additional factors can contribute to thrombocytopenia, such as viral-induced myeloid suppression. Thrombocytopenia is a common problem in patients with liver disease, with the extent of thrombocytopenia often worsening with the degree of cirrhosis.

Patient treatment decisions are guided by platelet count measurements, as well as by clinical judgment on the risk of bleeding. Patients with moderate to severe thrombocytopenia (<50 x 10^9/L) associated with liver disease are commonly administered platelet transfusions immediately prior to elective diagnostic or therapeutic procedures in order to mitigate the risk of bleeding. The extent of the bleeding risk relates to the degree of thrombocytopenia, the extent of other coexisting coagulopathy(ies), and the type of elective procedure. While temporarily effective, platelet transfusion therapy can have significant health and economic consequences, including the development of refractoriness to subsequent platelet transfusions, potential transmission of infectious agents, transfusion reactions, and, in rare cases, fatality. Unfortunately, in patients requiring repeated platelet transfusions, both the magnitude of the platelet increase and the duration of that increase declines with increasing numbers of transfusions.[1] This refractoriness to treatment can pose a major challenge for patients undergoing procedures in preparation for liver transplant or other procedures pertinent to their care. For patients who have acquired refractoriness to platelet transfusion, an unintended consequence is often the need to delay or even cancel important procedures. Additionally, like all blood products, platelets are a precious commodity with a limited shelf life. Approximately 9 million units of platelets are transfused each year in the US;[2] 40% in surgical settings.[3] Liver disease patients are believed to represent a significant proportion of the patient population regularly receiving platelet transfusions.[4] A recent assessment at the University of Colorado Denver Medical School revealed that up to 20% of all platelet transfusions were given to liver disease patients.

E5501/avatrombopag (formerly known as AKR-501 monomaleate and YM477) is an orally administered, small molecule c-Mpl receptor agonist that mimics the biological effects of TPO in vitro and in vivo. Thrombopoietin, the principal physiologic regulator of platelet production, exerts its effect on megakaryocytopoiesis and thrombocytopoiesis via binding and activation of the c-Mpl receptor, which is expressed on hematopoietic stem cells, on cells of the megakaryocytic lineage, and on platelets. Like TPO, avatrombopag also binds to the human c-Mpl receptor and affects signal transduction through the induction of downstream signaling, thereby enhancing human megakaryocytic proliferation and differentiation.

A proof of concept (POC) study (E5501-G000-202) has demonstrated the efficacy, safety, and tolerability of avatrombopag in elevating platelet counts in this group of patients with

thrombocytopenia associated with liver disease prior to elective procedures. Modeling and simulation based on a final pharmacokinetic (PK)/pharmacodynamic (PD) model, of the POC study data, allowed an optimal dosing regimen for Phase 3 to be identified. These simulations showed that the achievement of the appropriate platelet count and a high response rate is affected by baseline platelet count and that dosing avatrombopag is best stratified by baseline platelet count. The simulations also demonstrated that there is no advantage in having a loading dose as was used in the POC study. Theses simulations have been important because in the POC study the primary endpoint only related to elevation in platelet count, whereas in Phase 3 the primary endpoint will link to the clinical endpoint of platelet transfusion.

The current study will evaluate avatrombopag in the treatment of thrombocytopenia associated with liver disease prior to an elective procedure to reduce the need for platelet transfusions due to procedural and postprocedural bleeding complications.

7.1.1 Current Therapeutic Options

Currently, platelet transfusion is the standard of care for patients with thrombocytopenia who must undergo an invasive procedure. While 2 TPO-receptor agonists (romiplostim [Amgen] and eltrombopag [GlaxoSmithKline]) are approved for use in adults with chronic immune (idiopathic) thrombocytopenic purpura (ITP), and eltrombopag is approved in the US for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy, neither product is approved for the treatment of thrombocytopenia associated with liver disease in patients undergoing an elective procedure. Avatrombopag is being developed to provide an alternative to the standard of care (platelet transfusion) by providing a 5-day course of once daily therapy and eliminating the need for platelet transfusions and the potential associated side effects.

7.1.2 Avatrombopag

7.1.2.1 Mechanism of Action

Avatrombopag is an orally administered, small molecule c-Mpl agonist that mimics the biological effects of TPO in vitro and in vivo. Avatrombopag activates human c-Mpl through a mechanism that is different from endogenous TPO binding, but is still capable of stimulating signal transduction and mimicking the biological effects of TPO.

7.1.2.2 Nonclinical Pharmacology

Nonclinical pharmacology studies show that avatrombopag stimulates proliferation of cultured human c-Mpl–Ba/F3 cells and promotes differentiation of human cord blood CD34+ cells to human megakaryocytes in a concentration-dependent manner with a maximum effect similar to that of recombinant human TPO. In vitro, avatrombopag has been shown to stimulate human megakaryocyte proliferation and differentiation without affecting platelet function, either activation or aggregation. The pharmacologic effect of avatrombopag is highly species-specific, with signaling occurring only in chimpanzees and humans but not in any other species tested. Avatrombopag was stable in mouse, dog, or human liver microsomal enzyme incubations in vitro, indicating slow metabolism.

In addition, avatrombopag (up to 10 μmol/L) did not inhibit the major human liver cytochrome P450 (CYP) isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4). Avatrombopag (0.1 to 5 μmol/L) did not induce CYP1A, CYP2B6, CYP2C19, or CYP3A. However, it weakly induced CYP2C8 and CYP2C9. Therefore, the potential for drug-drug interactions is low.

Absolute bioavailability was evaluated in the mouse, rat, dog, and monkey. Overall, avatrombopag was well absorbed, but highly variable, and the fraction absorbed ranged from approximately 50% to 90%.

Nonclinical toxicology studies have indicated that avatrombopag was well tolerated. The primary toxicity of avatrombopag was identified as dose-related changes in the stomachs of rats, mice, and monkeys, with an elevation of serum gastrin levels in repeated-dose studies. The gastric changes showed a clear trend towards recovery after a recovery period. Exposures (area under the concentration-time curve and maximum plasma concentration) at the no-observed-adverse-effect-levels in animals, in pivotal studies, are sufficiently above the clinical exposures at the current maximum therapeutic dose. Avatrombopag was negative in the standard battery of genotoxicity tests. Avatrombopag has no effect on reproductive toxicity, except for the higher sensitivity to toxicity in neonates/juvenile rats in the pre-and postnatal development study. In the 2-year carcinogenicity studies, neuroendocrine cell (enterochromaffin-like [ECL] cell) hyperplasia (rats only), and ECL cell tumors (carcinoids, both mice and rats) occurred in the stomach. The mechanism of action for gastric changes by avatrombopag was confirmed to be compatible with a gastrin hypothesis, similar to the cases of antisecretory agents such as proton pump inhibitors and H_2 blockers based on mechanistic studies, leading to the conclusion that the results are not relevant to humans. Avatrombopag had no ocular or dermal irritation, no dermal sensitization, and no phototoxicity potential in nonclinical studies.

Overall, nonclinical data suggest that avatrombopag is a promising candidate for use in the treatment of thrombocytopenia of diverse etiologies, including thrombocytopenia associated with liver disease.

7.1.2.3 Effects in Humans

Avatrombopag has been studied in humans in single- and multiple-dose Phase 1, dose-rising safety and tolerability studies. In healthy human subjects, single and multiple doses of avatrombopag oral suspension showed a dose-dependent increase in peripheral platelets and no safety issues were reported. A comparative bioavailability study of avatrombopag suspension and tablets showed that avatrombopag tablets produced significantly lower exposure (approximately 67%) than the oral suspension. A food-effect arm demonstrated a high-fat meal mildly increased avatrombopag exposure.

A total of 12 Phase 1 clinical pharmacology studies have been completed to date. Based on Phase 1 study results, avatrombopag was generally well tolerated and no major safety issues were identified during treatment. The subject population in the clinical pharmacology studies included 390 healthy volunteers, age 18 to 64, of which two-thirds were men (men: 263/390,

67.4%; women: 127/390, 32.6%). A total of 350 of the 390 subjects received at least 1 dose of avatrombopag.

Three Phase 2 efficacy and safety studies have been completed to date (Study 501-CL-003 and the rollover Study 501-CL-004, and Study E5501-G000-202).

Study E5501-G000-202 evaluated the efficacy, safety, and population PK of once-daily oral avatrombopag dosing, in subjects with chronic liver diseases and thrombocytopenia prior to elective surgical or diagnostic procedures. The primary efficacy endpoint was the proportion of responders with platelet count increases from baseline of $\geq 20 \times 10^9$/L and a platelet count of $\geq 50 \times 10^9$/L once from Day 4 through Day 8. The proportion of responders for all avatrombopag-treated subjects was 48.4% compared with 8.1% in the combined placebo group ($P<0.0001$). All doses of avatrombopag achieved a significantly higher proportion of responders compared with their respective cohort placebo arms and the highest platelet count responses were observed between Days 10 to 14 after first dose. In addition, avatrombopag appeared well tolerated in this patient population. There was no clear trend regarding the incidences of AEs between placebo and avatrombopag treatment groups, and the commonly reported treatment-emergent adverse events (TEAEs) and serious TEAEs were consistent with the disease state of the patient population. The findings from Study E5501-G000-202 suggest that avatrombopag would be an effective therapy for the treatment of thrombocytopenia in patients with chronic liver disease, prior to an elective procedure.

For more detailed information regarding effects in humans, please refer to the Investigator Brochure.

7.1.2.4 Common Serious Adverse Events Expected to Occur in the Study Population Even in the Absence of Study Drug Exposure

Thrombotic/thromboembolic complications may occur in patients with chronic liver disease. Portal vein thrombosis (PVT) is of particular concern in chronic liver disease patients who are prone this type of thrombosis and is often associated with poor portal vein flow. The presence of thrombocytopenia can increase the potential for bleeding, which results in an elevated morbidity and mortality risk in patients with liver disease. In cirrhotic patients undergoing abdominal surgery, bleeding accounts for up to 60% of all causes of death. Thrombocytopenic patients often require multiple platelet transfusions, which can be associated with complications such as systemic infections, iron overload, and platelet refractoriness.[4]

7.2 STUDY RATIONALE

The current study will evaluate avatrombopag in the treatment of thrombocytopenia associated with liver disease prior to an elective procedure to reduce the need for platelet transfusions or any rescue procedure for bleeding due to procedural and postprocedural bleeding complications Dose selection has been carefully focused on seeking to maintain an appropriate risk: benefit ratio in this patient population, removing the requirement for platelet transfusion, or any rescue procedure for bleeding, while minimizing the risk of thromboembolic events. The selected doses, based on modeling and simulation of the E5501-G000-202 study data, are aimed at

achieving sufficient efficacy (eliminating the need for platelet transfusion) while specifically limiting the proportion of subjects achieving platelet counts >200 × 10^9/L to less than 2%. The current study design employs a dosing regimen, according to baseline platelet count, that is anticipated to lead to a similar rise in platelet counts irrespective of baseline platelet count. Subjects will be enrolled into 2 cohorts according to mean baseline platelet count (<40 × 10^9/L or from 40 to <50 × 10^9/L) and dosed with 60 mg avatrombopag versus placebo for subjects with platelet count <40 × 10^9/L and 40 mg avatrombopag versus placebo for subjects with platelet count from 40 to <50 × 10^9/L.

This is 1 of 2 duplicate global pivotal studies that will overlap geographically to ensure that minor differences in clinical practices between regions will be balanced across the studies.

7.2.1 Risk Mitigation

Patients with liver disease have a significant risk of thromboembolic and bleeding events. As platelet counts decline, cirrhotic patients tend to become more susceptible to bleeding following an inciting event such as trauma, rather than spontaneous bleeding as seen in other thrombocytopenic conditions such as ITP. This apparent discrepancy is mainly due to coagulation abnormalities seen in patients with cirrhosis.[5,6] Despite an apparent 'balance' between pro- and anti-coagulation factors in plasma, the coagulation system in the cirrhotic patient is associated with an increased tendency towards thrombosis, regardless of observed prolonged conventional coagulation test times, such as prothrombin time, activated partial thromboplastin time, and INR. As a result, especially in patients with thrombocytopenia associated with liver disease, excessive elevations in platelet counts may potentially trigger thrombotic/thromboembolic events in the background of known coagulation abnormalities. Perhaps, the most significant thrombotic event seen in patients with thrombocytopenia associated with liver disease is PVT.

Portal vein thrombosis in the general population is a rare event. However, it is a relatively common complication in patients with liver cirrhosis (4% - 15%)[7], with frequencies increasing with the degree of cirrhosis and a prevalence as high as approximately 30% in candidates for liver transplantation. Although even complete occlusion of the portal vein may not result in overt clinical manifestations, due to rapid development of collateral veins bypassing the thrombosed segment, patients can experience acute and chronic onset of a variety of clinical symptoms. These include increased variceal bleeding, refractory ascites and abdominal pain, presumably from small bowel ischemia or infarction due to the involvement of the superior mesenteric vein.[8] Furthermore, the occurrence of PVT is known to increase the risk of mortality both prior to and post liver transplantation.[9] Eltrombopag, a currently marketed TPO-receptor agonist for the treatment of ITP, has been reported to have been associated with the occurrence of PVT in patients with chronic liver disease and thrombocytopenia.[10] In the ELtrombopag EValuated for its Ability to overcome Thrombocytopenia and Enable procedures (ELEVATE) study, aimed at decreasing the requirement for platelet transfusion prior to elective procedures, there was an imbalance in the incidence of PVT and mesenteric thrombosis between the active and placebo arms.[10] In addition to very high and prolonged elevations in platelet counts (26% of eltrombopag-treated subjects reached >200 × 10^9/Land 5% reached >400 × 10^9/L); 6 (4%) subjects in the eltrombopag arm and 1 (1%) in the placebo arm experienced a thrombotic event

of the portal venous system, leading to early termination of the study.[11,12] In the current Phase 3 program, avatrombopag doses and treatment duration have been selected so that platelet count elevations are transient and not excessive, with the projected percentage of subjects who reach >200 × 10^9/L limited to <2%. During this study, if a potential PVT is suspected, subjects will undergo confirmation of diagnosis and appropriate treatment as per local guidelines.

Development of PVT is recognized as a multifactorial complication, which involves both inherited and acquired thrombotic risk factors. One of the strongest risk factors predisposing patients to the development of a PVT may be a reduced flow in the portal vein. Literature and meeting reports indicate that a portal vein flow rate of 10 to 15 cm/second is a good predictor of future risk for PVT.[13] Doppler sonography, which is routinely used in patients with liver disease, can be used to assess portal vein flow rates and guidelines have been developed that can reduce interobserver variability in measuring flow rates to low levels.[14] Therefore, in the Phase 3 program, portal vein flow rate will be performed during the Screening Period, to pre-identify and exclude subjects with low portal flow. In addition, subjects with a history of arterial or venous thrombosis and subjects with current evidence of thrombosis will be excluded. For subjects whose preprocedural platelet count is >200 × 10^9/L on the Procedure Day, the elective procedure may be delayed at the discretion of the investigator until platelet counts are below 200 × 10^9/L. All subjects whose platelet count exceeds 200 × 10^9/L on the Procedure Day will be required to have a Doppler assessment following the procedure. For any subjects where the presence of a PVT is suspected, confirmation of diagnosis, via computerized tomography (CT) scan or magnetic resonance imaging (MRI), should be performed and treatment for PVT initiated per local guidelines. As part of the protocol, guidance on use of Doppler sonography for assessment of portal flow will be included in Appendix 3.

8 STUDY OBJECTIVES

8.1 PRIMARY OBJECTIVE

The primary objective of the study is to confirm that avatrombopag (60 mg avatrombopag for subjects with platelet count $<40 \times 10^9$/L and 40 mg avatrombopag for subjects with platelet count from 40 to $<50 \times 10^9$/L) is superior to placebo in removing the need for platelet transfusions or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure in subjects with chronic liver disease who have thrombocytopenia.

8.2 SECONDARY OBJECTIVES

The secondary objectives of the study are: (revised per Amendment 04)

- To confirm that avatrombopag is superior to placebo in achieving a platelet count of $\geq 50 \times 10^9$/L on Procedure Day in the proposed target population
- To confirm that avatrombopag is superior to placebo in elevating platelet counts from baseline on Procedure Day in the proposed target population
- To evaluate the safety of avatrombopag in the proposed target population

8.3 EXPLORATORY OBJECTIVES

The exploratory objectives of the study are:

- To characterize the pharmacokinetics and the relationship between avatrombopag plasma concentrations and platelet count using the population approach
- To characterize platelet count changes from baseline, the extent of platelet transfusion use, evaluate the incidence of bleeding events, and assess the severity of any bleeding events (revised per Amendment 04)
- To assess the health economic impact associated with minimizing the need for platelet transfusions and any rescue procedure for bleeding associated with an elective procedure

9 INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN

This is a Phase 3, global, multicenter, randomized, double-blind, placebo-controlled, parallel-group study using avatrombopag to treat adults with thrombocytopenia associated with liver disease prior to an elective procedure. Subjects will be enrolled into 2 cohorts according to mean baseline platelet count and, within each baseline platelet count cohort, will be further stratified by risk of bleeding associated with the elective procedure (low, moderate or high) and hepatocellular carcinoma (HCC) status (Yes or No). Neither baseline platelet count cohort will comprise greater than 55% of the total number of subjects enrolled into the study. The estimated study duration to enroll and complete all subjects is approximately 20 months.

Within the **lower** baseline platelet count cohort ($<40 \times 10^9$/L) and each stratum, subjects will be randomized by an interactive voice and web response system (IxRS) in a 2:1 ratio to receive avatrombopag or placebo as follows:

- 60 mg avatrombopag on Days 1 to 5 (Group A: avatrombopag, lower baseline platelet count)
- Matching placebo on Days 1 to 5 (Group B: placebo, lower baseline platelet count)

Within the **higher** baseline platelet count cohort (from 40 to $<50 \times 10^9$/L) and each stratum, subjects will be randomized in a 2:1 ratio to receive avatrombopag or placebo as follows:

- 40 mg avatrombopag on Days 1 to 5 (Group C: avatrombopag, higher baseline platelet count)
- Matching placebo on Days 1 to 5 (Group D: placebo, higher baseline platelet count)

Platelet counts must be measured on 2 separate occasions, during the Screening Period and at Baseline, and must be performed at least 1 day apart with neither platelet count $>60 \times 10^9$/L. The mean of these 2 platelet counts (mean baseline platelet count $<50 \times 10^9$/L) will be used for entry criteria.

The elective procedure must be scheduled to be performed within 10 to 13 days of first dose of study drug and after Visit 4 assessments have been performed.

This study will consist of 3 phases: Prerandomization, Randomization, and a Follow-up Phase.

The Prerandomization Phase consists of a Screening Period that will take place from Day -14 through Day -1.

The Randomization Phase includes the Baseline Period, Treatment Period, and Procedure Day (5 to 8 days after last dose of study drug, [Study Day 10 to 13]). During the Baseline Period, subjects who have met all entry criteria, provided signed informed consent, and been randomized will be instructed to take study drug on Days 1 to 5.

The elective procedure for those subjects whose preprocedural platelet count is >200 × 10^9/L on Visit 4 (Procedure Day) may be delayed at the discretion of the investigator until platelet counts are below 200 × 10^9/L. All subjects whose platelet count exceeds 200 × 10^9/L will be required to have a Doppler assessment at Visit 5. For any subjects where the presence of a PVT is suspected, confirmation of diagnosis, via CT scan or MRI, should be performed and treatment for PVT initiated per local guidelines.

The Follow-up Phase encompasses 2 visits: 7 days postprocedure day and 30 days after receiving the last dose of study drug.

An independent Data Safety Monitoring Board (DSMB) will be established to monitor the ongoing safety data.

The end of the study will be the date of the clinical database lock (ie, when all study data are collected and data validation is completed).

An overview of the study design is presented in Figure 1.

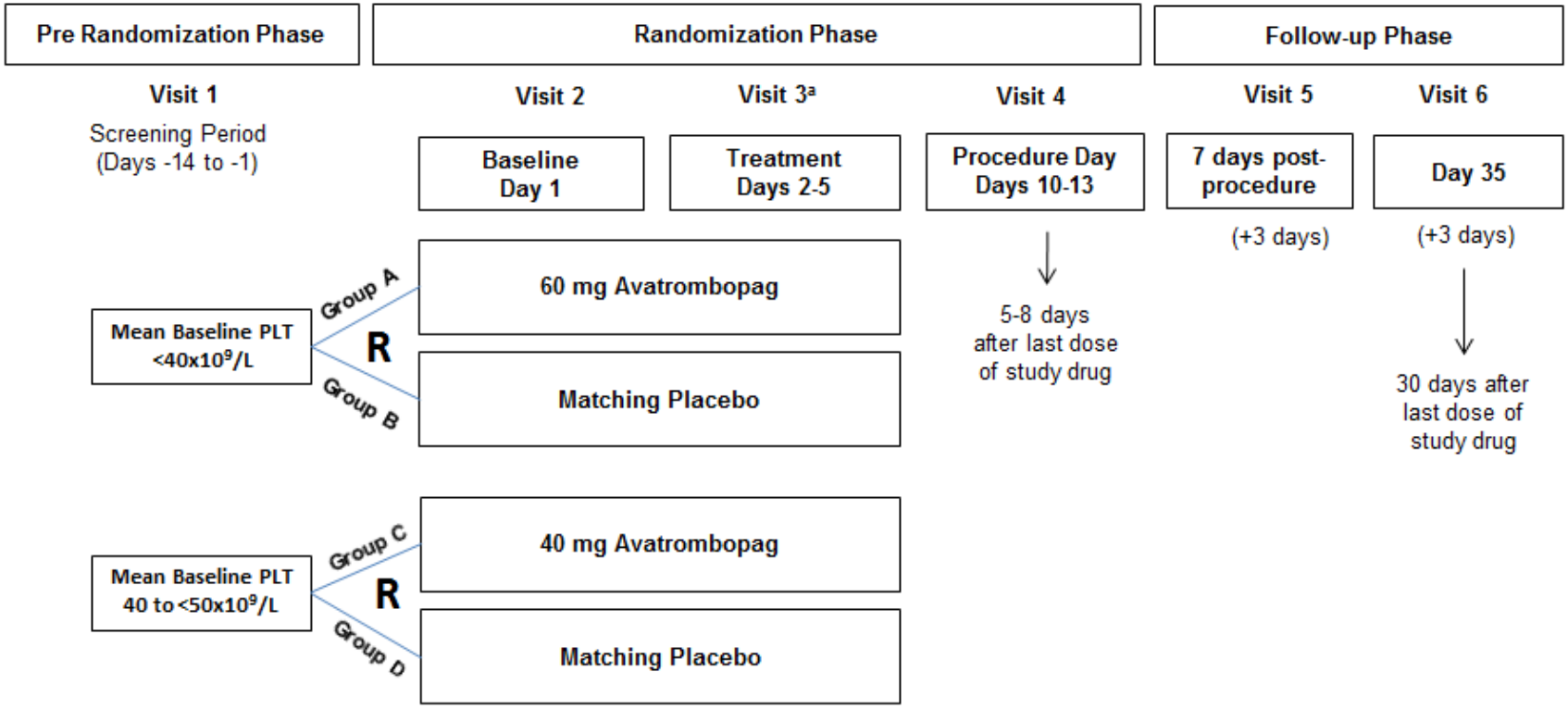

Figure 1 Study Design

PLT=platelet count; R = randomization

Platelet counts must be measured on 2 separate occasions, during the Screening Period and at Baseline, and must be performed at least 1 day apart with neither platelet count >60 × 10^9/L. The mean of these 2 platelet counts (mean baseline platelet count <50 × 10^9/L) will be used for entry criteria and determination of baseline platelet count.

[a]: Visit 3 occurs on Day 4 (±1 day) during the Treatment Period.

9.1.1 Prerandomization Phase

The Prerandomization Phase consists of a Screening Period that will last up to 14 days.

9.1.1.1 Screening Period (Visit 1)

Screening will occur between Day -14 and Day -1.

The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Subjects must have a diagnosis of thrombocytopenia associated with liver disease and be scheduled to undergo an elective procedure. Only subjects who, in the opinion of the investigator, are expected to require platelet transfusion to address a risk of bleeding associated with the procedure will be recruited into this study.

Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3.

After providing informed consent, all subjects will undergo screening assessments to ensure that they meet all of the inclusion and none of the exclusion criteria, as described in Section 9.3.1 and Section 9.3.2. Screening assessments and timing are shown in Section 9.5.2.1 (Table 5).

During this phase, the type and schedule of the elective procedure will be confirmed.

The Screening Disposition case report form (CRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

Rescreen of subjects will only be allowed under the following circumstances:

- Scheduled procedure is cancelled or delayed
- Platelet count inclusion criteria is not met as platelet count tends to fluctuate
- Unable to complete the Screening Period due to administrative, logistical issues
- Previously screen failed due to criteria no longer in the protocol (added per Amendment 01)

Repeat of screening laboratory evaluations are allowed in cases where abnormal result(s) are noted during the Screening Period that are believed to be related to a potential laboratory error or a transient and/or reversible condition (eg, clumped platelets or hemolyzed sample for complete blood count). Results of the repeated assessment must be available before randomization. If additional blood samples are sent to the central laboratory during the Screening Period, eligibility must be assessed based on the most recent laboratory values. The 2 most recent values will be used to determine the mean platelet count value for entry criteria and for assignment to the low or high baseline platelet count cohort.

9.1.2 Randomization Phase

The duration of the Randomization Phase will be 10 to 13 days and will include 3 periods: Baseline, Treatment, and Procedure Day. Subjects whose screening assessments and evaluations are completed and reviewed by the principal investigator and who continue to meet all of the inclusion and none of the exclusion criteria will enter the Randomization Phase.

9.1.2.1 Baseline Period (Visit 2)

The Baseline Period will occur on Study Day 1. Subjects who meet all the inclusion criteria and none of the exclusion criteria, (Sections 9.3.1 and 9.3.2) will be randomized and begin the Treatment Period.

Baseline assessments are shown in Section 9.5.2.1 (Table 5).

Platelet counts must be measured on 2 separate occasions, during the Screening Period and at Baseline, and must be performed at least 1 day apart with neither platelet count $>60 \times 10^9$/L. The mean of these 2 platelet counts (mean baseline platelet count $<50 \times 10^9$/L) will be used for entry criteria.

Upon confirmation of eligibility, subjects will be enrolled into 2 cohorts according to mean baseline platelet count ($<40 \times 10^9$/L or from 40 to $<50 \times 10^9$/L). Within each cohort, subjects will be further stratified by risk of bleeding associated with the elective procedure (low, moderate or high) and presence of HCC (Yes or No). Neither baseline platelet count cohort will comprise greater than 55% of the total number of subjects enrolled into the study.

Within the **lower** baseline platelet count cohort ($<40 \times 10^9$/L) and each stratum, subjects will be randomized in a 2:1 ratio to receive avatrombopag or placebo as follows:

- Group A (avatrombopag, lower baseline platelet count): 60 mg avatrombopag (3 × 20-mg tablets) once daily on Days 1 through 5
- Group B (placebo, lower baseline platelet count): placebo (3 × 20-mg matching placebo tablets) once daily on Days 1 through 5

Within the higher baseline platelet count cohort (from 40 to $<50 \times 10^9$/L) and each stratum, subjects will be randomized in a 2:1 ratio to receive avatrombopag or placebo as follows:

- Group C (avatrombopag, higher baseline platelet count): 40 mg avatrombopag (2 × 20-mg tablets) once daily on Days 1 through 5
- Group D (placebo, higher baseline platelet count): placebo (2 × 20-mg matching placebo tablets) once daily on Days 1 through 5

Subjects will receive a dosing diary in which they are to record the dates and times of their study drug doses.

9.1.2.2 Treatment Period (Visit 3)

During the Treatment Period, subjects will take avatrombopag (60 or 40 mg) or placebo daily from Days 1 to 5. There will be a visit on Day 4 (±1 day) (Visit 3). Subjects are to record the dates and times of their study drug doses in the dosing diary.

Assessments to be conducted are shown in Section 9.5.2.1 (Table 5).

9.1.2.3 Procedure Day (Visit 4)

This will occur 5 to 8 days after the last dose of study drug (on Study Day 10 to 13).

All Procedure Day assessments are to be completed prior to the procedure and include assessments shown in Section 9.5.2.1 (Table 5).

In addition, all subjects are required to return study drug and the dosing diary at this visit.

The elective procedure for those subjects whose preprocedural platelet count is $>200 \times 10^9$/L on Visit 4 (Procedure Day) may be delayed at the discretion of the investigator until platelet counts are below 200×10^9/L. All subjects whose platelet count exceeds 200×10^9/L will be required to have a Doppler assessment at Visit 5. For any subjects where the presence of a PVT is suspected, confirmation of diagnosis, via CT scan or MRI, should be performed and treatment for PVT initiated per local guidelines.

Permitted procedures and the risk of bleeding associated with each procedure are listed in Table 1. It is planned that no fewer than 10% of subjects will be enrolled into the high risk group and no more than 60% of subjects in the low-risk group.

Table 1 Permitted Procedures and the Risk of Bleeding Associated with Each Procedure (revised per Amendment 02)

Risk of Bleeding Associated with Procedure	Procedure
Low risk	Paracentesis
	Thoracentesis
	Gastrointestinal endoscopy with or without plans for biopsy, colonoscopy, polypectomy, or variceal banding
Moderate risk	Liver biopsy
	Bronchoscopy with or without plans for biopsy
	Ethanol ablation therapy or chemoembolization for HCC
High risk	Vascular catheterization (including right side procedures in subjects with pulmonary hypertension)
	Transjugular intrahepatic portosystemic shunt
	Dental procedures
	Renal biopsy
	Biliary interventions
	Nephrostomy tube placement
	Radiofrequency ablation
	Laparoscopic interventions

Level of risk based on KOL input and Malloy PC, Grassi CJ, Kundu S, Gervais DA, Miller DL, Osnis RB, et al. for the Standards of Practice Committee with Cardiovascular and Interventional Radiological Society of Europe (CIRSE) Endorsement. Consensus Guidelines for Periprocedural Management of Coagulation Status and Hemostasis Risk in Percutaneous Image-guided Interventions (2009)[15]

Subjects who have an International Normalization Ratio (INR) >1.6 should be treated with fresh frozen plasma (FFP) or other appropriate therapies, where indicated, as per local guidelines and practices.

The following are considered as rescue procedures when used specifically for bleeding:

- Platelet transfusion
- FFP
- Cryoprecipitate
- Vitamin K (phytonadione)
- Desmopressin
- Recombinant activated factor VII
- Aminocaproic acid
- Tranexanic acid (added per Amendment 01)
- Whole blood transfusion
- Packed red cell transfusion

- Surgical intervention or interventional radiology

9.1.3 Follow-up Phase (Visits 5 and 6)

Upon completion of the Procedure Day period, all subjects will enter the Follow-up Phase comprised of 2 visits: 7 days postprocedure Day and Day 35.

Assessments and timing are shown in Section 9.5.2.1 (Table 5).

9.2 DISCUSSION OF STUDY DESIGN, INCLUDING CHOICE OF CONTROL GROUPS

The current study will evaluate avatrombopag in the treatment of thrombocytopenia associated with liver disease prior to an elective procedure to reduce the need for platelet transfusions or any rescue procedure for bleeding due to procedural and postprocedural bleeding complications. The study design employs a dosing regimen, according to baseline platelet count, that is anticipated to lead to a similar rise in platelet counts irrespective of baseline platelet count. Subjects will be enrolled into 2 cohorts according to mean baseline platelet count ($<40 \times 10^9$/L or from 40 to $<50 \times 10^9$/L) and dosed with 60 mg avatrombopag versus placebo for subjects with platelet count $<40 \times 10^9$/L and 40 mg avatrombopag versus placebo for subjects with platelet count from 40 to $<50 \times 10^9$/L. Within each cohort, subjects will be further stratified by risk of bleeding associated with the elective procedure (low, moderate, or high) and HCC status. From previous studies, it is anticipated that the 2 baseline platelet count cohorts ($<40 \times 10^9$/L and from 40 to $<50\times 10^9$/L) will be equally represented. However, neither baseline platelet count cohort will be permitted to comprise greater than 55% of the total number of subjects enrolled into the study.

The clinical primary endpoint is based on reducing the need for platelet transfusions or any rescue procedure for bleeding due to procedural and postprocedural bleeding complications. A similar primary endpoint has already been used for eltrombopag, another TPO agonist. Based on the clinical grounds and the available literature, the primary endpoint of "proportion of subjects who do not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure," is considered to be clinically relevant.

The secondary and exploratory endpoints surrounding World Health Organization (WHO) bleeding scores and BARC bleeding scale in the current study are also clinically relevant, as bleeding is considered a complication of thrombocytopenia that can lead to increased morbidity, mortality, and use of medical resources. Information obtained from these secondary and exploratory endpoints can provide important information regarding bleeding scores and associated medical interventions in patients with thrombocytopenia associated with liver disease and thrombocytopenia.

An independent DSMB will be established to monitor the ongoing safety data. If there are excessive serious adverse events (SAE) in a dose arm, further subject enrollment to that dose arm may be suspended at the discretion of the DSMB. The study will continue to its end with the remaining dose until follow-up is completed for all enrolled subjects.

Randomization will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

It is envisaged that 2 global pivotal studies will overlap geographically to ensure that minor differences in clinical practices between regions will be balanced across both studies.

9.3 SELECTION OF STUDY POPULATION

Approximately 200 subjects with thrombocytopenia associated with liver disease who are scheduled to undergo an elective surgical or diagnostic procedure will be randomized at approximately 80 to 100 sites in regions that may include Asia/Pacific, Europe, Middle East, Africa, Latin America, and North America. (revised per Amendment 04) Only subjects who, in the opinion of the investigator, are expected to require platelet transfusion to address a risk of bleeding associated with the procedure will be recruited into this study. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Subjects ≥18 years of age at Screening with chronic liver disease
2. Subjects who have a mean baseline platelet count of $<50 \times 10^9$/L. Platelet counts must be measured on 2 separate occasions, during the Screening Period and at Baseline, and must be performed at least 1 day apart with neither platelet count $>60 \times 10^9$/L. The mean of these 2 platelet counts (mean baseline platelet count) will be used for entry criteria and for assignment to the low or high baseline platelet count cohort.
3. Subjects scheduled to undergo a permitted elective procedure and who, in the opinion of the investigator, will otherwise require a platelet transfusion to address a risk of bleeding associated with the procedure unless there is a clinically significant increase in platelet count from baseline (revised per Amendments 02 and 03)
4. Model For End-stage Liver Disease (MELD) score ≤24 at Screening
5. If taking inhibitors of P glycoprotein (P-gp), except for verapamil, dose must be stable for 7 days prior to Screening (see Appendix 2 for the list of P-gp Inhibitors)
6. Provide written informed consent
7. Willing and able to comply with all aspects of the protocol

9.3.2 Exclusion Criteria
(revised per Amendment 02)

Subjects who meet any of the following criteria will be excluded from this study:

1. Any history of arterial or venous thrombosis, including partial or complete thrombosis
2. Evidence of thrombosis (partial or complete) in the main portal vein, portal vein branches, or any part of the splenic mesenteric system at Screening
3. Portal vein blood flow velocity rate <10 cm/second at Screening
4. Hepatic encephalopathy that cannot be effectively treated
5. Subjects with HCC and Barcelona Clinic Liver Cancer (BCLC) staging classification C or D
6. Platelet transfusion or receipt of blood products containing platelets within 7 days of Screening. However packed red blood cells are permitted
7. Heparin, warfarin, nonsteroidal anti-inflammatory drugs (NSAID), aspirin, verapamil, and antiplatelet therapy with ticlopidine or glycoprotein IIb/IIIa antagonists (eg, tirofiban) within 7 days of Screening
8. Use of erythropoietin stimulating agents within 7 days of Screening
9. Interferon (IFN) use within 14 days of Screening
10. Estrogen-containing hormonal contraceptive or hormone replacement therapy use within 30 days of Screening
11. Active infection requiring systemic antibiotic therapy within 7 days of Screening. However, prophylactic use of antibiotics is permitted.
12. Alcohol abuse, alcohol dependence syndrome, drug abuse, or drug dependence within 6 months of the study start (unless participating in a controlled rehabilitation program) or acute alcoholic hepatitis (chronic alcoholic hepatitis is allowed) within 6 months of the study start
13. Elective procedure performed prior to Visit 4 (Procedure Day)
14. Known to be human immunodeficiency virus (HIV) positive
15. Any clinically significant acute or active bleeding (gastrointestinal, central nervous system, etc.)

16. Known history of any primary hematologic disorder (eg, ITP, myelodysplastic syndrome, etc.)

17. Known medical history of genetic prothrombotic syndromes (eg, Factor V Leiden; prothrombin G20210A; ATIII deficiency etc.) (revised per Amendment 01)

18. Subjects with a history of significant cardiovascular disease (eg, congestive heart failure New York Heart Association Grade III/IV, arrhythmia known to increase the risk of thromboembolic events [eg, atrial fibrillation], coronary artery stent placement, angioplasty, and coronary artery bypass graft [CABG])

19. Females of childbearing potential who have had unprotected sexual intercourse within 30 days before study entry and who do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a progesterone-only contraceptive implant/injection, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 30 days after study drug discontinuation. If currently abstinent, the subject must agree to use a double-barrier method as described above if she becomes sexually active during the study period or for 30 days after study drug discontinuation. All females will be considered to be of childbearing potential unless they are postmenopausal (at least 12 months consecutive amenorrhea in the appropriate age group and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, hysterectomy, or bilateral oophorectomy) at least 1 month before dosing.

20. Females who are lactating or pregnant at Screening or Baseline (as documented by a positive serum beta-human chorionic gonadotropin [β-hCG] test with a minimum sensitivity 25 IU/L or equivalent units of β-hCG). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.

21. Post liver transplant subjects

22. Any subject who has previously received avatrombopag

23. Hypersensitivity to avatrombopag maleate or any of its excipients

24. Hemoglobin levels ≤8.0 or ≥18.0 g/dL for men and >15 for women at Screening, with hematocrit ≥54% for men and ≥45% for women

25. Current malignancy including solid tumors and hematologic malignancies (except HCC)

26. Any history of concomitant medical condition that, in the opinion of the investigator(s), would compromise the subject's ability to safely complete the study

27. Currently enrolled in another clinical trial with any investigational drug or device within 30 days of Screening

9.3.3 Removal of Subjects From Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason. A subject who discontinues study treatment, but does not withdraw consent, should be followed for subsequent protocol-specified visits and procedures.

In these subjects, the Visit 4 (Procedure Day) assessments for the study will be performed as an end of study visit as outlined in Section 9.5.2.1 (Table 5), with the exception of the elective procedure, which may take place outside the study. The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug should be collected on the Subject Disposition CRF page.

These subjects will also be required to complete a follow-up visit, Visit 6 (Day 35) assessments, which will be conducted approximately 30 days after the last dose of study drug.

9.4 TREATMENTS

In this study, the test drug is avatrombopag. The study drugs are avatrombopag, expressed as the amount of free base, and placebo.

9.4.1 Treatments Administered

Subjects will be instructed to take avatrombopag 20-mg tablets or matching placebo orally, once daily, with a meal, as follows:

- Group A (avatrombopag, lower baseline platelet count): 60 mg avatrombopag (3 × 20-mg tablets) once daily on Days 1 through 5
- Group B (placebo, lower baseline platelet count): placebo (3 × 20-mg matching placebo tablets) once daily on Days 1 through 5
- Group C (avatrombopag, higher baseline platelet count): 40 mg avatrombopag (2 × 20-mg tablets) once daily on Days 1 through 5
- Group D (placebo, higher baseline platelet count): placebo (2 × 20-mg matching placebo tablets) once daily on Days 1 through 5

On Day 4 (Visit 3), subjects will take their study medication after the predose PK sample has been taken.

9.4.2 Identity of Investigational Products

Avatrombopag and matching placebo will be supplied by the sponsor in labeled containers. The product release certificates for avatrombopag will be included in the clinical study report for this study.

The sponsor will provide the study drugs packaged in a double-blind configuration. Each subject's study drug will consist of avatrombopag or corresponding matching placebo.

9.4.2.1 Generic and Chemical Name

- Test drug code: E5501
- Generic name: avatrombopag maleate
- Chemical name: 1-(3-Chloro-5-{[4-(4-chlorothiophen-2-yl)-5-(4-cyclohexylpiperazin-1-yl)-1,3-thiazol-2-yl]carbamoyl}pyridin-2-yl)piperidine-4-carboxylic acid maleate

9.4.2.2 Comparator Drug

The comparator drug is matching placebo, which will be provided as matching 20-mg tablets.

9.4.2.3 Labeling for Study Drugs

Study drugs (ie, avatrombopag and placebo) will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required languages for each of those countries.

9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be enrolled into 2 cohorts according to mean baseline platelet count ($<40 \times 10^9$/L or from 40 to $<50 \times 10^9$/L), with neither baseline platelet count cohort comprising greater than 55% of the total number of subjects enrolled into the study. Within each cohort, subjects will be further stratified centrally by risk of bleeding associated with the elective procedure (low, moderate, or high) and HCC status (Yes or No), in order to ensure balance between treatments within each cohort and each further stratum. Within each cohort and each further stratum, subjects will be assigned in a 2:1 ratio to receive avatrombopag or placebo once a day for 5 days

based on a computer-generated randomization scheme using permuted-block randomization. It is planned that no fewer than 10% of subjects will be enrolled into the high risk group and no more than 60% of subjects in the low-risk group. The randomization scheme and identification for each subject will be kept strictly confidential before the database lock and final unblinding, and will be included in the final clinical study report for this study.

Approximately 200 subjects who meet all the eligibility requirements will be randomized. (revised per Amendment 04)

Randomization will be performed centrally by an IxRS. The IxRS or clinical supply vendor will generate the randomized study drug identification numbers. After successful completion of Visit 1, the investigator or designee will call or access via web the IxRS to register the subject information and the IxRS will assign each subject a unique 6-digit randomization number at Visit 2.

9.4.4 Selection of Doses in the Study

Dose selection has been carefully focused on seeking to maintain an appropriate risk:benefit ratio balance in this patient population, removing the requirement for platelet transfusion, or any rescue procedure for bleeding, while minimizing the risk of thromboembolic events. The selected doses, based on modeling and simulation of the E5501-G000-202 study data, are aimed at achieving sufficient efficacy (eliminating the need for platelet transfusion) while specifically limiting the proportion of subjects achieving platelet counts $>200 \times 10^9$/L to less than 2%.

The current study design employs a dosing regimen according to baseline platelet count that is anticipated to lead to a similar overall rise in platelet counts irrespective of baseline platelet count.

9.4.5 Selection and Timing of Dose for Each Subject

Subjects will be instructed to take avatrombopag 20-mg tablets or matching placebo orally, once daily, with a meal. On Day 4 (Visit 3), subjects will take their study medication after the predose PK sample has been taken.

9.4.6 Blinding

During the study, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes. Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per SOP.

A master list of all treatments and the subject numbers associated with them will be maintained in a sealed envelope by the IxRS vendor, and the sponsor. In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5.

A subject's treatment should only be unblinded when knowledge of the treatment is essential for further management of the subject. A subject whose treatment is unblinded will not receive any further study medication. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject during the study and used by the subject within 30 days before Visit 1 will be recorded on the Prior & Concomitant Medication CRF or Non-Pharmacological Procedures CRF. The investigator will record on the Adverse Event CRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition CRF.

9.4.7.1 Permitted Prior Therapy

Subjects who have taken IFN previously, but who have discontinued use for at least 14 days before Screening, are eligible for this study. Subjects who have taken erythropoietin-stimulating agents, but who have discontinued use for at least 7 days before Screening, are eligible for this study. Subjects who have taken heparin, warfarin, NSAIDs, aspirin, verapamil, or antiplatelet therapy with ticlopidine or glycoprotein IIb/IIIa antagonists (eg, tirofiban), but who have discontinued use for at least 7 days before Screening, are eligible for this study. Subjects who are taking inhibitors of P-gp (excluding verapamil) and are on a stable dose for at least 7 days before Screening are eligible for this study. Subjects who have received platelet transfusion or blood products containing platelets, but who have had their last treatment at least 7 days prior to Screening, are eligible for this study; however packed red blood cells are permitted throughout.

9.4.7.2 Permitted Concomitant Therapy

Subjects should be instructed to contact site personnel before starting any new medications or treatments. Medications or treatments not specified as prohibited (see below) are permitted during the study.

All prescription drugs, herbal products, nutritional supplements (including vitamins), and over the counter medications are to be recorded, as well as any changes in concomitant medications, including dose, after Visit 1 and while the subject is in the study. Stable doses of inhibitors of P-gp are permitted during the study. The dose of these medications should remain unchanged until the first postprocedure visit (Visit 5). Please refer to Appendix 2 for a list of P-gp inhibitors.

Subjects may receive therapy if clinically indicated as rescue therapy for bleeding.

9.4.7.3 Prohibited Concomitant Therapy

Erythropoietin stimulating agents are prohibited throughout the study. Interferon use is prohibited during the study; however, at the investigator's discretion, subjects may restart IFN therapy if clinically indicated during the Follow-up Phase (ie, after Visit 4 [Procedure Day]).

Eltrombopag, romiplostim, heparin, warfarin, NSAIDs, aspirin, verapamil, estrogen, and antiplatelet therapy with ticlopidine or glycoprotein IIb/IIIa antagonists (eg, tirofiban) are prohibited. (revised per Amendment 02) Aspirin, for antiplatelet therapy, can be prescribed at the discretion of the investigator in subjects in which the platelet count rises and who are believed to have an increased risk of thrombosis. In subjects where use of aspirin is contraindicated, an alternate antiplatelet therapy such as a platelet adenosine diphosphate receptor inhibitor (eg, clopidogrel) can be prescribed. It should be noted that clopidogrel should be used with due consideration in subjects with liver disease. Lack of activation due to liver disease could lead to a reduction in activation of the prodrug. In addition, as clopidogrel is activated by the CYP system, care is required when administering clopidogrel to subjects with liver disease and co-administering clopidogrel with agents that are substrates or inhibitors of CYP.

9.4.8 Treatment Compliance

Subjects will receive a dosing diary in which they are to record the dates and times of their study drug doses.

Records of treatment compliance for each subject will be kept during the study. Clinical research associates will review treatment compliance during site visits and at the completion of the study.

9.4.9 Drug Supplies and Accountability

The investigator and the study staff will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of study drugs that occurs at the site. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, Food and Drug Administration, Medicines and Healthcare Products Regulatory Agency). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be

returned to the investigator by the subject and together with unused study drugs that were shipped to the site but not dispensed to subjects are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed and sealed and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 STUDY ASSESSMENTS

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth, age, sex, race, and ethnicity.

9.5.1.2 Baseline Assessments

MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history and current medical conditions will be recorded at the Screening Visit. All significant medical and surgical history must be noted in the Medical History and Current Medical Conditions CRF.

Physical examinations (both comprehensive and targeted) will be performed as designated on the Schedule of Procedures/Assessments (Table 5). A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and neurologic examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. A targeted physical examination will include evaluations of the heart and lungs, abdomen, and limbs. Examinations of other regions will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

CONFIRMATION OF ELECTIVE PROCEDURE

Elective procedure(s) will be recorded at the Screening Visit.

CHILD–TURCOTTE-PUGH (CTP) SCORE

The subject's Child–Turcotte-Pugh (CTP) score will be calculated based on the screening laboratory values and physical examination.

MODEL FOR END-STAGE LIVER DISEASE (MELD) SCORE

The subject's MELD score (based on serum bilirubin, serum creatinine, and INR for prothrombin time at Screening) will be calculated. The MELD score must be ≤24 for inclusion into the study.

BARCELONA-CLINIC LIVER CANCER (BCLC) STAGE

For subjects with HCC, the BCLC stage will be collected at Screening. The BCLC staging classification must be 0, A, or B for inclusion in the study. Therefore, HCC subjects with a staging classification of C or D will be excluded from the study as these subjects have a higher risk of developing a PVT complication. The BCLC staging classification guides treatment, particularly in early tumors. The BCLC staging system links tumoral stage with a treatment strategy, and is aimed at incorporating prognosis estimation and potential treatment advancements in 1 unified proposal, with Stage 0 and additional stages ranging from A to D. The system may be applied to most subjects with HCC, although individual cases might warrant special consideration.[16]

DOPPLER SONOGRAPHY WITH FLOW RATE

Subjects will be screened for evidence of PVT, including portal vein flow rate, using Doppler sonography before study entry. All subjects whose platelet count exceeds 200 x 10^9/L will be required to have a Doppler assessment at Visit 5. Three main portal vein blood flow velocity measurements, lasting no less than 4 seconds, will be recorded, and the mean of the 3 values recorded as the final reading. Subjects will be required to have a main portal vein blood flow velocity rate of ≥10 cm/second at Screening to be eligible for the study. The Doppler sonography and flow rate assessment can be completed at any time during the Screening Period with results available prior to randomization.

Guidelines have been developed to reduce inter-observer variability in measuring flow rates[14] to ensure uniformity of flow rate measurements. Every effort should be made to have the same sonography operator at the study site perform all ultrasound evaluations throughout the study. Please refer to Appendix 3 for additional information.

9.5.1.3 Efficacy Assessments

The timing of assessments is described in the Schedule of Assessments/Procedures (Table 5).

NUMBER OF PLATELET TRANSFUSIONS

The incidence of platelet transfusions will be monitored by the investigator (or appropriately delegated study site personnel) from randomization. The number of transfusions administered (if used), along with date and start/stop times, will be specified and recorded in the CRF. In order to minimize missing data for the primary endpoint, "Not Done" (or "Not Applicable") will be collected on the CRF to indicate subjects who did not receive a platelet transfusion.

ANY RESCUE PROCEDURE FOR BLEEDING

Any rescue procedure for bleeding will be monitored by the investigator (or appropriately delegated study site personnel) from randomization onwards. Any rescue procedure for bleeding, including number of transfusions administered (if used), along with start and end dates/times, will be recorded. In order to minimize missing data for the primary endpoint, "Not Done" (or "Not Applicable") will be collected on the CRF to indicate subjects who did not receive rescue therapy.

The following are considered as rescue procedures when used specifically for bleeding:

- Platelet transfusion
- FFP
- Cryoprecipitate
- Vitamin K (phytonadione)
- Desmopressin
- Recombinant activated factor VII
- Aminocaproic acid
- Tranexanic acid (added per Amendment 01)
- Whole blood transfusion
- Packed red cell transfusion
- Surgical intervention or interventional radiology

PLATELET COUNTS

Platelet count by local laboratory will be measured in all subjects at Screening (Days -14 to -1) and at Baseline (Day 1), then on the Procedure Day (Day 10), 7 days postprocedure and Day 35. Screening and Baseline platelet counts must be measured at least 1 day apart with neither platelet count $>60 \times 10^9$/L for eligibility. The mean of these 2 platelet counts (mean baseline platelet count $<50 \times 10^9$/L) will be used for entry criteria.

BLEEDING EVENTS

All bleeding events will be assessed by the investigator (or appropriately delegated study site personnel) from randomization utilizing the WHO bleeding score (Table 2) and the Bleeding Academic Research Consortium (BARC) bleeding scale (Table 3).

Table 2 WHO Bleeding Score Categories

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

Table 3 BARC Bleeding Scale Categories

Bleeding Type	Description
Type 0	No bleeding
Type 1	Minor bleeding (not requiring medical attention)
Type 2	Mild blood loss (clinically significant - requiring evaluation or intervention)
Type 3a	Overt bleeding plus hemoglobin drop 3 to < 5 g/dL, requires transfusion
Type 3b	Overt bleeding plus hemoglobin drop ≥ 5 g/dL, requires IV vasoactive agents
Type 3c	Intracranial hemorrhage, intraocular bleed compromising vision
Type 4	Coronary artery bypass graft-related bleeding (CABG)[a]
Type 5a	Probable fatal bleeding; no autopsy or imaging confirmation
Type 5b	Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

a: CABG is not a permitted procedure (see Section 9.3.2)

BARC bleeding scale based on Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. (2011) [17]

9.5.1.4 Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic/Pharmacogenetic Assessments

PHARMACOKINETIC ASSESSMENTS

The pharmacokinetics of avatrombopag and effects of covariates will be assessed using population modeling. A total of 3 blood samples for PK analysis will be collected. One sample will be collected on Day 1 between 2 to 6 hours postdose. Two samples will be collected on Day 4 (±1 day): a predose sample within 2 hours prior to dosing and a second sample between 2 to 6 hours postdose.

Please refer to the Laboratory Manual for a description of collection, handling, and shipping procedures for PK samples.

Plasma samples will be assayed for avatrombopag concentrations using a validated liquid chromatography-tandem mass spectrometry method with a lower limit of quantification of 1.00 ng/mL.

Blood will also be drawn where possible at the first report of an SAE or severe unexpected AE and at its resolution.

PHARMACODYNAMIC ASSESSMENTS

Platelet count by local laboratory will be measured in all subjects at least 1 day apart at Screening (Days -14 to -1) and Baseline (Day 1), then on the Procedure Day (Day 10), 7 days postprocedure, and Day 35.

PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

The relationship between avatrombopag plasma concentrations and platelet count will be evaluated using population PK/pharmacodynamic (PD) modeling. Effects of covariates on the PD parameters will be evaluated.

PHARMACOGENOMIC/PHARMACOGENETIC ASSESSMENTS

Not applicable

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, including all Common Terminology Criteria for Adverse Events (CTCAE) v4.0 grades (for both increasing and decreasing severity), and SAEs including platelet transfusion-related complications; regular monitoring of hematology, blood chemistry, and urine values; periodic measurement of vital signs and electrocardiograms (ECG); the performance of physical examinations; and Doppler sonography as detailed in Table 5.

An independent DSMB will be established in order to ensure the safety of the subjects.

ADVERSE EVENTS AND OTHER EVENTS OF INTEREST

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is avatrombopag

The criteria for identifying AEs are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product

- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present at pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, whether prescribed in the protocol or not.

A laboratory result should be considered by the investigator to be an AE if it:

- Results in the withdrawal of study drug
- Results in withholding of study drug pending some investigational outcome
- Results in an intervention, based on medical evaluation (eg, potassium supplement for hypokalemia)
- Results in any out of range laboratory value that in the investigator's judgment fulfills the definitions of an AE with regard to the subject's medical profile
- Increases in severity compared with baseline by ≥2 CTCAE grades (see Appendix 1 for CTCAE v 4.0), with the exception of lymphocytes, albumin, cholesterol, glucose, and phosphate. For these tests, any change of ≥2 grades will be evaluated by the investigator to determine if it is of clinical significance and, if so, will be considered an AE.

All AEs observed during the study will be reported on the CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit. Serious AEs will be collected for 30 days after the last dose.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.

It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

Abnormal ECG (QTc, corrected for heart rate) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is >450 ms and there is an increase of >60 ms from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

All AEs must be followed for 30 days after the subject's last dose, or until resolution, whichever comes first.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

ASSESSING SEVERITY OF ADVERSE EVENTS

Adverse events will be graded on a 5-point scale according to CTCAE v4.0[18] as follows:

Grade 1 = Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2 = Moderate: minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living

Grade 3 = Severe or medically significant but not immediately life threatening hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living

Grade 4 = Life-threatening consequences: urgent intervention indicated

Grade 5 = Death related to AE

Investigators will report CTCAE grades for all AEs (for both increasing and decreasing severity). All AEs reported using CTCAE classification and graded as 4 or 5 are to be considered serious. The criteria for assessing severity are different from those used for seriousness (see Serious Adverse Events and Other Events of Interest for the definition of an SAE).

ASSESSING RELATIONSHIP TO STUDY TREATMENT

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

CLASSIFICATION OF CAUSALITY

Not Related A causal relationship between the study treatment and the AE is not a reasonable possibility.

Related A causal relationship between the study treatment and the AE is a reasonable possibility. The investigator must further qualify the degree of certainty as "possible" or "probable."

SERIOUS ADVERSE EVENTS AND OTHER EVENTS OF INTEREST

A SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent 1 of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

In addition to the above, other events of interest include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error; any treatment-emergent significant laboratory abnormality; recurrence of thrombocytopenia (defined as a platelet count of $<10 \times 10^9$/L and 10×10^9/L less than baseline count within 30 days of discontinuation); thromboembolic events; bleeding events (WHO Grade 2 to 4); and platelet transfusion-related complications. These events of interest are to be captured using the SAE procedures but are to be considered as SAEs only if they meet 1 of the above criteria. All AEs associated with events of interest are to be reported on the CRF whether or not they meet the criteria for SAEs. All liver transplantations are to be captured as SAEs.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration).
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 4. The Schedule of Procedures/Assessments (Table 5) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 4 Clinical Laboratory Tests

Category	Parameters
Hematology	
Complete Blood Count	hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (basophils, eosinophils, lymphocytes, monocytes, total neutrophils [segmented and bands])
Coagulation panel	prothrombin time, activated partial thromboplastin time, international normalized ratio
Chemistry	
Electrolytes	bicarbonate, chloride, potassium, sodium
Liver function tests	alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, direct bilirubin, total bilirubin, gamma-glutamyl transpeptidase
Renal function parameters	blood urea nitrogen, creatinine
Other	albumin, calcium, cholesterol, creatine phosphokinase with fractionation, globulin, glucose, lactate dehydrogenase, phosphorus, total protein, triglycerides, uric acid
Urinalysis	bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs
Protocol specified	human immunodeficiency virus serology, serum thrombopoietin
Females only	serum beta-human chorionic gonadotropin pregnancy tests, urine pregnancy tests
Platelet function tests [a]	eg, p-selectin and integrin IIbβ3 with and without an agonist. The following agonists will be used: 0.5 μM ADP, 20 μM ADP, 1.5 μM TRAP, or 20 μM TRAP (eg, platelet aggregation with an agonist. ADP will be used as the agonist) (revised per Amendment 02)

ADP = adenosine diphosphate, RBC = red blood cell, TRAP = thrombin receptor agonist peptide, WBC = white blood cell

a: Performed only at selected sites

Clinical laboratory tests during the study will be performed by the designated central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. When a hematology test is required, 2 blood samples will be collected: 1 for central laboratory analysis and 1 for local laboratory analysis. Investigators will utilize the platelet count result received from the local laboratory hematology test analysis to qualify subject's entry into the study, and also for clinical assessments.

Only platelet count data from local laboratories, including the date and clock time of collection of the sample, will be collected and entered into the CRF for analysis. All other hematological parameters will be collected and loaded into the database for analysis according to results derived from the designated central laboratory.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Adverse Events and Other Events of Interest) and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

For laboratory abnormalities meeting the criteria of SAEs (see Serious Adverse Events and Other Events of Interest), the site must fax or email the SAE report including the laboratory report (as regionally required) to the sponsor using the SAE form (see Reporting of Serious Adverse Events [Section 9.5.4.1]).

VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic blood pressure [BP] [mmHg], pulse [beats per minute], respiration rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated on the Schedule of Procedures/Assessments (Table 5) by a validated method. Blood pressure and pulse will be measured after the subject has been sitting for 5 minutes. Preferably, all blood pressure measurements will be performed on the same arm and by the same person.

PHYSICAL EXAMINATIONS

Physical examinations will be performed as designated on the Schedule of Procedures/Assessments (Table 5). Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated on the Schedule of Procedures/Assessments (Table 5). Subjects must be in the supine position for a period of 5 minutes before the ECG.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Adverse Events and Other Events of Interest) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

For ECG abnormalities meeting criteria of an SAE (see Serious Adverse Events and Other Events of Interest), the site must fax or email the SAE report including the ECG report to the sponsor using the SAE form (see Reporting of Serious Adverse Events [Section 9.5.4.1]).

OTHER SAFETY ASSESSMENTS

DOPPLER SONOGRAPHY

Subjects will be screened for evidence of PVT and portal vein flow rate using Doppler sonography at Screening. Only subjects whose preprocedural platelet count is $>200 \times 10^9$/L on Visit 4 (Procedure Day) will be required to have a Doppler assessment at Visit 5. For any subjects where the presence of a PVT is suspected, confirmation of diagnosis, via CT scan or

MRI, should be performed and treatment for PVT initiated per local guidelines. Please refer to Appendix 3 for additional information.

VIRAL TESTS

A blood sample will be taken to test for HIV antibodies at Screening.

PREGNANCY TEST

At the Screening Visit, a serum β-hCG test will be performed for females of childbearing potential or who have been amenorrheic for less than 12 months. All females will be considered to be of childbearing potential unless they are postmenopausal (at least 12 months consecutive amenorrhea in the appropriate age group and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, hysterectomy, or bilateral oophorectomy) at least 1 month before dosing. A urine β-hCG test will be performed at other time points during the study, as specified in the Schedule of Procedures/Assessments (Table 5).

PLATELET FUNCTION

At selected sites, blood samples will be collected on Day 1 (Visit 2) before dosing (Baseline), on Day 4 (Visit 3), and on the Procedure Day (Day 10) for platelet function assessment. Platelet function will be assessed using specified flow cytometric markers or platelet aggregometry at selected sites (Table 4). Flow cytometry will be performed at Visits 2, 3, and 4. Platelet aggregometory will be conducted on Day -14 to 1 (Visit 1 or 2) before dosing and on the Procedure Day (Day 10). (revised per Amendment 02)

9.5.1.6 Other Assessments

HEALTH ECONOMIC ASSESSMENTS

Health economic parameters will be collected at each visit (as appropriate). Health care resource utilization, including any rescue treatment, procedure, and laboratory test for bleeding including the number of transfused platelet units, the supply from which the transfused platelet units were procured including whole blood platelets from a random donor pool (if known) with or without leukocyte depletion, as an apheresis product (as platelets alone) from a single donor and/or autologous blood donation, number of hospital days, number of intensive care bed-days, number of outpatient visits to the hospital's outpatient department, the clinic, the physician's office, home health care or other place of service, and health care resource utilization related to other transfusion-related complications during all scheduled and unscheduled visits will be collected in the CRF.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 5 presents the schedule of procedures/assessments for the study.

Table 5 Schedule of Procedures/Assessments in Study E5501-G000-311

Phase	Prerandomization	Randomization			Follow-Up	
Period	Screening	Baseline	Treatment	Procedure Day		
Visit	1	2	3	4[a, b]	5	6[c]
Day	Days -14 to -1	Day 1	Day 4 (±1 day)	Day 10 (+3 days)	7 Days Postprocedure (+3 days)	Day 35 (+3 days)
Procedures/Assessments						
Subject informed consent	X					
Inclusion/Exclusion criteria	X	X				
Demographics	X					
Medical history	X					
CTP and MELD Scores	X					
BCLC grade[d]	X					
Prior/concomitant medications	X	X	X	X	X	X
Health care resource use		X	X	X	X	X
Adverse events	X	X	X	X	X	X
Physical examination[e]	X			X	X	X
Vital signs (including height, weight)	X [f]	X		X	X	X
ECG (12-lead)	X	X	X			X
Hematology (including platelet count by local laboratory)[g]	X[h]	X[h]	X	X	X	X
Coagulation	X			X		X
Serum chemistry, liver function tests, CPK with fractionation, urinalysis[i]	X			X		X

Table 5 Schedule of Procedures/Assessments in Study E5501-G000-311

continued

Phase	Prerandomization	Randomization			Follow-Up	
Period	Screening	Baseline	Treatment	Procedure Day	Postprocedure	
Visit	1	2	3	4 [a,b,c]	5	6[d]
Day	Days -14 to -1	Day 1	Day 4 (±1 day)	Day 10 (+3 days)	7 Days Postprocedure (+3 days)	Day 35 (+3 days)
HIV serology	X					
Pregnancy testing[j]	X	X		X		X
Doppler sonography	X[k]				X[l]	
Assessment of platelet transfusion[m]		X	X	X	X	
Assessment of any rescue procedure for bleeding[n]		X	X	X	X	
Serum TPO		X		X		X
Platelet function tests[o]		X	X	X		
Randomization		X				
PK blood sampling		X[p]	X[p,q]			
Study drug dosing[r,s]		X	X			
Dispense dosing diary[t]		X				
Retrieve/review dosing diary			X	X		
Collect study drug, if applicable				X		
Bleeding assessment (WHO and BARC)		X	X	X	X	X

BARC = Bleeding Academic Research Consortium; BCLC = Barcelona Clinic Liver Cancer; CPK = creatine phosphokinase; CTP = Child-Turcotte-Pugh; ECG = electrocardiogram; HIV = human immunodeficiency virus; MELD = Model For End-stage Liver Disease; PK =

Table 5 Schedule of Procedures/Assessments in Study E5501-G000-311

pharmacokinetics; TPO = thrombopoietin; WHO = World Health Organization

a: Subjects will undergo their elective procedure within 5 to 8 days of their last dose of study drug (ie, Study Day 10 to13), and after completing the Procedure Day assessments.

b: Visit 4 (Procedure Day) assessments will also occur when any subject has been withdrawn or discontinued early from the study for any reason.

c: Visit 6 (Day 35) assessments will also occur when any subject has been withdrawn or discontinued early from the study for any reason.

d: BCLC grade is only for subjects with hepatocellular carcinoma.

e: Comprehensive physical examination at Screening and targeted physical examination at all subsequent visits.

f: Height will be recorded at Screening (Visit 1) only.

g: Hematology must be taken prior to any platelet transfusion

h: Independent platelet counts performed by a local laboratory at Screening and Baseline must be at least 1 day apart with neither platelet count $>60 \times 10^9$/L. The mean of these 2 platelet counts (mean baseline platelet count) must be $<50 \times 10^9$/L (as per Inclusion Criterion #2), to be eligible to participate in the study.

i: Complete urinalysis will be performed at Screening and dipstick analysis at all subsequent visits. If urine dipstick is abnormal, a complete urinalysis will be required. After the Screening measurement, fractionation will only be analyzed by the central laboratory in the event CPK level is abnormal.

j: For females of childbearing potential or who have been amenorrheic for less than 12 months. Serum beta-human chorionic gonadotropin pregnancy testing will be performed at Screening (Visit 1). Urine pregnancy testing will be performed at Visits 2, 4, and 6.

k: Portal vein flow velocity will be assessed at this visit. Subjects will be required to have a main portal vein blood flow velocity rate of ≥10 cm/second at Screening to be eligible for the study.
Three main portal vein blood flow velocity measurements, lasting no less than 4 seconds, will be recorded, and the mean of the 3 values recorded as the final reading.
The Doppler sonography and flow rate assessment can be completed at any time during the Screening Period with results available prior to randomization.

l: Only subjects whose preprocedural platelet count exceeds 200×10^9/L will be required to have a Doppler assessment at Visit 5. For any subjects where the presence of a portal vein thrombosis (PVT) is suspected, confirmation of diagnosis via computerized tomography scan or magnetic resonance imaging, should be performed and treatment for PVT initiated per local guidelines.

m: Number of transfusions administered (if used), along with start and end dates/times, will be recorded.

n: Any rescue procedure for bleeding, including number of transfusions administered (if used), along with start and end dates/times, will be

Table 5 Schedule of Procedures/Assessments in Study E5501-G000-311

recorded.

o: Platelet function tests will be performed at selected sites. Flow cytometry will be performed at Visits 2, 3, and 4. Platelet aggregometory will be performed on Day -14 to 1 (Visit 1 or 2) before dosing and on the Procedure Day (Day 10) (revised per Amendment 02).

p: On Visit 2 (Day 1), 1 PK sample will be collected between 2 to 6 hours after dosing.

q: On Visit 3 (Day 4 ±1), 2 PK samples will be collected: predose (within 2 hours prior to dosing) and between 2 to 6 hours after dosing.

r: Subjects will be randomized to receive placebo or avatrombopag as follows:

Group A (avatrombopag, lower baseline platelet count): 60 mg avatrombopag (3 × 20-mg tablets) once daily on Days 1 through 5
Group B (placebo, lower baseline platelet count): placebo (3 × 20-mg matching placebo tablets) once daily on Days 1 through 5
Group C (avatrombopag, higher baseline platelet count): 40 mg avatrombopag (2 × 20-mg tablets) once daily on Days 1 through 5
Group D (placebo, higher baseline platelet count): placebo (2 × 20-mg matching placebo tablets) once daily on Days 1 through 5

s: All doses of study drug will be taken with a meal.

t: Subjects will receive a dosing diary in which they are to record the dates and times of their study drug doses.

9.5.3 Appropriateness of Measurements

All clinical assessments, including platelet counts, are standard measurements commonly used in studies of subjects with thrombocytopenia associated with liver disease.

The safety assessments to be performed in this study, including but not limited to hematology analyses, blood chemistry tests, urinalysis, physical examinations, ECGs, Doppler sonography, vital signs, and assessment of AEs, are standard evaluations to ensure subject safety.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Other Events of Interest

9.5.4.1 Reporting of Serious Adverse Events

All SERIOUS ADVERSE EVENTS, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.

Deaths and life-threatening events should be reported immediately by telephone. The immediate report should be followed up within 24 hours by emailing or faxing the completed SAE form.

Serious adverse events, regardless of causality assessment, must be collected through the last visit and for 30 days after the subject's last dose. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE, in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 30 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 30 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Serious Adverse Events [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

9.5.4.3 Reporting of Other Events of Interest

REPORTING OF ADVERSE EVENTS ASSOCIATED WITH STUDY DRUG OVERDOSE, MISUSE, ABUSE, OR MEDICATION ERROR

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with an overdose should be captured on the Adverse Event CRF. Adverse events associated with overdose, misuse, abuse, or medication error should be reported using the

procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

REPORTING OF SIGNIFICANT LABORATORY ABNORMALITY

Any significant treatment-emergent laboratory abnormality observed during the clinical study should be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the laboratory abnormality does not meet serious criteria. If the significant laboratory abnormality does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

A laboratory result should be considered a treatment-emergent significant abnormality if the result:

- Is within normal limits at baseline and has increased in severity to meet the sponsor's grading criteria for laboratory values of Grade 3 or above
- Is outside normal limits at baseline and increases in severity to the sponsor's grading criteria for laboratory values of Grade 4 or above. These abnormalities are automatically considered to be serious, with the exception of expected and reproducible hematologic abnormalities.
- Is otherwise considered by the investigator to meet serious criteria as defined in Section 9.5.1.5 (Serious Adverse Events and Other Events of Interest)

Significant laboratory abnormalities should not be listed as separate AEs or SAEs if they are considered to be part of the clinical syndrome that is being reported as an AE or SAE.

REPORTING OF STUDY-SPECIFIC EVENTS

Study-specific events (ie, recurrence of thrombocytopenia [defined as a platelet count of $<10 \times 10^9$/L and 10×10^9/L less than baseline count within 30 days of discontinuation]); thromboembolic events; bleeding events (WHO Grade 2 to 4); and platelet transfusion-related complications should be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), even if the study-specific event does not meet serious criteria. If the event does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF. All liver transplantations will be captured as SAEs.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific

time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All suspected unexpected serious adverse reactions will be reported, as required, to the CAs of all involved European member states.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue the study at any time for any reason. All subjects who discontinue the study are to complete the study's early discontinuation procedures the Visit 4 (Procedure Day) assessments for the study will be performed as an end of study visit.

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms. This information will be recorded in the CRF.

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, inadequate therapeutic effect, withdrawal of consent, pregnancy, study terminated by sponsor, or administrative/other. In addition to the primary reason, the subject may indicate 1 or more of secondary reasons for discontinuation. Study disposition information will be collected on the Subject Disposition CRF.

A subject removed from the study for any reason may not be replaced.

9.5.6 Abuse or Diversion of Study Drug

Not applicable

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 DATA QUALITY ASSURANCE

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 STATISTICAL METHODS

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding. However, unblinded safety analyses for review by a DSMB will be conducted by an independent statistical group prior to database lock. Statistical analyses will be performed using SAS® software or other validated statistical software

as required. Details of the planned statistical analyses are outlined below; further details will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before the unblinded interim safety analyses, final database lock and treatment unblinding, and will be included in the clinical study report. An interim statistical analysis plan, describing the safety analyses planned for the purposes of review by the DSMB, will also be produced.

9.7.1.1 Study Endpoints

PRIMARY ENDPOINTS

The primary efficacy endpoint is the proportion of subjects who do not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure.

SECONDARY ENDPOINTS

The secondary efficacy endpoints are:

- Proportion of responders defined as subjects who achieve platelet counts of $\geq 50 \times 10^9$/L on Procedure Day (ie, prior to receiving a platelet transfusion or undergoing the elective procedure)
- Change from baseline in platelet count on Procedure Day (ie, prior to receiving a platelet transfusion or undergoing the elective procedure)

(revised per Amendment 04)

EXPLORATORY ENDPOINTS

The exploratory endpoints are:

- Platelet count and change from baseline in platelet count at each visit
- Proportion of subjects who achieve platelet count of $\geq 50 \times 10^9$/L, $\geq 75 \times 10^9$/L, or $\geq 200 \times 10^9$/L at each visit
- Number of platelet units used per platelet transfusion episode
- Severity of bleeding events assessed by WHO bleeding score and BARC bleeding scale
- Proportion of subjects with a WHO bleeding score ≥2 after randomization and up to 7 days following an elective procedure (revised per Amendment 04)
- Health economics assessed by resource use

9.7.1.2 Definitions of Analysis Sets

Full Analysis Set (FAS): The FAS is the group of randomized subjects. The FAS will be analyzed "as randomized".

Per Protocol Set (PP): The PP Set is the group of all randomized subjects who receive protocol-assigned study drug and do not meet any of the following criteria:

- Subjects who have any major protocol violations (major inclusion/exclusion violations or other major protocol violations that impact the evaluation of efficacy)
- Subjects who use a prohibited concomitant medication that affects the assessment of study endpoints
- Subjects who are noncompliant in terms of study medication

A comprehensive list of subjects to be excluded from the PP will be agreed upon by the study team prior to database lock. The PP will be analyzed "as randomized".

Safety Analysis Set: The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment. This set will be analyzed "as treated."

PK Analysis Set: The PK Analysis Set is the group of randomized subjects who receive at least 1 dose of avatrombopag and have at least 1 quantifiable avatrombopag concentration with a documented dosing history.

PK/PD Analysis Set: The PK/PD Analysis Set is the group of randomized subjects who receive at least 1 dose of avatrombopag, have at least 1 quantifiable avatrombopag concentration, and at least 1 platelet count, with a documented dosing history.

9.7.1.3 Subject Disposition

Subject disposition will be summarized by treatment group for the FAS and Safety Analysis set. The number (percentage) of subjects who completed or discontinued prematurely from the study and their reason for discontinuation will be summarized by treatment group. In addition, the number of subjects screened and the number and percentage of subjects who failed screening and the reasons for screen failure will be summarized, based on data recorded on the Screening Disposition CRF.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the FAS and Safety Analysis set will be summarized for each treatment group using descriptive statistics or frequency count. Continuous demographic and baseline variables include age, weight, height, body mass index, MELD score, CTP score, and baseline platelet count; categorical variables include sex, race, ethnicity group, baseline platelet count stratification level, risk of bleeding associated with the elective procedure, and HCC status.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded using the WHO Drug Dictionary. The number and percentage of subjects who took prior and concomitant medications will be summarized for the Safety Analysis set by treatment group, Anatomical Therapeutic Chemical class (indicating therapeutic class) and WHO Drug Dictionary preferred term. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the subject's last dose.

9.7.1.6 Efficacy Analyses

The FAS will be used as the primary population for the efficacy analyses, while the PP will be used as a supportive analysis. All analyses of platelet counts will be based on local laboratory results.

PRIMARY EFFICACY ANALYSIS

The primary efficacy variable is the proportion of subjects who do not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure.

The null hypothesis is that the proportion of subjects not requiring a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure is the same between the avatrombopag and placebo treatment groups. The corresponding alternative hypothesis is that the proportion of subjects not requiring a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure is not the same between avatrombopag and placebo. This hypothesis will be tested separately within each baseline platelet cohort.

The proportion of subjects not requiring a platelet transfusion or any rescue procedure for bleeding will be tested between the individual avatrombopag treatment group (40 or 60 mg) and matching placebo within each baseline platelet count cohort ($<40 \times 10^9$/L or from 40 to $<50 \times 10^9$/L), each at a significance level of α=0.05, using the generalized Cochran Mantel Haenszel (CMH) test adjusting for risk of bleeding associated with the elective procedure (low, moderate, or high based on Amendment 02 categorization).

- For subjects with platelet count $<40 \times 10^9$/L at baseline, the treatment comparison will be carried out between the 60 mg avatrombopag treatment group versus matching placebo.
- For subjects with platelet count from 40 to $<50 \times 10^9$/L at baseline, the treatment comparison will be carried out between the 40 mg avatrombopag treatment group versus matching placebo.

This study will be considered as positive if statistical significance is achieved for the primary efficacy endpoint for both baseline platelet count cohorts.

The 95% confidence interval (CI) for the proportion of subjects not requiring a platelet transfusion or any rescue procedure for bleeding will be calculated for each treatment group within each baseline platelet count cohort. In addition, the 95% CI for the difference between avatrombopag and matching placebo will be provided within each baseline platelet count cohort.

Since the HCC status is included in the randomization stratification for safety purposes only, not for efficacy consideration, HCC will not be included in the CMH model for the primary efficacy analysis.

Subjects with missing information about the primary efficacy outcome due to early withdrawal or other reasons will be considered as having received a transfusion for the primary analysis.

The following analyses will be considered as sensitivity analyses:

- PP analysis: The same primary efficacy analyses described above will be repeated based on the PP analysis set.

- Observed case: The same primary efficacy analyses described above will be repeated based on observed data. Subjects with missing information about the primary efficacy outcome will be excluded from this analysis.

- Fisher's exact Test: The same primary efficacy analyses described above will be carried out using Fisher's exact test.

- Modified primary efficacy endpoint: Proportion of subjects who do not require a platelet transfusion after randomization and up to 7 days following an elective procedure. This efficacy endpoint will be analyzed using the same approach as primary efficacy analysis using FAS.

Additional sensitivity analyses may also be explored, if deemed appropriate.

SECONDARY EFFICACY ANALYSES

There are 2 secondary efficacy endpoints in this study: (revised per Amendment 04)

- Proportion of responders defined as subjects who achieve target platelet counts of $\geq 50 \times 10^9$/L on Procedure Day (prior to receiving a platelet transfusion or undergoing the elective procedure)

- Change from baseline in platelet count on Procedure Day (prior to receiving a platelet transfusion or undergoing the elective procedure)

The analysis of the secondary efficacy variables as defined above will proceed following a sequential gatekeeping testing procedure with the multiplicity adjustment to control the Type I error rate at significance level $\alpha=0.05$.

The proportion of subjects who achieve platelet counts of $\geq 50 \times 10^9$/L on the Procedure Day will be analyzed first. The proportion of subjects with platelet counts of $\geq 50 \times 10^9$/L on the Procedure Day will be tested between the individual avatrombopag treatment group (40 or 60 mg) and matching placebo separately within each baseline platelet count cohort ($< 40 \times 10^9$/L or from 40 to $< 50 \times 10^9$/L), each at a significance level of $\alpha=0.05$, using the generalized CMH test adjusting for risk of bleeding associated with the elective procedure (low, moderate, or high based on Amendment 02 categorization).

The second secondary efficacy variable, change from baseline in platelet count on the Procedure Day, will be analyzed only if the test for the first secondary efficacy variable is statistically significant for both baseline platelet count cohorts. The change from baseline in platelet count will be analyzed using the Wilcoxon rank sum test separately within each baseline platelet count cohort ($< 40 \times 10^9$/L or from 40 to $< 50 \times 10^9$/L), each at a significance level of $\alpha=0.05$.

(REVISED PER AMENDMENT 04)

EXPLORATORY EFFICACY ANALYSES

The following efficacy variables are considered exploratory:

- Platelet count and change from baseline in platelet count at each visit
- Proportion of subjects who achieve platelet count of $\geq 50 \times 10^9$/L, $\geq 75 \times 10^9$/L, or $\geq 200 \times 10^9$/L at each visit
- Number of platelet units used per platelet transfusion episode
- Severity of bleeding events assessed by WHO bleeding score and BARC bleeding scale
- Proportion of subjects with a WHO bleeding score ≥2 after randomization and up to 7 days following an elective procedure (revised per Amendment 04)

In general, the continuous variables will be analyzed within an analysis of covariance framework or Wilcoxon rank sum test, as appropriate. Categorical variables will be analyzed using CMH, Chi-square or Fisher's exact test. Additional analysis may be performed as needed using appropriate statistical methodologies as specified in the SAP.

Subgroup analyses will be performed on the primary efficacy variable, including age group (<65 and ≥65 years old); sex (male and female); race (white, black, asian and other); geographic region; bleeding risk associated with the elective procedure (low, moderate, or high based on Amendment 02 categorization); MELD score (<10, 10-14, and >14); and CTP grade (A, B, and C). Additional subgroups may be explored, if deemed appropriate.

No adjustment for multiplicity is planned for exploratory, subgroup and sensitivity analyses.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic/Pharmacogenetic Analyses

PHARMACOKINETIC ANALYSES

Plasma concentration versus time data will be listed. The data will be analyzed using a population PK approach to estimate population PK parameters and the effect of covariates on the PK parameters will be evaluated.

For the population PK analysis, data from this study will be pooled with PK data from two Phase 2 studies in subjects with thrombocytopenia associated with liver disease, including hepatitis C, and possibly with data from Phase 1 studies.

The population PK analysis will be performed to characterize the PK of avatrombopag in subjects with thrombocytopenia associated with liver disease, and to screen for potential covariates with any significant and clinically relevant effects on avatrombopag PK. The PK model will be parameterized for absorption rate constant, apparent clearance, and apparent volume of distribution. Derived exposure parameters will be area under the concentration-time curve and maximum plasma concentration.

PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

The relationship between avatrombopag concentration and platelet count will be analyzed using a population PK/PD approach to estimate population PD parameters and the effect of covariates on the PD parameters will be evaluated.

For the PK/PD modeling, data from this study will be pooled with PK/PD data from two Phase 2 studies in subjects with thrombocytopenia associated with liver disease, including hepatitis C, and possibly with data from Phase 1 studies.

The population PK and PK/PD analyses will be detailed in a separate analysis plan.

PHARMACOGENOMIC/PHARMACOGENETIC ANALYSES

Not applicable

9.7.1.8 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety assessment will be summarized for overall and within each baseline platelet count cohort as appropriate. Safety assessments including AEs, laboratory tests, vital signs, and ECG will be summarized by treatment groups using descriptive statistics (mean, standard deviation, median, minimum and maximum) or frequency count as appropriate. No hypothesis testing will be performed for safety assessment.

Study Day 1 for all safety analyses will be defined as the date of the first dose of study drug.

EXTENT OF EXPOSURE

The extent of exposure to study drug will be characterized by duration of exposure (in days) for each treatment group.

Duration of exposure will be defined as the number of days between the date the subject received the first dose of study drug and the date the subject received the last dose of study drug. Duration of exposure will be summarized using descriptive statistics by treatment group. In addition, the duration of exposure will be categorized and will be summarized using frequency count by treatment group.

ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 15.1 or higher) lower level term closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A treatment-emergent AE (TEAE) is defined as an AE that emerges during treatment (up to 30 days after the last dose of study drug), having been absent at pretreatment (Baseline) or

- Reemerges during treatment (up to 30 days after the last dose of study drug), having been present at pretreatment (Baseline) but stopped before the last dose of study drug plus 30 days, or
- Worsens in severity during treatment (up to 30 days after the last dose of study drug) relative to the pretreatment state, when the AE is continuous.

Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

Treatment-emergent AEs will be summarized by treatment group. The following summaries will be reported for TEAEs:

- Incidence of TEAEs by SOC and PT
- Incidence of treatment-related TEAEs by SOC and PT
- Incidence of TEAEs by SOC, PT, and CTCAE Grade
- Incidence of TEAEs by SOC, PT, and relationship to treatment.

A subject will be counted only once within a SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT.

The following summaries will also be presented for the treatment-emergent SAEs:

- Incidence of treatment-emergent SAEs by SOC and PT
- Incidence of treatment-related treatment-emergent SAEs by SOC and PT
- Incidence of treatment-emergent SAEs by SOC, PT, and relationship to treatment

In addition, subjects with TEAEs, treatment-related TEAEs leading to discontinuation from study treatment, and AEs of special interest for this study (including recurrence of thrombocytopenia, thromboembolic events and bleeding events [WHO Grade 2 to 4]) will also be summarized for each treatment group.

LABORATORY VALUES

Laboratory results will be summarized using Système International units, as appropriate. With the exception of urinalysis, platelet function tests, and platelet count (which is considered as an efficacy parameter), for all quantitative parameters listed in Section 9.5.1.5 Safety Assessments (Laboratory Measurements), the actual value and the change from baseline to Procedure Day and to the end of the Follow-up Phase will be summarized by treatment group using descriptive statistics. Analysis of changes from baseline will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Shifts from baseline (LNH) to Procedure Day and to the end of the Follow-up Phase will be presented for each laboratory parameter. Similar shift tables from baseline (LNH) to the highest/lowest postbaseline LNH classification will also be provided.

Appendix 1 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAV). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a grade of 3 or higher. The number and percentage of subjects with TEMAVs will be presented by treatment group; each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable. Markedly abnormal laboratory values will be flagged in the subject data listings.

VITAL SIGNS

Descriptive statistics for vital sign parameters (i.e. diastolic and systolic blood pressure, pulse, respiration rate, body temperature, and weight) and changes from baseline will be presented by visit and treatment group.

ELECTROCARDIOGRAMS

Descriptive statistics for ECG parameters and changes from baseline will be presented by visit and treatment group. ECG interpretation (categorized as normal; abnormal, not clinically

significant; and abnormal, clinically significant) will be presented by visit and treatment group using frequency count.

OTHER SAFETY ANALYSES

Results from Doppler sonography and platelet function tests will be presented.

9.7.1.9 Other Analyses

HEALTH ECONOMIC ANALYSES

The health outcome economics, as measured by healthcare resources utilization, will be summarized by item and by treatment group. The categorical variables will be tested using CMH, Chi-squared or Fisher's exact test, while continuous variables may be analyzed by t-test or Wilcoxon rank sum test as appropriate.

Details of these analyses will be provided in a separate analysis plan.

9.7.2 Determination of Sample Size

The proposed sample size is based on comparisons of the primary efficacy variable, with the response rate defined as the proportion of subjects who do not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure. Based on clinical opinion and the published results of a similar compound in adults with thrombocytopenia associated with liver disease (ELEVATE study),[10] the response rate in the placebo group is assumed to be 18%. With each baseline platelet count cohort, a sample size of 100 randomized subjects, 67 subjects for avatrombopag and 33 subjects for placebo, will have greater than 90% power to detect an absolute difference of 35% between the avatrombopag response rate and the placebo response rate assuming 18% response rate for placebo using Fisher's Exact tests with a 2-sided α=0.05. (revised per Amendment 04) The hypothesized treatment group difference is based on platelet count changes found in the Phase 2 study (E5501-G000-202) and dose-response modeling using data from that study and others in the project development. Based on the baseline data in the Phase 2 study and assuming these are projected to be similar for this study, it is anticipated that this study will enroll roughly half of the total number of subjects in each of the 2 baseline platelet count cohorts to make the total sample size of 200 randomized subjects, 133 subjects for avatrombopag and 67 subjects for placebo. (revised per Amendment 04)

9.7.3 Interim Analysis

No interim efficacy analysis is planned, and therefore no adjustment of the *P*-value for the final efficacy analysis is needed. However, to protect subjects' safety, an independent DSMB will be established to monitor the ongoing safety data. Some of the safety parameters that DSMB will review will include variables that are also being assessed in this study for efficacy (eg, platelet count to ensure there are not too many subjects with a platelet count that exceeds 200×10^9/L and bleeding). The DSMB interim safety analysis will be performed by an independent

statistician and governed by an external DSMB. To maintain the blinding and integrity of the study, procedures will be implemented to ensure the DSMB and independent statistician have sole access to unblinded interim safety data.

Full details of the DSMB procedures, including primary responsibilities of the DSMB, its relationship with other study components, its membership, and its purpose and timings of its meetings, will be documented in a DSMB Charter. These details will also include procedures to ensure confidentiality and proper communication, the guidelines to be implemented by the DSMB, and an outline of the content of the closed reports (unblinded) and open reports (blinded) that will be provided to the DSMB.

9.7.4 Other Statistical/Analytical Issues

Further statistical and analytical issues will be described in the SAP.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

10 REFERENCE LIST

1. Slichter SJ. Evidence-based platelet transfusion guidelines. Hematology. Am Soc Hematol Educ Program. 2007:172-8.

2. Schiffer C, Anderson KC, Bennett CL, Bernstein S, Elting LS, Goldsmith M, et al. Platelet transfusion for patients with cancer: Clinical Practice Guidelines of the American Society of Clinical Oncology. J Clin Oncol. 2001;19:1519-38.

3. Kuter DJ. Thrombopoietin: biology and potential clinical applications. In: McCrae KR, editor. Thrombocytopenia. New York: Taylor & Francis Group; 2006. p. 17-53.

4. Poordad F, Theodore D, Sullivan J, Grotzinger K. Evaluating medical resource utilization and costs associated with thrombocytopenia in chronic liver disease patients. J Med Econ. 2012;15(1):112-24.

5. Tripodi A, Primignani M, Chantarangkul V, Dell'era A, Clerici M, De Franchis R, et al. An imbalance of pro- vs. anti-coagulation factors in plasma from patients with cirrhosis. Gastroenterol. 2009;137:2105-11.

6. Lisman T, Caldwell SH, Burroughs AK, Northup PG, Senzolo M, Stravitz RT, et al. Hemostasis and thrombosis in patients with liver disease: the ups and downs. J Hepatol. 2010;53:362-71.

7. Ponziani FR, Zocco MA, Campanale C, Rinninella E, Tortora A, Di Maurizio L, et al. Portal vein thrombosis: insights into physiopathology, diagnosis and treatment. World J Gastroenterol. 2010;16(2):143-55.

8. Fimognari FL, Violi F. Portal vein thrombosis in liver cirrhosis. Intern Emerg Med. 2008;3:213-8.

9. Englesbe MJ, Kubus J, Muhammad W, Sonnenday CJ, Welling T, Punch JD. Portal vein thrombosis and survival in patients with cirrhosis. Liver Trans. 2010;16:83-90.

10. Afdhal NH, Giannini EG, Tayyab G, Mohsin A, Lee JW, Andriulli A, et al. Eltrombopag before procedures in patients with cirrhosis and thrombocytopenia. N Engl J Med. 2012;367:716-24.

11. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm211796.htm

12. http://clinicaltrials.gov/ct2/show/results/NCT00678587?term=promacta+elevate&rank=1&sect=Xa015#outcome4

13. Zocco MA, Di Stasio E, De Cristofaro R, Novi M, Ainora ME, Ponziani F, et al. Thrombotic risk factors in patients with liver cirrhosis: correlation with MELD scoring system and portal vein thrombosis development. J Hepatol. 2009;51:682-9.

14. Sabba C, Merkel C, Zoli M, Ferraioli G, Gaiani S, Sacerdoti D, et al. Interobserver and interequipment variability of echo-doppler examination of the portal vein: effect of a cooperative training program. Hepatol. 1995;21:428-33.

15. Malloy PC, Grassi CJ, Kundu S, Gervais DA, Miller DL, Osnis RB, et al. for the Standards of Practice Committee with Cardiovascular and Interventional Radiological Society of Europe (CIRSE) Endorsement. Consensus guidelines for periprocedural management of coagulation status and hemostasis risk in percutaneous image-guided interventions. J Vasc Interv Radiol 2009; 20:S240–9.

16. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet. 2003;362:1907-17.

17. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011;123:2736-47.

18. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [published 28 May 2009 (v4.03: June 14, 2010)].

11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 CHANGES TO THE PROTOCOL

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs of all investigational sites. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the CA detailing such changes.

11.2 ADHERENCE TO THE PROTOCOL

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 MONITORING PROCEDURES

The CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes which have been certified for accuracy after production

- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports, (eg, sonograms, CT scans, MRIs, radioactive images, ECGs, rhythm strips, electroencephalograms, polysomnographs, pulmonary function tests, aggregation tracing at selected sites) regardless of how these images are stored, including microfiche and photographic negatives (revised per Amendment 02)
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 RECORDING OF DATA

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

Data will be recorded electronically (See Section 9.6.1).

11.5 IDENTIFICATION OF SOURCE DATA

All data to be recorded on the CRF must reflect the corresponding source documents.

11.6 RETENTION OF RECORDS

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). In addition, the sponsor will send a list of treatment

codes by study subject to the investigator after the clinical database for this study has been locked. The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 AUDITING PROCEDURES AND INSPECTION

In addition to the routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 HANDLING OF STUDY DRUG

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA.

11.9 PUBLICATION OF RESULTS

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 DISCLOSURE AND CONFIDENTIALITY

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 DISCONTINUATION OF STUDY

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 SUBJECT INSURANCE AND INDEMNITY

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Sponsor's Grading for Laboratory Values

(revised per Amendment 02)

Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	< LLN – 10.0 g/dL < LLN – 100 g/L < LLN – 6.2 mmol/L	< 10.0 – 8.0 g/dL < 100 – 80 g/L < 6.2 – 4.9 mmol/L	< 8.0 g/dL < 80 g/L < 4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	< LLN – 3.0 x 10^9/L < LLN – 3000/mm^3	< 3.0 – 2.0 x 10^9/L < 3000 – 2000/mm^3	< 2.0 – 1.0 x 10^9/L < 2000 – 1000/mm^3	< 1.0 x 10^9/L < 1000/mm^3
Lymphocytes	< LLN – 800/mm^3 < LLN – 0.8 x 10^9/L	< 800 – 500/mm^3 < 0.8 – 0.5 x 10^9/L	< 500 – 200/mm^3 < 0.5 – 0.2 x 10^9/L	< 200/mm^3 < 0.2 x 10^9/L
Neutrophils	< LLN – 1.5 x 10^9/L < LLN – 1500/mm^3	< 1.5 – 1.0 x 10^9/L < 1500 – 1000/mm^3	< 1.0 – 0.5 x 10^9/L < 1000 – 500/mm^3	< 0.5 x 10^9/L < 500/mm^3
Platelets	< LLN – 75.0 x 10^9/L < LLN – 75,000/mm^3	< 75.0 – 50.0 x 10^9/L < 75,000 – 50,000/mm^3	< 50.0 – 25.0 x 10^9/L < 50,000 – 25,000/mm^3	< 25.0 x 10^9/L < 25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	< LLN – 3 g/dL < LLN – 30 g/L	< 3 – 2 g/dL < 30 – 20 g/L	< 2 g/dL < 20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
ALT	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
AST	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
Bicarbonate, serum-low	< LLN – 16 mmol/L	< 16 – 11 mmol/L	<11 – 8 mmol/L	< 8 mmol/L
Bilirubin (hyperbilirubinemia)	> ULN – 1.5 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 10.0 x ULN	> 10.0 x ULN
Calcium, serum-low (hypocalcemia)	< LLN – 8.0 mg/dL < LLN – 2.0 mmol/L	< 8.0 – 7.0 mg/dL < 2.0 – 1.75 mmol/L	< 7.0 – 6.0 mg/dL < 1.75 – 1.5 mmol/L	< 6.0 mg/dL < 1.5 mmol/L
Calcium, serum-high (hypercalcemia)	> ULN – 11.5 mg/dL > ULN – 2.9 mmol/L	> 11.5 – 12.5 mg/dL > 2.9 – 3.1 mmol/L	> 12.5 – 13.5 mg/dL > 3.1 – 3.4 mmol/L	> 13.5 mg/dL > 3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	> ULN – 300 mg/dL > ULN – 7.75 mmol/L	> 300 – 400 mg/dL > 7.75 – 10.34 mmol/L	> 400 – 500 mg/dL > 10.34 – 12.92 mmol/L	> 500 mg/dL > 12.92 mmol/L
Creatinine	> ULN – 1.5 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 6.0 x ULN	> 6.0 x ULN
GGT (γ-Glutamyl transpeptidase)	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: > ULN – 160 mg/dL > ULN – 8.9 mmol/L	Fasting glucose value: > 160 – 250 mg/dL > 8.9 – 13.9 mmol/L	Fasting glucose value: > 250 – 500 mg/dL; > 13.9 – 27.8 mmol/L; hospitalization indicated	Fasting glucose value: > 500 mg/dL; > 27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	< LLN – 55 mg/dL < LLN – 3.0 mmol/L	< 55 – 40 mg/dL < 3.0 – 2.2 mmol/L	< 40 – 30 mg/dL < 2.2 – 1.7 mmol/L	< 30 mg/dL < 1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low (hypophosphatemia)	< LLN – 2.5 mg/dL < LLN – 0.8 mmol/L	< 2.5 – 2.0 mg/dL < 0.8 – 0.6 mmol/L	< 2.0 – 1.0 mg/dL < 0.6 – 0.3 mmol/L	< 1.0 mg/dL < 0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	> ULN – 5.5 mmol/L	> 5.5 – 6.0 mmol/L	> 6.0 – 7.0 mmol/L hospitalization indicated	> 7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	< LLN – 3.0 mmol/L	< LLN – 3.0 mmol/L; symptomatic; intervention indicated	< 3.0 – 2.5 mmol/L hospitalization indicated	< 2.5 mmol/L life-threatening consequences

Sponsor's Grading for Laboratory Values				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Sodium, serum-high (hypernatremia)	> ULN – 150 mmol/L	> 150 – 155 mmol/L	> 155 – 160 mmol/L hospitalization indicated	> 160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	< LLN – 130 mmol/L	N/A	< 130 – 120 mmol/L	< 120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	> 300 – 500 mg/dL > 3.42 – 5.7 mmol/L	> 500 – 1000 mg/dL >5.7 – 11.4 mmol/L	> 1000 mg/dL > 11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	> ULN – 10 mg/dL ≤ 0.59 mmol/L without physiologic consequences	N/A	> ULN – 10 mg/dL ≤ 0.59 mmol/L with physiologic consequences	> 10 mg/dL > 0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.
Based on Common Terminology Criteria for Adverse events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

Appendix 2 List of P-glycoprotein Inhibitors

Inhibitor	Therapeutic Class
amiodarone	Antiarrhythmics
azithromycin	Antibiotics
captopril	ACE Inhibitors
carvedilol	α/β Adrenergic Antagonists
clarithromycin	Antibiotics
conivaptan	Diuretics
cremophor	RH40 Transporter Modulators
cyclosporine	Immunosuppressive
diltiazem	Calcium Channel Blockers
dronedarone	Antiarrhythmics
elacridar (GF120918)	Transporter Modulators
erythromycin	Antibiotics
felodipine	Calcium Channel Blockers
ginkgo	Herbal Medications
indinavir and ritonavir	Protease Inhibitors
itraconazole	Antifungals
ketoconazole	Antifungal
lopinavir and ritonavir	Protease Inhibitors
mibefradil	Calcium Channel Blockers
milk thistle	Herbal Medications
nifedipine	Calcium Channel Blockers
nitrendipine	Calcium Channel Blockers
quinidine	Antiarrhythmics
ranolazine	Cardiovascular Drugs
ritonavir	Protease Inhibitors
talinolol	α/β Adrenergic Antagonists
telaprevir	Antivirals
telmisartan	Angiotensin II Inhibitors
tipranavir/ritonavir	Protease Inhibitors
tolvaptan	Vasopressin Antagonist
valspodar (PSC 833)	Transporter Modulators
verapamil	Calcium Channel Blockers

Source: University of Washington Drug Drug Interaction database (except for cyclosporine and ketoconazole)

Appendix 3 Guidelines for Doppler Sonography Measurements

The key to collecting relevant ultrasound data is consistency. The following measures are adopted to minimize the variability of data obtained.

Minimize subject variability:

- The subject should be fasting for at least 4 hours prior to the Doppler sonography
    - *Rationale: Portal vein flow rate increases after food intake*
- The subject should be in the supine position for at least 15 minutes prior to the Doppler sonography
    - *Rationale: Posture has an impact on portal vein flow rate. Standardizing posture across study sites can minimize variability*
- The subject should be instructed to take a full inspiration and hold his/her breath for a few seconds during portal vein flow measurement
    - *Rationale: Measuring portal vein flow rate at the same point in the respiratory cycle can minimize variability*

Minimize operator variability:

In order to minimize operator variability, the following instructions are provided:

- When possible, the same trained sonography operator will perform all of the Doppler sonography testing on all subjects at the study site throughout the study.
- The portal vein should be scanned longitudinally
- Sample volume should be positioned in the center of the vessel, in the tract underneath the hepatic artery, covering 50% of the vessel diameter
- The Doppler angle should be 55º or just below
- Pulse repetition frequency should be 4 kHz; the high pass filter should be adjusted to 100 Hz
- The Doppler and B-mode tracings should be recorded simultaneously
- The average portal blood maximum velocity should be obtained by manual tracing of the upper limit of the Doppler waveforms
- The Doppler waveform calculation should be obtained by covering 2 cardiac cycles between 3 arterial wall artifacts

- Portal vein diameter should be measured from the inner anterior to the inner posterior wall

Three main portal vein blood flow velocity measurements, lasting no less than 4 seconds, will be recorded, and the mean of the 3 values recorded as the final reading.

Minimize equipment variability:

Different equipment may furnish different results due to interequipment variability. Therefore, the sponsor recommends that the same Doppler equipment should be used at the study site throughout the study.

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	E5501-G000-311
Study Protocol Title:	A Randomized, Global, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Once-daily Oral Avatrombopag for the Treatment of Adults with Thrombocytopenia Associated with Liver Disease Prior to an Elective Procedure
Investigational Product Name:	E5501/avatrombopag maleate
IND Number:	76,680
EudraCT Number:	2013-000934-36

SIGNATURES (revised per Amendment 02)
Authors:

PPD

Date

Eisai Inc.

PPD

Date

Eisai Ltd.

PPD

Date

Eisai Inc.

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E5501-G000-311
Study Protocol Title:	A Randomized, Global, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Once-daily Oral Avatrombopag for the Treatment of Adults with Thrombocytopenia Associated with Liver Disease Prior to an Elective Procedure
Investigational Product Name:	E5501/avatrombopag maleate
IND Number:	76,680
EudraCT Number:	2013-000934-36

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date