CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210238Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	210238
Priority or Standard	Priority
Submit Date(s)	September 21, 2017
Received Date(s)	September 21, 2017
PDUFA Goal Date	May 21, 2018
Division/Office	DHP/OHOP
Review Completion Date	February 21, 2018
Established Name	Avatrombopag
(Proposed) Trade Name	Doptelet
Pharmacologic Class	Thrombopoietin receptor agonist
Code name	E5501
Applicant	AkaRx Inc.
Formulation(s)	Tablets
Dosing Regimen	40 mg or 60 mg (based on baseline platelet count) orally once daily for 5 consecutive days starting 10-13 days prior to a planned procedure
Applicant Proposed Indication(s)/Population(s)	DOPTELET (avatrombopag) is indicated for the treatment of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a procedure.
Recommendation on Regulatory Action	Regular approval
Recommended Indication(s)/Population(s) (if applicable)	Patients with thrombocytopenia secondary to chronic liver disease undergoing a (b) (4) procedure with associated bleeding risk

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse event of special interest
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CLD	chronic liver disease
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DILI	drug induced liver injury
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice

GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PBO	placebo
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	preferred term
PVT	portal vein thrombosis
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	system organ class
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Avatrombopag maleate (E5501, DOPTELET®), hereafter avatrombopag, is an orally administered second generation thrombopoietin (TPO) receptor (c-MPL) agonist that promotes megakaryocyte production, maturation, and the formation of platelets. Avatrombopag activates human c-MPL by binding to a site on the TPO receptor distinct from that of endogenous TPO but remains capable of inducing signal transduction thereby increasing platelet counts.

Avatrombopag is a new molecular entity (NME). The proposed indication is for the treatment of thrombocytopenia in adult patients with chronic liver disease (CLD) who are scheduled to undergo a procedure. Avatrombopag is provided in a 20-mg oral tablet formulation to be taken with food. Dosing should begin 10-13 days prior to a scheduled procedure. The recommended daily dose of avatrombopag is based on a patient's baseline platelet count prior to a scheduled procedure. Patients with a platelet count less than 40,000/µL will receive avatrombopag 60 mg orally once daily for 5 consecutive days 10-13 days prior to a scheduled procedure whereas those with a platelet count of 40,000/µL to less than 50,000/µL will receive avatrombopag 40 mg orally once daily for 5 consecutive days 10-13 days prior to a scheduled procedure.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The applicant has provided substantial evidence of effectiveness given that a greater proportion of patients who received avatrombopag treatment as compared to placebo did not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following a procedure. Furthermore, a greater proportion of patients treated with avatrombopag as compared to placebo achieved a pre-specified target platelet count of ≥50,000/µL on the procedure day. This conclusion was based on results from two identically designed, international, double-blind, placebo-controlled, parallel-group studies with the same primary endpoint (E5501-G000-310 and E5501-G000-311, or Studies 310 and 311, respectively).

Studies 310 and 311 support efficacy claims for both the 60 mg and 40 mg doses of avatrombopag. Patients with a platelet count less than 40,000/µL received avatrombopag 60 mg orally once daily for 5 consecutive days 10-13 days prior to a scheduled procedure whereas those with a platelet count of 40,000/µL to less than 50,000/µL received avatrombopag 40 mg orally once daily for 5 consecutive days 10-13 days prior to a scheduled procedure.

In Study 310 and 311, the proportion of responders was shown to be significantly higher in the avatrombopag treatment groups as compared to placebo in both the low and high baseline platelet count cohorts.

In the pooled efficacy analysis of Studies 310 and 311, the proportion of patients who did not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following a procedure was 66.9% in the avatrombopag treatment group and 28.6% in the placebo treatment group among those patients with low baseline platelet counts ($p<0.0001$) and was 88% in the avatrombopag treatment group compared to 35.8% in the placebo treatment group among those patients with high baseline platelet counts ($p<0.0001$).

The proportion of patients in Study 310 who achieved the target platelet count (≥50,000/µL) on procedure day in the low baseline platelet count cohort was higher for the 60 mg avatrombopag treatment group (68.9%) as compared to placebo-treated patients (4.2%) ($p<0.0001$). Similarly, in the high baseline platelet count cohort, the majority of patients achieved the target platelet count of ≥50,000/µL in the 40 mg avatrombopag treatment group (88.1%) as compared to placebo-treated patients (20.6%) which was significant ($p<0.0001$).

Paralleling the result in Study 310, the proportion of patients in Study 311 who achieved the target platelet count (≥50,000/µL) on procedure day in the low baseline platelet count cohort was higher for the 60 mg avatrombopag treatment group (67.1%) compared to 7% of placebo-treated patients ($p<0.0001$). Similarly, in the high baseline platelet count cohort, the majority of patients achieved the target platelet count of ≥ 50,000/µL in the 40 mg avatrombopag treatment group (93.1%) compared to placebo-treated patients (39.4%, $p<0.0001$).

1.3. Benefit-Risk Assessment:

Benefit-Risk Summary and Assessment

Thrombocytopenia in patients with CLD who require invasive procedures is a serious condition due to the increased risk of bleeding in this patient population. Platelet transfusions have historically been the mainstay of treatment for thrombocytopenia in CLD patients undergoing procedures. Patients with CLD may require multiple platelet transfusions prior to a procedure and may not have adequate increases in platelet counts secondary to alloimmunization or splenic sequestration. Transfusion of blood products is associated with increased risk of infection, volume overload, transfusion reactions, and alloimmunization, specifically platelet refractoriness. Furthermore, appropriate matched blood products are often limited in supply resulting in transfusion of mismatched blood products which can increase risk for hemolytic reactions and transfusion-associated acute lung injury.

There are no therapies that are approved for the treatment of thrombocytopenia in patients with CLD who are scheduled to undergo an invasive procedure. Other interventions that can increase platelet counts in patients with liver disease include splenectomy, splenic artery embolization and transjugular intrahepatic portosystemic shunt (TIPS); however, these interventions confer significant procedural risks that make them a less desirable treatment option for patients.

Two identically designed, international, double-blind, placebo-controlled, parallel-group studies with the same primary endpoint (E5501-G000-310 and E5501-G000-311, or Studies 310 and 311, respectively) demonstrated that avatrombopag treatment was superior to placebo based on the proportion of patients who did not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following a procedure. Both studies enrolled patients aged 18 years or older with a history of CLD and a mean baseline platelet count of less than 50,000/µL.

In the pooled efficacy analysis of Studies 310 and 311, the proportion of patients who did not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following a procedure was 66.9% in the avatrombopag treatment group and 28.6% in the placebo treatment group among those patients with low baseline platelet counts ($p<0.0001$) and was 88.1% in the avatrombopag treatment group compared to 35.8% in the placebo treatment group among those patients with high baseline platelet counts ($p<0.0001$).

Furthermore, a greater proportion of patients treated with avatrombopag as compared to placebo achieved a pre-specified target platelet count of ≥50,000/μL on the procedure day. Avatrombopag results in a significant improvement in the management of this condition.

Generally, avatrombopag was well tolerated. Safety results were presented in a pooled fashion from Studies 310 and 311. Similar proportions of patients treated with avatrombopag and respective matched placebo reported adverse events (AEs). 54% (18/274) of patients in the combined avatrombopag treatment group (patients treated with the 40 or 60 mg dose) experienced a treatment emergent AE (TEAE) as compared to 55.1% (81/156) of patients in the combined placebo group. The most common TEAEs (occurring in greater than 3% of the safety population) for both the combined avatrombopag and placebo treatment groups included nausea, abdominal pain, procedural-related pain, diarrhea, fatigue, dizziness, and pyrexia. Serious adverse events (AEs) occurred in 7.3% (20/274) of the combined avatrombopag treated patients versus 9% (14/156) of patients in the combined placebo group.

Thromboembolic events were pre-defined as an adverse event of special interest (AESI) given previous experience with other TPO receptor agonists and observed thrombotic events on clinical trials. In the thromboembolic category, treatment-emergent AESIs were reported in 0.4% (1/274) of avatrombopag-treated patients and 1.3% (2/156 patients) of patients who received placebo. The treatment emergent thromboembolic AESIs included portal vein thrombosis (PVT) in a subject treated with 40 mg avatrombopag; pulmonary embolism and myocardial infarction occurred in 2 patients who received placebo. In addition, there was 1 nontreatment-emergent AESI of portal vein thrombosis in a subject who was treated with 60 mg avatrombopag which was confounded by complications secondary to splenic artery embolization and sepsis, and was deemed not related to study drug.

Of note, while the observed incidence of thromboembolic events in avatrombopag treated patients was low, the study only assessed a 5-day treatment period and excluded patients with a prior history of arterial or venous thrombotic events.

Table 1: Benefit Risk Assessment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Thrombocytopenia (platelet count <150,000/µL) is one of the most common hematologic abnormalities observed in patients with CLD. Moderate to severe thrombocytopenia is associated with increased risk of bleeding secondary to invasive procedures. • Thrombocytopenia can impact routine care of patients with CLD, potentially postponing or interfering with diagnostic and therapeutic procedures.	Thrombocytopenia in patients with CLD who require invasive procedures is a serious condition due to the increased risk of bleeding in this patient population.
Current Treatment Options	• There are no therapies that are approved for the treatment of thrombocytopenia in patients with CLD who are scheduled to undergo an invasive procedure. • Platelet transfusions have historically been the mainstay of treatment for thrombocytopenia in CLD patients undergoing procedures. Transfusion of blood products is associated with increased risk of infection, volume overload, blood product associated transfusion reactions, and alloimmunization, specifically platelet refractoriness. • Other interventions that can increase platelet counts in patients with liver disease include splenectomy, splenic artery embolization and transjugular intrahepatic portosystemic shunt (TIPS); however, these interventions confer significant procedural risks that make them a less desirable treatment option.	There is unmet medical need and limited therapeutic options for patients with liver disease and thrombocytopenia undergoing procedures.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Two identically designed, international, double-blind, placebo-controlled, parallel-group studies with the same primary endpoint (E5501-G000-310 and E5501-G000-311, or Studies 310 and 311, respectively) demonstrated that avatrombopag treatment was superior to placebo based on the proportion of patients who did not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following a procedure. Furthermore, a greater proportion of patients treated with avatrombopag as compared to placebo achieved a pre-specified target platelet count of ≥50,000/µL on the procedure day.	Avatrombopag treatment effectively raised platelet counts prior to a scheduled procedure and reduced the need for platelet transfusion as compared to placebo. Furthermore, the proportion of avatrombopag-treated patients who required a rescue procedure or medication for bleeding from randomization and up to 7 days post-procedure was less than placebo-treated patients.
Risk and Risk Management	• Generally, avatrombopag was well tolerated. • 54% of patients in the combined avatrombopag treatment group (patients treated with the 40 or 60 mg dose) experienced a TEAE as compared to 55.1% of patients in the combined placebo group. The most common TEAEs (occurring in greater than 3% of the safety population) for both the combined avatrombopag and placebo treatment groups included nausea, abdominal pain, procedural-related pain, diarrhea, fatigue, dizziness, and pyrexia. • SAEs occurred in 7.3% of the combined avatrombopag treated patients versus 9% of patients in the combined placebo group. • Four deaths occurred in the pooled safety population. There were 3 treatment emergent deaths. One death was deemed nontreatment-emergent. Of the 3 treatment-emergent deaths, 2 (0.7%) occurred in patients in the combined avatrombopag treatment group and 1	In patients with CLD, the safety profile of avatrombopag was comparable to that of placebo. The most commonly reported adverse events in avatrombopag treated patients included nausea, abdominal pain, procedural-related pain, diarrhea, fatigue, dizziness, and pyrexia. There were two events of PVT in the avatrombopag-treatment group as compared to none in the placebo group. While the overall incidence of thromboembolic events was low, patients were only exposed to the drug for 5 days. Furthermore, CLD patients with a prior history of thrombotic events were excluded from these trials.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(0.6%) occurred in a subject in the combined placebo treatment group. • Overall, there were a low number of observed thromboembolic events in the pooled safety population. Treatment-emergent thromboembolic events were reported in 0.4% (1/274) of avatrombopag-treated patients and 1.3% (2/156 patients) of patients who received placebo. The treatment emergent thromboembolic AESIs included portal vein thrombosis (PVT) in a subject treated with 40 mg avatrombopag; pulmonary embolism and myocardial infarction occurred in 2 patients who received placebo. In addition, there was 1 nontreatment-emergent AESI of portal vein thrombosis in a subject who was treated with 60 mg avatrombopag which was confounded by complications secondary to splenic artery embolization and sepsis, and was deemed not related to study drug. • Platelet function assays performed in a small cohort of patients did suggest increased platelet activation or platelet reactivity secondary to avatrombopag treatment.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable

	☐	Clinical outcome assessment (COA) data, such as		[e.g., Section 6.1 Study endpoints]
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Section 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that was not submitted in the application, but was considered in this review.			

X

Andrew Dmytrijuk
Acting Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1 Analysis of Condition

Thrombocytopenia (platelet count <150,000/µL) is one of the most common hematologic abnormalities observed in patients with CLD and occurs in 64%–84% of patients with a history of cirrhosis or fibrosis.[1,2,3] In patients undergoing diagnostic bone marrow biopsies for evaluation of thrombocytopenia, the prevalence of cirrhosis is estimated to be as high as 35%.[4] A low platelet count is an indicator of advanced hepatic disease and is associated with a poor prognosis.[5] Thrombocytopenia can impact routine medical management of patients with CLD, potentially delaying or interfering with necessary diagnostic and therapeutic procedures. [1]

Historically, thrombocytopenia in CLD was attributed to hypersplenism, in which circulating platelets are sequestered in a spleen enlarged by congestive splenomegaly secondary to portal hypertension.[6] However, efforts to reduce or eliminate splenomegaly and resultant platelet sequestration via splenectomy, splenic artery embolization or intrahepatic portosystemic stent shunting failed to consistently markedly increase circulating platelet counts in patients with CLD.

There have been substantial advances in the understanding of thrombopoiesis over the past decade, which has led to an improved understanding of thrombocytopenia in CLD.[1] Multiple factors have been implicated in the development of thrombocytopenia in the cirrhotic patient. Decreased hepatic production of thrombopoietin, inadequate production of platelets due to bone marrow suppression, as well as increased platelet destruction secondary to shear stress, immunologic destruction, and increased fibrinolysis all contribute to decreased platelet counts.[1,7] Furthermore, immune-mediated drug-induced thrombocytopenia is a common occurrence in CLD patients. Medications commonly prescribed to the cirrhotic patient that are associated with impaired thrombopoiesis include azathioprine, antibiotics, and interferon (IFN).[8,9]

The presence of mild thrombocytopenia (>75,000/µL to <150,000/µL) usually does not interfere with procedural interventions or management decisions. Moderate thrombocytopenia (50,000/µL–75,000/µL) is observed in 13% of cirrhotic patients although this figure may underestimate the prevalence of moderate thrombocytopenia in CLD patients.[2] Severe thrombocytopenia (<50,000/µL) is associated with significant morbidity in patients with hepatic dysfunction and often complicates their medical management and procedural interventions.

While mild to moderate thrombocytopenia rarely leads to spontaneous bleeding during invasive procedures, severe thrombocytopenia significantly increases the risk of bleeding. This bleeding risk is further increased by concomitant coagulopathy that often occurs in patients

with advanced liver disease.

Available data suggest that the invasive procedures may be performed in patients with platelet counts $\geq$ 50,000/µL with little risk of bleeding. There is no consensus on the safety of procedures in patients with platelet counts $\leq$ 20,000/µL.

2.2 Analysis of Current Treatment Options

Currently there are no approved therapies for the treatment of thrombocytopenia secondary to CLD in patients scheduled to undergo a procedure with associated bleeding risk. Current treatment options for severe thrombocytopenia include platelet transfusion, splenectomy, splenic artery embolization, and placement of a transjugular intrahepatic portosystemic stent shunt (TIPS).

Patients with thrombocytopenia secondary to CLD who require a procedure are most often treated with platelet transfusions. There is no consensus on the appropriate threshold values for prophylactic platelet transfusions in CLD patients.[10] The cut-off value for platelet transfusion varies significantly depending on the clinical setting and planned procedure. While low cut-off values may be appropriate for uncomplicated thrombocytopenic patients undergoing minor procedures, other patients may require higher platelet transfusion triggers, particularly in the setting of co-morbidities and high risk procedures or surgical interventions that confer greater bleeding risk.[10] Platelet transfusions are associated with febrile nonhemolytic and allergic reactions, risk of infection, and platelet refractoriness due to HLA alloimmunization which occurs in up to 40% of patients. In addition, platelet transfusions do not guarantee a hemostatic platelet level, especially when the risk of bleeding is highest. [11]

Surgical approaches to increase platelet counts in patients with CLD include splenectomy, splenic artery embolization, and transjugular intrahepatic portosystemic shunt (TIPS) with the goal of decreasing splenic platelet sequestration. Splenic artery embolization has been demonstrated to increase platelet counts in patients with portal hypertension but this does not always occur consistently in individual CLD patients. Possible complications of this procedure include bleeding, septicemia, splenic abscesses, splenic rupture, portal vein thrombosis, Budd-Chiari syndrome or complete hepatic failure. [10] TIPS placement can decrease sinusoidal portal pressure, but portal decompression does not consistently reduce the degree of thrombocytopenia in cirrhotic patients. TIPS is associated with risk of acute hemorrhage, tipsitis, liver laceration or hematoma formation, hepatic encephalopathy, biliary obstruction, and liver failure. Furthermore, acute shunt occlusion or migration often necessitate repeat TIPS procedures in patients with liver disease.[10-11]

While splenectomy typically results in increased platelet counts, the invasiveness of the procedure coupled with potential surgical risks makes it a less preferred method to address

thrombocytopenia. Furthermore, infectious risks and vulnerability to encapsulated microorganisms once a patient is asplenic make it a less desirable option.

Approved TPO receptor agonist therapies for the treatment of thrombocytopenia include eltrombopag and romiplostim. Of note, neither eltrombopag or romiplostim has been approved for the treatment of thrombocytopenia in CLD patients undergoing procedures.

Eltrombopag is an orally administered c-MPL TPO receptor agonist (tablet presentation) that received accelerated approval for marketing on November 20, 2008 (under NDA 22291) for the treatment of thrombocytopenia in adult and pediatric patients one year and older with chronic immune (idiopathic) thrombocytopenia (ITP) refractory to corticosteroids, immunoglobulins, or splenectomy (conversion to full approval granted on February 25, 2011). Eltrombopag was approved on November 16, 2012 for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of IFN-based therapy and was approved on August 26, 2014 for treatment of patients with severe aplastic anemia with inadequate response to immunosuppressive therapy. An eltrombopag oral suspension presentation was approved for marketing on August 24, 2015 (under NDA 207027) and has the same indications as the eltrombopag tablet presentation.

A phase 3 trial with eltrombopag (Eltrombopag Evaluated for its Ability to Overcome Thrombocytopenia and Enable Procedures [ELEVATE]) in patients with thrombocytopenia and CLD was prematurely terminated by an Independent Data and Safety Monitoring Committee due to safety concerns. In the ELEVATE trial, there was an approximate 6-fold increase in the incidence of portal vein thrombosis (PVT) in patients treated with eltrombopag as compared to placebo, 4.2% (6/143) of patients versus 0.7% (1/145) of patients, respectively.[12] It was noted in the study that 83% (5/6) of the eltrombopag-treated patients who developed PVT had platelet counts greater than or equal to 200,000/µL.

Romiplostim is a subcutaneously injected c-MPL TPO receptor agonist that received full marketing approval on August 22, 2008 (under BLA 125268) for the treatment of thrombocytopenia in patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Lusutrombopag (Shionogi), another TPO receptor agonist, is approved in Japan for patients with CLD and thrombocytopenia prior to elective invasive surgery, and has recently completed a phase 3 study in the United States but is not currently approved.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Avatrombopag is a new molecular entity (NME) is not currently marketed.

3.2. Summary of Presubmission/Submission Regulatory Activity

The sponsor submitted a marketing application for avatrombopag under NDA 210238 supporting document 1 letter dated September 21, 2017. The submission was received in eCTD format. The sponsor requested priority review which was granted by the agency. The application was filed on October 30, 2017.

APPEARS THIS WAY ON ORIGINAL

Table 2: Pre-Submission Regulatory History

Date	Meeting or Event
December 17, 2012	**Type B End of Phase 2 Meeting** - Agreement on GMP starting materials, adequacy of nonclinical program, and planned Phase 3 program for treatment of thrombocytopenia in CLD patients undergoing a procedure
September 19, 2013	**Special Protocol Assessment (SPA) Agreement** - Agency agreement that proposed design and analysis plan for Study 310 adequately assessed objectives to support regulatory submission
December 5, 2013; June 17, 2014; August 2, 2016	**SPA Modification Agreements** - Agency agreement to changes on Study 310 protocol including revision of doppler sonography measurements, addition of tranexamic acid to rescue procedures, addition of genetic prothrombotic conditions to exclusion criteria in Study 310, and revisions to risk level assigned to permitted procedures
November 14, 2016	**Type C Meeting** - Discussion of reduction of sample size in Studies 310 and 311 and adequacy of safety database to support regulatory submission
August 4, 2014	**Initial Pediatric Study Plan (iPSP) Agreement** - Agency agreement on pediatric assessments in children with thrombocytopenia secondary to CLD
July 12, 2017	**Amended Pediatric Study Plan (PSP) Agreement** - Agency agreed to revised timelines and deferred pediatric assessments
August 6, 2014	**Type C Meeting (Written Response)** - Agency agreed upon the sufficiency of platelet function data to be included in the NDA submission
August 13, 2014	**Type C Meeting (Written Response)** - Agency agreed on data submission plan and integrated safety analysis
May 10, 2017	**Type B Pre-NDA Meeting** - Discussion of topline safety data from Studies 310 and 311 and content and format of planned NDA
September 21, 2017	NDA 210238 Submitted to Agency and received **Priority Review Designation**

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Dr. Min Lu (Medical Officer in the Office of Scientific Investigations (OSI)) states in her review (final signature date March 14, 2018) of the avatrombopag application for the treatment of thrombocytopenia in adult patients with chronic liver disease (CLD) who are scheduled to undergo a procedure (NDA 210238 supporting document 1 letter date September 21, 2017 (received September 21, 2017)) that two clinical study sites, i.e., Drs. Zeid Kayali (Site #1004, San Bernardino, CA) and Dr. Tarek Hassanein (Site #1101, Coronado, CA), were selected for inspections for Protocol E5501-G000-310 and E5501-G000-311, respectively. Dr. Lu states that 10 patients were enrolled at study site #1004 and 18 patients were enrolled at study site #1101.

Dr. Lu states in her review that for study site #1004 the screening doppler sonography reports did not include the first, second, and third portal vein blood flow velocity rates individually for 7 patients ((b) (6)). The average of the 3 rates were yielded instead. These protocol deviations were considered clinically insignificant. Additional minor protocol deviations included incomplete laboratory tests recorded in two patients, adverse event grades were not accurately recorded for three patients, inaccurate recording of concomitant medications for three patients, inaccurate reporting of vital signs for three patients and investigational product storage temperature was out of acceptable range for eight hours due to the air conditioner breaking down. Dr. Lu states in her review that the observations appear unlikely to have significant impact on the primary efficacy endpoint and safety results of the study. Dr. Lu states in her review that for study site #1101 that data submitted by this clinical site appear acceptable in support of this application.

Dr. Lu concludes that the study data derived from these clinical sites, based on the inspections, are considered reliable in support of this application. The preliminary classification for the inspection for study site #1004 is Voluntary Action Indicated (VAI). Although protocol deviations were noted, they appear unlikely to have significant impact on the overall efficacy and safety of the study. The preliminary classification for the inspection for study site #1101 is No Action Indicated (NAI).

Reviewer comment: The clinical review team agrees with Dr. Lu's review and recommendations (final signature date March 14, 2018) for the avatrombopag application submitted under NDA 210238 supporting document 1 letter date September 21, 2017 (received September 21, 2017).

4.2. Product Quality

Novel excipients: No
Any impurity of concern: No

Dr. Sherita McLamore (Chemistry Reviewer in the Office of Product Quality (OPQ)) states in her review (final signature date February 14, 2017) of NDA 210238 supporting document 1 letter date September 21, 2017 (received September 21, 2017) for avatrombopag that based on the information provided in this application (original submission and in responses to information requests), OPQ considers all review issues adequately addressed and potential risks to patient safety, product efficacy, and product quality mitigated appropriately. OPQ recommends approval of the sponsor's application for avatrombopag submitted under NDA 210238 supporting document 1 letter date September 21, 2017 (received September 21, 2017)

4.3. Clinical Microbiology

Dr. Sherita McLamore (Chemistry Reviewer in the Office of Product Quality) states in her review (final signature date February 14, 2017) of NDA 210238 supporting document 1 letter date September 21, 2017 (received September 21, 2017) that no microbiology testing is required for this application for avatrombopag.

Reviewer comment for sections 4.2 Product Quality and 4.3 Clinical Microbiology: The clinical review team agrees with Dr. McLamore's review and recommendations (final signature date February 14, 2017) for the avatrombopag application.

4.4. Devices and Companion Diagnostic Issues

There are no companion diagnostic or devices proposed with the application, i.e., NDA 210238 supporting document 1 letter date September 21, 2017 (received September 21, 2017).

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The nonclinical development program for avatrombopag was conducted in various cellular assay systems, and in the mouse, rat, rabbit, dog, and monkey, to evaluate the pharmacology, pharmacokinetics, general toxicology, reproductive and developmental effects, the genotoxic potential, and carcinogenicity of avatrombopag. Avatrombopag is a thrombopoietin receptor agonist, which is the established pharmacological class. Thrombopoietin is a glycoprotein hormone that regulates the production of platelets by stimulating the production and differentiation of megakaryocytes, the bone marrow progenitor cells for platelets.

Avatrombopag stimulated the proliferation of cells expressing the human thrombopoietin receptor (c-Mpl) with an EC_{50} value of 3.3 nM and promoted the differentiation of human

hematopoietic progenitor cells (cord blood $CD34^+$ cells) to megakaryocytes with an EC_{50} value of 25.0 nM. The proliferation effect was 50-fold weaker and the differentiation effect was 200-fold weaker than the activities of recombinant human thrombopoietin (rhTPO), but the maximum activities of avatrombopag on proliferation and differentiation were similar to those of rhTPO. Avatrombopag did not inhibit rhTPO binding to human c-Mpl in human platelets, indicating that the binding site for avatrombopag on human c-Mpl is different from that of rhTPO. The addition of avatrombopag to a TPO concentration that produced maximal stimulation increased the number of megakaryocytes to approximately 2-fold the number generated with TPO alone. The combination of avatrombopag and TPO also enhanced the expansion of human hematopoietic progenitor cells and megakaryocytic progenitor cells. These results indicate that the effects of avatrombopag were at least additive to that of TPO.

Avatrombopag induced tyrosine phosphorylation of STAT2 and STAT5 in human platelets and induced tyrosine or threonine phosphorylation of STAT3, STAT5, and ERK in murine cells transfected with human c-Mpl. This data suggests that avatrombopag activates the JAK-STAT and the SHC-Ras-Raf-ERK signaling pathways via human c-Mpl. Oral administration of avatrombopag for 14 days to NOD/SCID mice engrafted with human fetal liver $CD34^+$ cells dose-dependently increased the number of human platelets on Day 14, indicating that avatrombopag can increase human platelets in an in vivo system.

Tyrosine phosphorylation of STAT5 was evaluated in the platelets of multiple toxicology species including the mouse, rat, dog, and Cynomolgus monkey, and avatrombopag appears to induce tyrosine phosphorylation of STAT5 only in chimpanzee and human platelets. Avatrombopag did not stimulate the proliferation of cells expressing murine c-Mpl and did not increase platelets in mice, rats, or monkeys in the general toxicology and carcinogenicity studies. Taken together, these findings suggest that avatrombopag does not produce the same pharmacological activity in the animals used in the toxicology studies as in humans and that there are no pharmacologically relevant species for toxicological testing.

Safety pharmacology studies assessed the effects avatrombopag on the cardiovascular, central nervous system (CNS), and respiratory function. Following single oral doses, avatrombopag had no effects on respiratory or cardiovascular function in telemetered dogs, and had no effects on neurobehavioral function in a CNS study conducted in male rats.

Systemic exposures following single or repeated administration of avatrombopag were evaluated in the toxicokinetics assessments in the toxicology studies. Exposures to avatrombopag (C_{max} and AUC) increased with an increase in dose in an approximately dose-proportional or slightly less than dose proportional manner and increased with repeated administration, indicating accumulation of the drug. The oral bioavailability of free base avatrombopag was 89 to 94% in rats and 49 to 67% in monkeys. Avatrombopag bound to protein in the plasma of various species in a concentration-independent manner; binding was 96% in human plasma. In a distribution study in rats following a single oral administration of radiolabeled avatrombopag, the drug was widely distributed with the highest radioactivity

observed in the small intestine (the main site of absorption), liver, adrenal gland, kidney, submandibular gland, heart, pancreas, stomach, lung, and hypophysis (pituitary). Of note, the $T_{1/2}$ in the eyeball in pigmented rats was 351 hours. In an elimination study conducted in bile duct-cannulated rats, hepatic clearance and biliary excretion was the primary route of elimination of avatrombopag with 83% in the feces, 8% in the bile, and 3% in the urine. The assessment of the metabolic profile of avatrombopag in this study indicated that avatrombopag was extensively metabolized with 17, 3, and 20 quantifiable metabolites in bile, feces, and urine, respectively. The primary biotransformation pathways were amino acid conjugation of the carboxylic acid moiety of radiolabeled avatrombopag with taurine as the most abundant conjugate and glycine and glucuronic acid conjugation also occurring. Following single oral doses of avatrombopag in rats and monkeys, the terminal elimination phase half-life ($T_{1/2}$) of the drug ranged from 3.9 to 7.2 hours.

Repeat-dose toxicology studies were conducted to assess the chronic toxicity of avatrombopag. The studies were conducted using the oral route of administration, which is consistent with the intended clinical route of administration. In the 26-week study in Sprague-Dawley rats, avatrombopag was administered by oral gavage at 0, 20, 80, or 160 mg/kg/day once daily for 26 weeks with a 4-week recovery period. In the 52-week study in Cynomolgus monkeys, avatrombopag was administered by nasogastric gavage at 0, 5, 15, or 45 mg/kg/day once daily for 52 weeks with a 4-week recovery period. The stomach is the main target organ of toxicity for avatrombopag in both rats and monkeys with increases in serum gastrin levels and histopathology changes of degeneration of glandular epithelium and atrophy of glandular mucosa observed in both species. Regenerative hyperplasia and intraluminal deposits were also observed in the stomach in rats. The kidney also appears to be a target organ in these studies with increases in kidney weights and a microscopic finding of mononuclear cell infiltration observed in both species and a slight increase in the incidences of chronic progressive nephropathy for the main study necropsy in rats.

In the 2-year carcinogenicity studies in mice and rats, avatrombopag-related non-neoplastic microscopic findings included changes in the stomach and increased incidences and severity of chronic nephropathy in the kidneys in both species. Findings in the stomach included hyperplasia of the mucosa in mice and degeneration of glandular epithelium, atrophy of glandular mucosa, regenerative hyperplasia, intraluminal deposits, and neuroendocrine cell hyperplasia in rats. The increases in the incidence and severity of chronic nephropathy in the kidneys resulted in a significantly decreased survival in females treated with the high dose of 160 mg/kg/day in both mice and rats. While abdominal pain and nausea were observed in the clinical studies, no clear stomach-related or renal toxicities have been observed in the trials for the current indication with a treatment duration of only 5 days. The relevance of the stomach toxicities and chronic nephropathy observed in animals with chronic administration of avatrombopag to humans is unknown at this time.

Separate fertility and early embryonic development studies were conducted in female and male rats. Female rats were administered avatrombopag (0, 100, 300, or 1000 mg/kg/day) orally

once daily starting 14 days prior to mating with untreated males through gestation day (GD) 7. Male rats were administered avatrombopag (0, 10, 30, or 100 mg/kg/day) orally once daily for 58 days starting 4 weeks prior to mating with untreated females. No effects on fertility or embryonic development were observed at any dose level of avatrombopag administered to female or male rats. Exposures at the doses of 100 mg/kg/day in males and 1000 mg/kg/day in females were approximately 22 times and 114 times, respectively, the human clinical exposure based on AUC at the highest recommended human dose.

Embryo-fetal development studies were conducted in female rats and rabbits. In the rat study, once daily administration of avatrombopag at doses of 0, 100, 300, or 1000 mg/kg/day on GD 7-17 resulted in maternal toxicity at 300 and 1000 mg/kg/day characterized by decreased food consumption, decreased body weight gain, and/or mortality. Fetal toxicity included minimally decreased fetal weight at 1000 mg/kg/day and increased incidences of skeletal variations including incidences of 14^{th} rib at 300 and 1000 mg/kg/day. The exposures at the 100 and 1000 mg/kg/day doses were approximately 53 and 190 times, respectively, the human clinical exposure based on AUC at the highest recommended human dose. In the embryo-fetal rabbit study, once daily administration of avatrombopag at doses of 0, 100, 300, or 600 mg/kg/day on GD 6-18 resulted in maternal toxicity at 300 and 600 mg/kg/day characterized by decreased food consumption and decreased body weight gain that lead to abortion in 4 dams at 300 mg/kg/day and 3 dams at 600 mg/kg/day. Abortion was also observed in one dam at 100 mg/kg/day. No effects on embryo-fetal development were observed at any dose. The exposures at the 100 and 600 mg/kg/day doses were approximately 10 and 35 times, respectively, the human clinical exposure based on AUC at the highest recommended human dose.

In a study evaluating placental transfer and excretion in milk, single doses of avatrombopag were administered orally to pregnant female rats on GD 13 or 18 or lactating rats on postpartum Day 10. The pharmacokinetic data confirmed placental transfer of avatrombopag and the presence of avatrombopag in fetal rat plasma, blood, and tissues (whole body, brain, heart, lung, liver, kidney, and digestive tract) on GD 18 and the presence of avatrombopag in maternal milk on postpartum Day 10.

In pre- and postnatal development studies in rats, avatrombopag was administered to female rats once daily from GD 6 through lactation day (LD) 20 at doses ranging from 5 to 600 mg/kg/day. In the first study, doses of 100, 300, and 600 mg/kg/day caused maternal toxicity leading to mortality and total litter losses. Body weight gain was decreased in pups at all doses compared to controls throughout the lactation/postnatal period. Increased pup mortality was also observed at all doses of avatrombopag with the majority of the pup mortality occurring between postnatal days (PND) 14 to 21. Due to the mortality, the study was terminated early and no post-weaning phase of the study was conducted. A second pre-and postnatal study was conducted with lower doses of avatrombopag (0, 5, 15, or 50 mg/kg/day). Although the 50 mg/kg/day dose did not produce clear maternal toxicity, 50 mg/kg/day avatrombopag caused increased pup mortality from PND 4 to 21, and mortality continued through PND 25.

The 50 mg/kg/day dose also decreased body weight gain in the pups, resulting in a delay in sexual maturation (balanopreputial separation and vaginal patency). There were no effects on behavioral or reproductive functions in the offspring. The 50 mg/kg/day dose resulted in maternal exposures 43 times and pup exposures approximately 3 times the AUC observed in patients at the recommended dose of 60 mg once daily.

In a 28-day dose-range finding toxicology study in juvenile rats, avatrombopag was administered by oral gavage at initial dose levels of 10, 100, and 300 mg/kg/day once daily for 28 days during PND 7-34 in Sprague Dawley rats. Due to the apparent absence of toxicity, additional dose levels of 600 and 1000 mg/kg/day were also evaluated in the study. No avatrombopag-related mortality was observed in this study. Decreased mean body weight gains were observed in both males and females at 600 and 1000 mg/kg/day throughout the treatment period compared to controls. Other toxicities included hematology changes at doses $\geq$300 mg/kg/day, gastric mucosal changes in the stomach similar to those observed in adult rats at $\geq$100 mg/kg/day and an increase in the incidences and severity of foci of the basophilic tubules in the kidney at 1000 mg/kg/day.

The results of the embryo-fetal development, pre-and postnatal development, and dose-range finding juvenile toxicology studies in rats have been carefully considered. The finding of increased pup mortality occurring during the postnatal period in the pre- and postnatal development study is a concerning toxicity; however, based on an absence of clear life threatening embryo-fetal toxicity and the absence of mortality in the dose-range finding juvenile toxicology study there is no clear explanation for pup mortality in the pre- and postnatal studies. Decreased body weight gain in the pups appears to be related to the pup mortality in the pre- and postnatal studies. Although pup mortality was observed at the 50 mg/kg/day dose, which did not produce clear maternal toxicity, there was clear maternal toxicity at the higher doses and the pup mortality and maternal toxicity both appear to be dose-dependent. Based on this information and data, the increased pup mortality observed in the pre- and postnatal development studies appears related to the maternal toxicity.

Avatrombopag was not mutagenic in the in vitro bacterial reverse mutation test or clastogenic in the in vitro chromosomal aberrations assay in peripheral human lymphocytes or in the in vivo bone marrow micronucleus assay in rats. Two-year (104-Week) carcinogenicity studies with avatrombopag were conducted in mice and rats. Avatrombopag was administered by oral gavage once daily at doses of 0, 20, 60, or 160 mg/kg/day to CD-1 mice in the 2-year mouse study and doses of 0, 20, 50, or 160 mg/kg/day to Sprague-Dawley rats in the 2-year rat study. Discontinuation of dosing and early termination of animals occurred in both studies. Avatrombopag induced malignant neuroendocrine tumors in the stomach in one male at 160 mg/kg/day and 1 female at 60 mg/kg/day in mice and induced benign and malignant neuroendocrine tumors in the stomach at 160 mg/kg/day in rats. In female rats, the incidences of benign and malignant neuroendocrine cell tumors combined in the stomach were statistically significant and the finding is mentioned in the label.

The nonclinical pharmacology and toxicology data submitted to this NDA are adequate to support the approval of avatrombopag for the proposed indication.

5.2. Referenced NDAs, BLAs, DMFs

None.

5.3. Pharmacology

Primary Pharmacology

Table 3: Primary Pharmacology Findings

Study Title/Study No.	Findings
Proliferative Effect of YM-301477 Monomaleate in Ba/F3 Cells Expressing Human or Murine c-Mpl/ Study SK-971417	Avatrombopag stimulated the proliferation Ba/F3 cells expressing human c-Mpl with an EC_{50} value of 3.3 nM. This effect was 50-fold weaker than the activity rhTPO (EC_{50}=0.065 nM), but the maximum proliferative activity of avatrombopag was similar to that of rhTPO. Avatrombopag did not stimulate the proliferation of Ba/F3 cells expressing murine c-Mpl.
Effect of YM-301477 Monomaleate on rhTPO Binding to Human c-Mpl on Human Platelets/Study SK-971455	Avatrombopag (up to 100 µM) did not inhibit ^{125}I-rhTPO binding to human c-Mpl in human platelets, indicating that the binding site for avatrombopag on human c-Mpl is different from that of rhTPO.
The Site of Action of YM-301477 on Human c-Mpl /Study CRE140019	rhTPO stimulated the proliferation of Ba/F3 cells expressing human extracellular domain/murine intracellular domain chimeric c-Mpl; in contrast, avatrombopag did not support proliferation of these cells, but induced proliferation of cells transfected with intact human c-Mpl. These results suggest that avatrombopag requires the transmembrane domain of human c-Mpl for proliferative activity.
Effect of YM-301477 Monomaleate on Human Megakaryocyte Colony Formation from Human Cord Blood $CD34^+$ Cells/Study SK-971454	Avatrombopag promoted the differentiation of human hematopoietic progenitor cells (cord blood $CD34^+$ cells) to megakaryocytes with an EC_{50} value of 25.0 nM. This effect was 200-fold weaker than the activity rhTPO (EC_{50}=0.122 nM), but the maximum activity of avatrombopag was similar to that of rhTPO.
Effect of YM-301477 Monomaleate on Human Hematopoietic Colony Formation, Other than Megakaryocytic Lineage, from Human Cord Blood $CD34^+$ Cells/Study SK-971453	Avatrombopag (up to 3 µM) did not affect the differentiation of human cord blood $CD34^+$ hematopoietic progenitor cells into non-megakaryocytic lineages.
YM477 Promotes the Differentiation of Human Hematopoietic Progenitor Cells into Polyploid Megakaryocytes/Study SK-971628	As measured by flow cytometry, avatrombopag promoted the differentiation of human peripheral blood $CD34^+$ cells into $CD41^+CD45^+$ cells (megakaryocytes) in a concentration-dependent manner. Avatrombopag also promoted the ploidy level of the megakaryocytes to a similar level as rhTPO.
AKR-501 (YM477) in Combination with Thrombopoietin Enhances Human Megakaryocytopoiesis/Fukushima-Shintani, et al., 2008	The combination of 3 µM avatrombopag to a TPO concentration that produced maximal stimulation (3 nM) increased the number of megakaryocytes to approximately 2-fold the number generated with TPO alone. The combination of avatrombopag and TPO also enhanced the expansion of

	human hematopoietic progenitor cells and megakaryocytic progenitor cells. The effects of avatrombopag were at least additive to that of TPO.
YM-301477 Monomaleate Induces Tyrosine Phosphorylation of STAT3 and STAT5 in Human Blood Platelets/Study SK-971447	Avatrombopag (0.03, 0.3, or 3 µM) induced tyrosine phosphorylation of STAT3 and STAT5 in human blood platelets; the activity appears to be through the activation of human c-Mpl.
YM-301477 Monomaleate Induces Tyrosine or Threonine Phosphorylation of STAT3, STAT5, and ERK in Human c-Mpl Transfected Murine Ba/F3 Cells/Study SK-971493	Avatrombopag induced tyrosine or threonine phosphorylation of STAT3, STAT5, and ERK in human c-Mpl transfected murine Ba/F3 cells. Suggests that avatrombopag activates the JAK-STAT and the SHC-Ras-Raf-ERK signaling pathways via human c-Mpl.
YM-301477 Does Not Induce Tyrosine Phosphorylation of STAT5 in Cynomolgus Monkey, Rhesus Monkey, Squirrel Monkey, and Common Marmoset Blood Platelets/ Study SK-010014	rhTPO induced tyrosine phosphorylation of STAT5 in cynomolgus, rhesus, and squirrel monkey and common marmoset platelets, but avatrombopag did not induce phosphorylation in any of them.
YM-301477 Does Not Induce Tyrosine Phosphorylation of STAT5 in Beagle Dog, Guinea Pig, Rabbit, and Rat Blood Platelets/ Study SK-010015	rhTPO induced tyrosine phosphorylation of STAT5 in dog, guinea pig, rabbit, and rat platelets, but avatrombopag did not induce phosphorylation in any of them.
YM-301477 Monomaleate Induces Tyrosine Phosphorylation of STAT5 in Chimpanzee Blood Platelets/Study SK-971462	Avatrombopag (0.03 and 0.3 µM) induced tyrosine phosphorylation of STAT5 in chimpanzee platelets; avatrombopag appears to activate chimpanzee c-Mpl
Effect of YM-301477 Monomaleate on Human Platelet Production After Oral Administration to NOD/SCID Mice Transplanted with Human Fetal Liver $CD34^+$ Cells/Study SK-971435	Oral administration of avatrombopag for 14 days to NOD/SCID mice engrafted with human fetal liver $CD34^+$ cells dose-dependently increased the number of human platelets (2.7-fold increase at 1 mg/kg/day and 3-fold increase at 3 mg/kg/day) on Day 14. This result indicates that avatrombopag can increase human platelets in an in vivo system.

Secondary Pharmacology

Study title/ number: In Vitro Pharmacology: Study of E5501/ 929084

The effects of avatrombopag against a panel of 86 receptors, transporters, and ion channels were evaluated in various in vitro receptor binding, functional, and/or enzyme assays. No significant effects (>50% inhibition or activation) were observed at 1 µM. At 10 µM, avatrombopag showed >50% inhibition of specific ligand binding at adenosine A3 (A_3), angiotensin II type 1 (AT_1), cholecystokinin B (CCK_2), muscarinic 4 acetylcholine (M_4), neurokinin 2 (NK_2), neurokinin 3 (NK_3), and serotonin 5A ($5\text{-}HT_{5a}$) receptors and the N-type Ca^{2+} channel. Avatrombopag also had an antagonistic effect at the CCK_2 receptor in a functional assay with an IC_{50} value of 7 µM.

Safety Pharmacology

A. Central Nervous System

In a safety pharmacology study of CNS function conducted with good laboratory practice (GLP; Study SP-0350), male F344 rats (6/group) were administered a single oral dose of avatrombopag (1, 10, or 100 mg/kg, free base) or vehicle (0.5% methylcellulose aqueous solution). Animals were observed according to the Irwin's method prior to administration and 0.5, 1, 2, 4, 8, 24, and 48 hours after administration. Avatrombopag had no effects on general condition or neurobehavioral function following a single oral administration at doses up to 100 mg/kg.

B. Respiratory and Cardiovascular

The potential for avatrombopag to inhibit the human ether-a-go-go related gene (hERG) potassium channel was assessed in an in vitro GLP study (Study SP-0358). The effects of avatrombopag (0.1, 0.650, and 2.54 μM), vehicle (0.1% DMSO), and a positive control (E-4031; 0.1 μM) on the hERG tail current were measured in HEK293 cells transfected with hERG. Avatrombopag significantly suppressed the hERG current in a concentration-dependent manner (20.5%, 43.8%, and 65.4%, respectively) with an estimated IC_{50} of 1.4 μM; for comparison, the hERG current was suppressed 10.8% by the vehicle and 86.2% by the positive control.

In a GLP safety pharmacology study of both cardiovascular and respiratory function (Study SP-0351), male unanesthetized and telemetered Beagle dogs (4 total) were administered single oral doses of vehicle (0.5% methylcellulose aqueous solution) and avatrombopag (3, 30, and 300 mg/kg, free base) in ascending order with drug withdrawal intervals of 7 days. Blood pressure, heart rate, electrocardiogram, respiration rate, and body temperature were continuously measured. The time points for the analysis of these parameters and for blood collection for toxicokinetic analysis, and blood gas measurement were prior to administration and 0.5, 1, 2, 4, 8, 24, and 48 hours after administration. Avatrombopag had no effects on respiratory or cardiovascular function following a single oral administration at doses up to 300 mg/kg.

5.4. ADME/PK

Table 4: Nonclinical Pharmacokinetics and Toxicokinetics

Type of Study	Major Findings
Absorption	Systemic exposures following single and/or repeated administration of avatrombopag in the various key toxicology studies are listed in the table below.
Plasma Concentrations of Unchanged Drug after Single Oral and Intravenous Administrations of YM477 Monomaleate to Rats/Study PBC81-33	A single dose of avatrombopag was administered orally (0.3, 1, or 3 mg/kg) or by intravenous injection (1 mg/kg) to male Fischer (F344/DuCrj) rats. Following oral administration: Mean $T_{1/2}$ ranged from 3.9-4.4 hours

Type of Study	Major Findings
	Mean orally bioavailability of avatrombopag free base at doses of 0.3, 1, and 3 mg/kg was 94.3, 92.6, and 89.3%, respectively
Plasma Concentrations of Unchanged Drug after Single Oral and Intravenous Administrations of YM477 Monomaleate to Cynomolgus Monkeys/Study PBC81-32	A single dose of avatrombopag was administered orally (0.3, 1, or 3 mg/kg) or by intravenous injection (1 mg/kg) to Cynomolgus monkeys. Following oral administration: Mean $T_{1/2}$ ranged from 5.2-7.2 hours Mean orally bioavailability of avatrombopag free base at doses of 0.3, 1, and 3 mg/kg was 52.5, 49.2, and 66.9%, respectively
Distribution	
In Vitro Plasma Protein Binding of YM477 Monomaleate by an Ultracentrifugation Method/ME03171	Plasma protein binding of avatrombopag (0.05-50 µg/mL) was not concentration-dependent and was higher in dogs (97.3-97.9%), monkeys (97.0-97.6%), and humans (96.3-96.6%) than in mice (87.2-89.1%), rats (87.6-89.2%), and rabbits (88.3-92%).
Absorption, Distribution, Metabolism, and Excretion after Oral Administration of ^{14}C-YM477 Monomaleate to Rats/Study 030039	Tissue distribution of radioactivity following a single oral dose of 1 mg/kg of [^{14}C]avatrombopag with a specific radioactivity of 1.78 MBq/mg was evaluated in male albino (Fischer; F344/DuCrj) and pigmented (Long Evans) rats (3 animal/time point). At 0.5, 1, 4, and 24 hours after administration of [^{14}C]avatrombopag, F344/DuCrj or Long Evans rats were laparotomized under anesthesia, blood was collected via the inferior vena cava, and various tissues throughout the body were collected. Additionally, concentrations of radioactivity were also measured at 168, 336, 504, and 672 hours after [^{14}C]avatrombopag administration in Long Evans rats. Whole-body autoradioluminography was also conducted in both rat strains. In most tissues, radioactivity concentrations reached a maximum at 1 or 4 hours in F344/DuCrj rats and at 4 hours in Long Evans rats and radioactivity was eliminated relatively slowly. Tissue concentrations of radioactivity in Long Evans rats were approximately 2-5 times higher than those in F344/DuCrj rats in most tissues up to 4 hours after dosing and were almost the same concentrations at 24 hours after dosing, except for in the eyeball. The distribution profile of radioactivity in F344/DuCrj and Long Evans rats was similar except for the colored skin and eyeball of the Long Evans rats. At 4 hours after administration, tissue concentrations of radioactivity were highest in the small intestine (determined to be the main site of absorption) with a tissue/plasma radioactivity concentration ratio (T/P) of 13.24 followed by the liver (6.79), adrenal gland (3.86), kidney (2.58), submandibular gland (2.11), heart (2.09), pancreas (1.97), stomach (1.90), lung (1.65), and hypophysis (1.36). The $t_{1/2}$ in the eyeball was 351 hours.
Placental Transfer and Excretion in Milk After a Single Administration of [^{14}C]E5501 in Rats/ Study AE-7538-G	A single oral dose of [^{14}C]avatrombopag (3 mg/kg; 8.904 MBq/kg) was administered to pregnant rats (on Day 13 or 18 of pregnancy) or lactating rats (on postpartum Day 10). On Day 13 of pregnancy, the ratios for the radioactive concentrations in the fetus to the maternal plasma concentrations were 0.04, 0.12, and 0.42 at 1, 4, and 24 hours after dosing, respectively. Data for select maternal and fetal tissues on Day 18 of pregnancy are in the table below. The percentage distributions of radioactivity in the fetuses were $\leq$0.01% of the dose.

Type of Study	Major Findings

Ratios of Radioactive Concentrations in Tissues Relative to the Plasma on Day 18 of Pregnancy

Tissue	Ratio to radioactive concentration in plasma		
	1 hour	4 hours	24 hours
Liver	6.87	7.80	9.13
Kidney	2.36	3.90	4.27
Adrenal gland	3.79	4.58	4.75
Uterus	0.44	1.10	1.53
Placenta	0.79	1.25	1.71
Fetal membrane	0.20	0.67	2.65
Amniotic fluid	NC	0.01	0.06
Fetus (whole body)*	0.02	0.07	0.22
Fetal blood**	0.02	0.04	0.12
Fetal plasma**	0.02	0.05	0.15
Fetal brain**	0.01	0.04	0.12
Fetal heart**	0.04	0.12	0.21
Fetal lung**	0.04	0.17	0.39
Fetal liver**	0.05	0.18	0.40
Fetal kidney**	0.02	0.10	0.24
Fetal digestive tract**	0.02	0.09	0.30

*One fetus from each of 3 dams
**Fetal tissues collected from remaining fetuses
NC=Not calculated

Pharmacokinetics in Plasma and Milk in Lactating Rats on Postpartum Day 10

Parameter	$AUC_{(0\text{-}last)}$ (µg eq.·hr/mL)	$AUC_{(0\text{-}\infty)}$ (µg eq.·hr/mL)	$T_{1/2}$ (hr)
Plasma (P)	8.49	9.40	6.6
Milk (M)	7.69	9.00	7.5
M/P ratio	0.89	0.94	1.15

Metabolism

Species Comparison of the Metabolic Stability and Metabolite Profile of AKR-501 (YM477) Using Mouse, Rat, Rabbit, Beagle Dog, Cynomolgus Monkey, and Human Primary Hepatocytes/Study AA33893	Cryopreserved hepatocytes from CD-1 mice, Sprague-Dawley rats, New Zealand White rabbits, Beagle dogs, Cynomolgus monkeys, and humans were incubated with 1 or 10 µmol/L avatrombopag for 4 hours at 37°C and the avatrombopag remaining and metabolites formed were evaluated.

In Vitro Metabolism: Avatrombopag Remaining and Metabolites Formed after 4 Hours Incubation with Hepatocytes

Species	Remaining Avatrombopag (%)		Metabolites Formed			
	1 µmol/L	10 µmol/L	4-hydroxy metabolite	Ester glucuronide	3-hydroxy metabolite	Hydroxy metabolite
Mouse	92	97	-	+	-	-
Rat	82	97	+	+	+	-
Rabbit	93	86	+	-	+	+
Dog	53	96	-	+	+	+
Monkey	74	92	+	+	+	-
Human	86	91	+	-	+	-

+=Detected -=Not detected

Elimination of Radioactivity in Bile, Urine, and Feces Following Oral or Intravenous Administration of ^{14}C-AKR-501 to Rats/Study 7994-110	The in vivo metabolic profile of avatrombopag was investigated following a single oral dose of 10 mg/kg of [^{14}C]avatrombopag administered to bile duct-cannulated Sprague-Dawley male rats in an excretion study. The following results were observed following oral administration:

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td>Bile: Analysis of bile samples revealed the presence of unchanged avatrombopag and 17 quantifiable metabolites. The major metabolite in bile was M46 (avatrombopag taurine conjugate), which accounted for 2.25% of the radioactive dose.
Feces: In the feces, 3 metabolites and unchanged avatrombopag (68% of radioactivity) were observed. M46 accounted for 1% of the dose
Urine: Analysis of urine identified 20 quantifiable metabolites, each with no more than 0.16% of the dose following oral administration; no unchanged avatrombopag was detected in urine.

The 4-hydroxy-avatrombopag and 3-hydroxyavatrombopag metabolites were found in bile and feces, but were at levels that could not be quantitated by HPLC. The primary biotransformation pathways (Phase 2) were amino acid conjugation of the carboxylic acid moiety of [^{14}C]avatrombopag. The most abundant conjugate was taurine; glycine and glucuronic acid conjugation was also noted. Methylation was also indicated in the metabolism of [^{14}C]avatrombopag.</td></tr>
<tr><td colspan="2">Excretion</td></tr>
<tr><td>Elimination of Radioactivity in Bile, Urine, and Feces Following Oral or Intravenous Administration of ^{14}C-AKR-501 to Rats/Study 7994-110</td><td>A single oral dose of 10 mg/kg of [^{14}C]avatrombopag at a radioactive dose of 25.8 µCi/mg was administered to bile duct-cannulated Sprague-Dawley male rats (4 total). Excretion of radioactivity in bile, urine, and feces was determined through 120 hours. Hepatic clearance and biliary excretion of the absorbed radioactivity was the primary route of elimination. Most of the excretion of radioactivity (90.4%) occurred in the first 48 hours after dosing.
Elimination of Radioactivity in Rats
<table>
<tr><th rowspan="2">Sample</th><th>% of Radioactive Dose (Mean)</th></tr>
<tr><th>Males</th></tr>
<tr><td>Urine</td><td>2.98</td></tr>
<tr><td>Feces</td><td>82.8</td></tr>
<tr><td>Bile</td><td>8.10</td></tr>
<tr><td>Cage Rinse</td><td>0.06</td></tr>
<tr><td>Cage Wash, Cage Wipe, Bile cannula, Jacket Rinse, and Residual Carcass</td><td>0.57</td></tr>
<tr><td>Total</td><td>94.5</td></tr>
</table></td></tr>
<tr><td colspan="2">TK data from general toxicology studies</td></tr>
<tr><td>26-Week Study in Rats with 4-Week Recovery Period/Study (b) (4)-152-08</td><td>Peak avatrombopag plasma concentrations (T_{max}) were observed at 4 or 8 hours after dosing. $T_{1/2}$ values were not calculated/reported. Exposures (C_{max} and AUC_{last}) were greater (1.3- to 2.5-fold) in females than males.
Summary of Toxicokinetic Values in 26-Week Study in Rats
<table>
<tr><th rowspan="2">Dose (mg/kg/day)</th><th rowspan="2">Day</th><th colspan="2">C_{max} (ng/mL)</th><th colspan="2">AUC_{last} (hr·ng/mL)</th></tr>
<tr><th>Males</th><th>Females</th><th>Males</th><th>Females</th></tr>
<tr><td rowspan="2">20</td><td>1</td><td>2220</td><td>4120</td><td>33900</td><td>53600</td></tr>
<tr><td>183</td><td>3220</td><td>4920</td><td>41200</td><td>76900</td></tr>
<tr><td rowspan="2">80</td><td>1</td><td>5990</td><td>7680</td><td>82700</td><td>106000</td></tr>
<tr><td>183</td><td>8140</td><td>16900</td><td>101000</td><td>251000</td></tr>
<tr><td rowspan="2">160</td><td>1</td><td>7650</td><td>11600</td><td>98700</td><td>177000</td></tr>
<tr><td>183</td><td>12100</td><td>23200</td><td>199000</td><td>390000</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>52-Week Study in Monkeys with 4-Week Recovery Period/Study (b) (4) 152-07</td><td>Mean peak avatrombopag plasma concentrations (T_{max}) ranged from 3.3 to 12 hours after dosing. $T_{1/2}$ values were not calculated/reported. Exposures (C_{max} and AUC_{last}) tended to be greater in males than females, primarily in the mid and high dose groups on Day 364.
Summary of Toxicokinetic Values in 52-Week Study in Monkeys
<table>
<tr><th rowspan="2">Dose (mg/kg/day)</th><th rowspan="2">Day</th><th colspan="2">C_{max} (ng/mL)</th><th colspan="2">AUC_{last} (hr·ng/mL)</th></tr>
<tr><th>Males</th><th>Females</th><th>Males</th><th>Females</th></tr>
<tr><td rowspan="3">5</td><td>1</td><td>377</td><td>306</td><td>5561</td><td>4407</td></tr>
<tr><td>181</td><td>751</td><td>1074</td><td>12630</td><td>14416</td></tr>
<tr><td>364</td><td>1102</td><td>758</td><td>18585</td><td>11908</td></tr>
<tr><td rowspan="3">15</td><td>1</td><td>1433</td><td>1244</td><td>24544</td><td>19446</td></tr>
<tr><td>181</td><td>4002</td><td>3683</td><td>69200</td><td>63904</td></tr>
<tr><td>364</td><td>6193</td><td>3210</td><td>107170</td><td>55550</td></tr>
<tr><td rowspan="3">45</td><td>1</td><td>4298</td><td>2754</td><td>67386</td><td>43906</td></tr>
<tr><td>181</td><td>10470</td><td>9592</td><td>195051</td><td>170861</td></tr>
<tr><td>364</td><td>16750</td><td>11278</td><td>303285</td><td>192221</td></tr>
</table></td></tr>
<tr><td colspan="2">TK data from reproductive toxicology studies</td></tr>
<tr><td>Female Fertility and Early Embryonic Development/Study 303102</td><td>Summary of Toxicokinetic Values in Female Rats
<table>
<tr><th>Dose (mg/kg/day)</th><th>Day</th><th>C_{max} (ng/mL)</th><th>T_{max} (hr)</th><th>$AUC_{0\text{-}24hr}$ (ng·hr/mL)</th></tr>
<tr><td rowspan="2">100</td><td>1</td><td>10281</td><td>2</td><td>123776</td></tr>
<tr><td>14</td><td>11770</td><td>4</td><td>188517</td></tr>
<tr><td rowspan="2">300</td><td>1</td><td>13806</td><td>4</td><td>209108</td></tr>
<tr><td>14</td><td>13475</td><td>4</td><td>252238</td></tr>
<tr><td rowspan="2">1000</td><td>1</td><td>20470</td><td>4</td><td>357520</td></tr>
<tr><td>14</td><td>29850</td><td>4</td><td>548466*</td></tr>
</table>*: exposure used for comparison in label</td></tr>
<tr><td>Male Fertility and Early Embryonic Development/ Study R-886</td><td>Summary of Toxicokinetic Values in Male Rats
<table>
<tr><th>Dose (mg/kg/day)</th><th>Day</th><th>C_{max} (ng/mL)</th><th>T_{max} (hr)</th><th>$AUC_{0\text{-}24hr}$ (ng·hr/mL)</th></tr>
<tr><td>10</td><td>28</td><td>1375</td><td>2</td><td>13609</td></tr>
<tr><td>30</td><td>28</td><td>3186</td><td>4</td><td>41519</td></tr>
<tr><td>100</td><td>28</td><td>7015</td><td>4</td><td>104096*</td></tr>
</table>*: exposure used for comparison in label</td></tr>
<tr><td>Embryo-fetal Development in Rats/Study R-884</td><td>Summary of Toxicokinetic Values in Female Rats
<table>
<tr><th>Dose (mg/kg/day)</th><th>GD Day</th><th>C_{max} (ng/mL)</th><th>T_{max} (hr)</th><th>$AUC_{0\text{-}24hr}$ (ng·hr/mL)</th></tr>
<tr><td rowspan="2">100</td><td>7</td><td>10173</td><td>4</td><td>149050</td></tr>
<tr><td>17</td><td>16406</td><td>4</td><td>254882*</td></tr>
<tr><td rowspan="2">300</td><td>7</td><td>30445</td><td>4</td><td>381405</td></tr>
<tr><td>17</td><td>25865</td><td>4</td><td>385952</td></tr>
<tr><td rowspan="2">1000</td><td>7</td><td>31617</td><td>4</td><td>453976</td></tr>
<tr><td>17</td><td>49946</td><td>4</td><td>920057*</td></tr>
</table>GD=Gestational Day *: exposure used for comparison in label</td></tr>
<tr><td>Embryo-fetal Development in Rabbits/Study R-885</td><td>Summary of Toxicokinetic Values in Female Rabbits
<table>
<tr><th>Dose (mg/kg/day)</th><th>GD Day</th><th>C_{max} (ng/mL)</th><th>T_{max} (hr)</th><th>$AUC_{0\text{-}24hr}$ (ng·hr/mL)</th></tr>
<tr><td rowspan="2">100</td><td>6</td><td>1619</td><td>2</td><td>10182</td></tr>
<tr><td>18</td><td>2896</td><td>7</td><td>47596*</td></tr>
<tr><td rowspan="2">300</td><td>6</td><td>3402</td><td>2</td><td>31466</td></tr>
<tr><td>18</td><td>4053</td><td>4</td><td>55960</td></tr>
<tr><td rowspan="2">600</td><td>6</td><td>6301</td><td>2</td><td>72586</td></tr>
<tr><td>18</td><td>8479</td><td>4</td><td>168333*</td></tr>
</table>GD=Gestational Day *: exposure used for comparison in label</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Pre- and Postnatal Development in Rats/Study (b) (4) 779001</td><td>
Summary of Toxicokinetics in F0 Females and F1 Pups in Rat Pre- and Postnatal Study on LD 10
<table>
<tr><th rowspan="2">Animals</th><th rowspan="2">Parameter</th><th colspan="3">Dose (mg/kg/day)</th></tr>
<tr><th>5</th><th>15</th><th>50</th></tr>
<tr><td rowspan="2">F0 females</td><td>AUC_{last} (ng·hr/mL)</td><td>19223</td><td>65646</td><td>206491*</td></tr>
<tr><td>C_{max} (ng/mL)</td><td>1503</td><td>6093</td><td>12963</td></tr>
<tr><td rowspan="2">F1 males</td><td>AUC_{last} (ng·hr/mL)</td><td>1233</td><td>4199</td><td>11928*</td></tr>
<tr><td>C_{avg} (ng/mL)</td><td>103</td><td>350</td><td>994</td></tr>
<tr><td rowspan="2">F1 females</td><td>AUC_{last} (ng·hr/mL)</td><td>1275</td><td>3995</td><td>14400*</td></tr>
<tr><td>C_{avg} (ng/mL)</td><td>106</td><td>333</td><td>1200</td></tr>
</table>
LD=Lactation Day *: exposure used for comparison in label
C_{avg}=Average concentration of the compound in plasma at steady state
</td></tr>
<tr><td>Dose-range Finding Juvenile Toxicity Study in Rats/ Study (b) (4) 779002</td><td>
Summary of Toxicokinetic Values in Juvenile Rats
<table>
<tr><th rowspan="2">Dose (mg/kg/day)</th><th rowspan="2">PND</th><th colspan="2">C_{max} (ng/mL)</th><th colspan="2">AUC_{last} (ng·hr/mL)</th></tr>
<tr><th>Males</th><th>Females</th><th>Males</th><th>Females</th></tr>
<tr><td rowspan="2">10</td><td>7</td><td>2760</td><td>2800</td><td>56000</td><td>58700</td></tr>
<tr><td>34</td><td>1520</td><td>1910</td><td>12900</td><td>21200</td></tr>
<tr><td rowspan="2">100</td><td>7</td><td>11400</td><td>11900</td><td>203000</td><td>208000</td></tr>
<tr><td>34</td><td>10500</td><td>12300</td><td>117000</td><td>199000</td></tr>
<tr><td rowspan="2">300</td><td>7</td><td>13600</td><td>10000</td><td>261000</td><td>205000</td></tr>
<tr><td>34</td><td>14400</td><td>19500</td><td>207000</td><td>275000</td></tr>
<tr><td rowspan="2">600</td><td>7</td><td>9070</td><td>10500</td><td>185000</td><td>225000</td></tr>
<tr><td>34</td><td>24800</td><td>24500</td><td>384000</td><td>382000</td></tr>
<tr><td rowspan="2">1000</td><td>7</td><td>11400</td><td>13200</td><td>239000</td><td>257000</td></tr>
<tr><td>34</td><td>19200</td><td>32000</td><td>340000</td><td>428000</td></tr>
</table>
PND=Postnatal Day PND 7=Day 1 PND 34=Day 28
</td></tr>
<tr><td colspan="2">TK data from Carcinogenicity studies</td></tr>
<tr><td>104-Week Carcinogenicity Study in Rats/ (b) (4) -152-10</td><td>
Summary of Toxicokinetic Values in Carcinogenicity Study in Rats
<table>
<tr><th rowspan="2">Dose (mg/kg/day)</th><th rowspan="2">Week</th><th colspan="2">C_{max} (ng/mL)</th><th colspan="2">AUC_{last} (hr·ng/mL)</th></tr>
<tr><th>Males</th><th>Females</th><th>Males</th><th>Females</th></tr>
<tr><td rowspan="2">20</td><td>26</td><td>2890</td><td>5120</td><td>44900</td><td>62800</td></tr>
<tr><td>52</td><td>4400</td><td>5800</td><td>54400</td><td>93300</td></tr>
<tr><td rowspan="2">50</td><td>26</td><td>6560</td><td>12300</td><td>75900</td><td>150000</td></tr>
<tr><td>52</td><td>8080</td><td>16900</td><td>119000</td><td>230000</td></tr>
<tr><td rowspan="2">160</td><td>26</td><td>11400</td><td>24300</td><td>182000</td><td>426000</td></tr>
<tr><td>52</td><td>18300</td><td>33600</td><td>287000</td><td>565000*</td></tr>
</table>
*: exposure used for comparison in label
</td></tr>
</table>

5.5. Toxicology

5.5.1. General Toxicology

Study title/ number: A 26-Week Oral Gavage Toxicity Study with Toxicokinetics of AKR-501 (E5501) in Male and Female Sprague Dawley Rats Followed by a 4-Week Recovery Period/ (b) (4) 152-08

Key Study Findings

- The stomach appears to be the main target organ of toxicity for avatrombopag in the rat with increases in serum gastrin levels and histopathology changes

including degeneration of glandular epithelium, atrophy of glandular mucosa, regenerative hyperplasia, and intraluminal deposits.

- Other potential organs of toxicity are the heart and kidneys.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 20, 80 or 160 mg/kg/day once daily for 26 weeks; 4-week recovery period
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% methylcellulose solution
Species/Strain:	Rat/Sprague-Dawley
Number/Sex/Group:	Main Study: 10/sex/group Recovery: 5/sex/group (0 and 160 mg/kg/day only)
Age:	10 weeks at randomization
Satellite groups/ unique design:	Toxicokinetics: 9/sex/group
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

<table>
<tr><th>Parameters</th><th>Major findings</th></tr>
<tr><td>Mortality</td><td>No avatrombopag-related mortality</td></tr>
<tr><td>Clinical Signs</td><td>Unremarkable</td></tr>
<tr><td>Body Weights</td><td>Unremarkable</td></tr>
<tr><td>Ophthalmoscopy</td><td>Conducted but not all of the data was recorded; examiner provided a statement indicating that there were no ophthalmic lesions present in the rats, however, there is no raw data for audit; additional histopathological evaluations were conducted to evaluate the lens</td></tr>
<tr><td>Hematology</td><td>% Mean differences vs. concurrent controls on Day 184
<table>
<tr><th rowspan="3">Parameter</th><th colspan="3">Males</th></tr>
<tr><th colspan="3">Dose level (mg/kg/day)</th></tr>
<tr><th>20</th><th>80</th><th>160</th></tr>
<tr><td>White blood cells</td><td>↑68%*</td><td>↑49%*</td><td>↑66%*</td></tr>
<tr><td>Lymphocytes</td><td>↑84%*</td><td>↑56%*</td><td>↑75%*</td></tr>
<tr><td>Monocytes</td><td>↑100%*</td><td>↑110%*</td><td>↑140%*</td></tr>
</table>
*p<0.05 compared to control group</td></tr>
<tr><td>Clinical Chemistry</td><td>% Mean differences vs. concurrent controls on Day 184
<table>
<tr><th rowspan="3">Parameter</th><th colspan="3">Males</th><th colspan="3">Females</th></tr>
<tr><th colspan="3">Dose level (mg/kg/day)</th><th colspan="3">Dose level (mg/kg/day)</th></tr>
<tr><th>20</th><th>80</th><th>160</th><th>20</th><th>80</th><th>160</th></tr>
<tr><td>AST</td><td>↑146%</td><td>↑132%</td><td>↑210%*</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>ALT</td><td>↑169%</td><td>↑196%</td><td>↑300%*</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Gastrin</td><td>-</td><td>-</td><td>-</td><td>-</td><td>↑287%*</td><td>↑929%*</td></tr>
</table>
*p<0.05 compared to control group</td></tr>
<tr><td>Urinalysis</td><td>Unremarkable</td></tr>
</table>

<table>
<tr><td>Gross Pathology</td><td>Unremarkable</td></tr>
<tr><td>Organ Weights</td><td>% Mean differences vs. concurrent controls for main study necropsy
<table>
<tr><th rowspan="3">Organ and Weight</th><th colspan="3">Males</th><th colspan="3">Females</th></tr>
<tr><th colspan="3">Dose level (mg/kg/day)</th><th colspan="3">Dose level (mg/kg/day)</th></tr>
<tr><th>20</th><th>80</th><th>160</th><th>20</th><th>80</th><th>160</th></tr>
<tr><td>Heart</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Absolute</td><td>-</td><td>↑25%*</td><td>↑28*</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Relative to BWt</td><td>-</td><td>↑19%*</td><td>↑17%*</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>Kidneys</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Absolute</td><td>-</td><td>-</td><td>↑20%*</td><td>-</td><td>↑20%*</td><td>↑18%*</td></tr>
<tr><td>Relative to BWt</td><td>-</td><td>-</td><td>↑8</td><td>-</td><td>↑14%*</td><td>↑11%*</td></tr>
<tr><td>Spleen</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Absolute</td><td>-</td><td>↑14%</td><td>↑25%*</td><td>-</td><td>↑24%*</td><td>↑26%*</td></tr>
<tr><td>Relative to BWt</td><td>-</td><td>↑9%</td><td>↑13%</td><td>-</td><td>↑18%*</td><td>↑20%*</td></tr>
</table>
*p<0.05 compared to control group BWt= Body weight</td></tr>
<tr><td>Histopathology
Adequate battery: Yes</td><td>See histopathology table below</td></tr>
</table>

-: indicates reduction in parameters compared to control.

Table 5: Histopathology Changes in 26-week Toxicology Study in Rats

Treatment-Related Microscopic Findings			No. of animals affected (main/recovery)							
			Males				Females			
Dose (mg/kg/day)			0	20	80	160	0	20	80	160
Number of animals examined			9/4	8/NE	10/NE	10/5	10/5	10/NE	10/NE	10/5
Organ	Finding									
Heart	Cardiomyopathy	Total	1/2	5/NE	4/NE	4/1	1/0	1/NE	-	2/1
		Minimal	1/2	4/NE	4/NE	4/1	1/0	1/NE	-	2/1
		Mild	-	1/NE	-	-	-	-	-	-
Kidneys	Chronic progressive nephropathy	Minimal	2/3	5/NE	2/NE	5/1	1/0	1/NE	2 NE	1/1
	Mononuclear cell infiltration, interstitium/perivascular	Minimal	-	-	2/NE	1/0	-	1/NE	1/NE	-
Stomach	Degeneration of glandular epithelium with or without intraluminal deposits	Total	-	-	8/NE	10/0	-	-	10/NE	10/0
		Minimal	-	-	5/NE	8/0	-	-	6/NE	9/0
		Mild	-	-	3/NE	2/0	-	-	4/NE	1/0
	Atrophy of glandular mucosa	Total	-	-	-	4/0	-	-	2/NE	7/0
		Minimal	-	-	-	4/0	-	-	2/NE	3/0
		Mild	-	-	-	-	-	-	-	2/0
		Moderate	-	-	-	-	-	-	-	2/0
	Regenerative hyperplasia, glandular epithelium	Minimal	-	-	-	-	-	-	2/NE	2/0
	Intraluminal deposits, glandular epithelium	Minimal	-	-	-	0/4	-	-	-	0/5

- = no test-article related changes
NE= Not examined; recovery groups not conducted at this dose

Study title/ number: A 52-Week Oral (Nasogastric Gavage) Toxicity Study with Toxicokinetics of AKR-501 (E5501) in Male and Female Cynomolgus Monkeys Followed by a 4-Week Recovery Period/ (b) (4) -152-07

Key Study Findings

- The stomach appears to be the main target organ of toxicity for avatrombopag in the monkey with increases in serum gastrin levels and histopathology changes including degeneration of glandular epithelium and atrophy of glandular mucosa.
- Other potential organs of toxicity are the heart, kidneys, and liver.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 5, 15 or 45 mg/kg/day once daily for 52 weeks (365 days); 4-week recovery period
Route of administration:	Oral nasogastric gavage
Formulation/Vehicle:	0.5% methylcellulose solution
Species/Strain:	Monkey/Cynomolgus
Number/Sex/Group:	Main Study: 4/sex/group Recovery: 2/sex/group
Age:	3-6 years at pre-study physical examination
Satellite groups/ unique design:	None
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	None
Clinical Signs	Unremarkable
Body Weights	Unremarkable
Electrocardiography (ECG)	Unremarkable
Ophthalmoscopy	Unremarkable
Hematology	Unremarkable
Clinical Chemistry	**45 mg/kg/day:** Serum gastrin levels were increased in 2 males (↑3- to 9-fold) and one females (↑2- to 3-fold) on Days 177 and 359
Urinalysis	Unremarkable
Gross Pathology	Unremarkable
Organ Weights	**% Mean differences vs. concurrent controls for main study necropsy**

Organ and Weight	Males			Females		
	Dose level (mg/kg/day)			Dose level (mg/kg/day)		
	5	15	45	5	15	45
Kidneys						
Absolute	-	-	↑28%*	-	-	-
Relative to BWt	-	-	↑21%	-	-	-
Relative to BrWt	-	-	↑31%*	-	-	-
Liver						
Absolute	-	-	↑20%	↑21%	↑11%	↑23%
Relative to BWt	-	-	↑11%	↑23%*	↑18%*	↑23%*

	Relative to BrWt	-	-	↑25%	↑30%*	↑19%	↑34%*
	*p<0.05 compared to control group BWt = Body weight BrWt= Brain weight						
Histopathology **Adequate battery:** Yes	See histopathology table below						

-: indicates reduction in parameters compared to control.

Table 6: Histopathology Changes in 52-week Toxicology Study in Monkeys

Treatment-Related Microscopic Findings			No. of animals affected (main/recovery)							
			Males				**Females**			
Dose (mg/kg/day)			0	5	15	45	0	5	15	45
Number of animals examined			4/2	4/2	4/2	4/2	4/2	4/2	4/2	4/2
Organ	Finding									
Heart	Mononuclear cell infiltration, pericardium	Minimal	-	-	-	1/0	-	-	-	-
Kidneys	Mononuclear cell infiltration, interstitium/perivascular	Minimal	-	-	2/0	1/1	-	-	3/1	1/1
Stomach	Degeneration of glandular epithelium	Total	-	-	1/0	4/0	-	-	1/0	4/0
		Minimal	-	-	1/0	-	-	-	1/0	3/0
		Mild	-	-	-	2/0	-	-	-	-
		Moderate	-	-	-	2/0	-	-	-	1/0
	Atrophy of glandular mucosa	Total	-	-	-	2/1	-	-	-	2/0
		Minimal	-	-	-	0/1	-	-	-	-
		Mild	-	-	-	2/0	-	-	-	2/0

- = no test-article related changes

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: Bacterial Reverse Mutation Study of YM477 Monomaleate/B030544

Key Study Findings:

- Avatrombopag did not increase the number of revertant colonies in any of the tester strains with or without metabolic activation; therefore, avatrombopag was negative for mutagenicity in the reverse mutation assay.

GLP compliance: Yes

Test system: *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537; *Escherichia coli* tester strain WP2*uvrA*/pKM101; +/- S9 activation; tested at concentrations up to 5000 µg/plate in dose-finding test and due to microbial toxicity observed with *Salmonella typhimurium* strains, the main test was performed twice for TA98, TA100, TA1535, and TA1537 and once for WP2*uvrA*/pKM101 with the following highest concentrations (all concentrations were expressed as avatrombopag free base):

Test strain	Concentrations (µg/plate)	
	Without S9 mix	With S9 mix
TA100, TA1535, TA1537	39.1	156
TA98	156	313
WP2*uvrA*/pKM101	5000	5000

Study is valid: Yes

In Vitro Assays in Mammalian Cells

Study title/ number: Chromosomal Aberration Study of YM477 Monomaleate in Human Lymphocytes/ B030546

Key Study Findings:

- Avatrombopag did not induce chromosome aberrations in human peripheral blood lymphocytes with and without metabolic activation; therefore, avatrombopag was negative for clastogenicity in the in vitro chromosome aberrations assay.

GLP compliance: Yes

Test system: Human peripheral blood lymphocytes;+/- S9 activation; exposure to avatrombopag of 3 or 24 hours without S9 activation and 3 hours with S9 activation; for chromosomal aberration test, concentrations of up to 200 µg/mL for 3-hour assay and 100 µg/mL for 24-hour assay; concentrations were expressed as avatrombopag free base

Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/ number: Micronucleus Test of YM477 Monomaleate in Rats/ B030545

Key Study Findings:

- Avatrombopag did not induce an increase in the incidence of micronucleated polychromatic erythrocytes; therefore, avatrombopag was negative for micronucleus induction and in vivo clastogenicity.

GLP compliance: Yes

Test system: Sprague-Dawley rats; two orals doses of 70, 200, 600, or 2000 mg/kg/day avatrombopag administered at a 24-hour interval; 24-hour bone marrow collection; toxicokinetic analysis was also conducted in satellite groups; due to multiple deaths in males, an additional micronucleus test and toxicokinetics study was conducted in male rats at doses of 25, 50, or 100 mg/kg/day; avatrombopag doses were expressed as avatrombopag free base

Study is valid: Yes

In the first micronucleus test, deaths were observed prior to the second administration of avatrombopag in 2/5 males at 200 mg/kg, 1/5 males at 600 mg/kg, and 2/5 males and 1/5 females at 2000 mg/kg. Due to these deaths, a second micronucleus test was conducted in males only with a highest dose of 100 mg/kg/day. A necropsy was performed; however, the causes of the deaths were not determined.

5.5.3. Carcinogenicity

Study title/ number: A 104-Week Oral (Gavage) Carcinogenicity Study of AKR-501 (E5501) in Mice/ (b) (4) 152-09

and

Study title/ number: A 104-Week Oral (Gavage) Carcinogenicity Study of AKR-501 (E5501) in Rats/ (b) (4) 152-10

Two-year (104-Week) carcinogenicity studies with avatrombopag were conducted in mice and rats, and are reviewed in detail in a separate Pharmacology/Toxicology review. Avatrombopag was administered by oral gavage once daily at doses of 0, 20, 60, or 160 mg/kg/day to CD-1 mice in the 2-year mouse study and doses of 0, 20, 50, or 160 mg/kg/day to Sprague-Dawley rats in the 2-year rat study. Discontinuation of dosing and early termination of animals occurred in both studies. In the mouse study, females were dosed for 101-102 weeks and were necropsied during Weeks 101-103, but males were dosed for the entire study (104-105 weeks). In the rat study, the dosing period was 82 weeks in females at 160 mg/kg/day, 96 weeks in females at 50 mg/kg/day, and 98 or 99 weeks in the other groups. All rats were also terminated early with surviving males necropsied during Week 99 and surviving females necropsied during Weeks 91 (160 mg/kg/day) and 103 (all other female groups). Survival was significantly decreased in females treated with 160 mg/kg/day avatrombopag compared to controls in both species and the decreases in survival were attributed to increases in the incidence and severity of chronic nephropathy in the kidneys. Body weights were lower in female rats treated with 160 mg/kg/day compared to the control groups with mean weights 15% lower than the first control group at necropsy on Week 91. Avatrombopag-related non-neoplastic microscopic findings included changes in the stomach and increased incidences and severity of chronic nephropathy in the kidneys in both species. Findings in the stomach included hyperplasia of the mucosa in mice and degeneration of glandular epithelium, atrophy of glandular mucosa, regenerative hyperplasia, intraluminal deposits, and neuroendocrine cell hyperplasia in rats.

Avatrombopag induced malignant neuroendocrine tumors in the stomach in one male at 160 mg/kg/day and 1 female at 60 mg/kg/day in mice and induced benign and malignant neuroendocrine tumors in the stomach at 160 mg/kg/day in rats. Benign and malignant neuroendocrine cell tumors in the stomach were not observed in the concurrent controls (<1%); therefore, they are considered rare tumors. Based on the FDA criteria for a positive carcinogenicity response, the single incidences of malignant neuroendocrine cell tumors observed in mice and the incidences of benign and malignant neuroendocrine cell tumors observed in male rats at 160 mg/kg/day were not statistically significant. In female rats, the incidences of benign neuroendocrine cell tumors and benign and malignant neuroendocrine cell tumors combined in the stomach were statistically significant. Exposures in female rats at 160 mg/kg/day were approximately 117 times the human clinical exposure based on AUC at the highest recommended human dose.

The Executive Carcinogenicity Assessment Committee reviewed and discussed the findings for both the 2-year mouse and rat carcinogenicity studies. The Committee concurred that there were no drug-related neoplasms in the 2-year mouse carcinogenicity study in either males or females. For the rat study, the Committee concluded that the combined incidence of benign and malignant neuroendocrine cell tumors in the stomach was increased in rats at the 160 mg/kg/day dose in females, and was drug related.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Study title/ number: Study of Fertility and Early Embryonic Development to Implantation in Female Rats Administered YM477 Monomaleate Orally/ 303102

Key Study Findings

- Avatrombopag caused mortality in females at 300 and 1000 mg/kg/day. The cause of death was undetermined.
- No effects on fertility or early embryonic development were observed at any dose level; therefore, the NOAEL for female fertility and early embryonic development was 1000 mg/kg/day in rats. The exposures at the 1000 mg/kg/day dose were approximately 114 times the human clinical exposure based on AUC at the highest recommended human dose.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 100, 300, or 1000 mg/kg/day (free base YM477); once daily dosing starting 14 days prior to cohabitation through Gestation Day (GD) 7
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% methylcellulose aqueous solution
Species/Strain:	Rat/Sprague-Dawley
Number/Sex/Group:	20/sex/group; only females were dosed
Satellite groups:	Toxicokinetics (TK): 10 females/group at 100, 300, and 1000 mg/kg/day; dosing period of 14 days; blood collected on Days 1 and 14
Study design:	Females treated with avatrombopag were cohabitated with untreated males until evidence of mating; maximum cohabitation period of 2 weeks; day on which evidence of copulation was observed was considered GD 0; necropsy/cesarean section for females conducted on GD 13; due to the observed mortality, histopathological examination was conducted in the 300 and 1000 mg/kg/day TK groups.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	**300 mg/kg/day:** Two main study females and one TK female **1000 mg/kg/day:** One main study female and one TK female All of these females were found dead prior to the daily administration of drug between Days 2 and 4 of dosing; the cause of death in these animals was undetermined
Clinical Signs	**In females with mortality at 300 and 1000 mg/kg/day:** Decreased locomotor activity, bradypnea, piloerection, incomplete eyelid opening, and/or soiled fur **Surviving females at 300 and 1000 mg/kg/day:** Decreased locomotor activity on Day 2 of dosing
Body Weights	Unremarkable
Fertility	Unremarkable
Necropsy findings Cesarean Section Data	 Unremarkable
Histopathology in TK animals	**300 mg/kg/day:** Degeneration or necrosis of the muscle fiber in skeletal muscles and sporadic degeneration or necrosis of renal tubular epithelium in the ascending thick limb of Henle's loop in kidney **300 and 1000 mg/kg/day:** Diffuse degeneration or necrosis of the parietal cells, diffuse decreased number or loss of the chief cells, diffuse increased mitosis in the neck, and diffuse immature cell proliferation in the fundic gland of stomach of all animals

Study title/ number: Study of Fertility and Early Embryonic Development to Implantation in Male Rats Treated Orally with YM477 Monomaleate/ R-886

Key Study Findings

- No effects on fertility or early embryonic development were observed at any dose level; therefore, in this study, the NOAEL for male fertility and early embryonic development was 100 mg/kg/day in rats. The exposures at the 100 mg/kg/day dose were approximately 22 times the human clinical exposure based on AUC at the highest recommended human dose.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 10, 30, or 100 mg/kg/day (free base YM477); once daily dosing for 58 days starting 4 weeks prior to mating through the mating period until Day 58

Route of administration: Oral gavage

Formulation/Vehicle: 0.5% methylcellulose aqueous solution

Species/Strain: Rat/Sprague-Dawley

Number/Sex/Group:	20/sex/group; only males were dosed
Satellite groups:	Toxicokinetics (TK): 12 males/group; blood collected on Day 28 of administration; 0 and 100 mg/kg/day groups were subjected to laparotomy and necropsy, and full histopathology examination was conducted
Study design:	Males treated with avatrombopag were cohabitated/mated with untreated females from Day 29 until evidence of mating; maximum cohabitation period of 2 weeks; females that had not copulated during the first week were replaced by females that had not been used for mating for the second week of mating; day on which evidence of copulation was observed was considered GD 0; necropsy in males was conducted on Day 59; necropsy/cesarean section for females conducted on GD 14
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	None
Clinical Signs	Unremarkable
Body Weights	Unremarkable
Fertility	Unremarkable
Necropsy findings	
Males	Unremarkable
Cesarean Section Data (females)	Unremarkable
Histopathology in TK animals	Unremarkable

Embryo-Fetal Development

Study title/ number: Study of Effects on Embryo-fetal Development in Rats Treated Orally with YM477 Monomaleate/ R-884

Key Study Findings

- Avatrombopag caused maternal toxicity at 300 and 1000 mg/kg/day characterized by decreased food consumption, decreased body weight gain, and/or mortality.
- Fetal toxicity included decreased fetal weight at 1000 mg/kg/day and increased incidences of skeletal variations including incidences of 14th rib at 300 and 1000 mg/kg/day.
- The NOAEL for maternal and developmental toxicity was 100 mg/kg/day in rats.

- The exposures at the 100 and 1000 mg/kg/day doses were approximately 53 and 190 times, respectively, the human clinical exposure based on AUC at the highest recommended human dose.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 100, 300, or 1000 mg/kg/day (free base YM477); once daily dosing from GD 7-17

Route of administration: Oral gavage

Formulation/Vehicle: 0.5 w/v% methylcellulose aqueous solution

Species/Strain: Rat/Sprague-Dawley

Number/Sex/Group: 24 females/group

Satellite groups: Toxicokinetics (TK): 24 females/group at 100, 300, and 1000 mg/kg/day; blood collected on GD 7 and 17

Study design: Female rats were paired with male rats until evidence of mating; day on which evidence of copulation was observed was considered GD 0; pregnant rats were administered avatrombopag once daily on GD 7-17 and necropsy/cesarean section was conducted on GD 20

Deviation from study protocol affecting interpretation of results: No

Observations and Results

<table>
<tr><th>Parameters</th><th>Major findings</th></tr>
<tr><td>Mortality</td><td>300 mg/kg/day: One female was found dead before dosing on GD8
1000 mg/kg/day: One female was found dead before dosing on GD9</td></tr>
<tr><td>Clinical Signs</td><td>1000 mg/kg/day: Decrease in spontaneous movement observed on GD 8 in female found dead on GD9</td></tr>
<tr><td>Body Weights</td><td>1000 mg/kg/day: Body weight gain ↓14% for GD 7-18 period compared to controls</td></tr>
<tr><td>Food Consumption</td><td>1000 mg/kg/day: Food consumption ↓ 33% for GD 7-8 and ↓9-13% for GD 8-9, GD 9-10, and GD 10-11 compared to controls</td></tr>
<tr><td>Necropsy findings
Cesarean Section Data</td><td>Cesarean section data findings: Embryo-fetal deaths
<table>
<tr><th rowspan="2">Dose (mg/kg/day)</th><th rowspan="2">No. of Dams</th><th colspan="4">No. of embryo-fetal deaths</th></tr>
<tr><th>Total</th><th>Mean total %</th><th>Early</th><th>Late</th></tr>
<tr><td>0</td><td>24</td><td>15</td><td>4.4</td><td>15</td><td>0</td></tr>
<tr><td>100</td><td>24</td><td>12</td><td>3.1</td><td>11</td><td>1</td></tr>
<tr><td>300</td><td>21</td><td>15</td><td>4.5</td><td>14</td><td>1</td></tr>
<tr><td>1000</td><td>21</td><td>25</td><td>7.5</td><td>24</td><td>1</td></tr>
</table></td></tr>
</table>

Necropsy findings
Offspring

Fetal body weights and placental weights

Dose (mg/kg/day)	No. of Dams	Mean fetal body weight (g)		Placental weight (g)	
		Male	Female	Male	Female
0	24	4.20	4.00	0.49	0.47
100	24	4.17	3.94	0.46	0.45
300	21	4.12	3.92	0.46	0.44
1000	21	4.06	3.78* (↓6%)	0.45 (↓8%)	0.43* (↓9%)

*=p<0.05, different from control

The incidence of live fetuses with skeletal variations was significantly higher in the 300 and 1000 mg/kg/day groups.

Skeletal variations in live fetuses

Parameter	No. of fetuses affected (%)			
Dose mg/kg/day)	0	100	300	1000
No. of fetuses examined	179	190	163	155
No. of dams with variations	7	8	12	11
No. of fetuses with variations	13 (7.3)	14 (7.4)	26 (16.0)*	23 (14.8)*
14th rib (rudimentary rib)	11 (6.1)	8 (4.2)	20 (12.3)	21 (13.5)*
Bilateral	7 (3.9)	2 (1.1)	12 (7.4)	11 (7.1)
Unilateral	4 (2.2)	6 (3.2)	8 (4.9)	10 (6.5)

*=p<0.05, different from control

Study title/ number: Study for Effects on Embryo-fetal Development in Rabbits Treated Orally with YM477 Monomaleate/ R-885

Key Study Findings

- Avatrombopag caused maternal toxicity at 300 and 600 mg/kg/day characterized by decreased food consumption and decreased body weight gain that lead to abortion in 4 dams at 300 mg/kg/day and 3 dams at 600 mg/kg/day. Abortion was also observed in one dam at 100 mg/kg/day.
- No effects on embryo-fetal development were observed at any level; therefore, the NOAEL for embryo-fetal toxicity was 600 mg/kg/day in rabbits.
- The exposures at the 100 and 600 mg/kg/day doses were approximately 10 and 35 times, respectively, the human clinical exposure based on AUC at the highest recommended human dose.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 100, 300, or 600 mg/kg/day (free base YM477); once daily dosing from GD 6-18
Route of administration: Oral gavage
Formulation/Vehicle: 0.5 w/v% methylcellulose aqueous solution
Species/Strain: Rabbit/New Zealand White
Number/Sex/Group: 20 females/group

Satellite groups:	Toxicokinetics (TK): 6 females/group at 100, 300, and 600 mg/kg/day; blood collected on GD 6 and 18
Study design:	Female rabbits were mated with male rabbits; mating continued until 98 females copulated successfully at 17 or 18 weeks of age and the day was designated GD 0; pregnant rabbits were administered avatrombopag once daily on GD 6-18 and necropsy/cesarean section was conducted on GD 28
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	None
Clinical Signs	A decrease in the number of feces was observed in all groups with higher incidences of the finding observed at 300 mg/kg/day (in 9 females) and 600 mg/kg/day (in 7 females) **300 mg/kg/day:** No feces observed in 3 females **600 mg/kg/day:** Yellow-white feces observed in 2 females
Body Weights and Food Consumption	**Aborting dams:** Consumed almost no food from GD 14 or 15 until abortion, exhibited low body weight gain from GD 6-19, and lost weight during this time period **300 and 600 mg/kg/day:** Low food consumption starting on GD 14; for non-aborting females, 3 at 300 mg/kg/day and 1 at 600 mg/kg/day showed low body weight gain and lost weight from GD 6-19; body weight in most of these animals increased in post-administration period; 1 female at 300 mg/kg/day consumed almost no food from GD 14-28 and continued to lose weight
Necropsy findings Cesarean Section Data	**Abortions:** One dam in the 100 mg/kg/day group, 4 dams in the 300 mg/kg/day group, and 3 dams in the 600 mg/kg/day group aborted between GD 21-25. Macroscopic findings in these animals included focal discoloration (dark red) of mucosa of the stomach at 300 and 600 mg/kg/day, focal discoloration (green/dark green) mucosa of gallbladder at 100 and 600 mg/kg/day, and yellowish white content in cecum or cortical cyst in both kidneys at 600 mg/kg/day. Unremarkable
Necropsy findings Offspring	Unremarkable

Prenatal and Postnatal Development

Study title/ number: A Study of the Effects of AKR-501 on Pre- and Postnatal Development, Including Maternal Function in Rats/ (b) (4) 617003

Key Study Findings

- Avatrombopag caused maternal toxicity at 100, 300 and 600 mg/kg/day characterized by decreased food consumption and decreased body weight gain leading to mortality and total litter losses. Increased pup mortality/decreased survival was observed at all doses of avatrombopag with most of the mortality observed between PND 14-21. Due to the mortality, the study was terminated early.
- Body weight gain was decreased in both male and female pups at all doses compared to controls throughout the lactation/postnatal period.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0, 100, 300, or 600 mg/kg/day (free base AKR-501); once daily dosing from GD 6 through lactation day (LD) 20
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Rat/Sprague-Dawley
Number/Sex/Group:	25 females/group
Satellite groups:	None
Study design:	Pregnant females (F0 dams) were administered avatrombopag once daily from GD 6 through LD 20; females were allowed to deliver the F1 litters and rear the F1 pups to weaning on LD/postnatal day (PND) 21 to evaluate the effects on the F0 dams and F1 generation pups through weaning; standardization of litter size (culling) to 8 pups/litter (4/sex when possible), occurred on PND 4; study was originally designed with a post-weaning phase to evaluate the effects on developmental landmarks, sensory function, and behavior in the offspring and reproductive performance of the F1 generation, however, because of significant mortality, the surviving dams and their pups were euthanized on or around LD/PND 21
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

<table>
<tr><th>Generation/Finding</th><th>Major findings</th></tr>
<tr><td colspan="2">F0 Dams</td></tr>
<tr><td>Mortality</td><td>
Summary of Dispositions of the F0 Females
<table>
<tr><th>Parameter</th><th colspan="4">No. of dams affected</th></tr>
<tr><th>Dose (mg/kg/day)</th><th>0</th><th>100</th><th>300</th><th>600</th></tr>
<tr><td>No. of F0 dams at study initiation</td><td>25</td><td>25</td><td>25</td><td>25</td></tr>
<tr><td>Females found dead</td><td>0</td><td>0</td><td>1</td><td>3</td></tr>
<tr><td>Females euthanized in extremis</td><td>0</td><td>1</td><td>1</td><td>2</td></tr>
<tr><td>Females with total litter loss of delivered pups</td><td>0</td><td>4</td><td>5</td><td>8</td></tr>
<tr><td>Non-gravid females euthanized on post-mating Day 25</td><td>1</td><td>0</td><td>1</td><td>1</td></tr>
<tr><td>Females euthanized at study termination (LD 21)</td><td>24</td><td>20</td><td>17</td><td>11</td></tr>
</table>
One female in the 600 mg/kg/day group was found dead on GD 9, all other mortality and moribundity occurred between GD 21 and LD 2

Most of the total litter losses of delivered pups occurred during LD 16-21, the exceptions were 1 litter at 100 mg/kg/day and 2 litters at 300 mg/kg/day that died during LD 0-2
</td></tr>
<tr><td>Clinical Signs</td><td>Females with mortality/moribundity: Red material around nose, pale body, body cool to touch, hypoactivity, decreased defecation and/or yellow feces, and gasping
100 mg/kg/day: Yellow feces
300 and 600 mg/kg/day: Red material around nose, yellow feces, and decreased defecation</td></tr>
<tr><td>Body Weights and Food Consumption</td><td>Maternal total body weight gain for the GD 6-20 period was significantly decreased (↓15-25%) at all doses compared to controls; mean food consumption for the GD 6-20 period was also significantly decreased (↓13%) at 300 mg/kg/day and 600 mg/kg/day compared to controls and mean food consumption was generally lower (↓ up to 31%) at all doses compared to controls during the lactation period (LD 7-10, 10-14, 14-17, and 17-21)</td></tr>
<tr><td>Necropsy findings</td><td>A slight increase in the mean number of unaccounted for implantation sites (indicative of prenatal deaths) was observed at 300 and 600 mg/kg/day (1.7 and 2.2 per dam, respectively) compared to the control group (0.6 per dam)</td></tr>
<tr><td colspan="2">F1 Pups (Neonatal Parameters)</td></tr>
<tr><td>F1 mortality</td><td>
Summary of Postnatal survival
<table>
<tr><th>Time Period</th><th colspan="4">Mean % per litter</th></tr>
<tr><th>Dose (mg/kg/day)</th><th>0</th><th>100</th><th>300</th><th>600</th></tr>
<tr><td>PND 0 (relative to number born</td><td>99.7</td><td>99.2</td><td>94.5</td><td>96.7</td></tr>
<tr><td>PND 0-1</td><td>97.3</td><td>94.8</td><td>98.5</td><td>97.8</td></tr>
<tr><td>PND 1-4 (pre-selection)</td><td>97.4</td><td>94.2</td><td>92.5</td><td>93.6</td></tr>
<tr><td>PND 4 (post-selection)-PND 7</td><td>96.9</td><td>98.4</td><td>94.4</td><td>98.8</td></tr>
<tr><td>PND 7-14</td><td>98.4</td><td>94.0</td><td>91.7</td><td>87.2</td></tr>
<tr><td>PND 14-21</td><td>100.0</td><td>66.2</td><td>53.1*</td><td>27.2**</td></tr>
<tr><td>Birth-PND 4 (pre-selection)</td><td>94.5</td><td>89.7</td><td>86.7</td><td>86.6</td></tr>
<tr><td>PND 4 (post-selection)-PND 21</td><td>86.7</td><td>57.4</td><td>47.1</td><td>25.7**</td></tr>
</table>
*=p<0.05, different from control **=p<0.01, different from control
</td></tr>
</table>

Disposition/deaths of the F1 pups

Parameter	No. of pups affected			
Dose (mg/kg/day)	0	100	300	600
Found dead	20	49	65	83
Euthanized in extremis	0	0	3	3
Missing (presumed cannibalized)	6	7	22	29
Sent to necropsy due to death of dam	0	1	0	11

F1 clinical observations

100 mg/kg/day: Subcutaneous hemorrhage and hypothermia
300 and 600 mg/kg/day: Subcutaneous hemorrhage, pale body, hypothermia, small stature, and umbilical hernia

F1 body weight

Body weights were lower and body weight gain was decreased in both male and female pups at all doses compared to controls throughout the lactation/postnatal period; body weights for PND 17 (↓ up to 33%) and PND 21 (↓ up to 38%) and body weight gain for PND 17-21 (↓ up to 73%) are shown in the table below

Pup Body Weights and Body Weight Gain

Dose (mg/kg/day)	Mean body weight (g)				Body weight gain (g)	
	PND 17		PND 21		PND 17-21	
	Male	Female	Male	Female	Male	Female
0	39.0	37.0	48.4	45.1	9.8	9.3
100	29.8**	28.9**	33.3**	32.8**	3.8**	4.6**
300	25.0**	23.5**	31.3**	27.9**	4.6**	3.6**
600	26.9**	24.3**	35.0**	28.6**	3.6**	2.5**

**=p<0.01, different from control

Study title/ number: An Oral (Gavage) Study of the Effects of E5501 on Pre- and Postnatal Development, Including Maternal Function and Toxicokinetics in Rats/ (b) (4) 779001

Key Study Findings

- Avatrombopag caused increased pup/F1 mortality at 50 mg/kg/day from PND 4-21; mortality continued post-weaning with F1 pups found dead between PND 22-25.
- Toxicities observed at 50 mg/kg/day in the F1 generation included decreased body weight gain that resulted in the delay in balanopreputial separation and vaginal patency.
- The NOAEL for F1 developmental/neonatal toxicity and early postnatal development is 15 mg/kg/day. The NOAEL for F0 maternal toxicity, and F1 neurobehavior and reproductive toxicity is 50 mg/kg/day.
- The 50 mg/kg/day dose resulted in maternal exposures 43 times and pup exposures approximately 3 times the human clinical exposure based on AUC at the highest recommended human dose.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 5, 15, or 50 mg/kg/day (free base E5501); once daily dosing from GD 6 through LD 20
Route of administration: Oral gavage
Formulation/Vehicle: 0.5% methylcellulose
Species/Strain: Rat/Sprague-Dawley
Number/Sex/Group: 25 females/group

Satellite groups:	Toxicokinetics: 3 females/group for control and 8 females/group for 5, 15, and 50 mg/kg/day dosed from GD 6 to LD 10; plasma concentrations of E5501 determined in culled pups on LD 4 and dams and pups on LD 10
Study design:	Pregnant females (F0 dams) were administered avatrombopag once daily from GD 6 through LD 20; females were allowed to deliver the F1 litters and rear the F1 pups to weaning on LD/PND 21 to evaluate the effects on the F0 dams and F1 generation pups through weaning; standardization of litter size (culling) to 8 pups/litter (4/sex when possible), occurred on PND 4; selected F1 pups evaluated for auditory startle response on PND 20, locomotor activity on PND 61, learning and memory assessment (Biel maze) beginning on PND 62, and developmental landmarks; F1 animals were mated and uterine parameters were evaluated on GD 15
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

<table>
<tr><th>Generation/Finding</th><th>Major findings</th></tr>
<tr><td colspan="2">F0 Dams</td></tr>
<tr><td>Mortality</td><td>One female at 5 mg/kg/day was found dead on LD 19 and one female at 15 mg/kg/day was found dead on GD 23; due to no clinical findings, a lack of a dose-related response, and no apparent cause of death, these deaths were not attributed to avatrombopag administration</td></tr>
<tr><td>Clinical Signs and Body Weight</td><td>Unremarkable</td></tr>
<tr><td>Food Consumption</td><td>50 mg/kg/day: Mean food consumption was decreased compared to controls during LD 17-21 (↓10%) and for the entire lactation period (LD 1-21; ↓7%); these findings were not considered maternal toxicity, but were considered related to the increased pup mortality and decreased pup body weight gains during lactation at 50 mg/kg/day</td></tr>
<tr><td>Necropsy findings</td><td>Unremarkable</td></tr>
<tr><td colspan="2">F1 Pups/Rats</td></tr>
<tr><td>F1 mortality</td><td>50 mg/kg/day: Increased pup mortality was observed from PND 4-21; pup mortality continued post-weaning with a total of 4 (3 male and 1 female) F1 pups found dead between PND 22-25
Summary of Postnatal survival
<table>
<tr><th>Time Period</th><th colspan="4">Mean % per litter</th></tr>
<tr><th>Dose (mg/kg/day)</th><th>0</th><th>5</th><th>15</th><th>50</th></tr>
<tr><td>Birth-PND 4 (pre-selection)</td><td>98.7</td><td>97.7</td><td>93.6</td><td>94.9</td></tr>
<tr><td>PND 4 (post-selection)-PND 21</td><td>96.5</td><td>99.0</td><td>98.4</td><td>91.3 (↓5%)</td></tr>
</table></td></tr>
</table>

<table>
<tr><td></td><td>
Disposition/deaths of the F1 pups
<table>
<tr><th>Parameter</th><th colspan="4">No. of pups affected (No. of litters affected)</th></tr>
<tr><th>Dose (mg/kg/day)</th><th>0</th><th>5</th><th>15</th><th>50</th></tr>
<tr><td>Found dead</td><td>7(7)</td><td>6(6)</td><td>24(10)</td><td>30(14)</td></tr>
<tr><td>Euthanized in extremis</td><td>0(0)</td><td>0(0)</td><td>0(0)</td><td>1(1)</td></tr>
<tr><td>Missing (presumed cannibalized)</td><td>4(4)</td><td>5(4)</td><td>2(2)</td><td>5(4)</td></tr>
<tr><td>Euthanized due to death of dam</td><td>0(0)</td><td>8(1)</td><td>0(0)</td><td>0(0)</td></tr>
</table>
</td></tr>
<tr><td>F1 clinical observations</td><td>50 mg/kg/day: Small stature and umbilical hernia</td></tr>
<tr><td>F1 body weight</td><td>50 mg/kg/day: Body weights were significantly lower (↓13-14%) in both male and female pups compared to controls on PND 7, PND 10, PND 14, PND 17, and PND 21, resulting in decreased body weight gain (↓16%) compared to controls for the PND 4-21 period; body weight gain was still significantly decreased (↓11-13%) for the PND 28-35 period and body weights remained significantly lower than controls during PND 28-63 for males (↓7-14%) and PND 28-56 for females (↓7-12%)</td></tr>
<tr><td>F1 developmental landmarks</td><td>50 mg/kg/day: The ages of balanopreputial separation in males and vaginal patency in females were significantly higher than in the concurrent control group but within the (b) (4) historical control range for balanopreputial separation (42.3-49.0 days) and vaginal patency (31.3-37.0 days); the delay in balanopreputial separation and vaginal patency in the 50 mg/kg/day group was attributed to delayed growth and lower body weights (↓9-12%) noted for these animals
Balanopreputial Separation and Vaginal Patency
<table>
<tr><th colspan="4">Mean PND observed</th></tr>
<tr><th colspan="2">Balanopreputial separation</th><th colspan="2">Vaginal patency</th></tr>
<tr><th>0 mg/kg/day</th><th>50 mg/kg/day</th><th>0 mg/kg/day</th><th>50 mg/kg/day</th></tr>
<tr><td>45.1</td><td>47.2*</td><td>32.2</td><td>34.0**</td></tr>
</table>
*p<0.05, different from control **=p<0.01, different from control</td></tr>
<tr><td>Auditory startle response, locomotor activity, and Biel maze</td><td>Unremarkable</td></tr>
<tr><td>Reproductive performance</td><td>Unremarkable</td></tr>
<tr><td>F2 Generation</td><td>Unremarkable</td></tr>
</table>

Juvenile Toxicity

Study title/ number: E5501: A 28-Day Dose Range-Finding Oral (Gavage) Toxicity Study in Juvenile Rats/ (b) (4) 779002

In this dose-range finding study in juvenile rats, avatrombopag was administered by oral gavage at initial dose levels of 10, 100, and 300 mg/kg/day once daily for 28 days during PND 7-34 in Sprague Dawley rats. Due to the apparent absence of toxicity, additional dose levels of 600 and 1000 mg/kg/day were also evaluated in the study. Toxicokinetics were evaluated in satellite groups with blood samples collected on Days 1 and 28 (PND 7 and 34). No avatrombopag-related mortality was observed in this study. Decreased mean body weight gains were observed in both males (↓ up to 14%) and females (↓ up to 10%) at 600 and 1000 mg/kg/day throughout the treatment period compared to controls. Hematology changes included decreases in hemoglobin, hematocrit, mean corpuscular volume, and mean corpuscular hemoglobin and alterations in red blood morphology (hypo/polychromia, anisocytosis, or

poikilocytosis) at doses ≥300 mg/kg/day. Histopathology findings were observed in the stomach and kidney. Gastric mucosal changes in the stomach (degeneration and single cell necrosis of the glandular epithelium, regenerative epithelial cell hyperplasia, and atrophy of glandular mucosa) similar to those observed in adult rats were observed at ≥100 mg/kg/day. An increase in the incidences and severity of foci of the basophilic tubules in the kidney were observed at 1000 mg/kg/day.

5.5.5. Other Toxicology Studies

Genetic Toxicology Studies with Impurities

Multiple in vitro bacterial reverse mutation (Ames) assays were conducted to assess the potential for the impurities to induce mutagenicity. All studies were conducted with *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 *uvr*A, with and without S9 activation (+/- S9), and were valid. These studies, methods, maximum concentrations, and the results are listed in the table below. Impurities (b) (4) were positive for mutagenicity in bacterial reverse mutation assays and impurity (b) (4) was inconclusive for mutagenicity.

Table 7: Results of Bacterial Reverse Mutation Assays Conducted with Impurities present in Avatrombopag

Study #	Impurity tested	Method/Concentrations	Results
14K3678G	(b) (4)	Pre-incubation method; concentrations up to 5000 µg per plate	Positive; maximum mean increase in revertant colonies of 2.2-fold (+ S9) with strain TA100
14K3688G		Pre-incubation method; concentrations up to 5000 µg per plate	Inconclusive; in first assay, increases in revertant colonies of 2.2-fold (+ S9) with strain TA98 and less than 2-fold (+ S9) with strain TA100; in confirmatory assay, 2.1-fold increase (+ S9) in strain TA 98 with no dose dependency and less than 2-fold increase with strain TA100
15K3898G		Pre-incubation method; concentrations up to 5000 µg per plate	Negative
964106		Plate incorporation and pre-incubation methods; concentrations up to 5000 µg per plate	Negative
964107		Plate incorporation and pre-incubation methods; concentrations up to 5000 µg per plate	Positive; with both methods (+ S9); maximum increases in revertant colonies with strains TA98 (3-fold), TA100 (7.8-fold), and WP2 *uvr*A (3.1-fold)
K12006		Pre-incubation method; concentrations up to 1000 µg per plate	Negative
K12014		Pre-incubation method; concentrations up to 5000 µg per plate	Negative

Study #	Impurity tested	Method/Concentrations	Results
K12015	(b) (4)	Pre-incubation method; concentrations up to 5000 µg per plate	Negative

Qualification of Mutagenic Impurities

Based on the principles in the ICH M7 guidance, the threshold of toxicological concern (TTC) limit for daily intake of mutagenic impurities in drugs with less than 1 month duration of treatment is 120 µg/day. This TTC is acceptable for mutagenic impurities in avatrombopag for the proposed indication of thrombocytopenia (platelet count <50 x 10^9/L) in adult patients with chronic liver disease who are scheduled to undergo a procedure with a treatment duration of 5 days. For the proposed maximum dose of 60 mg/day avatrombopag, the TTC is 2000 ppm or 0.20%.

Assessments of mutagenicity were conducted for all actual and potential process related impurities using in silico software (Case ultra: Version 1.5.0.0; DEREK Nexus: Derek Nexus version 3.0.1 and Nexus version 1.5.0) and the in vitro bacterial reverse mutation (Ames) assays reviewed above. The mutagenic or potentially mutagenic impurities based on these assessments are listed in the table below.

Table 8: Control and Batch History of Mutagenic Impurities

(b) (4)

According to the Impurities document submitted to Module 3.3.S.3.2., the impurity (b) (4) is being controlled with a specification of not more than (b) (4) %. The other impurities are being controlled through the specifications (b) (4) and are at levels below the

TTC. Based on this information, there are no concerns with the levels of the mutagenic impurities in avatrombopag for the proposed indication.

X X

Brenda J Gehrke, PhD
Primary Reviewer

Christopher M Sheth, PhD
Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant seeks approval of DOPTELET (avatrombopag) for the treatment of thrombocytopenia in patients with chronic liver disease (CLD) who are scheduled to undergo a procedure. The proposed DOPTELET dosing regimen is 60 mg daily for 5 consecutive days for patients with baseline platelet count <40 x 10^9 /L (low baseline platelet count cohort) and 40 mg daily for 5 consecutive days for patients with baseline platelet count within 40 x 10^9 /L and < 50 x 10^9 /L (high baseline platelet count cohort), with food, beginning 10 to 13 days prior to a scheduled procedure.

The Clinical Pharmacology section of the NDA is supported by the following evaluations and analyses:

- Single and repeat dose pharmacokinetics (PK) of avatrombopag,
- PK/pharmacodymanic (PD) relationship between avatrombopag concentrations and platelet count response,
- Population PK, and food effect on avatrombopag PK,
- Potential PK drug-drug interactions (DDI) between avatrombopag and cytochrome P450 (CYP) 3A and CYP2C9 modulators and P-glycoprotein (P-gp) inhibitors, and
- Potential for QT/QTc prolongation.

Based on the PK/PD relationship between change in platelet count from baseline and avatrombopag concentration, and the efficacy results in the registration trials, the proposed DOPTELET dosing regimen of 60 mg and 40 mg daily for 5 consecutive days for the low and high baseline platelet count cohorts, respectively is reasonable. No exposure-safety relationships were evaluated from the registration trials due to overall low incidence of safety related events. The adverse reactions were similar between DOPTELET and placebo, with no meaningful differences in safety profiles between patients dosed with 40 mg or 60 mg DOPTELET and no dose modifications in the registration trials. The overall efficacy and safety profiles in the registration trials support the use of the proposed DOPTELET dosing regimens (60 mg daily for 5 consecutive days for the low baseline platelet count cohort and 40 mg daily for 5 consecutive days for the high baseline platelet count cohort) for the treatment of thrombocytopenia in patients with CLD who are scheduled to undergo a procedure.

The population PK analyses did not identify clinically important covariates influencing avatrombopag PK, including any hepatic impairment and mild to moderate renal impairment.

No dose adjustment of DOPTELET is needed with modulators of CYP3A and CYP2C9, inhibitors of P-gp, and for patients with organ impairment.

Recommendations
The proposed DOPTELET dosing regimens of 60 mg daily for 5 consecutive days for patients with baseline platelet counts <40 x 10^9 /L and 40 mg daily for 5 consecutive days for patients

with baseline platelet count of 40 x 10^9 /L and < 50 x 10^9/L are acceptable and are supported by the efficacy and safety results. From a Clinical Pharmacology standpoint, the NDA is approvable provided the Applicant and the FDA reach an agreement regarding the labeling language.

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness[†]	The pivotal Trials G000-310 and -311 demonstrated that a high proportion of patients with baseline platelet counts < 50 x 10^9/L in the DOPTELET arm did not require a platelet transfusion or rescue measures for bleeding up to 7 days post-procedure and achieved platelet counts $\geqslant$ 50 x 10^9/L on procedure day compared to the placebo arm.
General dosing instructions	• 60 mg daily for 5 consecutive days with food for patients with baseline platelet count <40 x 10^9 /L. • 40 mg daily for 5 consecutive days with food for patients with baseline platelet count between 40 x 10^9 /L and < 50 x 10^9 /L.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose adjustments are recommended in patients with any hepatic impairment and mild-to-moderate renal impairment. No dose adjustments are recommended with concomitant use of CYP3A and CYP2C9 modulators, and P-gp inhibitors, considering the short treatment duration and lack of significant safety concerns.
Labeling	(b) (4)
Bridge between the to-be-marketed and clinical trial formulations	Not applicable. The to-be-marketed formulation (2G tablet) was used in the registration trials (G000-310 and -311), supportive trials (G000-202, -204) in patients, and the pertinent clinical pharmacology studies.

Postmarketing Requirements and Commitments

No postmarketing requirements or commitments.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Avatrombopag (molecular weight of 650 g/mol as free base) is a thrombopoetin (TPO) receptor (c-Mpl) agonist. Like TPO, avatrombopag increased proliferation of recombinant Ba/F3- human c-Mpl (EC_{50} 3.3 nM), and promoted the differentiation of human hematopoietic progenitor cells, cord blood (CB) CD34+ cells, to human megakaryocytes (EC_{50} 25.0 nM).

The following is a summary of the clinical pharmacokinetics (PK) of avatrombopag:

Pharmacodynamics (Platelet Response)

Administration of avatrombopag resulted in dose- and exposure-dependent elevations in platelet counts. The onset of effect was observed within 3 to 5 days of administration, with peak platelet response within 10 to 13 days relative to the initiation of a 5-day treatment with DOPTELET.

Dose proportional increase in area under the effect curve for platelet count over 28 days ($AUEC_{0\text{-}28d}$) was observed after a single dose between 20 mg and 60 mg with food. Maximal platelet count (Emax) showed a modest increase between 20 mg and 60 mg with food, and median time to Emax was between 8-11 hours.

Pharmacokinetics

The PK of avatrombopag were similar in healthy subjects and patients with CLD. After a single dose, systemic exposure was dose proportional over the dose range of 10 mg to 80 mg. Steady-state was achieved within 5 to 7 days, with a geometric mean accumulation ratio of 1.8- to 2-fold at 7 days, following avatrombopag daily dosing. Avatrombopag was the major circulating component.

Absorption

The median Tmax was 5-6 hours following administration of avatrombopag.

Effect of Food: A low-fat or high-fat meal did not affect avatrombopag $AUC_{0\text{-}inf}$ and C_{max}, but reduced the intra-subject variability by 50 to 70% and inter-subject variability by 40 to 49%. Median T_{max} was unchanged or reduced up to 2 hours with low-fat or high-fat meal. Dose proportionality of avatrombopag was also demonstrated with high-fat meal between 20 mg and 60 mg (highest dose tested).

Distribution

Avatrombopag was 96 to 99% bound to human plasma proteins at concentrations ranging from 50 to 50000 ng/mL in vitro. The human blood-to-plasma concentration ratio was 0.58 in vitro. The geometric mean (%CV) apparent volume of distribution (V_d/F) of avatrombopag at steady-state was 180 L (25%).

Elimination

The mean terminal elimination half-life (%CV) of avatrombopag was 18 hours (4%). The geometric mean (% CV) clearance (CL/F) was 6.9 L/hr (29%).

Metabolism: Avatrombopag was primarily metabolized by CYP2C9 and CYP3A in vitro. Oxidative metabolism (4-hydroxyl metabolite) was the metabolic clearance pathway. No metabolites detected in plasma.

Excretion: Following a single 20 mg oral dose of ^{14}C-avatrombopag, 88% of the dose was recovered in feces (34% of dose as unchanged avatrombopag) and 6% of the dose was recovered in urine.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant proposes DOPTELET dosing regimens of 60 mg daily for 5 consecutive days for patients with baseline platelet count <40 x 10^9/L and 40 mg daily for 5 consecutive days for patients with baseline platelet count within 40 x 10^9/L and < 50 x 10^9/L, with food, beginning 10 to 13 days prior to a scheduled procedure.

The proposed DOPTELET dosing regimen was evaluated in the placebo-controlled Trials G000-310 (n=231) and G000-311 (n=204). The dosing regimen were chosen using PK/PD simulations and PK/PD modeling (based on data from Trial G000-202 that tested different dosing regimens) that described the target platelet response as a function of the total DOPTELET dose and a function of baseline platelet count. Following administration of the proposed DOPTELET dosing regimen in Trials G000-310 and -311, a high proportion of patients with low baseline platelet counts or high baseline platelet counts did not require a platelet transfusion or rescue measures for bleeding up to 7 days post-procedure and achieved platelet counts $\geqslant$ 50 x 10^9/L on procedure day compared to the placebo arm, supporting the recommended dosing strategy. Although food did not affect avatrombopag exposure, DOPTELET is recommended to be administered with food to reduce PK variability of avatrombopag.

Therapeutic Individualization

CYP3A and CYP2C9 Modulators and Pg-p Inhibitors: Although changes in avatrombopag exposure were observed with CYP3A and CYP2C9 modulators and P-gp inhibitors, no dose adjustments are recommended with CYP3A and CYP2C9 modulators and P-gp inhibitors.

Organ impairment: A lower starting dose is not recommended for patients with any hepatic impairment (Child-Turcotte-Pugh grade A, B, and C) and mild to moderate renal impairment (creatinine clearance (CLcr) ≥30 mL/min) as avatrombopag PK were similar in these patient populations compared to subjects with normal hepatic function and normal renal function (CLcr

≥90 mL/min), and no clinically meaningful effect in response was observed. The PK and safety of avatrombopag in patients with severe renal impairment (CLcr <30 mL/min) have not been studied adequately.

Patients requiring subsequent procedures: For second and subsequent procedures, no changes to the dosing regimen are recommended. The platelet response for various dosing regimens within a short time post procedure were evaluated to determine if patients who would receive a full 5-day dosing regimen in a 2- to 4-week period after the first dose would experience adversely high platelet counts. See Appendix 19.4.5 for further details on the simulation results.

Outstanding Issues

None.

Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling concepts to be included in the final package insert:

- (b) (4)
-
- Recommend including in Section 12.2 a subsection for platelet response that includes dose/exposure-response and time course of platelet response at the proposed DOPTELET dosing regimen.

Section 12.3

- Describe the dose proportionality of avatrombopag, exposure parameters at the proposed doses, and PK in healthy subjects and patients.
- Include information of avatrombopag exposure with standard and high fat meal (with description of standard and high fat meal).
- State that avatrombopag PK is not affected by age, race, sex, any hepatic impairment, and mild-to-moderate renal impairment. Population PK showed no changes in PK with changes in CLcr ≥30 mL/min and with any hepatic impairment at steady state. (b) (4)
- State that in vitro studies indicate that avatrombopag inhibits breast cancer resistance protein (BCRP) and organic anion transporter (OAT)3, but does not inhibit CYP1A, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A, OAT1, organic cation transporter (OCT)2, organic anion transporting polypeptide (OATP)1B1, OATP1B3, (b) (4) Also, state that avatrombopag weakly induces CYP2C8 and CYP2C9, and does not induce CYP1A2, CYP2B6, and CYP3A in vitro.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The PK parameters listed in Table 9 are from the clinical pharmacology studies in healthy subjects and patients.

Table 9: Summary of General Pharmacology and Pharmacokinetic Characteristics of Avatrombopag

<table>
<tr><th colspan="2">Pharmacology</th></tr>
<tr><td>Mechanism of Action</td><td>Avatrombopag (molecular weight of 650 g/mol):
• Is a thrombopoetin receptor (c-Mpl) agonist.
• Increased (EC_{50} 3.3 nmol/L) proliferation of Ba/F3-human c-Mpl cells.
• Promoted (EC_{50} 25.0 nmol/L) the differentiation of human hematopoietic progenitor cells to human megakaryocytes.</td></tr>
<tr><td>Active Moieties</td><td>No active metabolites and no metabolites detected in plasma. Unchanged avatrombopag was the major circulating component in plasma.</td></tr>
<tr><td>QT Prolongation</td><td>Avatarombopag inhibited hERG current with an IC_{50} of 1.4 µM in vitro.
The QT interval prolongation potential of avatrombopag was assessed using data from Trials 310 and 311 in patients with CLD who received DOPTELET of 40 mg or 60 mg daily x 5 days (n=274) or placebo (n=156). Linear regression analysis was used for evaluating the relationship between drug concentration and baseline corrected QTcF (ΔQTcF) or mean placebo response corrected ΔQTcF (ΔΔQTcF). The analyses showed no large mean QTc prolongation effects (>20 ms) are anticipated with the highest recommended therapeutic dosing regimen.</td></tr>
<tr><th colspan="2">General Information</th></tr>
<tr><td>Bioanalysis</td><td>Avatrombopag was measured using validated LC-MS/MS assay methods.</td></tr>
<tr><td>Healthy vs. Patients</td><td>PK characteristics were similar between healthy subjects and target patient population mean apparent oral clearance (CL/F) (%CV) was 6.86 (32%) L/hr in healthy subjects and 7.29 (18%) L/hr in patients.</td></tr>
<tr><td>Drug Exposure at Steady State Following the Therapeutic Dosing Regimen</td><td>The following table provides a summary of PK following daily dosing in patients with CLD:
<table>
<tr><th rowspan="2">PK Parameter</th><th colspan="2">Repeat Dose, Once Daily*</th></tr>
<tr><th>40 mg
(n=115)</th><th>60 mg
(n=160)</th></tr>
<tr><td>$AUC_{0\text{-}tau}$, ng·h/mL</td><td>3717 (62%)</td><td>4820 (85%)</td></tr>
<tr><td>C_{max}, ng/mL</td><td>214 (43%)</td><td>352 (47%)</td></tr>
<tr><td colspan="3">* at Day 5 in Trials G000-310 & G000-311 (with food)
Source: Pop PK Report E5501-005R</td></tr>
</table></td></tr>
<tr><td>Dose Proportionality</td><td>After single doses, avatrombopag PK was approximately dose proportional over the range of 10 mg to 80 mg in healthy subjects.
<table>
<tr><th>PK Parameter</th><th>10 mg
n=26</th><th>40 mg
n=25</th><th>80 mg
n=25</th></tr>
</table></td></tr>
</table>

	$AUC_{0\text{-}inf}$, ng·h/mL: 1195 (56%); 4198 (83%); 7562 (106%) C_{max}, ng/mL: 42 (71%); 166 (84%); 293 (106%) Source: Table 10, Study A001-006 Dose proportionality was also demonstrated between 10 and 80 mg in patients: similar mean clearance (CL/F) (%CV) ranging from 6.8 (14%) to 7.4 (23%) L/hr. After a single dose, AUEC of platelet counts was dose proportional over the range of 10 mg to 80 mg in healthy subjects. **PD Parameter** / **Placebo** n=9 / **10 mg** n=8 / **40 mg** n=9 / **80 mg** n=9 $AUEC_{0\text{-}17d}$, 10^9.d/L: 259 (100%); 357 (202%); 715 (85%); 1283 (37%) E_{max}, 10^9/L: 219 (12%); 268 (16%); 291 (24%); 344 (57%) Source: Table 14.2.4.7, Study A001-006
Accumulation	The mean accumulation ratio following avatrombopag 10 mg QD for 7 days was 2-fold.
Variability	• Following a single dose of 40 mg, the between-subject variability (%CV) for avatrombopag C_{max} was 46% to 79% and AUC_{inf} was 56 to 81%. The within-subject variability (%CV) for avatrombopag C_{max} was 63% to 73% and AUC_{inf} was 60 to 75%.
Absorption	
Bioavailability	88% oral radioactivity (34% as unchanged) recovered in excreta in humans.
T_{max}	With 40 mg single dose, median T_{max} was 5 - 6 hr (range 3-24 hr)
Food effect [a] (Fed/fasted)	Avatrombopag exposure ($AUC_{0\text{-}inf}$) increased by 10-21% with a high fat meal (~918 calories: 59 g carbohydrate, 59 g fat, and 39 g protein) and was not affected with a low-fat meal (~500 calories: 3 g fat, 15 g proteins, and 108 g carbohydrates). T_{max} was delayed by 0 to 2 hours (median T_{max} 5 to 8 hours) with food. Variability in avatrombopag exposure was decreased by 40-70% with high-fat or low-fat meal.
Distribution	
Volume of Distribution	Mean Vd/F (%CV) of 180 L (25%).
Plasma Protein Binding	>96% bound to human plasma proteins between 50 to 50000 ng/mL in vitro.
Blood to Plasma Ratio	0.58 in vitro
As Substrate of Transporters	• Substrate of P-glycoprotein (P-gp). • Not a substrate of breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP1B1, OATP1B3), organic anion transporter (OAT1, OAT3), organic cation transporter (OCT2), and multidrug and toxin extrusion proteins (MATE1, MATE2K).
Elimination	
Terminal Elimination Half-Life	The arithmetic mean (%CV) elimination half-life ($t_{1/2}$) of avatrombopag was 18 hours (4%). The mean (%CV) apparent oral clearance (CL/F) of avatrombopag is 6.9 L/h (29%).
Metabolism	
Fraction Metabolized (% dose)	Based on the mean percentage of the dose recovered as metabolites in the excreta, the fraction metabolized is 45%.

Primary Metabolic Pathway(s)	Primarily metabolized by CYP2C9 and CYP3A to form 4-hydroxyl metabolite in vitro.
Excretion	
Primary Excretion Pathways (% dose) ±SD	• Feces: 88% ± 2% (34% unchanged avatrombopag). • Urine: 6% ± 19% (negligible unchanged avatrombopag).
Interaction liability (Drug as Perpetrator)	
Inhibition/Induction of Metabolism	• Clinical studies with a single dose of DOPTELET show that avatrombopag exposure increased by 1.4-fold with strong CYP3A inhibitor, increased by 2.2-fold with a dual moderate CYP3A and CYP2C9 inhibitor, and decreased by 40% with a dual strong CYP3A and moderate CYP2C9 inducer. • In vitro data suggests that avatrombopag weakly induces CYP2C8 and CYP2C9, does not induce CYP1A2, CYP2B6, and CYP3A, and does not inhibit CYP1A, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A.
Inhibition/Induction of Transporter Systems	• Clinical studies with a single dose of DOPTELET show that avatrombopag exposure decreases by 20% with a P-gp inhibitor and increases by 1.6-fold with a P-gp and moderate CYP3A inhibitor. • In vitro data suggests that avatrombopag inhibits BCRP and OAT3, but does not inhibit OAT1, OCT2, OATP1B1, OATP1B3, MATE1, and MATE2K.

*PK parameters are presented as geometric mean (%CV) or median (minimum, maximum) unless otherwise noted

6.3.2. Clinical Pharmacology Questions

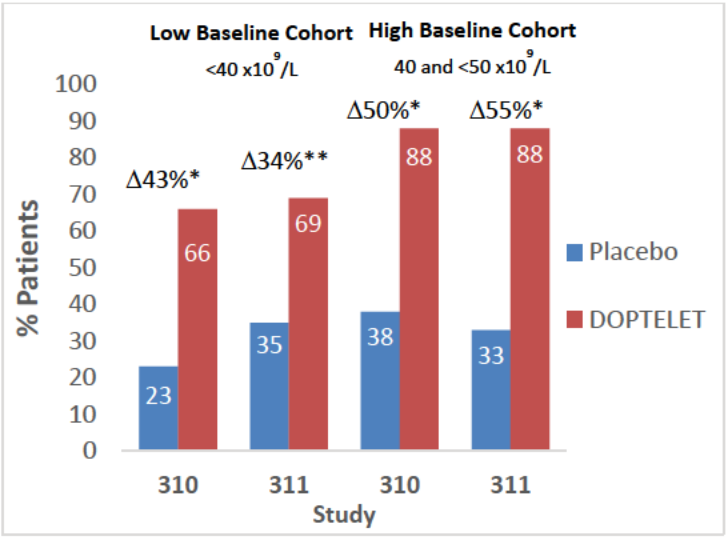
Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes, the clinical pharmacology information was adequate to provide supportive evidence of effectiveness of avatrombopag on platelet response in patients with CLD with thrombocytopenia. The Clinical Pharmacology program, including the PK/PD analysis provided in Appendix 19.4.5, supported the following:

- An increase in avatrombopag concentrations resulted in a corresponding increase in platelet count from baseline.
- Based on data from Trial G000-202 that tested different DOPTELET dosing regimen, the degree of response to avatrombopag dose was a function of baseline platelet count. As such, a higher dose is required for patients with lower baseline platelet count to attain a comparable target platelet profile as patients with higher baseline platelet counts.
- Platelet response was a function of the total dose, and a loading dose was not necessary.
- The selected daily 5-day dosing regimens of 60 mg for patients with baseline platelet count $<40 \times 10^9$ cells/mL and 40 mg for patients with baseline platelet count within 40×10^9 cells/mL and $< 50 \times 10^9$ cells/mL was supported by the results of the placebo-controlled trials.
- At least 90% of patients were expected to have target platelet counts $> 50 \times 10^9$ cells/mL with a low incidence of patients with platelet counts $>200 \times 10^9$ cells/mL at the selected dosing regimen.

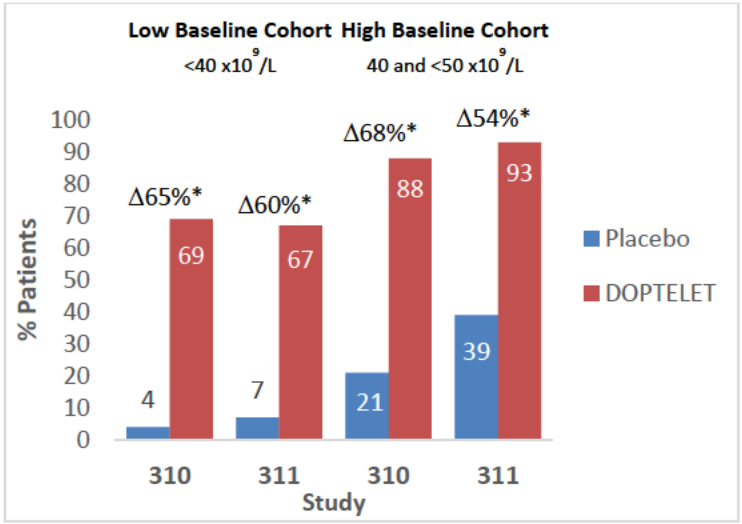
As shown in Figure 1, in Trials G000-310 and G000-311, 66 to 69% of patients with low baseline platelet counts and 88% of patients with high baseline platelet counts did not require a platelet transfusion or rescue measures for bleeding up to 7 days post-procedure compared to less than 38% in the placebo arm. These data are supported by the high proportion of patients who achieved platelet counts ≥50 x 10^9/L on procedure day compared to placebo as shown in Figure 2.

Figure 1: Proportion of Patients Who do not Require a Platelet Transfusion / Rescue Procedure for Bleeding from Randomization to 7 days Post-Procedure in Trials G000-310 and -311



Source: Generated by the reviewer based on Tables 14.2.2.1 (CSR 310) and 14.2.2.1 (CSR 311). *p<0.0001, **p<0.0006

Figure 2: Proportion of Patients Who Achieved Platelet Counts ≥50 x 10^9/L on Procedure Day in Trials G000-310 and -311



Source: Generated by the reviewer based on Tables 14.2.2.1 (CSR 310) and 14.2.2.1 (CSR 311). *p<0.0001

Overall, there was a low incidence of adverse events in Trials G000-310 and -311, and the adverse events were similar between DOPTELET and placebo, with no meaningful differences in safety profiles between patients dosed with 40 mg or 60 mg DOPTELET and no dose modifications for DOPTELET (Table 10).

Table 10: Summary of Adverse Events (AE) in Studies G000-310 and -311

Category	Low Baseline Platelet Count Cohort (<40×10^9/L)		High Baseline Platelet Count Cohort (≥40 to <50×10^9/L)		Combined Treatment Group Totals	
	Placebo (N=91) n (%)	Avatrombopag 60 mg (N=159) n (%)	Placebo (N=65) n (%)	Avatrombopag 40 mg (N=115) n (%)	Placebo (N=156) n (%)	Avatrombopag (N=274) n (%)
Patients with Any AE	53 (58.2)	89 (56.0)	33 (50.8)	59 (51.3)	86 (55.1)	148 (54.0)
Treatment-Related AE	16 (17.6)	18 (11.3)	4 (6.2)	8 (7.0)	20 (12.8)	26 (9.5)
AE Grade 3 or More	12 (13.2)	13 (8.2)	4 (6.2)	17 (14.8)	16 (10.3)	30 (10.9)
Serious AE	12 (13.2)	11 (6.9)	2 (3.1)	9 (7.8)	14 (9.0)	20 (7.3)
Deaths	0	0	1 (1.5)	2 (1.7)	1 (0.6)	2 (0.7)
Other	12 (13.2)	11 (6.9)	1 (1.5)	7 (6.1)	13 (8.3)	18 (6.6)
AE Leading to Study Drug Withdrawal	0	2 (1.3)	0	0	0	2 (0.7)
Source: Summary of Clinical Safety, Table 2.7.4-11, Module 2.7.4						

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen of 60 mg orally QD for 5 days for the low baseline cohort and 40 mg QD for 5 days for the high baseline cohort, are appropriate for the indicated patient population. The dose was selected based on the PK/PD analyses and supported by the efficacy and safety data from the pivotal trials. Less than 1% of the patients were discontinued during the study.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No. Based on the results of the population PK analysis, avatrombopag PK were similar among patients with mild hepatic impairment (Child-Turcotte-Pugh Class A: n=212), moderate hepatic impairment (Child-Turcotte-Pugh Class B, n=151), severe hepatic impairment (Child-Turcotte-Pugh Class B: n=31), and patients with normal hepatic function (n=391). Also, avatrombopag PK were similar among subjects or patients with mild (CLcr 60 to <90 mL/min: n=142) renal impairment, moderate renal impairment (CLcr 30 to <60 mL/min: n= 33) and normal renal function (CLcr ≥90 mL/min: n=606). Therefore, a lower starting dose is not recommended for patients with any hepatic impairment and mild to moderate renal impairment. However, the

effect of severe renal impairment (CLcr < 30 mL/hr) is unknown, as only 2 patients with severe renal impairment received avatrombopag during the clinical development.

There was no major difference in the PD response (i.e., change in platelet count from baseline) between patients with any hepatic impairment compared to patients with normal hepatic function, and between patients with mild to moderate renal impairment and patients or healthy subjects with normal renal function.

Age (18-86 years), sex, and race (Whites, African Americans, and East Asians (i.e., Japanese, Chinese and Koreans)), had no clinically meaningful effect on the PK of avatrombopag (Appendix 19.4.5).

Effect of CYP2C9 polymorphism

No dose adjustments are proposed with intermediate metabolizers (IMs), and poor metabolizers (PMs) of CYP2C9.

Among the 120 healthy subjects evaluated for CYP2C9 polymorphism across 3 single-dose studies [94 extensive metabolizers (EMs), 24 IMs, and 2 PMs], the avatrombopag exposures were 1.4-fold for CYP2C9 IMs and ~2-fold in CYP2C9 PMs compared to CYP2C9 EMs (Appendix 19.4.3). Also, physiologically based PK (PBPK) simulations with itraconazole suggested a 2-fold increase in avatrombopag exposure in PMs versus EMs with a single dose of avatrombopag alone (Appendix 19.4.6). Therefore, based on the limited dataset, the increase in single dose avatrombopag exposures with the IMs and PMs are comparable to those observed for strong CYP3A inhibitors and moderate CYP3A and CYP2C9 inhibitors (Appendix 19.4.3, Table 65). This increase in exposure is not considered clinically relevant given the short duration of therapy.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

No.

Food-Drug Interactions

Avatrombopag exposure ($AUC_{0\text{-}inf}$) increased by 21% with a high-fat meal and was not affected by a low-fat meal (Appendix 19.4.2, Table 62). However, food (high-fat or low-fat) decreased the variability of avatrombopag PK by 40-70% (Appendix 19.4.1, Table 61). In the registration trials, DOPTELET was administered with food to reduce the variability of PK.

Drug-Drug Interactions

Effects of Other Drugs on Avatrombopag

No dose management strategy is required for the co-administration of CYP3A and CYP2C9 modulators and P-gp inhibitors.

Strong CYP3A4 inhibitors, moderate CYP3A and CYP2C9 inhibitors, and a P-gp and moderate CYP3A inhibitor increased avatrombopag AUC by 1.4-fold and 2.2-fold, while P-gp inhibitor did not affect avatrombopag AUC after a single dose (20 mg) of DOPTELET. Also, a strong CYP3A

and moderate CYP2C9 inducer decreased avatrombopag AUC by 40% after a single DOPTELET dose (Appendix 19.4.3, Table 65).

The predicted proportion of patients with platelet counts < 50 x 10^9/L, >50 x 10^9/L and < 200 x 10^9/L, and > 200 x 10^9/L were simulated for DOPTELET alone, and with concurrent administration of CYP3A and CYP2C9 modulators and P-gp inhibitors for a range of dosing regimens and the results are shown in Table 11. Based on the results of the PK/PD simulations, the changes in avatrombopag exposure with CYP3A and CYP2C9 modulators and P-gp inhibitors do not result in a large effect on the proportion of patients with platelet counts < 50 x 10^9/L, >50 x 10^9/L and < 200 x 10^9/L, and > 200 x 10^9/L to warrant dose adjustments. While fewer patients are predicted to have platelet counts > 50 x 10^9/L when DOPTELET is administered concurrently with a strong CYP3A and moderate CYP2C9 inducer, 58% of patients are predicted to benefit and minimize platelet transfusion.

Table 11: PK/PD Simulations of the Effect of DOPTELET and Co-administered Drugs on the Platelet Response

Treatment	DOPTELET Dosing Duration	Percentage of Simulated Patients with Maximum Platelet Counts (x 10^9 cells/mL)		
		< 50	50 < Max Plt < 200	> 200
DOPTELET alone	5 days	25 %	73 %	2.2 %
+ Strong CYP3A inhibitor	5 days 4 days	21 % 24 %	76 % 74 %	3.5 % 2.1 %
+ Moderate CY3A & CYP2C9 inhibitor	5 days 4 days 3 days ↓ dose by 50% x 5 days	14 % 17 % 22 % 22 %	78 % 78 % 75 % 76 %	8.4 % 5.3 % 2.7 % 2.5 %
+ 2C9 inhibitor	5 days 4 days	18 % 22 %	77 % 75 %	4.8 % 2.9 %
+ P-gp inhibitor	5 days	26 %	70 %	1.3 %
+ P-gp & Moderate CY3A inhibitor	5 days	22 %	75 %	2.9 %
+ Strong CY3A & Moderate CYP2C9 inducer	5 days	42%	58%	0.2 %
Source: Appendix 19.4.5				

Effect of Avatrombopag

On Transporters: In vitro, avatrombopag has the potential to inhibit BCRP (IC_{50} 5.4 µM) and OAT3 (IC_{50} of 0.2 µM). This may translate into clinically relevant inhibition at therapeutic doses (i.e., I_{gut}/IC_{50} = 68 for BCRP and [Imax, u]/IC_{50} = 0.1 for OATP3, with dose of 60 mg, C_{max} of 0.5 µM at 60 mg dose and fu of 0.04) according to the FDA guidance for drug interaction studies (2017) (Appendix 19.4.3, Table 68).

Does this drug prolong the QT or QTc interval?

The available data suggests that no large mean QTc effects (>20 ms) are anticipated with the proposed 5-day DOPTELET dosing regimen.

A through QT study in 45 healthy subjects administered a single dose of 100 mg of 1G tablet formulation did not reveal clinically significant prolongation of QT by avatrombopag. However, the exposures in the study with the 1G tablet were lower than those in the clinical trials with the 2G formulation (to-be-marketed). Therefore, the change from baseline in QTcF (ΔQTcF) and placebo-corrected ΔQTcF (ΔΔQTcF) with the avatrombopag concentration were further explored using data from Studies G000-310 and -311 in 274 patients with CLD who were dosed with 40 mg or 60 mg daily for 5 days. While the data cannot exclude small mean QTc effects (10 ms) at the maximal concentrations with the proposed dosing regimen, the data suggest that no large mean QTc effects (>20 ms) are anticipated with the proposed therapeutic dosing regimens for this acute treatment (5 days) (Appendix 19.4.7).

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7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Two phase 3 pivotal studies which were international, randomized, double-blind, placebo-controlled, parallel-group studies (E5501-G000-310 and E5501-G000-311, or Studies 310 and 311 respectively) were included in the application to support primary safety and efficacy claims. Further details for each study are provided in the table below.

The sponsor also conducted two phase 2 studies which were multicenter, randomized, double-blind, placebo-controlled, parallel-group studies conducted in adult subjects with thrombocytopenia associated with CLD. E5501-G000-202 (Study 202) was conducted in the United States and E5501-J081-204 (Study 204) was conducted in Japan. These studies, in addition to Studies 310 and 311, served as part of the supportive safety data for avatrombopag in the proposed indication. An independent FDA analysis was not performed, because the studies used a different formulation of avatrombopag (1st generation formulation) as well as a different dosing regimen.

Table 12: Clinical Trials Relevant to this NDA

Trial and Status	Trial Design	Regimen/Schedule/Route	Primary Endpoint	Treatment Duration and Follow Up	No. of Patients Enrolled	Study Population	Countries and No. of Sites
Controlled Studies to Support Efficacy and Safety							
E5501-G000-310 (Study 310)	**Phase 3 Study** Randomized, double-blind, placebo-controlled, parallel-group study	Once daily dosing with a meal as follows: **Low Baseline Platelet Count Cohort** ($<40\times10^9$/L) • 60 mg avatrombopag (3×20-mg tablets) • Placebo (3×20-mg matching placebo tablets) **High Baseline Platelet Count Cohort** (≥40 to $<50\times10^9$/L) • 40 mg avatrombopag (2×20-mg tablets) • Placebo (2×20-mg matching placebo tablets)	Proportion of patients who did not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following a procedure	Subjects were treated for 5 days consecutively with once daily dosing of avatrombopag Subjects were followed until Study Day 35	**Low Baseline Platelet Count Cohort** (Placebo): 48 entered, 46 completed **Low Baseline Platelet Count Cohort** (Avatrombopag 60 mg): 90 entered, 85 completed **High Baseline Platelet Count Cohort** (Placebo): 34 entered, 32 completed **High**	Thrombocytopenia in Chronic Liver Disease	Argentina (1), Australia (2), Austria (2) Belgium (2), Brazil (2), Canada (2), China (3), France (3), Germany (3), Hungary (4), Italy (5), Republic of Korea (13), Poland (4), Portugal (2), Spain (4), Taiwan (5), Thailand (4), United Kingdom (2), United States (12)

					Baseline Platelet Count Cohort (Avatromb opag 40 mg): 59 entered, 55 completed		
E5501-G000-311 (Study 311)	**Phase 3 Study** Randomized, double-blind, placebo-controlled, parallel-group study	Once daily dosing with a meal as follows: **Low Baseline Platelet Count Cohort** ($<40\times10^9$/L) • 60 mg Avatrombopag (3×20-mg tablets) • Placebo (3×20-mg matching placebo tablets) **High Baseline Platelet Count Cohort** (≥40 to $<50\times10^9$/L) • 40 mg Avatrombopag (2×20-mg tablets) • Placebo (2×20-mg matching placebo tablets)	Proportion of patients who did not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following a procedure	Subjects were treated for 5 days consecutively with once daily dosing of avatrombopag Subjects were followed until Study Day 35	**Low Baseline Platelet Count Cohort** (placebo): 43 entered, 37 completed **Low Baseline Platelet Count Cohort** (Avatromb opag 60 mg): 70 entered, 68 completed **High Baseline Platelet Count Cohort** (Placebo): 33 entered, 31 completed	Thrombocytopenia in Chronic Liver Disease	Argentina (3), Australia (3), Belgium (3), Brazil (1), China (2), Czech Republic (2), France (3), Germany (2), Israel (7), Italy (7), Japan (16), Mexico (5), Romania (4), Russia (4), Spain (1), United States (11)

					High Baseline Platelet Count Cohort (Avatrombopag 40 mg): 58 entered, 55 completed		

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7.2. Review Strategy

The key materials used for the review of efficacy and safety included:

- NDA datasets (raw and derived), clinical study reports, and responses to the review team's information requests.
- Relevant published literature.
- Relevant information in the public domain.

Clinical data was provided in the Clinical Data Interchange Standards Consortium (CDISC) Foundational Standards SDTM (Study Data Tabulation Model) and ADaM (Analysis Data Model Implementation). Also submitted were the define files for the variables and the corresponding SAS programs for the primary ADaM data derivation to document the analysis results. The reviewers were able to duplicate the analysis results based on the applicant's submitted datasets.

This review was primarily based on analyses of Studies 310 and 311. These two trials provide efficacy and safety data for 231 and 204 patients respectively, who received the proposed marketing doses of avatrombopag or placebo treatment. Results were presented in a pooled fashion utilizing the two studies.

Results from the phase 3 controlled trials (Studies 310 and 311) listed in Table 3 were used in the analysis of safety. The review emphasis was placed on the avatrombopag 40 mg and 60 mg doses administered once daily for 5 days 10-13 days prior to a procedure proposed for marketing.

Sections 6 and 7 of this Review were performed jointly by Dr. Laurel Menapace, MD and Dr. Yaping Wang, PhD. Analysis by Dr. Wang was performed using SAS 9.4 (SAS Institute, Inc.).

Analyses by Dr. Menapace were performed utilizing JMP 13.0 (SAS Institute, Inc.) and JMP Clinical 6.1. The clinical safety review was conducted with assistance of the FDA Internal JMP Start Program. The JMP Start Program provided information regarding overall data fitness and integrity of the sponsor's submitted datasets as well as preliminary safety findings which were subsequently validated by Dr. Menapace. MedDRA Adverse Events Diagnostic (MAED) 1.3 (Clinical Trials and Surveys Corporation & FDA) was used to assess safety signals. Unless specifically referenced, all analyses and presentation of findings are the work of FDA reviewers.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study 310

Trial Design

Study 310 was an international, multicenter, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy of once daily oral avatrombopag versus placebo treatment in patients with thrombocytopenia and a history of concomitant CLD scheduled to undergo a procedure with associated bleeding risk. The study was conducted at 75 sites in the following countries: Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, France, Germany, Hungary, Italy, Republic of Korea, Poland, Portugal, Spain, Taiwan, Thailand, United Kingdom, and the United States.

The study enrolled adult male and female patients aged 18 years or older with severe thrombocytopenia (platelet count <50,000/µL), a history of concomitant CLD with a MELD score of 24 or less, who were scheduled to undergo a procedure that would typically require platelet transfusion unless there was a clinically significant increase in platelet count from baseline.

The key inclusion criteria were as follows:

- Adults with CLD and MELD score ≤ 24 scheduled to undergo an elective procedure and would require a platelet transfusion
- Mean baseline platelet count < 50,000/µL

The key exclusion criteria were as follows:

- Screening doppler ultrasound with portal vein blood flow velocity rate < 10 cm/second
- History of prior arterial or venous thrombosis, including partial or complete thrombosis
- History of main portal vein, portal vein branches, or splenic mesenteric system thrombosis, including partial or complete thrombosis
- Poorly controlled hepatic encephalopathy
- HCC staging classification C or D as per the Barcelona-Clinic Liver Cancer Staging System
- History of malignancy other than HCC
- Use of any anticoagulant (heparin, warfarin), antiplatelet (aspirin, ticlopidine or glycoprotein IIa/IIIb antagonists), verapamil, or non-steroidal anti-inflammatory drug (NSAID) within 7 days of screening
- Use of erythropoietin stimulating agent (ESA) within 7 days or interferon (IFN)

within 14 days of screening
- Use of eltrombopag or romiplostim
- Clinically significant acute or active bleeding
- Platelet transfusion or use of blood products, other than red blood cell transfusion, within 7 days of screening
- History of HIV infection
- Alcohol or drug abuse within 6 months of enrollment
- Other primary hematologic disorders (ITP, MDS, etc.)
- History of genetic prothrombotic syndromes (Factor V Leiden, ATIII Deficiency, etc.)
- New York Heart Association Grade III or IV heart failure or arrhythmia
- History of liver transplant
- Hemoglobin (Hgb) ≤ 8.0 g/dL or ≥ 18.0 g/dL for men and > 15.0 g/dL for women, or a hematocrit ≥ 54% for men or ≥ 45% for women at screening
- Female patients who were pregnant or lactating
- Female patients of reproductive potential who did not agree to the use of highly effective contraceptive methods during the entire study

The study consisted of a screening period from Day -14 through Day -1, a baseline, treatment and procedure period from Day 1 to Day 13, and a follow-up period which consisted of 2 follow-up visits scheduled 7 days after the procedure and 30 days after the last dose of study drug. The procedure day occurred 5 to 8 days after the last dose of study drug was administered (Study Days 10-13, respectively).

Baseline platelet counts were measured on two separate occasions during the screening period at least one day apart with neither platelet count measuring greater than 60,000/µL to meet study eligibility criteria. The mean of these two platelet counts (mean baseline platelet count) was used for study entry and was defined as < 50,000/µL.

Subjects were randomized in a 2:1 fashion to avatrombopag (2nd generation formulation) or matched placebo (PBO). Randomization occurred via an interactive voice and web response system (IxRS). Patients with mean baseline platelet counts <40,000/µL received oral avatrombopag 60 mg once daily (3 x 20 mg tablets) or PBO on study Days 1-5. Patients with baseline platelet counts between 40,000/µL to <50,000/µL received oral avatrombopag 40 mg once daily (2 x 20 mg tablets) or PBO on study Days 1-5. The rationale for differential dosing was to identify a dosing regimen that would result in approximately 90% of patients achieving a platelet count of at least 50,000/µL during the scheduled procedure window period and to minimize the number of patients reaching a platelet count of 200,000/µL or greater during the study period. Study drug or PBO was administered with a meal once daily during days 1-5. All subjects received a dosing diary in which they recorded the dates and times of their study drug doses. Clinical research associates reviewed compliance at each study visit and at study completion.

Erythropoietin stimulating agents were prohibited throughout the study. IFN use was prohibited during the study; however, at the investigator's discretion, subjects could

restart IFN therapy if clinically indicated during the follow-up phase after Visit 4. Eltrombopag, romiplostim, heparin, warfarin, NSAIDs, aspirin, verapamil, estrogen, and antiplatelet therapy with ticlopidine or glycoprotein IIb/IIIa antagonists (e.g., tirofiban) were prohibited per study protocol. Aspirin, for antiplatelet therapy, could be prescribed at the discretion of the investigator in subjects in which the platelet count rose and who were believed to have an increased risk of thrombosis. In subjects where use of aspirin was contraindicated, alternate antiplatelet therapy such as a platelet adenosine diphosphate (ADP) receptor inhibitor (e.g., clopidogrel) could be prescribed.

Platelet counts were assessed on Day 4 (Visit 3), Day 10-13 (Visit 4, Procedure Day), 7 days post-procedure (Visit 5) and on Day 35 (Visit 6). At select sites, blood samples from a subset of patients were collected on Day 1 (Visit 2) before dosing (baseline), on Day 4 (Visit 3) and on Procedure Day (Days 10-13) for platelet function assays (PFAs).

Patients were stratified according to hepatocellular cancer (HCC) status (yes or no) and risk of bleeding associated with the elective procedure (low, moderate, or high). Level of risk associated with a given procedure was established utilizing key opinion leader input, the Standards of Practice Committee with Cardiovascular and Interventional Radiological Society of Europe endorsement, and consensus guidelines for periprocedural management of coagulation and hemostasis risk in percutaneous image-guided interventions. It was pre-specified that no fewer than 10% of enrolled subjects were to be enrolled into the high-risk procedure cohort and no more than 60% of subjects would be enrolled into the low risk procedure cohort.

The following were the permitted procedures and respective assigned procedure bleeding risk levels:

Low Bleeding Risk: Paracentesis, thoracentesis, gastrointestinal (GI) endoscopy with or without biopsy, esophageal variceal banding, colonoscopy, polypectomy

Moderate Bleeding Risk: Liver biopsy, ethanol ablation or chemoembolization for hepatocellular carcinoma (HCC), bronchoscopy with or without biopsy

High Bleeding Risk: Vascular catheterization (including right sided procedures in the setting of pulmonary hypertension), transjugular intrahepatic portosystemic shunt (TIPS), biliary interventions, renal biopsy, nephrostomy tube placement, radiofrequency ablation, laparoscopic interventions, dental procedures

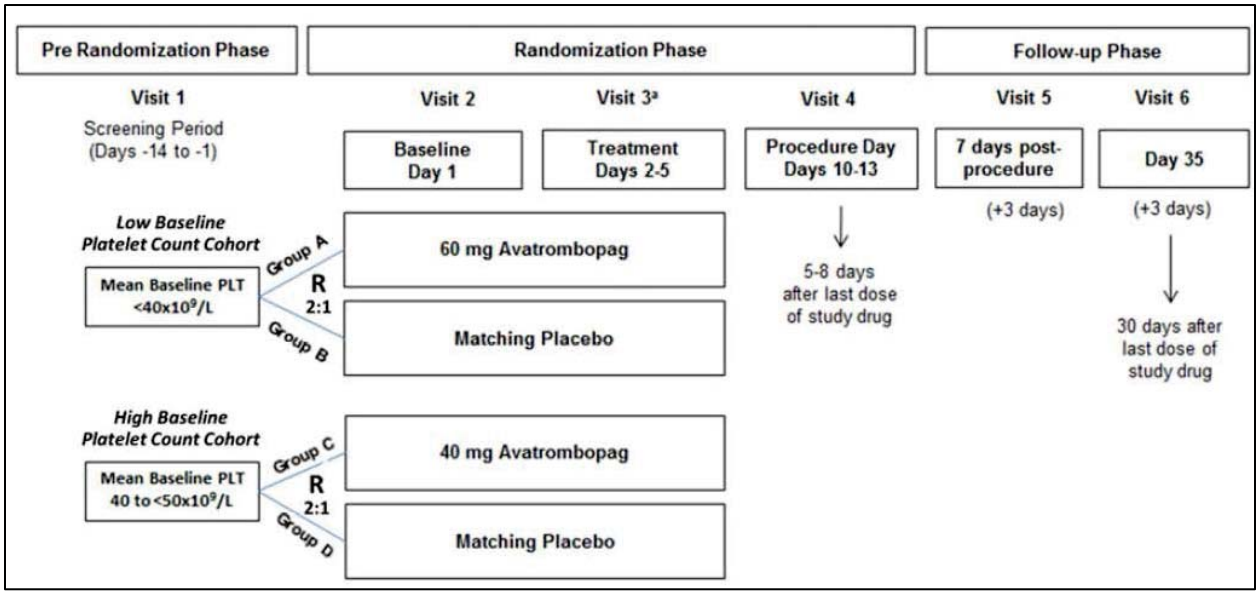
Patients with an international normalized ratio (INR) greater than 1.6 on the day of a scheduled procedure (Visit 4) received Fresh Frozen Plasma (FFP) or standard of care to reverse liver induced coagulopathy.

All subjects who obtained a platelet count ≥200,000/µL on the day of the procedure were

required to have a doppler ultrasound assessment of portal vein blood flow at Visit 5. If portal vein thrombus (PVT) was suspected based on doppler ultrasonography, further imaging with computerized tomography (CT) scan or magnetic resonance imaging (MRI) was performed.

The following figure depicts the study design.

Figure 3: Study 310 Schema



Source: Figure reproduced from Applicant's Integrated Summary of Efficacy (ISE), Figure 2.7.4.2

Study Endpoints

Efficacy measurements in Study 310 included platelet counts as measured at screening (Day -14 to -1), baseline (Visit 1), Day 4, Procedure Day (Days 10-13), 7 days post-procedure (Visit 5), and on Day 35 (Visit 6) as well as the number of transfusions administered, any rescue procedure performed for bleeding, and the occurrence of bleeding as measured by the World Health Organization (WHO) Bleeding Score and Bleeding Academic Research Consortium (BARC) score.

The incidence of platelet transfusions was monitored from randomization and the number of transfusions administered (if used), date(s), and start/stop times were recorded in the CRF. Any rescue procedure initiated for bleeding was monitored from randomization and recorded in the CRF. Any observed bleeding event on study was assessed by the clinical investigator utilizing the WHO Bleeding and BARC scores.

The following were considered recue procedures to manage risk of bleeding associated with a procedure: whole blood transfusion, packed red blood cell (RBC) transfusion, platelet transfusion, fresh frozen plasma (FFP) or cryoprecipitate administration, Vitamin

K, desmopressin, recombinant activated factor VII, aminocaproic acid, tranexamic acid, or surgical or interventional radiology procedures performed to achieve hemostasis and control blood loss.

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

Responders were defined as the subjects who did not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following a scheduled procedure.

The proportion of responders was tested between the individual avatrombopag treatment groups (60 mg or 40 mg) and matching placebo within each respective platelet count cohort (low baseline platelet count cohort or high baseline platelet count cohort) each at a significance level of α=0.05, using the generalized Cochran-Mantel-Haenszel test adjusting for risk of bleeding associated with the scheduled procedure (low, moderate, or high).

The secondary efficacy endpoints included:

- The proportion of patients who achieved platelet counts of >50,000/µL on the day of procedure (Visit 4)
- Change from baseline in platelet count on the day of procedure (Visit 4)

An exploratory endpoint included the proportion of subjects with a World Health Organization (WHO) bleeding score ≥2 after randomization and up to 7 days following the procedure.

Safety assessments included monitoring and recording of all AEs and SAEs that occurred on study, including bleeding events, complications secondary to platelet transfusion(s), routine hematologic laboratory evaluations, serum chemistry and urine values, periodic vital sign and ECG monitoring, as well as physical examinations and doppler ultrasonography. AEs were graded on a 5-point scale according to CTCAE 4.0. All AEs were followed for 30 days after the patient's last dose of study drug or until resolution, whichever came first. SAEs were followed to resolution, or if resolution was not expected, stabilization. AEs of special interest (AESIs) were pre-specified as reoccurrence of thrombocytopenia (defined as a platelet count <10 x 10^9/L or less than 10 x 10^9/L less than the baseline platelet count within 30 days of discontinuation), thromboembolic events, and bleeding events (WHO Grade 2 to 4). An independent Data and Safety Monitoring Board (DSMB) monitored all safety data in the study.

At select study sites, platelet activation was assessed by measuring platelet surface activated glycoprotein (GP) IIb-IIIa and platelet surface P-selectin on circulating activated platelets. Platelet reactivity was assessed by the platelet response to low and high concentrations of adenosine diphosphate (ADP) and low and high thrombin receptor activating peptide (TRAP).

The applicant's schedule of procedures and assessments for Study 310 is listed below for reference.

Table 13: Schedule of Procedures and Assessments in Study 310

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

Phase	Prerandomization	Randomization			Follow-Up	
Period	Screening	Baseline	Treatment	Procedure Day	Postprocedure	
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)
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 = pharmacokinetics, TPO = thrombopoietin, WHO = World Health Organization.

a Subjects underwent their scheduled procedure within 5 to 8 days of their last dose of study drug (ie, Study Day 10 to 13), and after completing the Procedure Day assessments.

b Visit 4 (Procedure Day) assessments also occurred when any subject had been withdrawn or discontinued early from the study for any reason.

c Visit 6 (Day 35) assessments also occurred when any subject had 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 was to be recorded at Screening (Visit 1) only.

g Hematology was to be taken prior to any platelet transfusion

h Independent platelet counts performed by a local laboratory at Screening and Baseline were to be at least 1 day apart with neither platelet count greater than 60×10^9/L. The mean of these 2 platelet counts (mean Baseline platelet count) were to be less than 50×10^9/L (as per Inclusion Criterion #2), to be eligible to participate in the study.

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

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

k Portal vein flow velocity was to be assessed at this visit. Subjects were had to have a main portal vein blood flow velocity rate of equal or greater than 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, were recorded, and the mean of the 3 values recorded as the final reading. The Doppler sonography and flow rate assessment were to be completed at any time during the Screening Period with results available prior to randomization.

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

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

n Any rescue procedures for bleeding, including number of transfusions administered (if used), along with start and end dates/times, were to be recorded.

o Platelet function tests were to be performed at selected sites. Flow cytometry was to be performed at Visits 2, 3, and 4. Platelet aggregometry was to be performed on Day -14 to 1 (Visit 1 or 2) before dosing and on the Procedure Day (Day 10).

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

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

Source: Figures and footnotes reproduced from Study Report Body for Study E5501-G000-310, Section 5.3.5.1, Table 3

Routine laboratory evaluations conducted on the study are listed in the following table.

Table 14: Study 310 Routine Laboratory Evaluations

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)

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

a: Performed only at selected sites. Results are addressed in a separate platelet function test report.

Source: Figure reproduced from Study Report Body for Study E5501-G000-310, Section 5.3.5.1, Table 2

Statistical Analysis Plan

Definitions of Analysis Sets

Full Analysis Set (FAS): the group of all randomized subjects. The FAS was analyzed "as randomized."

Per Protocol Analysis Set (PPAS): the group of all randomized patients who received protocol-assigned study drug and did not meet any of the following criteria:

- Patients who had any major protocol violations (major inclusion/exclusion violations or other major protocol violations that impact the evaluation of efficacy)
- Patients who used a prohibited concomitant medication that affected the assessment of study endpoints
- Patients who were noncompliant in terms of study medication

- Baseline platelet count of greater than 50×10^9/L
- Patients who were enrolled in the study despite not being planned for transfusion even in the event of no significant increase of platelet count
- Took prohibited prior medications or prior transfusion
- Presence of significant bleeding at Baseline
- Did not have a protocol permitted procedure on Days 8 to 15.
- Received a dose different than intended dose
- Patient received platelet transfusion before knowing the Visit 4 platelet count
- Patient refused platelet transfusion

The PPAS was analyzed "as randomized."

Safety Analysis Set: the group of patients who received at least 1 dose of study drug and had at least 1 post-dose safety assessment. This set was analyzed "as treated."

Analysis of Primary Endpoint

The FAS was used as the primary population for the efficacy analyses, while the PPAS was used as one of the supportive, sensitivity analyses.

The null hypothesis for the primary efficacy endpoint was that the proportion of patients not requiring a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following a scheduled procedure was the same between the avatrombopag and placebo treatment groups.

- For patients in the Low Baseline Platelet Count Cohort, the treatment comparison was carried out between the 60 mg avatrombopag treatment group and its matching placebo.
- For patients in the High Baseline Platelet Count Cohort, the treatment comparison was carried out between the 40 mg avatrombopag treatment group and its matching placebo.

The difference of proportion of patients not requiring a platelet transfusion or any rescue procedure for bleeding was tested at a two-side significance level of α=0.05, using the generalized Cochran-Mantel-Haenszel (CMH) test adjusting for the risk of bleeding associated with the scheduled procedure (low, moderate, or high). Since HCC status was included in the randomization stratification for safety purposes only, not for efficacy consideration, HCC was not included in the adjustment for the CMH model for the primary efficacy analysis.

This phase 3 study was to be considered positive if statistical significance was achieved for the primary efficacy endpoint for both baseline platelet count cohorts.

Patients with missing information about the primary efficacy outcome due to early withdrawal or other reasons were considered as having received a transfusion, i.e., a Non-Responder, for the primary analysis.

Sensitivity Analysis: The following sensitivity analyses were conducted:

- Per Protocol Analysis: The same primary efficacy analyses were repeated on the PPAS.
- Observed Case Analysis: Efficacy analyses repeated on "observed data"; excluded subjects with missing primary efficacy data.
- Fisher's Exact Test: Efficacy analyses repeated on the FAS using Fisher's Exact Test.
- Modified Primary Efficacy Endpoint Analysis: Efficacy analysis on the FAS for the proportion of patients who did not require a platelet transfusion after randomization and up to 7 days following a scheduled procedure. This analysis excluded patients who received other rescue procedures for bleeding.

Subgroup Analysis: The primary efficacy endpoint was also assessed for each of the subgroups listed below:

- Age group (<65 and ≥65 years old)
- Sex (male and female)
- Race (White, Black, Asian)
- Geographic region

Analysis of Secondary Endpoint(s)

There were 2 secondary efficacy endpoints:

- Proportion of Responders defined as patients who achieved the target platelet counts of equal or greater than 50×10^9/L on Procedure Day (prior to receiving a platelet transfusion or undergoing the scheduled procedure).
- Change in platelet count from Baseline to Procedure Day (prior to receiving a platelet transfusion or undergoing the scheduled procedure)

The analysis of efficacy endpoints followed a sequential gatekeeping testing procedure was followed to analyze efficacy endpoints, with the multiplicity adjustment to control the Type I error rate at significance level $\alpha = 0.05$. The secondary efficacy endpoints were only to be analyzed if the primary efficacy endpoint was statistically significant for both Baseline platelet count cohorts.

The proportion of patients who achieved the target platelet count of equal to or greater than 50×10^9/L on the Procedure Day was analyzed first, as the first secondary efficacy endpoint. It was analyzed within each Baseline platelet count cohort, each at a significance level of $\alpha=0.05$

using the generalized CMH test adjusting for the risk of bleeding associated with the scheduled procedure (low, moderate, or high).

The 95% CI for the proportion of subjects with platelet counts of equal to or greater than 50×10^9/L on the Procedure Day was calculated for each treatment group within each Baseline platelet count cohort. In addition, the 95% CI for the treatment difference was also provided within each Baseline platelet count cohort using the normal approximation method. Patients with a missing platelet count on Procedure Day were considered as not achieving the platelet count of equal to or greater than 50×10^9/L in this analysis.

The second secondary efficacy endpoint, the change in platelet count from Baseline to Procedure Day, was analyzed only if the test for the first secondary efficacy endpoint was statistically significant for both Baseline platelet count cohorts. The change from Baseline in platelet count was analyzed using the Wilcoxon Rank Sum Test separately within each Baseline platelet count cohort ($<40\times10^9$/L or ≥40 to $<50\times10^9$/L), each at a significance level of $\alpha=0.05$. Last observation carried forward (LOCF) was used for analysis of platelet count change from Baseline to procedure day.

Determination of Sample Size

The phase 3 protocol was originally designed to enroll a total of 300 patients, with 200 subjects in the avatrombopag treatment groups and 100 subjects in the placebo treatment groups. It was anticipated that this study would enroll roughly 150 subjects into each of the 2 Baseline platelet count cohorts. This sample size was based on comparisons of the primary efficacy endpoint between treatment groups. The response rate in the placebo treatment group was expected to be 18%, based on the clinical consensus of study PIs and published results of a similar TPO receptor agonist in adults with thrombocytopenia associated with CLD (Eltrombopag Evaluated for its Ability to overcome Thrombocytopenia and Enable procedures [ELEVATE] study). The hypothesized treatment group difference was based on platelet count changes observed in the avatrombopag phase 2 study (E5501-G000-202), and dose-response modeling using data from that study and other studies in the avatrombopag clinical development program. As originally sized, the study had greater than 99% power and a two-sided type-I error of $\alpha=0.05$ for the assessment of efficacy.

The sample size was reduced from 300 to 200 patients (Protocol Amendment 04), given the low reported incidence of AESI. The power can still be maintained at no less than 90% for the primary efficacy endpoint after the sample size reduction. Within each baseline platelet count cohort, the reduced sample size of 100 randomized patients (avatrombopag: 67; placebo: 33) retained greater than 90% power to detect an absolute difference of 35% between the avatrombopag response rate and the projected 18% placebo response rate, using Fisher's Exact tests with a 2-sided $\alpha = 0.05$.

Protocol Amendments

Four amendments to the original protocol (dated March 21, 2013) were made by the applicant. A summary of significant changes made to the protocol is provided below.

Table 15: Review of Study 310 Protocol Amendments

Date	Amendment(s)
December 2, 2016	• Sample size reduced from approximately 300 patients to approximately 200 patients after consultation with the FDA that the current study had reached adequate enrollment to demonstrate the safety and efficacy of avatrombopag • The secondary endpoint, proportion of patients with a World Health Organization (WHO) bleeding score ≥2 after randomization and up to 7 days following an elective procedure, was changed to an exploratory endpoint given the low occurrence of bleeding events observed
May 31, 2016	• Clarification to Inclusion Criteria #3: replaced the word "change" with the word "increase" as per FDA request
June 22, 2015	• Ongoing study observations, supported by key opinion leader (KOL) review and current literature review resulted in additional updates in the bleeding risk categories classification • Clarification of Inclusion #3 that patients 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 • 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. Patients who screen failed previously were permitted to rescreen due to removal of these criteria. • Addition of eltrombopag and romiplostim as prohibited medications • Added an evaluation for platelet aggregation measurement at select sites
November 12, 2013	• Tranexamic acid was defined as a rescue procedure when used specifically for bleeding • Specific genetic prothrombotic syndromes (Factor V Leiden; prothrombin G20210A; ATIII deficiency etc.) were added to exclusion criteria

Source: FDA Table generated from Protocol and Protocol Amendments for Study E5501-G000-310, Section 5.3.5.1

Study Results

Compliance with Good Clinical Practices

The applicant provided attestation that this study was conducted in accordance with U.S. regulations governing the protection of human patients, Institutional Review Boards, and the obligations of clinical investigators in accordance with good clinical practice (GCP).

Financial Disclosure

Patient Disposition

A total of 370 patients signed informed consent for Study 310. Of these patients, there were 139 screen failure and 231 patients were randomized into the study. The majority of screen failures did not meet the study inclusion and exclusion criteria (n=120, 32.4%). Other reasons for screening failure included withdrawal of consent and AEs.

A total of 138 (59.7%) and 93 (40.3%) patients were randomized into the low and high baseline platelet count cohorts, respectively.

A total of 149 patients were randomized to receive avatrombopag treatment in the two baseline platelet count cohorts. 98.7% of patients randomized to avatrombopag were treated (147/149) and 95.2% (140/149) completed the study. Of the 82 patients randomized to placebo, 97.6% (80/82) were treated and 97.5% (78/80) completed the study.

Table 16: Study 310 Disposition by Treatment Arm

	Low Baseline Platelet Cohort				High Baseline Platelet Cohort			
N (%)	Placebo (N=48)		60 mg Avatrombopag (N=90)		Placebo (N=34)		40 mg Avatrombopag (N=59)	
Informed Consent Obtained	48	100.00	90	100.00	34	100.00	59	100.00
Randomized	48	100.00	90	100.00	34	100.00	59	100.00
Completed	46	95.83	85	94.44	32	94.12	55	93.22
Withdrawal By Subject	1	2.08	3	3.33	1	2.94	1	1.69
Lost To Follow-Up	0	0.00	0	0.00	1	2.94	3	5.08
Adverse Event	0	0.00	2	2.22	0	0.00	0	0.00
Other	1	2.08	0	0.00	0	0.00	0	0.00

Source: FDA Reviewer JMP Clinical 6.1 Analysis

Protocol Violations/Deviations

A total of 56 patients (56/231, 24.2%) on the study had major protocol violations. The most common violation on the study was that enrolled patients never underwent an elective procedure. This included 4.0% (6/149) of patients in the combined avatrombopag treatment group and 9.8% (8/82) patients in the combined placebo group.

Other common violations on the study included administration of platelet transfusions despite a significant increase in platelet count prior to a procedure and in patients who did not have a clinically significant increase in platelet count prior to a procedure, omitting platelet transfusion(s) on the day of the procedure. This included 5.4% (8/149) patients in the combined avatrombopag treatment group; no patients in the combined placebo treatment group had such violations. These patients were removed from the PPAS analysis of the primary efficacy endpoint.

Demographic Characteristics

The overall mean (SD) age was 56.3 (10.06) years with a higher proportion of male patients (158, 68.4% patients) compared to female patients (73, 31.6%). The majority of patients were White, followed by Asian patients. The majority of patients were from Europe and Asia,

followed by the US.

Table 17: Trial 310 Demographic Characteristics; All Treated Analysis Set

Demographic Parameters	Low Baseline Platelet Cohort		High Baseline Platelet Cohort	
	Placebo (N=48)	**Avatrombopag 60 mg (N=90)**	**Placebo (N=34)**	**Avatrombopag 40 mg (N=59)**
Sex (N, %)				
Male	32 (66.7)	65 (72.2)	24 (70.6)	37 (62.7)
Female	16 (33.3)	25 (27.8)	10 (29.4)	22 (37.3)
Age				
Mean years (SD)	55.1 (11.02)	55.6 (9.12)	57.8 (11.05)	57.5 (10.06)
Median (years)	55.0	57.0	59.0	58.0
Min, max (years)	25, 76	29, 78	30, 76	19, 77
Age Group (N, %)				
< 65 years	41 (85.4)	77 (85.6)	24 (70.6)	44 (74.6)
≥ 65 years	7 (14.6)	13 (14.4)	10 (29.4)	15 (24.8)
Race (N, %)				
White	28 (58.3)	50 (55.6)	19 (55.9)	31 (52.5)
Black or African American	0 (0.0)	3 (3.3)	0 (0.0)	2 (3.4)
Asian	18 (37.5)	32 (35.6)	15 (44.1)	24 (40.7)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other[1]	2 (4.2)	1 (1.1)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	4 (4.4)	0 (0.0)	2 (3.4)
Ethnicity (N, %)				
Hispanic or Latino	10 (20.8)	10 (11.1)	3 (8.8)	7 (11.9)
Not Hispanic or Latino	37 (77.1)	77 (85.6)	31 (91.2)	51 (86.4)
Missing	1 (2.1)	3 (3.3)	0 (0.0)	1 (1.7)
Region (N, %)				
United States	10 (20.8)	21 (23.3)	6 (17.6)	10 (16.9)
Europe	18 (37.5)	31 (34.4)	12 (35.3)	24 (40.7)
East Asia	17 (35.4)	30 (33.3)	15 (44.1)	24 (40.7)
Rest of World	3 (6.3)	8 (8.9)	1 (2.9)	1 (1.7)

Source: Table derived from Applicant's Integrated Summary of Efficacy (ISE) and FDA Reviewer JMP Clinical 6.1 Analysis

In general, the distribution of baseline characteristics was comparable between treatment arms, except for an imbalance in the baseline disease etiology in the high baseline platelet count cohort (more patients had chronic viral hepatitis in the avatrombopag arm while more patients in control arm had alcoholic liver disease).

The majority of enrolled patients had a history of CLD secondary to chronic viral hepatitis (143 patients, 62.7%), followed by other causes of CLD (38 patients, 16.7%), and alcoholic liver

disease (33 patients, 14.5%). Of the patients with chronic viral hepatitis, the majority had chronic hepatitis C as demonstrated in the table below.

The majority of patients did not have a concomitant diagnosis of HCC (status of 'no', 173 patients, 75.5%).

For the low baseline platelet count cohort, the mean baseline platelet counts for the avatrombopag and placebo groups were similar, 31.1×10^9/L and 30.7×10^9/L, respectively. For the high baseline platelet count cohort, the mean baseline platelet counts for the avatrombopag and placebo groups were also similar, 44.3×10^9/L and 44.9×10^9/L, respectively.

Table 18: Trial 310 Baseline Characteristics; All Treated Analysis Set

Baseline Characteristics	Low Baseline Platelet Cohort		High Baseline Platelet Cohort	
	Placebo (N=48)	**Avatrombopag 60 mg (N=90)**	**Placebo (N=34)**	**Avatrombopag 40 mg (N=59)**
Disease Etiology, (N, %)				
Alcoholic liver disease	7 (14.6)	13 (14.6)	2 (5.9)	11 (19.3)
Chronic viral hepatitis	30 (62.5)	50 (56.2)	27 (79.4)	36 (63.2)
Chronic hepatitis B	10 (20.8)	14 (15.7)	8 (23.5)	14 (24.6)
Chronic hepatitis C	20 (41.7)	36 (40.4)	19 (55.9)	21 (36.8)
Chronic hepatitis B and C	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)
Nonalcoholic steatohepatitis	4 (8.3)	6 (6.7)	0 (0.0)	4 (7.0)
Other	7 (14.6)	20 (22.5)	5 (14.7)	6 (10.5)
Missing	0 (0.0)	1 (1.1)	0 (0.0)	2 (3.3)
Baseline Platelet Count (x 10^9/L)				
Mean	30.7 (7.1)	31.1 (7.3)	44.9 (3.1)	44.3 (2. 8)
Median	32.3	33.0	44.3	44.0
Range	11.5, 44.5	10, 40	40.5, 50.5	40, 49.5
HCC Status, (N, %)				
No	37 (77.1)	68 (76.4)	27 (79.4)	41 (70.7)
Yes	11 (22.9)	21 (23.6)	7 (20.6)	17 (29.3)
MELD Score (N, %)				
<10	19 (39.6)	31 (34.8)	15 (44.1)	19 (32.2)
≥10 to ≤14	20 (41.7)	44 (49.4)	16 (47.1)	28 (47.4)
>14	9 (18.8)	14 (15.7)	3 (8.8)	11 (18.6)
Missing	0 (0.0)	1 (1.1)	0 (0.0)	1 (1.7)

Source: Table derived from Applicant's Integrated Summary of Efficacy (ISE) and FDA Reviewer JMP Clinical 6.1 Analysis

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Nearly all patients in the combined avatrombopag treatment group (98%, 144/147 patients) and all patients in the combined placebo treatment group (100.0%, 80/80 patients) took

concomitant medications during the study.

The most common concomitant medications in the study included proton-pump inhibitors (pantoprazole, omeprazole, lansoprazole), lactulose, beta blockers, and potassium sparing diuretics.

Compliance rates were between 80% and 100% for almost all patients in the combined avatrombopag and placebo treatment groups (96.0% [143/149] patients and 97.6% [80/82] patients, respectively).

Efficacy Results – Primary Endpoint

In the Low Baseline Platelet Count Cohort (<40×10^9/L), the proportion of Responders was 65.6% (59/90) in the 60 mg avatrombopag treatment group compared to 22.9% (11/48) in placebo-treated patients. The treatment difference in the proportion of Responders (60 mg avatrombopag minus placebo) was 42.6% (95% CI [27.2%, 58.1%]), and was statistically significant with P <0.0001 by the CMH test (adjusted for bleeding risk associated with scheduled procedures).

In the High Baseline Platelet Count Cohort (≥40 to <50×10^9/L), the proportion of Responders was also larger in the 40 mg avatrombopag treatment group, 88.1% (52/59), compared to the placebo treatment group, 38.2% (13/34). The treatment difference (40 mg avatrombopag minus placebo) was 49.9% (95% CI [31.6%, 68.2%]), and was statistically significant favoring avatrombopag with P<0.0001 by the CMH test (adjusted for bleeding risk associated with scheduled procedures).

Table 19 Prop. of patients not requiring a platelet transfusion or any rescue procedure (Full Analysis Set)

	Low baseline PLT count cohort		High baseline PLT count cohort	
	Placebo N = 48	Avatrombopag 60 mg, N = 90	Placebo N = 34	Avatrombopag 40 mg, N = 59
Responder, n (%)	11 (22.9)	59 (65.6)	13 (38.2)	52 (88.1)
95% CI	(11.0, 34.8)	(55.7, 75.4)	(21.9, 54.6)	(79.9, 96.4)
Missing	5 (10.4)	5 (5.6)	2 (5.9)	3 (5.1)
95% CI of diff.		42.6 (27.2, 58.1)		49.9 (31.6, 68.2)
P-value (CMH)		<.0001		<.0001
P-value(Fisher's)		<.0001		<.0001

FDA reproduced the results from Applicant's data

Table 20 Prop. of patients not requiring a platelet transfusion or any rescue procedure (Sensitivity: worst scenario)

	Low baseline PLT count cohort		High baseline PLT count cohort	
	Placebo N = 48	Avatrombopag 60 mg, N = 90	Placebo N = 34	Avatrombopag 40 mg, N = 59
Responder, n (%)	16 (33.3)	59 (65.6)	15 (44.1)	52 (88.1)
95% CI	(20.0, 46.7)	(55.7, 75.4)	(27.4, 60.8)	(79.9, 96.4)
95% CI of diff.		32.2 (15.7, 48.8)		44.0 (25.4, 62.6)
P-value (CMH)		<.0001		0.0001
P-value(Fisher's)		<.0001		0.0003

FDA generated the results from Applicant's data

Reviewer's comments: FDA noticed differential missing data between treatment arm in the low baseline PLT cohort (10.4% vs 5.6%, respectively). However, the conclusions stay the same after worst-case calculation (assuming responders for patients with missing data in the placebo arm and non-responders for patients with missing data in the Avatrombopag arm).

Efficacy Results – Secondary and other relevant endpoints

The first secondary endpoint was the proportion of Responders, defined as patients who achieved platelet counts equal to or greater than the targeted 50×10^9/L on Procedure Day (Day 10 to Day 13).

In the Low Baseline Platelet Count Cohort ($<40\times10^9$/L), 68.9% (62/90) of the 60 mg avatrombopag-treated patients, and 4.2% (2/48) of patients who received placebo were Responders. The treatment difference (60 mg avatrombopag minus placebo) was 64.7% (95% CI [53.6%, 75.8%]), and was statistically significant with P <0.0001 by the CMH test (adjusted for bleeding risk associated with scheduled procedures).

Similarly, in the High Baseline Platelet Count Cohort (≥40 to $<50\times10^9$/L), 88.1% (52/59) of the 40 mg avatrombopag-treated patients, and 20.6% (7/34) of patients who received placebo were Responders. The treatment difference (40 mg avatrombopag minus placebo) was 67.5% (95% CI [51.6%, 83.4%]), and was statistically significant with P <0.0001 by the CMH test (adjusted for bleeding risk associated with scheduled procedures).

Table 21 Prop. of patients achieving platelet counts ≥ $50x10^9$/L on procedure day (Full Analysis Set)

	Low baseline PLT count cohort		High baseline PLT count cohort	
	Placebo N = 48	Avatrombopag 60 mg, N = 90	Placebo N = 34	Avatrombopag 40 mg, N = 59
Responder, n (%)	2 (4.2)	62 (68.9)	7 (20.6)	52 (88.1)
95% CI	(0.0, 9.8)	(59.3, 78.5)	(7.0, 34.2)	(79.9, 96.4)
Missing	6 (12.5)	10 (11.1)	3 (8.8)	3 (5.1)
95% CI of diff.		64.7 (53.6, 75.8)		67.5 (51.6, 83.4)
P-value (CMH)		<.0001		<.0001

FDA reproduced the results from Applicant's data

Table 22 Prop. of patients achieving platelet counts ≥ $50x10^9$/L on procedure day (Sensitivity: worst scenario)

	Low baseline PLT count cohort		High baseline PLT count cohort	
	Placebo N = 48	Avatrombopag 60 mg, N = 90	Placebo N = 34	Avatrombopag 40 mg, N = 59
Responder, n (%)	8 (16.7)	62 (68.9)	10 (29.4)	52 (88.1)
95% CI	(6.1, 27.2)	(59.3, 78.5)	(14.1, 44.7)	(79.9, 96.4)
95% CI of diff.		52.2 (38.0, 66.5)		58.7 (41.3, 76.1)
P-value (CMH)		<.0001		<.0001

FDA generated the results from Applicant's data

Reviewer's comments: The proportions of missing data appear small and comparable between treatment arms. The conclusions stay the same after worst case calculation (assuming responders for patients with missing data in the placebo arm and non-responders for patients with missing data in the Avatrombopag arm).

The second secondary endpoint was the change in platelet count from Baseline to Procedure Day (Day 10 to Day 13).

The mean change in Platelet count from Baseline to Procedure Day in the Low Baseline Platelet Count Cohort (<$40x10^9$/L) was $32.0x10^9$/L for the 60 mg avatrombopag treatment group compared to $0.8x10^9$/L for the placebo group. The treatment difference (60 mg avatrombopag minus placebo) in favor of avatrombopag was $27.5x10^9$/L (95% CI [22.5, 32.5]), and was statistically significant with P <0.0001 by the Wilcoxon Rank Sum Test.

In the High Baseline Platelet Count Cohort (≥40 to <50×10^9/L), the mean change from Baseline to Procedure Day was 37.1×10^9/L for the 40-mg avatrombopag treatment group compared to 1.0×10^9/L for the placebo group. The treatment difference (40 mg avatrombopag minus placebo) was 33.5×10^9/L (95% CI [25.5, 41.5]), and was statistically significant with P /<0.0001 by the Wilcoxon Rank Sum Test.

Table 23 Change from Baseline of platelet count on procedure day (Full Analysis Set)

Change from Baseline(x10^9/L)	Low baseline PLT count cohort		High baseline PLT count cohort	
	Placebo N = 48	Avatrombopag 60 mg, N = 90	Placebo N = 34	Avatrombopag 40 mg, N = 59
N	48	88	32	58
Mean (SD)	0.8 (6.36)	32.0 (25.53)	1.0 (9.30)	37.1 (27.41)
Median	0.5	28.3	0.0	33.0
Min, Max	-13, 17	-8, 139	-17, 33	-8, 131
Diff in Changes[†]		27.5		33.5
95% CI		(22.5, 32.5)		(25.5, 41.5)
P-value (Wilcoxon)		<.0001		<.0001

[†]Hodges Lehmann estimation

Reviewer's comments: Even though LOCF method is not recommended for the missing data imputation, due to small numbers of missing data in both cohorts, FDA considers the impact of using LOCF as the imputation method on the results may be minimum.

Additional Analyses Conducted on the Individual Trial

There were no additional analyses conducted for Study 310.

Table 24 Prop. of patients not requiring a platelet transfusion or any rescue procedure (Sensitivity: Per Protocol Analysis Set)

	Low baseline PLT count cohort		High baseline PLT count cohort	
	Placebo N = 36	Avatrombopag 60 mg, N = 77	Placebo N = 26	Avatrombopag 40 mg, N = 55
Responder, n (%)	7 (19.4)	55 (75.3)	7 (26.9)	52 (94.5)
95% CI	(6.5, 32.4)	(65.7, 55.0)	(9.9, 44.0)	(88.5, 100.0)

Missing	0	1 (1.3)	0	0
95% CI of diff.		55.9 (39.8, 72.0)		67.6 (49.5, 85.7)
P-value (CMH)		<.0001		<.0001

The subgroup analyses for the primary efficacy endpoints are presented by age, gender, ethnic subgroups and regions in the following tables. In general, there are more responders in the Avatrombopag arm cross all the subgroups.

Table 25 Summary of Proportion of Patients not Requiring a Platelet Transfusion or Any Rescue Procedure for Bleeding by Age Group (Full Analysis Set)

	Low baseline PLT count cohort		High baseline PLT count cohort	
	Placebo N = 48	Avatrombopag 60 mg, N = 90	Placebo N = 34	Avatrombopag 40 mg, N = 59
< 65 Years old				
Responder, n (%)	8 (19.5)	51 (66.2)	9 (37.5)	39 (88.6)
95% CI	(7.4, 31.6)	(55.7, 76.8)	(18.1, 56.9)	(79.3, 98.0)
95% CI of diff.		46.7 (30.6, 62.8)		51.1 (29.6, 72.6)
>= 65 to < 75 Years old				
Responder, n (%)	2 (33.3)	8 (66.7)	4 (50.0)	12 (85.7)
95% CI	(0.0, 71.1)	(40.0, 93.3)	(15.4, 84.6)	(67.4, 100.0)
95% CI of diff.		46.7 (-12.9, 79.5)		35.7 (-3.5, 74.9)
>= 75 Years old				
Responder, n (%)	1 (100)	0	0	1 (100)
95% CI	(100.0, 100.0)	(0.0, 0.0)	(0.0, 0.0)	(100.0, 100.0)

FDA reproduced the results from Applicant's data

Table 26 Summary of Proportion of Patients not Requiring a Platelet Transfusion or Any Rescue Procedure for Bleeding by Sex (Full Analysis Set)

	Low baseline PLT count cohort		High baseline PLT count cohort	
	Placebo N = 48	Avatrombopag 60 mg, N = 90	Placebo N = 34	Avatrombopag 40 mg, N = 59
Male				
Responder, n (%)	8 (25.0)	41 (63.1)	9 (37.5)	33 (89.2)
95% CI	(10.0, 40.0)	(51.3, 74.8)	(18.1, 56.9)	(79.2, 99.2)
95% CI of diff.		38.1 (19.0, 57.1)		51.7 (29.9, 73.5)
Female				
Responder, n (%)	3 (18.8)	18 (72.0)	4 (40.0)	19 (86.4)
95% CI	(0.0, 37.9)	(54.4, 89.6)	(9.6, 70.4)	(72.0, 100.0)
95% CI of diff.		53.3 (27.3, 79.2)		46.4 (12.8, 79.9)

FDA reproduced the results from Applicant's data

Table 27 Summary of Proportion of Patients not Requiring a Platelet Transfusion or Any Rescue Procedure for Bleeding by Race (Full Analysis Set)

	Low baseline PLT count cohort		High baseline PLT count cohort	
	Placebo N = 48	Avatrombopag 60 mg, N = 90	Placebo N = 34	Avatrombopag 40 mg, N = 59
White				
Responder, n (%)	7 (25.0)	34 (68.0)	9 (47.4)	30 (96.8)
95% CI	(9.0, 41.0)	(55.1, 80.9)	(24.9, 69.8)	(90.6, 100.0)
95% CI of diff.		43.0 (22.4, 63.6)		49.4 (26.1, 72.7)
Black				
Responder, n (%)	0	3 (100)	0	2 (100)
95% CI		(100.0, 100.0)		(100.0, 100.0)
95% CI of diff.				
Asian				
Responder, n (%)	3 (16.7)	18 (56.3)	4 (26.7)	18 (75.0)
95% CI	(0.0, 33.9)	(39.1, 73.4)	(4.3, 49.0)	(57.7, 92.3)
95% CI of diff.		39.6 (15.3, 63.9)		48.3 (20.0, 76.6)

FDA reproduced the results from Applicant's data

Table 28 Summary of Proportion of Patients not Requiring a Platelet Transfusion or Any Rescue Procedure for Bleeding by Region (Full Analysis Set)

	Low baseline PLT count cohort		High baseline PLT count cohort	
	Placebo N = 48	Avatrombopag 60 mg, N = 90	Placebo N = 34	Avatrombopag 40 mg, N = 59
North America				
Responder, n (%)	2 (20.0)	17 (81.0)	1 (16.7)	9 (90.0)
95% CI	(0.0, 44.8)	(64.2, 97.7)	(0.0, 46.5)	(71.4, 100.0)
95% CI of diff.		61.0 (31.0, 90.9)		73.3 (38.2, 100.0)
Europe				
Responder, n (%)	6 (33.3)	21 (67.7)	7 (58.3)	24 (100)
95% CI	(11.6, 55.1)	(51.3, 84.2)	(30.4, 86.2)	(100.0, 100.0)
95% CI of diff.		34.4 (7.1, 61.7)		41.7 (13.8, 69.6)
East Asia				
Responder, n (%)	2 (11.8)	16 (53.3)	4 (26.7)	18 (75.0)
95% CI	(0.0, 27.1)	(35.5, 71.2)	(4.3, 49.0)	(57.7, 92.3)
95% CI of diff.		41.6 (18.0, 65.1)		48.3 (20.0, 76.6)

FDA reproduced the results from Applicant's data

8.1.2. Study 311

Trial Design

E5501-G000-311, or Study 311 was an international, multicenter, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy of once daily oral avatrombopag versus placebo treatment in patients with thrombocytopenia and a history of concomitant CLD scheduled to undergo a procedure with associated bleeding risk. The study was conducted between December 5, 2013 and January 30, 2017 at 74 sites in Argentina, Australia, Belgium, Brazil, China, Czech Republic, France, Germany, Israel, Italy, Japan, Mexico, Romania, Russia, Spain, and the United States.

The trial design, eligible patient population, key inclusion and exclusion criteria, study protocol, schedule of procedures and assessments, safety monitoring, and endpoints were identical to those described for Study 310 in the previous section (refer to Section 8.1.1).

Study Endpoints

Refer to Section 8.1.1 for a description of primary and secondary endpoints.

Statistical Analysis Plan

Refer to the analysis sets definition for Study 310 (Section 8.1.1).

Protocol Amendments

A summary of significant changes made to the protocol is provided in Section 8.1.1.

Study Results

Compliance with Good Clinical Practices

The applicant provided attestation that this study was conducted in accordance with U.S. regulations governing the protection of human subjects, Institutional Review Boards, and the obligations of clinical investigators in accordance with good clinical practice (GCP).

Financial Disclosure

The applicant submitted financial disclosure information from all investigators for this trial. Site 5917 and 5920 were reported as having significant payments both >$35,000 but total enrollment for these two study sites was low (n=10). It is not expected that these two study sites would have a significant impact on study results.

Patient Disposition

A total of 346 patients signed informed consent for this study. Of these patients, there were 142 screen failures and 204 proceeded to randomization. Most screen failures did not meet the study eligibility criteria (119 patients, 34.4%) or withdrew consent (13 patients, 3.8%). Other reasons for screen failure included AEs and patients who were lost to follow-up.

Of the 204 randomized patients, 113 patients (55.4%) were randomized into the low baseline platelet count cohort and 91 patients (44.6%) were randomized into the high baseline platelet count cohort.

A total of 128 patients were randomized to receive avatrombopag treatment (70 patients in the low baseline platelet count cohort and 58 patients in the high baseline platelet count cohort), and 76 patients were randomized to receive placebo (43 patients in the low baseline platelet count cohort and 33 patients in the high baseline platelet count cohort).

100% of the patients randomized to avatrombopag were treated (128/128) and 96.1% (123/128) completed the study. 100% of patients randomized to receive placebo were treated (76/76) and 89.5% (68/76) completed the study.

Table 29: Study 311 Disposition by Treatment Arm

	Low Baseline Platelet Cohort				High Baseline Platelet Cohort			
N (%)	Placebo (N=43)		60 mg Avatrombopag (N=70)		Placebo (N=33)		40 mg Avatrombopag (N=58)	
Informed Consent Obtained	43	100.0	70	100.0	33	100.0	58	100.0
Randomized	43	100.0	70	100.0	33	100.0	58	100.0
Completed	37	86.1	68	97.1	31	93.9	55	94.8
Withdrawal By Subject	3	6.9	1	1.4	0	0.0	2	3.4
Lost To Follow-Up	3	6.9	0	0.0	1	3.0	1	1.7
Adverse Event	0	0.0	0	0.0	1	3.0	0	0.0
Other	0	0.0	1	1.4	0	0.0	0	0.0

Source: FDA Reviewer JMP Clinical 6.1 Analysis

Protocol Violations/Deviations

A total of 18.1% (37/204) of patients had major protocol deviations and the majority were under the category of Study Procedures across all treatment groups. The most frequent deviation was that patients who did not have a clinically significant increase in platelet count from baseline to procedure day had, at the investigator's discretion, the scheduled procedure without being given a platelet transfusion. This included 1.6% (2/128) of patients in the combined avatrombopag treatment group and 6.6% (5/76) of patients in the combined placebo treatment group. These patients were removed from the PPAS analysis of the primary efficacy endpoint, although they had been assessed as responders in the primary FAS efficacy analysis even though their platelet counts had not increased to $\geq 50\times10^9$/L on Procedure Day, since they had not received a transfusion or rescue procedure for bleeding.

A total of 5 (2.5%) patients received a platelet transfusion despite having achieved a significant increase in platelet count. This included 2.3% (3/128) of patients in the combined avatrombopag treatment group and 2.6% (2/76) of patients in the combined placebo group. These transfusions were performed immediately prior to a scheduled dental procedure. In all cases the dentist performing the procedure (not the PI), considered the platelet count insufficiently high for a dental procedure thus mandating transfusion.

Overall, the percentage of patients with protocol deviations was lower in the combined avatrombopag treatment group (14.8% [19/128] patients) compared to the combined placebo treatment group (23.7% [18/76] patients).

Demographic Characteristics

The following table outlines demographic characteristics of patients enrolled in Study 311.

Table 30: Study 311 Demographic Characteristics; All Treated Analysis Set

Demographic Parameters	Low Baseline Platelet Cohort		High Baseline Platelet Cohort	
	Placebo (N=43)	**Avatrombopag 60 mg (N=70)**	**Placebo (N=33)**	**Avatrombopag 40 mg (N=58)**
Sex (N, %)				
Male	27 (62.8)	50 (71.4)	17 (51.5)	33 (56.9)
Female	16 (37.2)	20 (28.6)	16 (48.5)	25 (43.1)
Age				
Mean years (SD)	57.3 (11.98)	58.6 (14.18)	59.2 (10.31)	57.9 (11.11)
Median (years)	58.0	61.5	60.0	59.0
Min, max (years)	27, 77	20, 86	39, 81	29, 77
Age Group (N, %)				
< 65 years	30 (69.8)	45 (64.3)	23 (69.7)	43 (74.1)
≥ 65 years	13 (30.3)	25 (35.7)	10 (30.3)	15 (25.9)
Race (N, %)				
White	27 (62.8)	40 (57.1)	24 (72.7)	40 (69.0)
Black or African American	2 (4.7)	2 (2.9)	0 (0.0)	2 (3.4)
Asian	10 (23.3)	26 (37.1)	8 (24.2)	12 (20.7)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other[1]	4 (9.3)	2 (2.9)	0 (0.0)	4 (6.9)
Missing	0 (0.0)	0 (0.0)	1 (3.0)	0 (0.0)
Ethnicity (N, %)				
Hispanic or Latino	12 (27.9)	10 (14.3)	7 (21.2)	15 (26.3)
Not Hispanic or Latino	29 (67.4)	57 (81.4)	25 (75.8)	41 (71.9)
Missing	2 (4.7)	3 (4.3)	1 (3.0)	1 (1.8)
Region (N, %)				
United States	12 (27.9)	16 (22.9)	3 (9.1)	11 (19.0)
Europe	12 (27.9)	16 (22.9)	12 (36.4)	20 (34.5)
East Asia	10 (23.3)	23 (32.9)	8 (24.2)	12 (20.7)
Rest of World	9 (20.9)	15 (21.4)	10 (30.3)	15 (25.9)

Source: Table derived from Applicant's Integrated Summary of Efficacy (ISE)and FDA Reviewer JMP Clinical 6.1 Analysis

For the low baseline platelet count cohort, the mean baseline platelet counts for the avatrombopag and placebo treatment groups were similar, 32.7×10^9/L and 32.5×10^9/L,

respectively. In the high baseline platelet count cohort, the mean baseline platelet counts for the avatrombopag and placebo treatment groups were also similar, 44.3×10^9/L and 44.5×10^9/L, respectively.

Table 31: **Study 311 Baseline Characteristics; All Treated Analysis Set**

Baseline Characteristics	Low Baseline Platelet Cohort		High Baseline Platelet Cohort	
	Placebo (N=43)	**Avatrombopag 60 mg (N=70)**	**Placebo (N=33)**	**Avatrombopag 40 mg (N=58)**
Disease Etiology, (N, %)				
Alcoholic liver disease	7 (16.3)	12 (17.1)	5 (15.2)	6 (10.3)
Chronic viral hepatitis	26 (60.5)	34 (48.6)	18 (54.5)	29 (50.0)
Chronic hepatitis B	6 (14.0)	4 (5.7)	3 (9.1)	2 (3.4)
Chronic hepatitis C	20 (46.5)	29 (41.4)	14 (42.4)	26 (44.8)
Chronic hepatitis B and C	0 (0.0)	1 (1.4)	1 (3.0)	1 (1.7)
Nonalcoholic steatohepatitis	5 (11.6)	10 (14.3)	5 (15.2)	6 (10.3)
Other	5 (11.6)	14 (20.0)	5 (15.2)	17 (29.3)
Missing	7 (16.3)	12 (17.1)	5 (15.2)	6 (10.3)
Baseline Platelet Count (x 10^9/L)				
Mean (SD)	32.5 (6.22)	32.7 (5.24)	44.5 (3.10)	44.3 (3.58)
Median	33.5	33.5	45.0	44.3
Range	12, 39.7	18, 39.5	36, 49	36.5, 50
HCC Status, (N, %)				
No	29 (67.4)	49 (70.0)	22 (66.7)	43 (74.1)
Yes	14 (32.6)	21 (30.0)	11 (33.3)	15 (25.9)
MELD Score (N, %)				
<10	14 (32.6)	25 (36.2)	14 (42.4)	25 (43.1)
≥10 to ≤14	23 (53.5)	34 (49.3)	14 (42.4)	21 (36.2)
>14	6 (14.0)	10 (14.5)	5 (15.2)	12 (20.7)
Missing	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)

Source: Table derived from Applicant's Integrated Summary of Efficacy (ISE) and FDA Reviewer JMP Clinical 6.1 Analysis

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Nearly all patients in the combined avatrombopag treatment group (99.2%, 126/127 patients) and all patients in the combined placebo treatment group (100.0%, 76/76 patients) took concomitant medications during the study.

The most common concomitant medications in the study included proton-pump inhibitors (pantoprazole, omeprazole), lactulose, ursodeoxycholic acid, beta blockers, furosemide, and potassium sparing diuretics (spironolactone).

Compliance rates ranged between 80% and 100% for almost all patients in the combined avatrombopag and placebo treatment groups (96.1% [123/128] patients and 98.7% [75/76] patients, respectively).

Efficacy Results – Primary Endpoint

In the Low Baseline Platelet Count Cohort (<40×10^9/L), the proportion of Responders was 68.6% (48/70) in the 60 mg avatrombopag treatment group compared to 34.9% (15/43) in placebo-treated patients. The treatment difference in the proportion of Responders (60 mg avatrombopag minus placebo) was 33.7% (95% CI [15.8%, 51.6%]), and was statistically significant with P <0.0006 by the CMH test (adjusted for bleeding risk associated with the scheduled procedures).

In the High Baseline Platelet Count Cohort (≥40 to <50×10^9/L), the proportion of Responders was also larger in the 40 mg avatrombopag treatment group, 87.9% (51/58), compared to the placebo treatment group, 33.3% (11/33). The treatment difference (40 mg avatrombopag minus placebo) was 54.6% (95% CI [36.5%, 72.7%]), and was statistically significant favoring avatrombopag with P<0.0001 by the CMH test (adjusted for bleeding risk associated with the scheduled procedures).

Table 32 Prop. of patients not requiring a platelet transfusion or any rescue procedure (Full Analysis Set)

	Low baseline PLT count cohort		High baseline PLT count cohort	
	Placebo N = 43	Avatrombopag 60 mg, N = 70	Placebo N = 33	Avatrombopag 40 mg, N = 58
Responder, n (%)	15 (34.9)	48 (68.6)	11 (33.3)	51 (87.9)
95% CI	(20.6, 49.1)	(57.7, 79.4)	(17.2, 49.4)	(79.5, 96.3)
Missing	3 (7.0)	2 (2.9)	1 (3.0)	1 (1.7)
95% CI of diff.		33.7 (15.8, 51.6)		54.6 (36.5, 72.7)
P-value (CMH)		0.0006		<.0001
P-value(Fisher's)		0.0008		<.0001

FDA reproduced the results from Applicant's data

Table 33 Prop. of patients not requiring a platelet transfusion or any rescue procedure (Sensitivity: worst scenario)

	Low baseline PLT count cohort		High baseline PLT count cohort	
	Placebo N = 43	Avatrombopag 60 mg, N = 70	Placebo N = 33	Avatrombopag 40 mg, N = 58

Responder, n (%)	18 (41.9)	48 (68.6)	12 (36.4)	51 (87.9)
95% CI	(27.1, 56.6)	(57.7, 79.4)	(20.0, 52.8)	(79.5, 96.3)
95% CI of diff.		26.7 (8.4, 45.0)		51.6 (33.1, 7.0)
P-value (CMH)		0.0069		<.0001
P-value(Fisher's)		0.0063		<.0001

FDA generated the results from Applicant's data

Reviewer's comments: FDA noticed small differential proportions of missing data between treatment arms in the low baseline PLT cohort (7.0% vs 2.9%, for placebo and Avatrombopag, respectively). However, the conclusions stay the same after worst case calculation (assuming responders for patients with missing data in the placebo arm and non-responders for patients with missing data in the Avatrombopag arm).

Efficacy Results – Secondary and other relevant endpoints

The first secondary endpoint was the proportion of Responders, defined as patients who achieved platelet counts equal to or greater than the targeted 50×10^9/L on Procedure Day (Day 10 to Day 13).

In the Low Baseline Platelet Count Cohort ($<40\times10^9$/L), 67.1% (47/70) of the 60 mg avatrombopag-treated patients compared to 7.0% (3/43) of patients who received placebo were Responders. The treatment difference (60 mg avatrombopag minus placebo) was 60.2% (95% CI [46.8%, 73.5%]), and was statistically significant with P <0.0001 by the CMH test (adjusted for bleeding risk associated with the scheduled procedures).

Similarly, in the High Baseline Platelet Count Cohort (≥40 to $<50\times10^9$/L), 93.1% (54/58) of the 40 mg avatrombopag-treated patients compared to 39.4% (13/33) of patients who received placebo were Responders. The treatment difference (40 mg avatrombopag minus placebo) was 53.7% (95% CI [35.8%, 71.6%]), and was statistically significant with P <0.0001 by the CMH test (adjusted for bleeding risk associated with the scheduled procedures).

Table 34 Prop. of patients achieving platelet counts ≥ $50x10^9$/L on procedure day (Full Analysis Set)

	Low baseline PLT count cohort		High baseline PLT count cohort	
	Placebo N = 43	Avatrombopag 60 mg, N = 70	Placebo N = 33	Avatrombopag 40 mg, N = 58
Responder, n (%)	3 (7.0)	47 (67.1)	13 (39.4)	54 (93.1)

95% CI	(0.0, 14.6)	(56.1, 78.2)	(22.7, 56.1)	(86.6, 99.6)
Missing	3 (7.0)	3 (4.3)	3 (9.1)	2 (3.4)
95% CI of diff.		60.2 (46.8, 73.6)		53.7 (35.8, 71.6)
P-value (CMH)		<.0001		<.0001

FDA reproduced the results from Applicant's data

Table 35 Prop. of patients achieving platelet counts ≥ 50x10^9/L on procedure day (Sensitivity: worst scenario)

	Low baseline PLT count cohort		High baseline PLT count cohort	
	Placebo N = 43	Avatrombopag 60 mg, N = 70	Placebo N = 33	Avatrombopag 40 mg, N = 58
Responder, n (%)	6 (14.0)	47 (67.1)	16 (48.5)	54 (93.1)
95% CI	(3.6, 24.3)	(56.1, 78.2)	(31.4, 65.5)	(86.6, 99.6)
95% CI of diff.		53.2 (38.1, 68.3)		44.6 (26.4, 62.9)
P-value (CMH)		<.0001		<.0001

FDA generated the results from Applicant's data

Reviewer's comments: FDA noticed differential proportions of missing data between treatment arm in both the low baseline PLT cohort (7.0% vs 4.3% for placebo and Avatrombopag arm, respectively) and the high baseline PLT cohort (9.1% and 3.4% for placebo and Avatrombopag arm, respectively). However, the conclusions stay the same after worst case calculation (assuming responders for patients with missing data in the placebo arm and non-responders for patients with missing data in the Avatrombopag arm).

The second secondary endpoint was the change in platelet count from Baseline to Procedure Day (Day 10 to Day 13).

The mean change in Platelet count from Baseline to Procedure Day in the Low Baseline Platelet Count Cohort (<40×10^9/L) was 31.3×10^9/L for the 60 mg avatrombopag treatment group compared to 3.0×10^9/L for the placebo group. The treatment difference (60 mg avatrombopag minus placebo) in favor of avatrombopag was 25.4×10^9/L (95% CI [19.5, 32.0]), and was statistically significant with P <0.0001 by the Wilcoxon Rank Sum Test.

In the High Baseline Platelet Count Cohort (≥40 to <50×10^9/L), the mean change from Baseline to Procedure Day was 44.9×10^9/L for the 40 mg avatrombopag treatment group compared to 5.9×10^9/L for the placebo group. The treatment difference (40 mg avatrombopag minus

placebo) was 36.3×10^9/L (95% CI [25.5, 45.5]), and was statistically significant with P<0.0001 by the Wilcoxon Rank Sum Test.

Table 36 Change from Baseline of platelet count on procedure day (Full Analysis Set)

	Low baseline PLT count cohort		High baseline PLT count cohort	
	Placebo N = 43	Avatrombopag 60 mg, N = 70	Placebo N = 33	Avatrombopag 40 mg, N = 58
Change from Baseline(x 10^9/L)				
N	43	69	33	58
Mean (SD)	3.0 (10.01)	31.3 (24.09)	5.9 (14.89)	44.9 (32.96)
Median	0.5	28.0	3.3	41.3
Min, Max	-10, 52	-12, 118	-12, 53	0, 173
Diff in Changes†		25.4		36.3
95% CI		(19.5, 32.0)		(25.5, 45.5)
P-value (Wilcoxon)		<.0001		<.0001

†Hodges Lehmann estimation

Reviewer's comments: Even though LOCF method is not recommended for the missing data imputation, due to small numbers of missing data in both cohorts, FDA considers the impact of using LOCF as the imputation method on the results may be minimum.

Additional Analyses Conducted on the Individual Trial

No additional efficacy considerations were explored for Study 311.

Table 37 Prop. of patients not requiring a platelet transfusion or any rescue procedure (Sensitivity: Per Protocol Analysis Set)

	Low baseline PLT count cohort		High baseline PLT count cohort	
	Placebo N = 34	Avatrombopag 60 mg, N = 61	Placebo N = 27	Avatrombopag 40 mg, N = 50
Responder, n (%)	9 (26.5)	45 (73.8)	9 (33.3)	47 (94.0)
95% CI	(11.6, 41.3)	(62.7, 84.8)	(15.6, 51.1)	(87.4, 100.0)
Missing	0	0	0	0
95% CI of diff.		47.3 (28.8, 65.8)		60.7 (41.7, 79.6)
P-value (CMH)		<.0001		<.0001

The subgroup analyses for the primary efficacy endpoints are presented by age, gender, ethnic subgroups and regions in the following tables. In general, there are more responders in the Avatrombopag arm across all the subgroups.

Table 38 Summary of Proportion of Patients not Requiring a Platelet Transfusion or Any Rescue Procedure for Bleeding by Age Group (Full Analysis Set)

	Low baseline PLT count cohort		High baseline PLT count cohort	
	Placebo N = 43	Avatrombopag 60 mg, N = 70	Placebo N = 33	Avatrombopag 40 mg, N = 58
< 65 Years old				
Responder, n (%)	13 (43.3)	32 (71.1)	8 (34.8)	36 (83.7)
95% CI	(25.6, 61.1)	(57.9, 84.4)	(15.3, 54.2)	(72.7, 94.8)
95% CI of diff.		27.8 (5.6, 49.9)		48.9 (26.6, 71.3)
>= 65 to < 75 Years old				
Responder, n (%)	2 (18.2)	12 (66.7)	3 (42.9)	12 (100)
95% CI	(0.0, 41.0)	(44.9, 88.4)	(6.2, 79.5)	(100.0, 100.0)
95% CI of diff.		48.5 (17.0, 80.0)		57.1 (20.5, 93.8)
>= 75 Years old				
Responder, n (%)	0 (100)	4	0	3 (100)
95% CI	(0.0, 0.0)	(20.5, 93.8)	(0.0, 0.0)	(100.0, 100.0)
95% CI of diff.		57.1 (20.5, 93.8)		100.0 (100.0, 100)

FDA reproduced the results from Applicant's data

Table 39 Summary of Proportion of Patients not Requiring a Platelet Transfusion or Any Rescue Procedure for Bleeding by Sex (Full Analysis Set)

	Low baseline PLT count cohort		High baseline PLT count cohort	
	Placebo N = 43	Avatrombopag 60 mg, N = 70	Placebo N = 33	Avatrombopag 40 mg, N = 58
Male				
Responder, n (%)	6 (22.2)	33 (66.0)	6 (35.3)	28 (84.8)
95% CI	(6.5, 37.9)	(52.9, 79.1)	(12.6, 58.0)	(72.6, 97.1)
95% CI of diff.		43.8 (23.3, 64.2)		49.6 (23.8, 75.4)
Female				
Responder, n (%)	9 (56.3)	15 (75.0)	5 (31.3)	23 (92.0)
95% CI	(31.9, 80.6)	(56.0, 94.0)	(8.5, 54.0)	(81.4, 100.0)
95% CI of diff.		53.3 (27.3, 79.2)		60.8 (35.7, 85.8)

FDA reproduced the results from Applicant's data

Table 40 Summary of Proportion of Patients not Requiring a Platelet Transfusion or Any Rescue Procedure for Bleeding by Race (Full Analysis Set)

	Low baseline PLT count cohort		High baseline PLT count cohort	
	Placebo N = 43	Avatrombopag 60 mg, N = 70	Placebo N = 33	Avatrombopag 40 mg, N = 58
White				
Responder, n (%)	10 (37.0)	27 (67.5)	9 (37.5)	33 (82.5)
95% CI	(18.8, 55.3)	(53.0, 82.0)	(18.1, 56.9)	(70.7, 94.3)
95% CI of diff.		30.5 (7.2, 53.8)		45.0 (22.3, 67.7)
Black				
Responder, n (%)	1 (50.0)	2 (100)	0	2 (100)
95% CI	(0.0, 100.0)	(100.0, 100.0)		(100.0, 100.0)
95% CI of diff.		50.0 (-19.3, 100.0)		
Asian				
Responder, n (%)	1 (10.0)	17 (68.0)	2 (25.0)	12 (100)
95% CI	(0.0, 28.6)	(49.7, 86.3)	(0.0, 55.0)	(100. 0, 100. 0)
95% CI of diff.		58.0 (31.9, 84.1)		75.0 (45.0, 100.0)

FDA reproduced the results from Applicant's data

Table 41 Summary of Proportion of Patients not Requiring a Platelet Transfusion or Any Rescue Procedure for Bleeding by Region (Full Analysis Set)

	Low baseline PLT count cohort		High baseline PLT count cohort	
	Placebo N = 43	Avatrombopag 60 mg, N = 70	Placebo N = 33	Avatrombopag 40 mg, N = 58
North America				
Responder, n (%)	4 (33.3)	12 (75.0)	2 (66.7)	9 (81.8)
95% CI	(6.7, 60.0)	(53.8, 96.2)	(13.3, 100.0)	(59.0, 100.0)
95% CI of diff.		41.7 (7.6, 75.7)		15.2 (-42.9, 73.2)
Europe				
Responder, n (%)	5 (41.7)	11 (68.8)	2 (16.7)	16 (80.0)
95% CI	(13.8, 69.6)	(46.0, 91.5)	(0.0, 37.8)	(62.5, 97.5)
95% CI of diff.		27.1 (-8.9, 63.1)		63.3 (35.9, 90.8)
East Asia				
Responder, n (%)	1 (10.0)	16 (69.6)	2 (25.0)	12 (100.0)
95% CI	(0.0, 28.6)	(50.8, 88.4)	(0.0, 55.0)	(100.0,100.0)
95% CI of diff.		59.6 (33.1, 86.0)		75.0 (45.0, 100.0)

FDA reproduced the results from Applicant's data

Integrated Review of Effectiveness

8.1.3. Assessment of Efficacy Across Trials

The integrated pivotal data (Study 310 and Study 311) includes 435 patients from 2 identically-designed randomized, double-blind, placebo controlled phase 3 studies in the target patient

population and indication that used the planned commercial avatrombopag formulation, doses, and dosing regimen with food.

Figure 4 Summary of Study 310 and Study 311

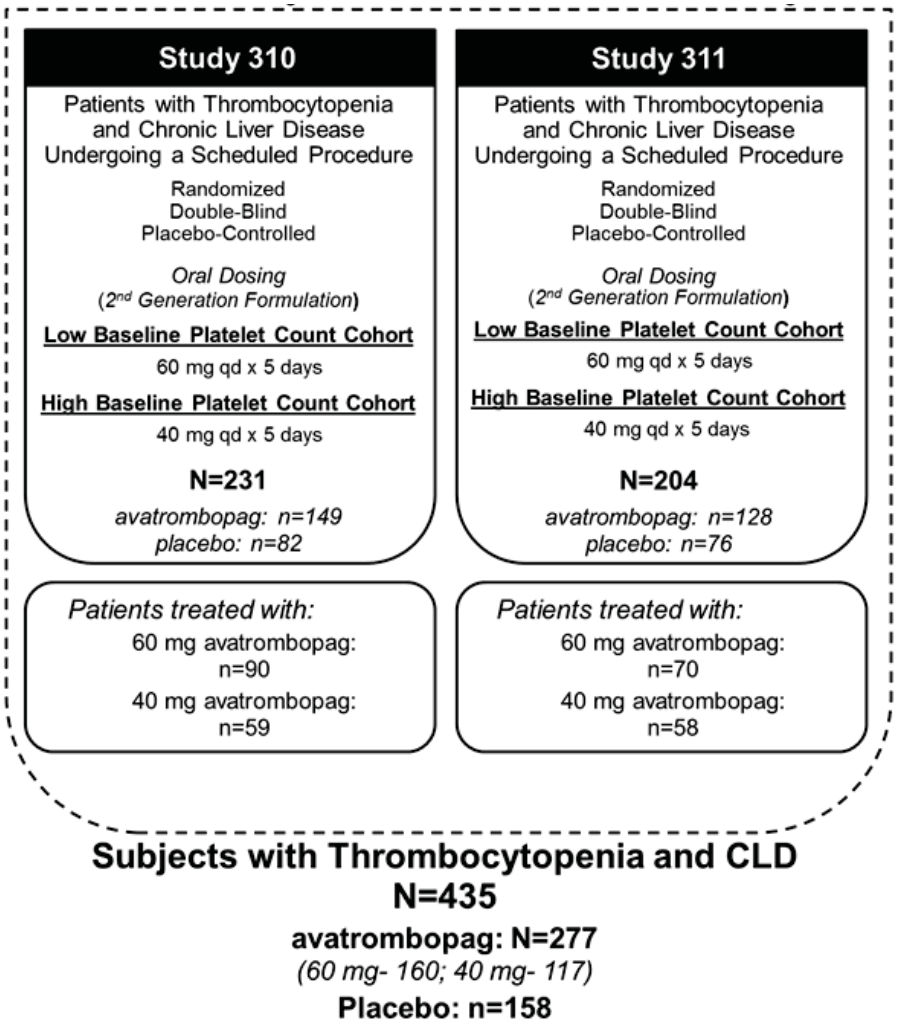


Figure modified from Eisai's AOM Slide November 2017

Primary Endpoints

Low Baseline Platelet Count Cohort (<40×10^9/L):

In Study 310, the proportion of Responders was 65.6% (59/90) in the 60 mg avatrombopag group compared to 22.9% (11/48) in patients who received placebo. The treatment difference in the proportion of Responders (60 mg avatrombopag minus placebo) was 42.6% (95% CI [27.2, 58.1]), and was statistically significant with P <0.0001 by the CMH test (adjusted for bleeding risk).

Consistent results are also shown in Study 311, the proportion of Responders was 68.6% (48/70) in the 60 mg avatrombopag group compared to 34.9% (15/43) in the placebo group. The treatment difference in the proportion of Responders (60 mg avatrombopag minus placebo) was 33.7% (95% CI [15.8, 51.6]), and was statistically significant with P <0.0006 by the CMH test (adjusted for bleeding risk).

High Baseline Platelet Count Cohort (≥40 to <50×10^9/L):

In Study 310, the proportion of Responders was also larger in the 40 mg avatrombopag group, 88.1% (52/59), compared to the placebo group, 38.2% (13/34). The treatment difference (40 mg avatrombopag minus placebo) was 49.9% (95% CI [31.6, 68.2]), and was statistically significant favoring avatrombopag with P<0.0001 by the CMH test (adjusted for bleeding risk).

Consistent results are also shown in Study 311, the proportion of Responders was also larger in the 40 mg avatrombopag group, 87.9% (51/58), compared to the placebo group, 33.3% (11/33). The treatment difference (40 mg avatrombopag minus placebo) was 54.6% (95% CI [36.5, 72.7]), and was statistically significant favoring avatrombopag with P<0.0001 by the CMH test (adjusted for bleeding risk).

Figure 5: Proportion of Patients Who Did Not Require Platelet Transfusion or Any Rescue Procedure for Bleeding

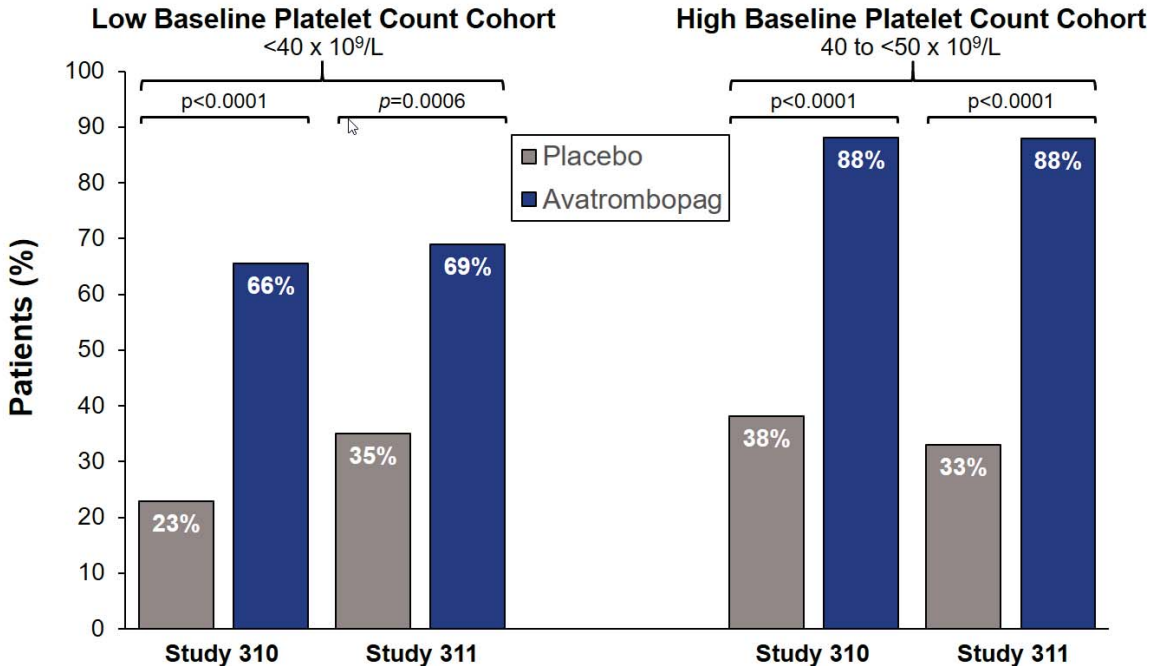


Figure modified from Eisai's AOM Slide November 2017

Secondary and Other Endpoints

Proportion of Patients Who Achieved Platelet Counts ≥ 50 x 10^9/L on Procedure Day

Low Baseline Platelet Count Cohort (<40×10^9/L):

In Study 310, 68.9% (62/90) of the 60 mg avatrombopag-treated patients, and 4.2% (2/48) of those who received placebo were Responders. The treatment difference (60 mg avatrombopag minus placebo) was 64.7% (95% CI [53.6, 75.8]), and was statistically significant with P <0.0001 by the CMH test (adjusted for bleeding risk).

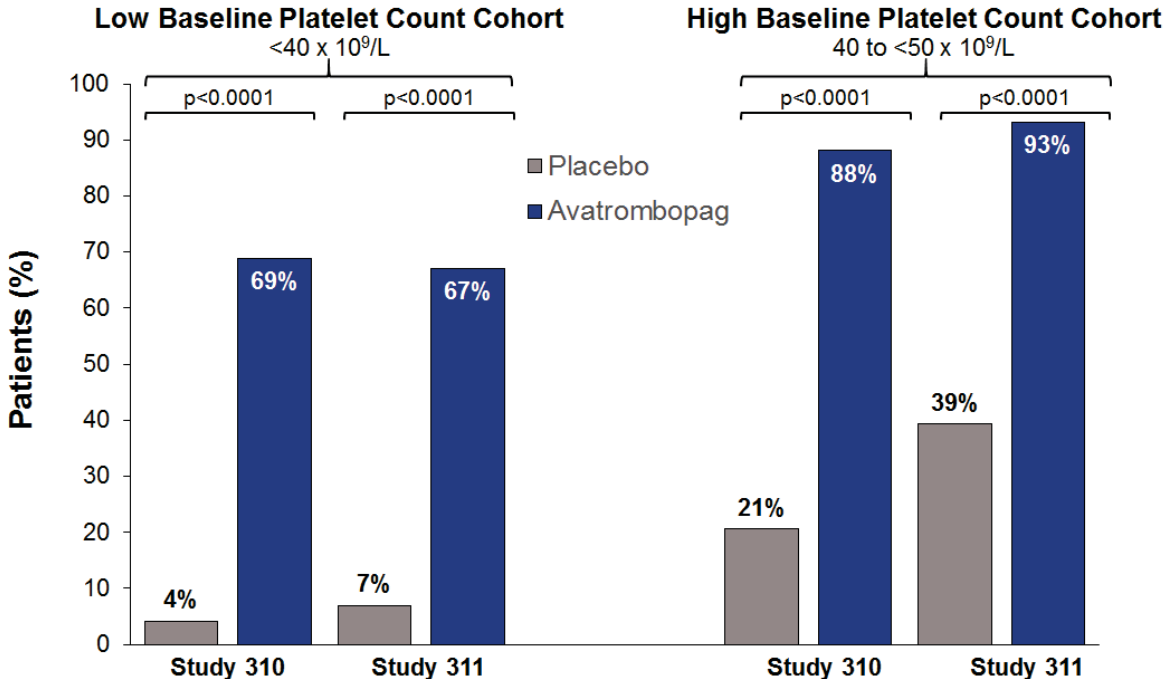
Consistent results are also shown in Study 311, 67.1% (47/70) of the 60 mg avatrombopag-treated patients compared to 7.0% (3/43) of those who received placebo were Responders. The treatment difference (60 mg avatrombopag minus placebo) was 60.2% (95% CI [46.8, 73.5]), and was statistically significant with P <0.0001 by the CMH test (adjusted for bleeding risk).

High Baseline Platelet Count Cohort (≥40 to <50×10^9/L):

In Study 310, 88.1% (52/59) of the 40 mg avatrombopag-treated patients, and 20.6% (7/34) of patients who received placebo were Responders. The treatment difference (40 mg avatrombopag minus placebo) was 67.5% (95% CI [51.6, 83.4]), and was statistically significant with P <0.0001 by the CMH test (adjusted for bleeding risk).

Consistent results are also shown in Study 311, 93.1% (54/58) of the 40 mg avatrombopag-treated patients compared to 39.4% (13/33) of patients who received placebo were Responders. The treatment difference (40 mg avatrombopag minus placebo) was 53.7% (95% CI [35.8, 71.6]), and was statistically significant with P <0.0001 by the CMH test (adjusted for bleeding risk).

Figure 6 Proportion of Patients Who Achieved Platelet Counts ≥ 50 x 10^9/L on Procedure Day



Change in Platelet Counts from Baseline to Procedure Day

Low Baseline Platelet Count Cohort (<40×10^9/L):

In Study 310, the mean change in platelet count from baseline to procedure day was 32.0×10^9/L for the 60 mg avatrombopag group compared to 0.8×10^9/L for the placebo group. The treatment difference (60 mg avatrombopag minus placebo) in favor of avatrombopag was 27.5×10^9/L (95% CI [22.5, 32.5]), and was statistically significant with P <0.0001 by the Wilcoxon Rank Sum Test.

Consistent results are also shown in Study 311, the mean change in platelet count from baseline to procedure day was 31.3×10^9/L for the 60 mg avatrombopag group compared to 3.0×10^9/L for the placebo group. The treatment difference (60 mg avatrombopag minus placebo) in favor of avatrombopag was 25.4×10^9/L (95% CI [19.5, 32.0]), and was statistically significant with P <0.0001 by the Wilcoxon Rank Sum Test.

High Baseline Platelet Count Cohort (≥40 to <50×10^9/L):

In Study 310, the mean change from baseline to procedure day was 37.1×10^9/L for the 40-mg avatrombopag group compared to 1.0×10^9/L for the placebo group. The treatment difference (40 mg avatrombopag minus placebo) was 33.5×10^9/L (95% CI [25.5, 41.5]), and was statistically significant with P <0.0001 by the Wilcoxon Rank Sum Test.

Consistent results are also shown in Study 311, the mean change from baseline to procedure day was 44.9×10^9/L for the 40 mg avatrombopag group compared to 5.9×10^9/L for the placebo

group. The treatment difference (40 mg avatrombopag minus placebo) was 36.3×10^9/L (95% CI [25.5, 45.5]), and was statistically significant with P<0.0001 by the Wilcoxon Rank Sum Test.

Additional Efficacy Considerations

No additional efficacy considerations were explored for this application.

8.1.4. Integrated Assessment of Effectiveness

The 2 phase 3 studies that provide the pivotal efficacy data were identically-designed, international studies that used the planned commercial formulation of avatrombopag, doses (40 mg or 60 mg), and dosing regimen in the target patient population and indication. Subjects were assigned to one of 2 baseline platelet count cohorts and received treatment once daily for 5 days, 10-13 days prior to a scheduled procedure. Individual data as well as pooled efficacy analyses of Study 310 and Study 311 support the efficacy of avatrombopag for the treatment of thrombocytopenia in patients with CLD who are scheduled to undergo a procedure. Both studies met their primary and secondary efficacy endpoints in both baseline platelet count cohorts. Of note, independent statistical analysis revealed small differential proportions of missing data between treatment arms in both Studies 310 and 311. However, further imputation implementing the LOCF method for missing data did not impact statistical conclusions.

Avatrombopag treatment demonstrated statistically significant increases in the proportion of patients who did not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following a scheduled procedure. These primary efficacy endpoint data were further supported in both studies by positive data for the 2 secondary efficacy endpoints. Avatrombopag treatment resulted in measured increases in platelet counts, with each study confirming that a greater proportion of avatrombopag-treated subjects achieved the pre-specified platelet count on procedure day and had a greater magnitude of the change in mean platelet counts from baseline to procedure day as compared to those subjects who received placebo.

The 40 mg and 60 mg avatrombopag dosing regimens resulted in a transient increase in platelet counts that peaked 5 to 8 days after the last dose (on the day of a procedure) at approximately 2 times the respective baseline platelet count for each combined avatrombopag treatment group, and then consistently started to decline within 7 days of the procedure, returning to baseline within 30 days of the last dose.

The treatment effect of avatrombopag was consistent across all major subgroups evaluated.

8.2. Review of Safety

8.2.1. Safety Review Approach

The clinical review of safety for this NDA was based on safety data from Studies 310 and 311. Further details regarding study design and protocols are provided in section 5.1 of this review. The applicant presented safety data in a pooled fashion from the 310 and 311 studies. All patients had a history of chronic liver disease with concomitant severe thrombocytopenia

(platelet count <50,000/µL) and were scheduled to undergo a procedure with associated bleeding risk. There were no key safety issues identified a priori.

8.2.2. Review of the Safety Database

Overall Exposure

The pooled Study 310 and 311 population included 435 patients. A total of 430 patients were included in the safety population analysis set, defined as those randomized patients who received at least 1 dose of study drug and had at least 1 post-dose safety assessment. A total of 250 patients were randomized to the low baseline platelet count cohort whereas 180 patients were randomized to the high baseline platelet cohort. There were 274 patients in the combined avatrombopag treatment group (40 mg or 60 mg avatrombopag) and 156 patients in the combined placebo group, respectively.

The majority of patients received the planned 5 days of treatment in both treatment groups, respectively. 98.2% of patients in the combined avatrombopag treatment group (269/274) and 98.7% (154/156) of patients in the combined placebo group completed the planned 5-day treatment period. Furthermore, exposure was comparable between the groups. Duration of exposure was defined as the number of days between the date the subject received the first dose of study drug and the date the patient received the last dose of study drug, inclusive. The table below provides further exposure data by treatment group.

The mean duration of exposure in days was 5.0 (SD 0.29) for the avatrombopag treatment group and 5.0 (SD 0.18) for patients who received placebo.

Table 42: Exposure Summary for Safety Population (Studies 310 and 311) by Treatment Arm

	Low Baseline Platelet Cohort		**High Baseline Platelet Cohort**	
Duration of Study Treatment (Days)	Placebo (N=91)	Avatrombopag 60 mg (N=159)	Placebo (N=65)	Avatrombopag 40 mg (N=115)
Mean	5	5	5	5
Median	5	5	5	5
Range (Min, Max)	3, 5	2, 5	5, 5	4, 5
Duration of Study Treatment by Category (N, %)				
Missing duration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1 Day	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2 Days	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
3 Days	1 (1.1%)	2 (1.3%)	0 (0.0)	0 (0.0)
4 Days	1 (1.1%)	0 (0.0)	0 (0.0)	2 (1.7%)
5 Days	89 (97.8%)	156 (98.1)	65 (100.0)	113 (98.3)

Source: FDA Reviewer Analysis, JMP Clinical 6.1

Table 43: Safety Population and Database for Avatrombopag

Safety Database for Avatrombopag Individuals Exposed to the Study Drug in this Development Program for the Indication under Review N= 430			
Clinical Trial Groups	Avatrombopag (n= 274)	Active Control (n=0)	Placebo (n=156)
Controlled trials conducted for this indication	274	0	156
All other than controlled trials conducted for this indication	0	0	0
Controlled trials conducted for other indications	0	0	0

Relevant Characteristics of the Safety Population

As described in previous sections of this review, Studies 310 and 311 enrolled a population of patients will CLD and concomitant severe thrombocytopenia scheduled to undergo a procedure with associated bleeding risk. Demographics and baseline characteristics of the safety population are described in the tables below.

Table 44: Pooled Safety Population Demographics (Studies 310 and 311)

Demographic Parameters	**Low Baseline Platelet Cohort**		**High Baseline Platelet Cohort**	
	Placebo (N=91)	**Avatrombopag 60 mg (N=159)**	**Placebo (N=65)**	**Avatrombopag 40 mg (N=115)**
Sex (N, %)				
Male	59 (64.8)	115 (72.3)	39 (60.0)	68 (59.1)
Female	32 (35.2)	44 (27.7)	26 (40.0)	47 (40.9)
Age				
Mean years (SD)	56.1 (11.47)	56.8 (11.71)	58.3 (10.74)	58.0 (10.39)
Median (years)	57.0	57.0	60.0	59.0
Min, max (years)	25.0, 77.0	20.0, 86.0	30.0, 81.0	19.0, 77.0
Age Group (N, %)				
< 65 years	71 (78.0)	121 (76.1)	46 (70.8)	85 (73.9)
65 to < 75 years	17 (18.7)	30 (18.9)	14 (21.5)	26 (22.6)
≥ 75 years	3 (3.3)	8 (5.0)	5 (7.7)	4 (3.5)

Race (N, %)				
White	55 (60.4)	90 (56.6)	43 (66.2)	69 (60.0)
Black or African American	2 (2.2)	5 (3.1)	0 (0.0)	4 (3.5)
Asian	28 (30.8)	57 (35.8)	21 (32.3)	36 (31.3)
Other	6 (6.6)	4 (2.5)	0 (0.0)	4 (3.5)
Missing	0 (0.0)	3 (1.9)	1 (1.6)	2 (1.7)
Ethnicity (N, %)				
Hispanic or Latino	22 (24.2)	20 (12.6)	10 (15.4)	21 (18.3)
Not Hispanic or Latino	66 (72.5)	134 (84.3)	54 (83.1)	92 (80.0)
Missing	3 (3.3)	5 (3.1)	1 (1.5)	2 (1.7)
Region (N, %)				
United States	24 (26.4)	40 (25.2)	14 (21.5)	26 (22.6)
Europe	30 (33.0)	47 (29.6)	24 (36.9)	43 (37.4)
East Asia	27 (29.7)	53 (33.3)	21 (32.3)	36 (31.4)
Rest of World	10 (11.0)	19 (11.9)	6 (9.2)	10 (8.7)

Source: FDA Reviewer Analysis, JMP Clinical 6.1

Table 45: Pooled Safety Population Baseline Characteristics (Studies 310 and 311)

Baseline Characteristics	Low Baseline Platelet Cohort		High Baseline Platelet Cohort	
	Placebo (N=91)	**Avatrombopag 60 mg (N=159)**	**Placebo (N=65)**	**Avatrombopag 40 mg (N=115)**
Disease Etiology, (N, %)				
Alcoholic liver disease	14 (15.4)	25 (15.7)	7 (10.8)	17 (14.9)
Chronic viral hepatitis	56 (61.5)	85 (53.5)	44 (67.7)	64 (56.1)
Chronic hepatitis B	16 (17.6)	18 (11.3)	10 (15.4)	16 (13.9)
Chronic hepatitis C	40 (44.0)	66 (41.5)	33 (50.8)	46 (40.0)
Chronic hepatitis B and C	0 (0.0)	1 (0.6)	1 (1.5)	2 (1.7)
Nonalcoholic steatohepatitis	9 (9.9)	15 (9.4)	5 (7.7)	10 (8.8)
Other	12 (13.2)	34 (21.4)	9 (13.8)	23 (20.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Baseline Platelet Count				
Mean (SD)	31.6 (6.73)	32.0 (6.65)	44.6 (3.04)	44.2 (3.16)
Median	33.0	33.5	44.5	44.0
Range	11.5, 44.5	10.0, 49.5	36.0, 49.5	36.5, 50.0
HCC Status, (N, %)				
No	66 (72.5)	116 (73.0)	48 (73.8)	84 (73.0)
Yes	25 (27.5)	43 (27.0)	17 (26.2)	31 (27.0)
MELD Score (N, %)				
<10	33 (36.3)	56 (35.2)	28 (43.1)	44 (38.3)
≥10 to ≤14	43 (47.3)	79 (49.8)	30 (46.2)	48 (41.7)
>14	15 (16.4)	23 (14.5)	7 (10.8)	23 (20.0)
Missing	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)

Source: FDA Reviewer Analysis, JMP Clinical 6.1

Overall, male patients (65.3% [281/430] patients) comprised more of the safety population than female patients (34.7% [149/430] patients) and the majority of patients were White (59.8% [257/430] patients) and Asian (33.0% [142/430] patients). The majority of patients had CLD secondary to chronic viral hepatitis (58.0% [249/430] patients), followed by other etiologies of CLD (18.2% [78/430] patients), and alcoholic liver disease (14.7% [63/430] subjects). Baseline platelet counts were comparable between treatment groups in both the low and high baseline platelet count cohorts.

Most patients in the pooled safety population did not have HCC (HCC Status of "no," 73.0% [314/430]).

Overall, the distribution of patients having procedures in each of the bleeding risk categories between the avatrombopag and placebo groups was comparable with some differences noted in the individual procedure categories. Most patients had procedures in the low risk bleeding category in both the combined avatrombopag and placebo treatment groups (61.4% and 59.7%, respectively). The percentage of patients with procedures in the moderate bleeding risk category (15.5% and 20.1%, respectively) and high bleeding risk category (23.1% and 20.1%, respectively) were similar between treatment groups.

Table 46: Pooled Safety Population Summary of Scheduled Procedures by Bleeding Risk (Studies 310 and 311)

	Low Baseline Platelet Count Cohort		High Baseline Platelet Count Cohort	
Bleeding Risk Scheduled Procedure Type	**Placebo (N=91)**	**Avatrombopag 60 mg (N=159)**	**Placebo (N=65)**	**Avatrombopag 40 mg (N=115)**
Low Bleeding Risk Procedures (N, %)	48 (60.0)	97 (63.8)	38 (59.4)	65 (58.0)
Paracentesis	0 (0.0)	2 (1.3)	2 (3.1)	1 (0.9)
Endoscopy	43 (53.8)	83 (54.6)	32 (50.0)	54 (48.2)
Upper Gastrointestinal Endoscopy with Biopsy	7 (8.8)	15 (9.9)	8 (12.5)	12 (10.7)
Upper Gastrointestinal Endoscopy Without Biopsy	16 (20.0)	24 (15.8)	14 (21.9)	22 (19.6)
Upper Gastrointestinal Endoscopy with Variceal Banding	17 (21.3)	30 (19.7)	9 (14.1)	20 (17.9)
Upper Gastrointestinal Endoscopy with Variceal Banding and Biopsy	2 (2.5)	8 (5.3)	0 (0.0)	0 (0.0)

Upper Gastrointestinal Endoscopy with Variceal Sclerotherapy	1 (1.3)	6 (3.9)	1 (1.6)	0 (0.0)
Colonoscopy	5 (6.3)	12 (7.9)	4 (6.3)	10 (8.9)
Colonoscopy with Polypectomy/ Biopsy	5 (6.3)	4 (2.6)	3 (4.7)	6 (5.4)
Colonoscopy Without Polypectomy/ Biopsy	0 (0.0)	8 (5.3)	1 (1.6)	4 (3.6)
Moderate Bleeding Risk Procedure	17 (21.3)	21 (13.8)	12 (18.8)	20 (17.9)
Liver Biopsy	3 (3.8)	3 (2.0)	3 (4.7)	7 (6.3)
Ethanol Ablation	0 (0.0)	1 (0.7)	0	1 (0.9)
Chemoembolization for HCC	14 (17.5)	17 (11.2)	9 (14.1)	12 (10.7)
High Bleeding Risk Procedures	15 (18.8)	34 (22.4)	14 (21.9)	27 (24.1)
Dental Procedures	5 (6.3)	13 (8.6)	8 (12.5)	13 (11.6)
TIPS Procedure	3 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)
Laparoscopic Interventions	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Radiofrequency Ablation	5 (6.3)	13 (8.6)	3 (4.7)	11 (9.8)
Vascular Catheterization	2 (2.5)	8 (5.3)	3 (4.7)	2 (1.8)
Missing	11	7	1	3

Source: Figure reproduced from Integrated Summary of Safety, Table 20.1 3.3.1

Adequacy of the Safety Database

The demographics of the safety population are adequately consistent with those of the intended patient population. The safety database enrolled a heterogeneous population of CLD patients with varying degrees of hepatic impairment so that pooled safety results are generalizable to the intended patient population.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No issues regarding data integrity were identified during the course of this review, or in the course of clinical investigational site inspections. Overall the applicant's submission was well-organized with appropriate analyses and detailed reports and patient summaries. Responses to information requests were rapid and complete.

Categorization of Adverse Events

In addition, subjects with TEAEs, treatment-related TEAEs leading to discontinuation from study treatment, and AESI for this study including recurrence of thrombocytopenia, thromboembolic events and bleeding events [WHO Grade 2 to 4] were summarized for each treatment group.

Routine Clinical Tests

The schedule of safety evaluations and clinical assessments for each protocol was described in Section 8.1.1. The frequency of monitoring was considered adequate within the context of Studies 310 and 311.

8.2.4. Safety Results

Deaths

Reviewer Comment: The information provided by the applicant is inadequate to determine the cause of death in this patient. An autopsy was not performed. No further details were available as per the original MEDWATCH report. In the absence of autopsy, the causal relationship between avatrombopag treatment and the patient's death cannot be assessed by this reviewer.

Case 2:

Patient (b) (6) was a 54-year-old white male. His medical history included chronic hepatitis C viral (HCV) infection with liver cirrhosis, hepatocellular carcinoma (HCC), portal hypertension, splenomegaly, esophageal varices, ascites, hepatic encephalopathy, peripheral edema, diabetes mellitus type 2, and depression.

The patient was randomized to the 40 mg avatrombopag treatment arm in the high baseline platelet cohort. He received the planned 5 days of avatrombopag treatment pre-procedure. The patient underwent chemoembolization for HCC. Twenty-seven days following the last dose of study drug, the subject presented with hematemesis and underwent upper endoscopy which revealed 5 actively bleeding esophageal varices which were banded. The patient was transfused with 5 units of packed red blood cells, 1 unit of platelets and seven units of FFP during his hospitalization. He subsequently developed multiorgan failure (acute liver failure, acute kidney injury and respiratory failure secondary to aspiration pneumonia) and despite aggressive medical intervention and intubation, he continued to deteriorate. The patient expired secondary to multiorgan failure 36 days after receiving study drug. An autopsy was not performed.

Adverse events that occurred within a +/- 3-day window of the onset of the SAE included headache (Grade 2), hyperkalemia (Grade 2), nausea (Grade 2), esophageal variceal hemorrhage (Grade 3), and aspiration pneumonia (Grade 3). Concomitant medications taken at

the onset of the SAE included: ceftriaxone, fentanyl, fresh frozen plasma (FFP), furosemide, granisetron, lactulose, magnesium, metronidazole, octreotide, pantoprazole, spironolactone, sumatriptan, tazocin, and terliprissin.

Reviewer Comment: This reviewer concurs with the applicant's assessment that the patient's death was not related to avatrombopag treatment.

Case 3:

Patient (b) (6) was a 53-year-old white male. His medical history included hepatocellular carcinoma with a baseline MELD score of 8. The patient was randomized to the 40 mg placebo treatment arm in the high baseline platelet count cohort. The patient underwent a low risk dental procedure without platelet transfusion. At the time of the procedure, platelet count was 95,000/µL (baseline 47,000/µL).

On Day 31, the patient experienced an acute myocardial infarction (Grade 5). He subsequently developed multiorgan failure and expired on Day 33. No autopsy was performed.

The investigator considered the AE to be not related to study medication.

Reviewer Comment: This patient death occurred in a placebo-treated patient. The inciting factors for a fatal myocardial infarction are unclear from the provided information and the patient had no documented pre-existing cardiovascular disease.

On Study Day 30, the patient was hospitalized for acute left upper quadrant abdominal pain and underwent repeat abdominal CT imaging which revealed hemorrhage and evidence of a retroperitoneal bleed. He was concomitantly diagnosed with hyperkalemia, stress polycythemia, hematemesis, and acute kidney injury. He was treated with intravenous fluids, bicarbonate drip, insulin, glucose, calcium gluconate, and sodium polystyrene sulfonate.

Flow cytometry performed on peripheral blood at time of hospitalization did not suggest a clonal plasma disorder or evidence of blast cells. On Study Day 35, a diagnostic bone marrow biopsy was performed with unrevealing pathologic findings.

On Study Day 37, the patient underwent repeat upper endoscopy and variceal banding. He was discharged on Day 38 from the hospital after resolution of acute abdominal pain, electrolyte imbalances and acute kidney injury.

The patient completed the study as planned on Day 42. On Day 50, the subject re-presented to the hospital with abdominal pain and hematemesis. His hemoglobin rapidly dropped from baseline (unknown value) and he developed Grade 4 hypotension and hemodynamic instability. He received packed red blood cell transfusion. A repeat endoscopy performed that night revealed Grade 3 oozing esophageal varices status post banding. No endoscopic procedures

were performed. After the procedure, the patient went into cardiopulmonary arrest, was successfully resuscitated, intubated and transferred to the intensive care unit.

Reviewer Comment: Massive splenomegaly secondary to portal hypertension in CLD patients can occur and is associated with non-traumatic splenic hemorrhage and rupture, although rare. This patient had documented CLD secondary to chronic viral hepatitis with evidence of portal hypertension and a history of esophageal varices and ascites. The patient's splenomegaly is unrelated to study treatment. In this reviewer's assessment, it is highly unlikely that the nontreatment-emergent death was related to avatrombopag treatment.

Serious Adverse Events

This section provides a summary of all non-fatal Serious Adverse Events (SAEs) that occurred in subjects who received at least one dose of study drug in all studies included in the safety database (Studies 310 and 311).

The overall incidence of TESAEs was low in the combined avatrombopag and placebo treatment groups. SAEs occurring within 30 days of the last dose of study drug were reported in 7.3% (20/274) of patients in the combined avatrombopag treatment group as compared to 9.0% (14/156) in the combined placebo group.

The most common treatment-emergent SAEs (TESAEs) in the combined avatrombopag treatment group occurred in the Gastrointestinal Disorders and Infections and Infestations SOCs (3.3% [9/274] patients; 1.8% [5/274] patients, respectively), which were higher compared to the combined placebo groups (0.6% [1/156] patients; 0% [0/156] patients, respectively).

The highest incidence of TESAEs for patients treated with placebo were reported in the Injury, Poisoning, and Procedural Complications SOC (3.8% [6/156] patients), which was higher as compared to subjects treated with avatrombopag (0.7% [2/274] patients). The table below provides numbers and percentages of patients with TESAEs by System Organ Class.

Table 47: Treatment-Emergent Serious Adverse Events by System Organ Class Occurring in at least 1 Patient, Pooled Safety Population (Studies 310 and 311)

	Low Baseline Platelet Count Cohort		**High Baseline Platelet Count Cohort**	
SOC	Placebo (N=91)	60 mg Avatrombopag (N=159)	Placebo (N=65)	40 mg Avatrombopag (N=115)
Gastrointestinal disorders	0 (0.0)	5 (3.1)	1 (1.5)	4 (3.5)
Injury, poisoning and procedural complications	6 (6.6)	2 (1.3)	0 (0.0)	(0.0)
General disorders and administration site conditions	2 (2.2)	0 (0.0)	2 (3.1)	1 (0.9)

Infections and infestations	0 (0.0)	1 (0.6)	0 (0.0)	4 (3.4)
Nervous system disorders	2 (2.2)	1 (0.6)	0 (0.0)	1 (0.9)
Metabolism and nutrition disorders	0 (0.0)	2 (1.3)	0 (0.0)	1 (0.9)
Blood and lymphatic system disorders	0 (0.0)	2 (1.3)	0 (0.0)	0 (0.0)
Investigations	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.9)
Renal and urinary disorders	0 (0.0)	2 (1.3)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	1 (1.1)	0 (0.0)	0 (0.0)	1 (0.9)
Cardiac disorders	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)

Source: FDA Reviewer Analysis, JMP Clinical 6.1
One subject in the ≥40 to <50×10^9/L High Baseline Platelet Count Cohort received 60 mg avatrombopag and hence is included in the <40×10^9/L Low Baseline Platelet Count Cohort in all safety analyses.

The table below provides further detail regarding TESAEs in the safety population, by preferred term (PT) and treatment group.

Within the Gastrointestinal Disorders SOC, it is noted that there were 2 SAEs of gastrointestinal hemorrhage in the combined avatrombopag treatment group (0.7% [2/274] patients) as compared to no patients in the combined placebo group (0% [0/156] subjects). In addition, there was 1 SAE of esophageal variceal hemorrhage in the 40 mg avatrombopag treatment group (0.4% [1/274] patients) as compared to no variceal bleeding events in the combined placebo group (0% [0/156] patients).

There were 2 SAEs (1.3%, [2/156]) of postprocedural bleeding that occurred in the combined placebo group. There were no postprocedural bleeding SAEs that occurred in the combined avatrombopag treatment group.

There were TESAEs of transfusion reactions and anaphylactic transfusion reactions reported in the combined placebo group as those patients received platelet transfusion(s) prior to a procedure.

Table 48: Treatment-Emergent Serious Adverse Events by Preferred Term Occurring in at least 1 Patient, Pooled Safety Population (Studies 310 and 311)

	Low Baseline Platelet Count Cohort		**High Baseline Platelet Count Cohort**	
Preferred Term	Placebo (N=91)	60 mg Avatrombopag (N=159)	Placebo (N=65)	40 mg Avatrombopag (N=115)
Gastrointestinal hemorrhage	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.9)
Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Ascites	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Esophageal variceal hemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Diarrhea	0 (0.0)	1 (0.6)	1 (1.5)	0 (0.0)
Hematemesis	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Left upper quadrant pain	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Paralytic ileus	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)

Transfusion reaction	3 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)
Post procedural bleeding	1 (1.1)	1 (0.6)	0 (0.0)	0 (0.0)
Anaphylactic transfusion reaction	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Postoperative pain	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Procedural bleeding	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Fever	1 (1.1)	0 (0.0)	1 (1.5)	0 (0.0)
Anasarca	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Multiple organ failure	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.9)
Cellulitis of leg	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Clostridium difficile infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Pneumonia	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Sepsis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Urinary tract infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Hepatic encephalopathy	2 (2.2)	1 (0.6)	0 (0.0)	0 (0.0)
Hepatic coma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Syncope	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Anemia	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Dehydration polycythemia	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Splenomegaly	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Hyperkalemia	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Hyponatremia	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Hyponatremia aggravated	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Clostridium difficile test positive	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Platelet count decreased	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Generalized muscle aches	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Muscle spasm	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Acute kidney injury	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Azotemia	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Acute respiratory failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Nose bleed	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
End stage liver disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Acute myocardial infarction	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)

Source: FDA Reviewer Analysis, JMP Clinical 6.1

One subject in the ≥40 to <50×10^9/L High Baseline Platelet Count Cohort received 60 mg avatrombopag and hence is included in the <40×10^9/L Low Baseline Platelet Count Cohort in all safety analyses.

The majority of observed SAEs were deemed unrelated to treatment by the applicant.

The incidence of treatment-related TESAEs was 0.4% (1/274 subjects) in the combined avatrombopag treatment group and 1.3% (2/156 patients) in the combined placebo treatment group. The only treatment-related TESAEs in avatrombopag-treated patients were anemia (0.4% [1/274] patients; placebo, 0% [0/156] patients) and myalgia (avatrombopag, 0.4% [1/274] patients; placebo, 0% [0/156] patients) in the low baseline platelet count cohort avatrombopag treatment group. There were no treatment-related TESAEs in the avatrombopag treated patients in the high baseline platelet count cohort.

In the placebo group, the only TESAEs deemed to be treatment-related were decreased platelet

count (avatrombopag, 0% [0/159] patients; placebo, 1.1% [1/91] patients) in the low baseline platelet count cohort, and diarrhea (avatrombopag, 0% [0/115] patients; placebo, 1.5% [1/65 patients) and pyrexia (avatrombopag, 0% [0/115] patients; placebo, 1.5% [1/65] patients) in the high baseline platelet count cohort.

Narrative of Non-Fatal Related Serious Adverse Event

Patient (b) (6) was a 78-year-old white male with a history of liver cirrhosis with a MELD Score of 12, esophageal varices, and insulin dependent diabetes mellitus. He was randomized to the low baseline platelet cohort 60 mg avatrombopag treatment group.

On follow up Study Day 4, the patient reported diffuse muscle pain and difficulty walking (Grade 3 myalgia) and was diagnosed with concomitant anemia (Grade 3). Hemoglobin was 7.4 g/dL on Study Day 4 (unknown baseline). There were no associated electrolyte abnormalities. Renal function was within normal limits, as well as LFTs. The patient discontinued the study after 3 days of avatrombopag treatment due to these events and was hospitalized. Therefore, no elective procedure was performed. Treatment included intravenous hydration and tramadol. The event of myalgia resolved on Study Day 7. At date of study discontinuation and last available report, the event of anemia was ongoing. The event of myalgia was listed as possibly related to study drug given that the patient had no prior history of myopathy, myalgia, or muscular pain, and had no history of rheumatologic disease or infection. Review of concomitant medications did not identify other drugs associated with myalgia or myopathy.

Reviewer Comment: The observed SAE of myalgia may be related to avatrombopag-treatment, I concur with the applicant's assessment. Review of concomitant medications did not identify other drugs associated with myalgia or myopathy. The etiology of the patient's anemia remains unclear as per information provided by the applicant. It cannot be elucidated as to whether the acute anemia was secondary to a gastrointestinal bleed in the setting of esophageal varices. The causal relationship between avatrombopag treatment and the SAE of acute anemia cannot be assessed by this reviewer.

Dropouts and/or Discontinuations Due to Adverse Effects

In the pooled safety population, 0.7% (2/274) of patients in the combined avatrombopag treatment group experienced a TEAE that led to study drug discontinuation. No patients in the combined placebo group had a TEAE that resulted in discontinuation of study placebo. Of the 2 patients who experienced a TEAE leading to study drug discontinuation, both patients were in the low baseline platelet cohort and randomized to the 60 mg avatrombopag treatment group. Subject (b) (6) experienced anemia and myalgia which were deemed to be treatment-related TESAEs. Patient (b) (6) experienced pyrexia which led to study drug being discontinued.

Only 0.4% (1/275) and 0.6% (1/156) of patients in the combined avatrombopag treatment and placebo groups experienced a TEAE that led to study discontinuation.

Reviewer Comment: Overall, there were very few patients who discontinued study treatment secondary to an adverse event in the pooled safety population.

Significant Adverse Events

Table 49: Grade 3-4 Adverse Events by System Organ Class and Preferred Term in at least 1 Patient, Safety Population (Studies 310 and 311)

		Low Baseline Platelet Count Cohort		High Baseline Platelet Count Cohort	
Primary System Organ Class	**Preferred Term**	60 mg Placebo (N=91)	60 mg Avatrombopag (N=159)	40 mg Placebo (N=65)	40 mg Avatrombopag (N=115)
Investigations	Neutrophil count decreased	0 (0.0)	1 (0.6)	0 (0.0)	2 (1.7)
	Absolute neutrophil count decreased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.87)
	White blood cell decreased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.87)
	AST increased	1 (1.1)	1 (0.6)	0 (0.0)	1 (0.87)
	Uric acid increased	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.87)
	Clostridium difficile test positive	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
	GGT increased	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Thrombocytopenia aggravated	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.87)
	Platelet count decreased	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Serum bilirubin increased	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	Hematemesis	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)
	Ascites	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
	Bleeding esophageal varices	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.87)
	Constipation	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
	Diarrhea aggravated	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
	Gastrointestinal hemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.87)
	Upper gastrointestinal bleeding	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
	Heartburn	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
	Hypochondrium pain right	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)

	Left upper quadrant pain	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
	Right upper quadrant pain	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
	Nausea	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Paralytic ileus	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.87)
Blood and lymphatic system disorders	Anemia	1 (1.1)	1 (0.6)	0 (0.0)	0 (0.0)
	Coagulopathy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.87)
	DIC	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)
	Dehydration polycythemia	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
	Hemorrhagic anemia	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
	Splenic infarction	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
	Splenomegaly	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	Electrolyte abnormality	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
	Hyperglycemia	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)
	Hyperkalemia	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
	Hyperuricemia	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Hypokalemia	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Hyponatremia	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
	Hyponatremia aggravated	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.87)
Nervous system disorders	Hepatic encephalopathy	2 (2.1)	2 (1.2)	0 (0.0)	0 (0.0)
	Headache	1 (1.1)	0 (0.0)	0 (0.0)	1 (0.87)
	Syncope	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Infections and infestations	Cellulitis of leg	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.87)
	Clostridium difficile infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.87)
	Pneumonia	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
	Sepsis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.87)
	Urinary tract infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.87)
Injury, poisoning and procedural complications	Anaphylactic transfusion reaction	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Hypotensive transfusion reaction	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Pain post biopsy	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
	Procedural bleeding	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatobiliary disorders	End stage liver disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.87)
	Hyperbilirubinemia	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)

	Portal vein thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.87)
Respiratory, thoracic and mediastinal disorders	Acute respiratory failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.87)
	Aspiration pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.87)
	Pulmonary embolism	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)
General disorders and administration site conditions	Multiple organ failure	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)
Psychiatric disorders	Anxiodepressive syndrome	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.87)
	Depressed state	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.87)
Vascular disorders	Hypertension aggravated	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Blood pressure increased	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Low blood pressure	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	Generalized muscle aches	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Renal and urinary disorders	Acute kidney injury	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)

Source: FDA Reviewer JMP Clinical 6.1 Analysis
One subject in the ≥40 to <50×10^9/L High Baseline Platelet Count Cohort received 60 mg avatrombopag and hence is included in the <40×10^9/L Low Baseline Platelet Count Cohort in all safety analyses.

Treatment Emergent Adverse Events and Adverse Reactions

Treatment emergent adverse events (TEAEs) were assessed through 30 days after the last administration of avatrombopag. The numbers of patients who experienced a TEAE are shown in the table below by SOC.

54.4% of patients (234/430 patients) in the safety population experienced a TEAE. The overall incidence of TEAEs was 54.0% (184/274 patients) in the combined avatrombopag treatment group as compared to 55.1% (81/156) patients in the combined placebo group. The most common TEAEs occurred in the Gastrointestinal Disorders and General Disorders and Administration Site Conditions SOCs in both the combined avatrombopag and placebo groups. There were slightly more patients who experienced TEAEs in the Gastrointestinal Disorders SOC in the combined avatrombopag treatment (27.7%, 76/274 patients) group versus the combined placebo group (26.9%, 42/156 patients), respectively.

Other common (>10%) TEAES in the combined placebo treatment group fell into the Nervous System Disorders and Injury, Poisoning, and Procedural Complications SOCs.

Table 50: Treatment Emergent Adverse Events by SOC in the Safety Population (Studies 310 and 311)

	Low Baseline Platelet Count Cohort		High Baseline Platelet Count Cohort	
System Organ Class	60 mg Placebo (N=91)	60 mg Avatrombopag (N=159)	40 mg Placebo (N=65)	40 mg Avatrombopag (N=115)
Gastrointestinal disorders	26 (28.5)	47 (29.6)	16 (24.6)	29 (25.2)
General disorders and administration site conditions	20 (22.0)	38 (23.9)	11 (16.9)	17 (14.8)
Nervous system disorders	13 (14.2)	14 (8.8)	5 (7.7)	9 (7.8)
Injury, poisoning and procedural complications	13 (14.2)	16 (10.1)	5 (7.7)	3 (2.6)
Infections and infestations	8 (8.8)	5 (3.1)	4 (6.2)	11 (9.6)
Respiratory, thoracic and mediastinal disorders	9 (9.9)	7 (4.4)	1 (1.5)	10 (8.7)
Investigations	7 (7.7)	11 (6.9)	2 (3.1)	6 (5.2)
Musculoskeletal and connective tissue disorders	4 (4.4)	11 (6.9)	1 (1.5)	6 (5.2)
Metabolism and nutrition disorders	7 (7.7)	6 (3.8)	1 (1.5)	6 (5.2)
Skin and subcutaneous tissue disorders	4 (4.4)	8 (5.0)	1 (1.5)	2 (1.7)
Blood and lymphatic system disorders	1 (1.1)	6 (3.8)	1 (1.5)	4 (3.5)
Psychiatric disorders	0 (0.0)	5 (3.1)	0 (0.0)	5 (4.3)
Renal and urinary disorders	1 (1.1)	2 (1.3)	2 (3.1)	4 (3.5)
Vascular disorders	2 (2.2)	4 (2.5)	0 (0.0)	1 (0.9)
Hepatobiliary disorders	0 (0.0)	3 (1.9)	1 (1.5)	2 (1.7)
Eye disorders	0 (0.0)	4 (2.5)	0 (0.0)	1 (0.9)
Cardiac disorders	1 (1.1)	1 (0.6)	1 (1.5)	1 (0.9)
Ear and labyrinth disorders	0 (0.0)	0 (0.0)	1 (1.5)	1 (0.9)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0 (0.0)	2 (1.2)	0 (0.0)	0 (0.0)
Congenital, familial and genetic disorders	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)
Endocrine disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)

Source: FDA Reviewer JMP Clinical 6.1 Analysis

One subject in the ≥40 to <50×10^9/L High Baseline Platelet Count Cohort received 60 mg avatrombopag and hence is included in the <40×10^9/L Low Baseline Platelet Count Cohort in all safety analyses.

Common TEAEs, defined as occurring in greater than 3% of the safety population are outlined in the following table. The most common TEAEs in all treatment groups included nausea, abdominal pain, diarrhea, peripheral edema, fatigue, headache, and dizziness. Of note, there were slightly more TEAES of pyrexia in the 60 mg avatrombopag treatment group as compared to placebo but this trend was not seen in the high baseline platelet cohort.

Table 51: Treatment Emergent Adverse Events by PT in >3% of Patients in the Safety Population (Studies 310 and 311)

	Low Baseline Platelet Count Cohort		High Baseline Platelet Count Cohort	
Preferred Term	60 mg Placebo (N=91)	60 mg Avatrombopag (N=159)	40 mg Placebo (N=65)	40 mg Avatrombopag (N=115)
Nausea	7 (7.7)	10 (6.3)	4 (6.1)	8 (7.0)
Abdominal pain	6 (6.6)	10 (6.3)	4 (6.1)	8 (7.0)
Abdominal pain upper	5 (5.5)	6 (3.8)	3 (4.6)	2 (1.7)
Diarrhea	4 (4.4)	7 (4.4)	2 (3.1)	3 (2.6)
Edema peripheral	2 (2.2)	5 (3.1)	1 (1.5)	4 (3.4)
Pyrexia	8 (8.8)	18 (11.3)	6 (9.2)	9 (7.8)
Fatigue	4 (4.4)	7 (4.4)	1 (1.5)	3 (2.6)
Headache	7 (7.7)	7 (4.4)	3 (4.6)	8 (7.0)
Dizziness	4 (4.4)	5 (3.1)	2 (3.1)	2 (1.7)
Procedural pain	2 (2.2)	8 (5.0)	0 (0.0)	0 (0.0)

Source: FDA Reviewer JMP Clinical 6.1 Analysis

One subject in the ≥40 to <50×10^9/L High Baseline Platelet Count Cohort received 60 mg avatrombopag and hence is included in the <40×10^9/L Low Baseline Platelet Count Cohort in all safety analyses.

Reviewer Comment: Adverse events including nausea, abdominal pain, diarrhea, and peripheral edema would not be unanticipated given that the patient population was comprised of patients with a history of CLD. There were more TEAES of pyrexia in the 60 mg avatrombopag treatment group as compared to placebo but this trend was not seen in the high baseline platelet cohort.

Treatment-Emergent Adverse Events of Special Interest (AESI)

There were 3 pre-defined AESI categories in studies 310 and 311 which included thromboembolic events, bleeding events (WHO Grade 2-4) and recurrence of thrombocytopenia (platelet count < 10^9/L or 10 x 10^9/L less than baseline platelet count within 30 days of discontinuation). There was concern for thromboembolic events in avatrombopag treated patients given previous experience with other TPO agonists and observed thrombotic events on clinical trials.

Overall, 3.6% of avatrombopag treated patients (10/274) developed TEASIs as compared to 5.8% (9/156) of patients receiving placebo.

In the thromboembolic category, treatment-emergent AESIs were reported in 0.4% (1/274) of avatrombopag-treated patients and in 1.3% (2/156 patients) of patients who received placebo. The treatment emergent thromboembolic AESIs included portal vein thrombosis (PVT) in a patient treated with avatrombopag; pulmonary embolism and myocardial infarction occurred in 2 patients who received placebo. In addition, there was 1 nontreatment-emergent AESI of portal vein thrombosis in a patient who was treated with avatrombopag. Narratives for both patients who developed portal vein thrombosis are provided below.

Summary of Portal Vein Thrombotic Events

Case 1: The 1 treatment-emergent AESI of PVT occurred in Patient (b) (6), a 71-year-old male randomized to the high baseline platelet count 40 mg avatrombopag treatment group. The patient's medical history included chronic hepatitis B virus (HBV) infection, liver cirrhosis, gastroesophageal varices, cholelithiasis, hypertension, prior aortic aneurysm and benign prostatic hypertrophy.

The patient's screening platelet count was 46,000/µL, followed by a baseline platelet count of 45,000/µL and Visit 3 platelet count of 45,000/µL. On Procedure Day (Study Day 11), the patient's peak platelet count was 77,000/µL, and he underwent upper gastrointestinal endoscopy with variceal banding.

Platelet count obtained 7 days post-procedure (Visit 5, Day 18) was 61,000/µL. On Study Day 18 (Visit 5), the patient was "asymptomatic" and a partial, non-occlusive PVT was identified by routine doppler examination. The event of PVT was deemed non-serious as the patient remained clinically asymptomatic and possibly related to study drug. The patient's platelets decreased to baseline (45,000/µL) at follow-up Visit 6 (Study Day 37). No significant liver function test derangements were observed after the event of non-occlusive PVT.

Reviewer Comment: The information provided by the applicant is inadequate to determine the cause of PVT in this patient. It is unclear why doppler ultrasonography was performed given that the patient's platelet count had not exceeded the designated threshold at Visit 5 and the patient was reportedly "asymptomatic." The causal relationship between avatrombopag treatment and the event of partial PVT cannot be assessed by this reviewer.

Case 2: One nontreatment-emergent AESI of PVT occurred in Patient (b) (6), a 46-year-old female randomized to the low baseline 60 mg avatrombopag treatment group. The patient's medical history included autoimmune hepatitis, esophageal varices, ascites, prior endoscopic ligation, gastroesophageal reflux disease and asthma. The patient's baseline platelet count was 13,500 /µL and on Study Day 4 was 19,000/µL. On procedure day (Day 12), the patient's platelet count was 23,000/µL and the patient was transfused with 2 units of platelets before undergoing splenic artery embolization. The patient developed post-procedure abdominal pain and sepsis with a platelet count on Day 15 of 86,000/µL. Platelet count on Day 26 was 178,000/µL. On Day 36 (31 days from last avatrombopag dose), the patient's platelet count was 93,000/µL when PVT was identified on routine computed tomography (CT) scan of the abdomen. The investigator assessed the event as serious and not related to avatrombopag, but secondary to the extensive splenic infarction resulting from splenic artery embolization. This case was confounded by its temporal relationship to study drug treatment, the administered platelet transfusions, sepsis, and the reported incidence of PVT as a complication of splenic artery embolization.

Reviewer Comment: This reviewer concurs with the applicant's assessment that study treatment was likely unrelated to the nontreatment-emergent event of PVT. The case was confounded by the study procedure, splenic artery embolization which is associated with development of PVT as well as the administered platelet transfusions prior to the procedure, and sepsis.

In the WHO Grade 2-4 AESI category, 3.3% (9/274) of patients in the combined avatrombopag treatment group experienced a bleeding event versus 4.9% (7/156) patients in the combined placebo group. Of note, gastrointestinal hemorrhage occurred in 2 avatrombopag treated patients (1 in the 60 mg treatment group and 1 in the 40 mg treatment group). There was only 1 patient

who developed gastrointestinal hemorrhage in the combined placebo group. In the combined placebo group, there were 2 patients with post-procedural hemorrhage. The applicant noted that 2 bleeding events occurred secondary to trauma in patients who received 60 mg avatrombopag; a varicose vein bleeding event secondary to a "cat scratch" and a bleeding event secondary to laceration. Further details regarding these events were not provided in narrative form.

There was only 1 AESI of recurrence of thrombocytopenia and that occurred in the placebo group.

Laboratory Findings

This section provides a summary of hematologic and non-hematologic laboratory parameters in the pooled safety population (Studies 310 and 311).

Mean values over time for hematology parameters (excluding platelet count) were generally similar between the combined avatrombopag and placebo treatment groups. Overall, the shifts from baseline to the highest and lowest post baseline value were normal. A higher percentage of patients in the combined avatrombopag treatment group had markedly abnormal low lymphocyte counts as compared to the combined placebo treatment group (37.6% [100/274] patients and 32.0% [49/156] patients, respectively), while a lower percentage had markedly abnormal low leukocytes when compared to placebo (32.1% [87/274] patients and 37.7% [58/156] patients, respectively).

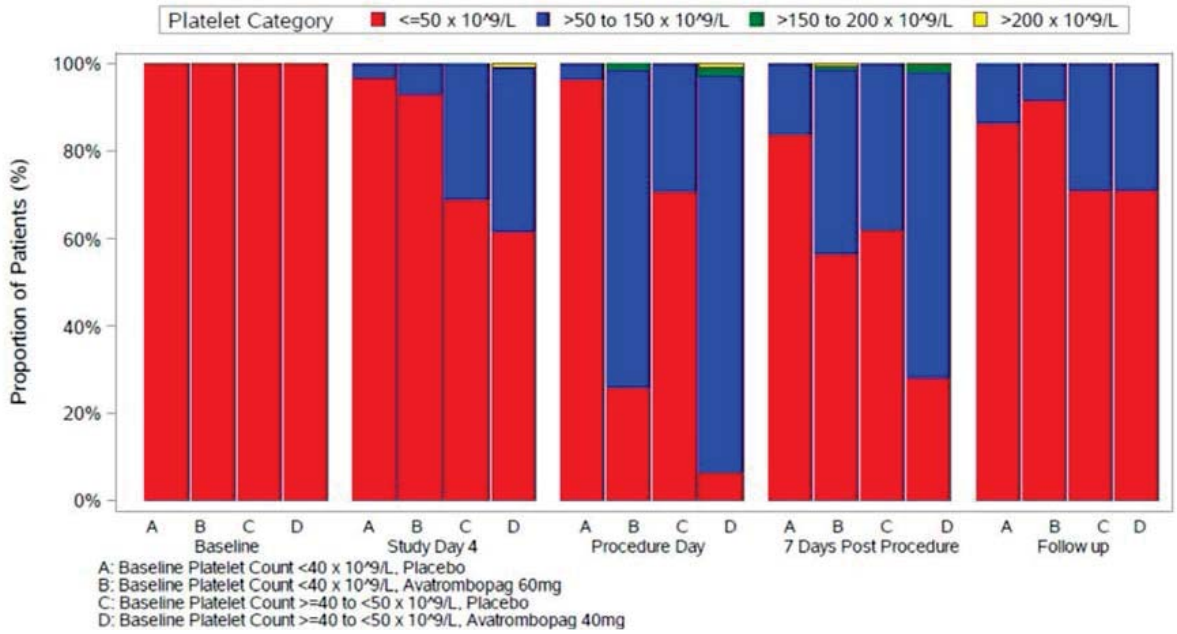
An extensive discussion regarding changes in platelet counts will not be presented as this is also presented in Section 8.1.3 of the review. The mean platelet count in the combined avatrombopag treatment groups in both baseline platelet count cohorts started to increase on Day 4 of treatment (Visit 3), peaked at Study Days 10 to 13 (Visit 4, Procedure Day), and then started to decrease by 7 days post procedure (Visit 5), returning to baseline values by Study Day 35 (Visit 6, Follow-up).

The peak mean platelet count on Procedure Day (Visit 4) for the combined 60 mg avatrombopag treated patients was 65,300/µL and 86,700/µL for the combined 40 mg avatrombopag treated patients, both groups had an approximate 2-fold increase from baseline mean platelet count.

Only 3 (1.1%) avatrombopag-treated patients had a platelet count greater than or equal to 200,000/µL at any visit.

The following figure depicts the proportion of patients who achieved platelet thresholds of less than 50,000/µL, greater than 50,000/µL to less than 150,000/µL, greater than 150,000/µL to less than 200,000/µL, and greater than 200,000/µL by respective treatment group.

Table 52: Bar Chart of Platelet Category by Study Day Visit



Source: Figure reproduced from Applicant's Integrated Summary of Safety, Figure 20.5.1.2

The following table outlines treatment-emergent events of worst post-baseline laboratory assessments at any visit for the pooled safety population.

Table 53: Treatment-Emergent Worst Post-Baseline Laboratory Assessments at Any Visit in the Pooled Safety Population (Studies 310 and 311)

	Low Baseline Platelet Count Cohort		High Baseline Platelet Count Cohort	
	60 mg Placebo	60 mg Avatrombopag	40 mg Placebo	40 mg Avatrombopag
Laboratory Test				
Alanine Aminotransferase Markedly Abnormal High	1	5	2	1
Albumin Markedly Abnormal Low	12	26	9	11
Alkaline Phosphatase Markedly Abnormal High	2	1	0	0
Aspartate Aminotransferase Markedly Abnormal High	7	10	6	5
Bicarbonate Decreased Markedly Abnormal Low	1	0	1	1
Bilirubin Markedly Abnormal High	12	14	13	15
Calcium	2	7	2	8

Markedly Abnormal Low				
Creatinine Markedly Abnormal High	0	0	0	3
Direct Bilirubin Markedly Abnormal High	9	14	3	13
Gamma Glutamyl Transferase Markedly Abnormal High	3	2	3	2
Glucose Markedly Abnormal Low	0	0	0	1
Glucose Markedly Abnormal High	3	8	2	6
Hemoglobin Markedly Abnormal Low	6	13	9	12
Leukocytes Markedly Abnormal Low	34	53	24	58
Lymphocytes Markedly Abnormal Low	28	53	21	47
Neutrophils Markedly Abnormal Low	22	56	23	32
Phosphate Markedly Abnormal Low	0	1	0	1
Potassium Markedly Abnormal High	0	1	0	2
Sodium Markedly Abnormal Low	0	2	2	4
Sodium Markedly Abnormal High	0	1	0	0
Triglycerides Markedly Abnormal High	0	2	1	0

Source: Data derived from Applicant's Integrated Summary of Safety Appendix 1 and confirmed via Reviewer JMP Clinical 6.1 Analysis
Note: There was variable missing laboratory data for each respective test at follow up from baseline so percentages are not represented in the above table, only raw event numbers for each treatment group.

Liver Function Tests

The applicant provided shift from baseline to highest post-baseline value at any visit for the laboratory parameters of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase and total bilirubin.

Table 54: Shift from Baseline to Highest Post-Baseline Value at any Visit for LFTs in the Pooled Safety Population (Studies 310 and 311)

Laboratory Test (Unit) / Baseline Platelet Count Cohort / Treatment / Category	Low (n) (%)	Normal (n) (%)	High (n) (%)	Total (n) (%)
Alkaline Phosphatase (U/L)				
Baseline Platelet Count <40 x 10^9/L				
Placebo (N=91)				
Low	0	0	0	0
Normal	0	43 (49.4)	3 (3.4)	46 (52.9)
High	0	9 (10.3)	32 (36.8)	41 (47.1)
Total	0	52 (59.8)	35 (40.2)	87 (100)
Avatrombopag 60mg (N=159)				
Low	0	0	0	0
Normal	0	88 (56.4)	4 (2.6)	92 (59.0)
High	0	13 (8.3)	51 (32.7)	64 (41.0)
Total	0	101 (64.7)	55 (35.3)	156 (100)
Baseline Platelet Count >=40 to <50 x 10^9/L				
Placebo (N=65)				
Low	0	0	0	0
Normal	0	39 (61.9)	2 (3.2)	41 (65.1)
High	0	2 (3.2)	20 (31.7)	22 (34.9)
Total	0	41 (65.1)	22 (34.9)	63 (100)
Avatrombopag 40mg (N=115)				
Low	0	0	0	0
Normal	0	57 (50.0)	3 (2.6)	60 (52.6)
High	0	7 (6.1)	47 (41.2)	54 (47.4)
Total	0	64 (56.1)	50 (43.9)	114 (100)
Alanine Aminotransferase (U/L)				
Baseline Platelet Count <40 x 10^9/L				
Placebo (N=91)				
Low	0	0	0	0
Normal	0	52 (61.2)	4 (4.7)	56 (65.9)
High	0	6 (7.1)	23 (27.1)	29 (34.1)
Total	0	58 (68.2)	27 (31.8)	85 (100)
Avatrombopag 60mg (N=159)				
Low	0	0	0	0
Normal	0	90 (57.7)	7 (4.5)	97 (62.2)
High	0	8 (5.1)	51 (32.7)	59 (37.8)
Total	0	98 (62.8)	58 (37.2)	156 (100)
Baseline Platelet Count >=40 to <50 x 10^9/L				
Placebo (N=65)				
Low	0	0	0	0
Normal	0	34 (54.0)	0	34 (54.0)
High	0	4 (6.3)	25 (39.7)	29 (46.0)
Total	0	38 (60.3)	25 (39.7)	63 (100)
Avatrombopag 40mg (N=115)				
Low	0	0	0	0
Normal	0	60 (52.6)	5 (4.4)	65 (57.0)
High	0	6 (5.3)	43 (37.7)	49 (43.0)
Total	0	66 (57.9)	48 (42.1)	114 (100)

Source: Table Reproduced from Applicant's Integrated Summary of Safety Appendix 1, Table 20.5.2.1.2.1

Laboratory Test (Unit) / Baseline Platelet Count Cohort / Treatment / Category	Low (n) (%)	Normal (n) (%)	High (n) (%)	Total (n) (%)
Aspartate Aminotransferase (U/L)				
Baseline Platelet Count <40 x 10^9/L				
Placebo (N=91)				
Low	0	0	0	0
Normal	0	19 (22.6)	5 (6.0)	24 (28.6)
High	0	6 (7.1)	54 (64.3)	60 (71.4)
Total	0	25 (29.8)	59 (70.2)	84 (100)
Avatrombopag 60mg (N=159)				
Low	0	0	0	0
Normal	0	42 (27.1)	3 (1.9)	45 (29.0)
High	0	10 (6.5)	100 (64.5)	110 (71.0)
Total	0	52 (33.5)	103 (66.5)	155 (100)
Baseline Platelet Count >=40 to <50 x 10^9/L				
Placebo (N=65)				
Low	0	0	0	0
Normal	0	10 (15.9)	2 (3.2)	12 (19.0)
High	0	5 (7.9)	46 (73.0)	51 (81.0)
Total	0	15 (23.8)	48 (76.2)	63 (100)
Avatrombopag 40mg (N=115)				
Low	0	0	0	0
Normal	0	28 (24.8)	3 (2.7)	31 (27.4)
High	0	5 (4.4)	77 (68.1)	82 (72.6)
Total	0	33 (29.2)	80 (70.8)	113 (100)

Bilirubin (umol/L)				
Baseline Platelet Count <40 x 10^9/L				
Placebo (N=91)				
Low	0	0	0	0
Normal	0	21 (24.7)	3 (3.5)	24 (28.2)
High	0	10 (11.8)	51 (60.0)	61 (71.8)
Total	0	31 (36.5)	54 (63.5)	85 (100)
Avatrombopag 60mg (N=159)				
Low	0	0	0	0
Normal	0	40 (25.6)	11 (7.1)	51 (32.7)
High	0	14 (9.0)	91 (58.3)	105 (67.3)
Total	0	54 (34.6)	102 (65.4)	156 (100)
Baseline Platelet Count >=40 to <50 x 10^9/L				
Placebo (N=65)				
Low	0	0	0	0
Normal	0	14 (22.2)	2 (3.2)	16 (25.4)
High	0	8 (12.7)	39 (61.9)	47 (74.6)
Total	0	22 (34.9)	41 (65.1)	63 (100)
Avatrombopag 40mg (N=115)				
Low	0	0	0	0
Normal	0	28 (24.6)	4 (3.5)	32 (28.1)
High	0	13 (11.4)	69 (60.5)	82 (71.9)
Total	0	41 (36.0)	73 (64.0)	114 (100)

Source: Table Reproduced from Applicant's Integrated Summary of Safety Appendix 1, Table 20.5.2.1.2.1

FDA evaluation for clinically significant changes in liver function tests (LFTs) and potential cases of drug induced liver injury (DILI) was confounded by the fact that all enrolled patients in Studies 310 and 311 had a history of chronic liver disease with variable degrees of hepatic dysfunction as represented by changes in alkaline phosphatase level, transaminases, and hyperbilirubinemia. In addition, permitted procedures included transarterial hepatic chemoembolization (TACE) for HCC which can be associated with significant post-treatment LFT derangements. As such, significant changes in AST, ALT and total bilirubin were challenging to assess given the natural history and anticipated fluctuations in LFTs in this specific patient population.

No cases of potential DILI were identified by independent review with exception of 1 treatment-emergent adverse event of chronic hepatic failure/end-stage liver disease in the pooled safety population. A patient narrative is provided below.

Patient Narrative for Treatment-Emergent Adverse Event of Chronic Hepatic Failure/End-Stage Liver Disease

Patient (b) (6) was a 50-year-old white male. His medical history included chronic hepatitis C virus (HCV) infection and hepatic cirrhosis. The patient's baseline MELD score was 11 and Child Pugh Grade was B. The patient's baseline LFTs included slightly increased total bilirubin (27 µmol/L) and direct bilirubin (8 µmol/L); AST, ALT, GGT and alkaline phosphatase were within normal limits. The patient was randomized to the high baseline platelet 40 mg avatrombopag treatment group and received the planned 5-day treatment (completed avatrombopag on Study Day 5) prior to a scheduled dental procedure. The patient underwent an uncomplicated dental procedure on Study Day 13. On the day of the procedure, the patient's LFTs were all within normal limits.

On Study Day 28, the patient was diagnosed with chronic hepatic failure [end-stage liver disease] (Grade 4) which was considered a SAE and resulted in hospitalization. The patient underwent liver transplantation on the same day.

No LFT measurements were available on Study Day 28 or afterwards so it was not known if there was interval worsening of the patient's baseline hepatic function. It was not known from the case report form if the patient had been listed for hepatic transplantation or if the procedure occurred in an emergent situation secondary to hepatic decompensation.

No other AEs were recorded within a +/- 3-day window around the onset of the event. Concomitant medications taken at the onset of the SAE included furosemide, isosorbide mononitrate, lactulose, rabeprazole, and rifaximin.

The investigator considered the AE to be not related to study medication. The event ended on Day 43 with an outcome of recovered/resolved.

An information request was sent to the applicant regarding this patient case, specifying that further detail regarding the event of hepatic transplantation was required. The following response was received by the applicant on February 15, 2018:

"This 50-year-old subject (Subject # (b) (6)) with a history of hepatitis C (b) (6) and hepatic cirrhosis (b) (6) was randomized to the High Baseline Platelet Count Cohort in Study 310. He received 5 days of 40 mg avatrombopag with an increase in mean Baseline platelet count from 45,000 to 118,000 on Procedure Day (Day 13, Visit 4). The subject underwent the scheduled dental surgery with no transfusion or rescue procedures for bleeding. As requested, the full chronology of events for this subject is summarized in the table below, and tables of all available vital signs, laboratory results and concomitant medications are attached.

An SAE of "Liver Transplantation" was reported for this subject on Study Day 28, 25 days after the last dose of avatrombopag, that resolved on Day 43. Per the study protocol, "all liver transplantations are to be captured as SAEs." We are following-up with the investigator for confirmation, but believe that this subject was on the liver transplant list for his chronic liver disease resulting from viral hepatitis and cirrhosis, and was hospitalized on (b) (6) (Study Day 28), when a liver match was identified; there are no data to suggest there was an acute hepatic decompensation or that the liver transplant was done as an emergency procedure. Additional data regarding the liver transplant will be provided to the Agency if received from the investigator. The SAE was initially reported as "liver transplantation," but since that was a procedure and not an event, it was queried and the SAE was then subsequently updated to "end stage liver disease" with the date of onset kept as the date of the hospitalization.

The only liver function test (LFT) measurements available at this time are from screening and Study Day 13. The subject's baseline total and direct bilirubin were mildly elevated at screening (Study Day -13), and these elevations had normalized post-treatment by Study Day 13. Other than a Screening blood pressure of 130/90 mm Hg, his vital signs were normal throughout the study. His concomitant medications at screening included furosemide 75 mg PO BID (b) (6), isosorbide mononitrate 1 tablet PO QD (b) (6), lactulose 1 spoon PO QD (b) (6) rabeprazole 1 tablet PO QD (b) (6) rifaximin 200 mg PO

TID (b) (6) and canrenoic acid 100 mg PO TID (b) (6) and they were not reported to change after screening."

The following tables were provided to the agency by the applicant. They provide a summary of all recorded laboratory measurements, vital signs, and concomitant medications for the aforementioned patient.

Table 55: Subject # (b) (6) Study Summary

STUDY DAY	VISIT	DATE	Comments	Platelets x 10^9/L	LFTs
Day -13 Screening	Visit 1	(b) (6)		42	Increased total and direct bilirubin; other LFTs normal
Day 1 Baseline	Visit 2		First dose of avatrombopag	48	
Day 3	Visit 3			43	
Day 5			Last dose of avatrombopag		
Day 13 Procedure Day	Visit 4		**Procedure Day**- Dental Surgery	118	All LFTs normal
Day 20 Follow-up	Visit 5			57	
Day 28			"Liver transplantation" reported as an SAE (per protocol) due to hospitalization Assessed as **Not Related** to avatrombopag SAE term queried and subsequently changed to "end stage liver disease" (b) (6) Subject underwent liver transplant		
Day 38 Study Completion			Completed study as planned Ongoing AE of "end stage liver disease"		
Day 43			Discharged from hospital post-liver transplant		

			AE of "end stage liver disease" resolved		
Day 58		(b) (6)	Updated SAE term from "liver transplantation" to "end-stage liver disease" Assessed as **Not Related** to study medication		

Table 56: Subject # (b) (6) Laboratory Values

Test	Parameter Code	Screening Visit 1 (b) (6) (Study Day -13)	Visit 4 (b) (6) (Study Day 13)	Visit 6 (b) (6) Follow-up (Study Day 38)
Alanine Aminotransferase (U/L)	ALT	17	11	
Albumin (g/L)	ALB	38	34	
Alkaline Phosphatase (U/L)	ALP	86	82	
Aspartate Aminotransferase (U/L)	AST	20	13	
Bicarbonate (mmol/L)	BICARB	29.1	26.2	
Bilirubin (umol/L)	BILI	27 (High)	16	
Calcium (mmol/L)	CA	2.32	2.23	
Chloride (mmol/L)	CL	101	105	
Cholesterol (mmol/L)	CHOL	2.88	2.71	
Creatine Kinase (U/L)	CK	52	46	
Creatinine (umol/L)	CREAT	88	80	
Creatinine Clearance (mL/s)	CREATCLR	1.92	2.11	
Direct Bilirubin (umol/L)	BILDIR	8 (High)	6	
Gamma Glutamyl Transferase (U/L)	GGT	13	12	
Globulin (g/L)	GLOBUL	38	32	
Glucose (mmol/L)	GLUC	6.2	5.6	
Lactate Dehydrogenase (U/L)	LDH	131	126	
Phosphate (mmol/L)	PHOS	1.06	1.11	
Potassium (mmol/L)	K	3.9	4.0	
Protein (g/L)	PROT	76	66	
Sodium (mmol/L)	SODIUM	140	141	
Triglycerides (mmol/L)	TRIG	0.44	0.50	
Urate (umol/L)	URATE	529 (High)	486	
Urea Nitrogen (mmol/L)	UREAN	6.8	6.5	

Test	Parameter Code	Screening Visit 1 (b) (6) (Study Day -13)	Visit 4 (b) (6) (Study Day 13)	Visit 6 (b) (6) Follow-up (Study Day 38)
Prothrombin Intl. Normalized Ratio	INR	1.3	1.4	1
Prothrombin Time (sec)	PT	14.1	14.5	11.1

Reviewer Comment: At this juncture, the available data do not suggest that DILI was a contributor to this event. However, the agency is awaiting confirmation from the applicant as to whether the patient was listed for transplant and underwent non-emergent hepatic transplantation while on study.

There were 2 Grade 3 AEs of increased AST in the combined avatrombopag treatment group as compared to only 1 Grade 3 adverse event of increased AST in the combined placebo group. In the avatrombopag treatment group, both Grade 3 AEs of increased AST occurred in the setting of recent transarterial chemoembolization for HCC (Patients (b) (6)).

Platelet Function

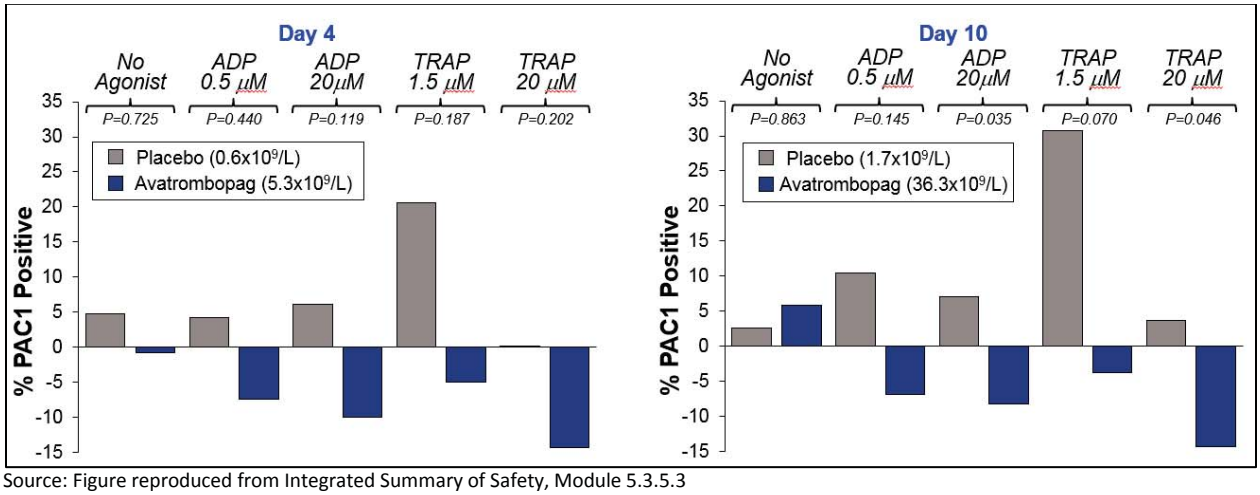
A subset of enrolled patients (n=30) underwent platelet function testing at baseline (Day 1, pre-drug) and after treatment (Day 4 and Day 10).

Platelet activation was evaluated by whole blood flow cytometry with and without in vitro stimulation with adenosine diphosphate (ADP) and thrombin receptor activating peptide (TRAP). Measured endpoints included platelet surface activated glycoprotein (GP) IIb-IIIa (as reported by the activation-dependent monoclonal antibody PAC1) and platelet surface P-selectin.

Platelet reactivity was not increased in avatrombopag-treated patients compared with those who received placebo, as judged by response to low and high concentrations of adenosine diphosphate (ADP) and low and high thrombin receptor activating peptide (TRAP).

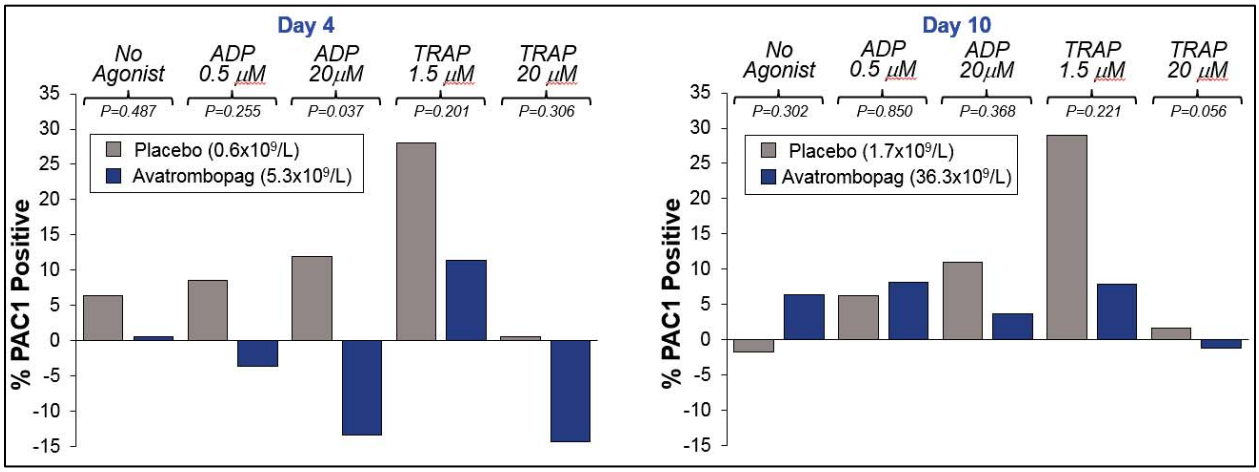
ADP and TRAP-stimulated platelet surface activated GPIIb-IIIa and P-selectin were similar for avatrombopag and placebo patients, supporting that the platelets in avatrombopag-treated patients function normally.

Figure 7: Activated GPIIb-IIIa (PAC1) in Avatrombopag and Placebo Treated Patients



Source: Figure reproduced from Integrated Summary of Safety, Module 5.3.5.3

Figure 8: Platelet Surface P-Selectin in Avatrombopag and Placebo Treated Patients



Source: Figure reproduced from Integrated Summary of Safety, Module 5.3.5.3

Vital Signs

The applicant obtained routine vital signs including temperature, respiratory rate, pulse, systolic and diastolic blood pressure at the screening visit (Day -14 to -1), baseline (Day 1), procedure day (Day 10-13), 7 days after the procedure, and 30 days after the last dose of study drug. The applicant provided mean changes in vital signs from baseline for each visit. Mean changes from baseline for each respective visit were similar between the combined avatrombopag and combined placebo groups. An independent analysis utilizing JMP Clinical 6.1 did not reveal any safety signals or significant derangements in vital signs.

Electrocardiograms (ECGs)

ECGs were obtained in all subjects at baseline and at each study visit. No clinically meaningful changes in QTc were identified in the combined avatrombopag or placebo groups. There were

no cardiac arrhythmia TEAEs in the combined avatrombopag treatment group identified during independent safety review. There one event of Grade 5 myocardial infarction in a patient who received placebo treatment, refer to the patient death narrative for further details. The mean and mean change from baseline ECG results were similar between the combined avatrombopag and combined placebo groups.

QT

The Interdisciplinary Review Team for QT Studies was consulted to review the submitted QT information. This included the study reports for Study 310 and 311, the electronic datasets, and waveforms submitted to the ECG warehouse. The team's findings are summarized as per below:

"The sponsor's ECG assessments from the submitted studies (TQT study E5501-A001-001 submitted to IND (b) (4) and the Phase 3 studies 310 and 311 submitted to NDA 210238) are not adequate to exclude small mean QTc effects (10 ms) at the mean C_{max} corresponding to the proposed therapeutic dosing regimens (40 mg or 60 mg QD for 5 consecutive days). However, the data suggest that no large mean QTc effects (>20 ms) are anticipated with the proposed therapeutic dosing regimens for this acute treatment (5 days)."

After consultation with clinical pharmacology, it was determined that although the data was unable to exclude small mean QTc effects, given the short duration of dosing (5 days), clinically significant changes in QTc are not anticipated with avatrombopag administration.

Immunogenicity

There were no immunogenicity concerns in relation to avatrombopag exposure.

8.2.5. Analysis of Submission-Specific Safety Issues

There are no submission-specific safety issues to address for this application.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

There were no COA analyses that informed safety or tolerability.

8.2.7. Safety Analyses by Demographic Subgroups

There were no demographic subgroup safety concerns identified for this application.

8.2.8. Specific Safety Studies/Clinical Trials

No studies or trials were conducted to evaluate a specific safety concern.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Review of the applicant's pre-clinical data and need for further carcinogenicity studies is deferred to the Pharmacology/Toxicology reviewer.

Pediatrics and Assessment of Effects on Growth

There has been no avatrombopag exposure in pediatric patients.

Drug Abuse Potential

There is no abuse potential for avatrombopag. Avatrombopag is an orally administered thrombopoietin (TPO) receptor (c-MPL) agonist.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Avatrombopag is not marketed in any country. There are no post-market safety data.

Expectations on Safety in the Postmarket Setting

A similar safety profile for avatrombopag is expected in the postmarket setting compared to that observed in the clinical trials. Studies 310 and 311 enrolled a heterogeneous population of patients with CLD with varying degrees of hepatic impairment so that pooled safety results are generalizable to the intended patient population. In the pivotal studies (310 and 311), the safety profile of avatrombopag was comparable to that of placebo. The most commonly reported adverse events in avatrombopag treated patients included nausea, abdominal pain, procedural-related pain, diarrhea, fatigue, dizziness, and pyrexia. SAEs occurred in 7.3% of the combined avatrombopag treated patients versus 9% of patients in the combined placebo group.

8.2.11. Integrated Assessment of Safety

Safety results were presented in a pooled fashion from Studies 310 and 311. A total of 430 patients were included in the safety population analysis set, defined as those randomized patients who received at least 1 dose of study drug and had at least 1 post-dose safety assessment. Patients were randomized in a 2:1 fashion to avatrombopag (differential dosing based on baseline platelet count) or matched placebo. The majority of patients received the planned 5 days of treatment across all treatment groups.

Overall, male patients (65.3%) comprised more of the safety population than female patients (34.7%) and the majority of patients were White (59.8%) and Asian (33.0%). The majority of patients had CLD secondary to chronic viral hepatitis (58.0%), followed by 'other' etiologies of CLD (18.2%), and alcoholic liver disease (14.7%). Baseline platelet counts were comparable between treatment groups in both the low and high baseline platelet count cohorts. Most patients in the pooled safety population did not have a concomitant diagnosis HCC (73.0%).

Similar proportions of patients treated with avatrombopag and respective matched placebo reported adverse events (AEs) (54% (18/274) of patients in the combined avatrombopag treatment group (patients treated with the 40 or 60 mg dose) experienced a treatment emergent AE (TEAE) as compared to 55.1% (81/156) of patients in the combined placebo group). The most common TEAEs (occurring in greater than 3% of the safety population) for both the combined avatrombopag and placebo groups included nausea, abdominal pain, procedural-related pain, diarrhea, fatigue, dizziness, and pyrexia. It is noted that most of the TEAEs observed on both studies would not be unexpected for the study population and no new safety signals were identified.

Serious adverse events (AEs) occurred in 7.3% (20/274) of the combined avatrombopag treated patients versus 9% (14/156) of patients in the combined placebo group.

Thromboembolic events were pre-defined as an adverse event of special interest (AESI) given previous experience with other TPO receptor agonists and observed thrombotic events on clinical trials. In the thromboembolic category, treatment-emergent AESIs were reported in 0.4% (1/274) of avatrombopag-treated patients and 1.3% (2/156 patients) of patients who received placebo. The treatment emergent thromboembolic AESIs included portal vein thrombosis (PVT) in a patient treated with 40 mg avatrombopag; pulmonary embolism and myocardial infarction occurred in 2 patients who received placebo. In addition, there was 1 nontreatment-emergent AESI of portal vein thrombosis in a patient who was treated with 60 mg avatrombopag which was confounded by complications secondary to splenic artery embolization and sepsis, and was deemed not related to study drug. Of note, while the observed incidence of thromboembolic events in avatrombopag treated patients was low, the study only assessed a 5-day treatment period and excluded patients with a prior history of arterial or venous thrombotic events.

No hepatoxicity was identified in avatrombopag treated patients. Furthermore, there was no evidence of increased incidence of clinically significant bleeding and no rebound thrombocytopenia was observed in avatrombopag treated patients as compared to placebo.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

Two statistical issues were identified during the course of this review and were addressed in detail in Section 8.1. In summary, independent statistical review highlighted differential proportions of missing data between treatment arms in both the primary and secondary endpoint assessments. Even though the conclusions stay the same based on the sensitivity analyses, the treatment effect estimates may be biased due to the differential proportions of missing data. The sponsor utilized the LOCF method to impute the missing data for the analysis of change from baseline in platelet counts. In general, the LOCF method for missing data imputation is not recommended. However, due to the small numbers of missing data in both studies, the agency considers the impact of using LOCF as the imputation method to be minimal.

8.4. Conclusions and Recommendations

This clinical reviewer recommends regular approval of avatrombopag (DOPTELET®) for the treatment of thrombocytopenia in patient with chronic liver disease (CLD) undergoing procedures. Approval was based on the proportion of avatrombopag-treated patients who required platelet transfusions or rescue procedures for bleeding from randomization until 7 days after a procedure as well as the proportion of patients who achieved a pre-specified platelet count threshold on the procedure day as compared to patients who received placebo.

This conclusion is supported by the comparable safety profile of avatrombopag as compared to placebo in Studies 310 and 311.

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Yaping Wang, PhD — Primary Statistical Reviewer

Yuan-Li Shen, Dr. P.H. — Statistical Team Leader

X X

Laurel A. Menapace, M.D.
Primary Clinical Reviewer

Andrew Dmytrijuk, M.D.
Acting Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

This application was not presented to an Advisory Committee or any other external consultants.

10 Pediatrics

An Agreed Amended Initial Pediatric Study Plan (iPSP) Agreement Letter was issued on July 12, 2017 under IND 76680 for avatrombopag. The following proposed Postmarketing Requirement (PMRs) under the Pediatric Research Equity Act (PREA) for the avatrombopag new medical entity (NME) should be forwarded to the sponsor. The final wording and milestone dates of PMRs is dependent on sponsor agreement.

- PMR-1: Conduct a study in juvenile rats with avatrombopag administration starting on Day 7 post-partum. Dosing duration should be 10 weeks to cover the entire pediatric age range from neonate through adolescence to adulthood. A minimum 4-week recovery period will be included upon completion of dosing to assess reversibility of any adverse effects or delays in development.
  Final Report Submission: August 2018

- PMR-2: Conduct a study to evaluate the bioavailability of an avatrombopag age appropriate formulation relative to the 20 mg tablet formulation in the fed condition, and to evaluate the effect of food on the bioavailability of the age appropriate formulation in healthy adults. Subjects should undergo serial blood sampling for avatrombopag plasma concentrations at scheduled intervals during each treatment period.
  Final Protocol submission: January 2019
  Final Report Submission: July 2019

- PMR-3: Conduct an open-label study to evaluate the pharmacokinetics, pharmacodynamics, safety, and tolerability of single doses of avatrombopag in pediatric patients (ages 2 to 17 years) with thrombocytopenia associated with liver disease to determine an appropriate dose. Enroll patients to 3 age cohorts: 2 to 6 years, 7 to 11 years, and 12 to 17 years. Patients aged 11 years and younger should receive the age appropriate formulation and patients aged 12 years and older should receive the oral tablet formulation, when appropriate. Subjects should undergo serial blood sampling for avatrombopag plasma concentrations and platelets at scheduled intervals during the study.
  Draft protocol submission: July 2019
  Final Protocol Submission: October 2019
  Enrollment completion: December 2021
  Final Report Submission: April 2022

- PMR-4: Conduct a study to evaluate the efficacy and safety of once-daily oral avatrombopag for the treatment of thrombocytopenia associated with liver disease prior to an elective procedure in pediatric patients ages 2 to 17 years.
  Draft Protocol Submission: April 2022

Final Protocol Submission: June 2022
Enrollment completion: December 2026
Final Report Submission: June 2027

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The following are recommended major changes to prescribing information based on this review:

Table: Significant Labeling Changes

Summary of Significant Labeling Changes		
Section	**Proposed Labeling**	**Approved Labeling**
Highlights, Product Title	DOPTELET (avatrombopag) tablets for oral use	DOPTELET (avatrombopag) tablets, for oral use *Rationale: We added a comma after "tablets" to be consistent with the draft "Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products—Content and Format Guidance for Industry".*
Highlights	n/a	Revised highlights to reflect changes in FPI and for brevity to achieve the ½ page Highlights requirement.
Indications and Usage	DOPTELET (avatrombopag) is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a procedure.	DOPTELET (avatrombopag) is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia (b) (4) in adult patients with chronic liver disease who are scheduled to undergo a procedure. *Rationale: The indication was revised to reflect the (b) (4) "adult" was added to provide clear and consistent communication to HCPs about*

		the indicated population for which we are granting approval.
Dosage and Administration	n/a	FDA proposed the inclusion of text to advise against dosing to normal platelet counts: DOPTELET should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts. Relocated the sentence "Begin Doptelet dosing 10-13 days prior to (b) (4) procedure" to beginning of 2.1 to provide the most important information first. FDA replaced the ≤≥ symbols with text in this section to avoid dosing errors as these symbols are on the ISMPs List of Error Prone Symbols as being frequently misinterpreted and involved in harmful medication errors. FDA deleted proposed (b) (4) We also added a sentence advising clinician to obtain platelet counts prior to therapy and on the day of procedure to ensure adequate increase in platelet count.
Dosage Forms and Strengths	(b) (4) 20 mg tablet, round, biconvex, yellow, film-coated (b) (4) debossed with "AVA" on one side and "20" on the other side.	Tablets: (b) (4) 20 mg avatrombopag as (b) (4), round, biconvex, yellow, film-coated tablets (b) (4) debossed with "AVA" on one side and "20" on the other side. Rationale: Dosage Forms and Strengths has been revised to include limited packaging that facilitates prescribing. (b) (4) the non-proprietary name is permitted.
Warnings and Precautions	5.1 Thrombotic/Thromboembolic (b) (4)	5.1 Thrombotic/Thromboembolic Complications: DOPTELET is a thrombopoietin (TPO) receptor agonist and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease.

	(b) (4)	Portal vein thrombosis has been reported in patients with chronic liver disease treated with TPO receptor agonists. There was 1 event of portal vein thrombosis in a patient with chronic liver disease and thrombocytopenia treated with DOPTELET. Consider the potential increased thrombotic risk when administering DOPTELET to patients with known risk factors for thromboembolism, including genetic prothrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency or Protein C or S deficiency). Rationale: The Warning was revised to Avoid distancing the product from the risk and to inform readers that there was 1 event of portal vein thrombosis in an avatrombopag treated patient.
Adverse Reactions	n/a	FDA added recommendation from the Adverse Reactions guidance to add a sample database description. FDA recommended that Applicant see the Adverse Reactions guidance for advice regarding how to select adverse reactions for selection for the labeling. FDA recommended deletion (b) (4)
Drug Interactions	(b) (4)	FDA recommended deletion (b) (4) .
Use in Specific Populations (8.1)	(b) (4)	FDA revised this section substantially to reflect the PLLR Final Rule and PLLR Guidance recommendations and our current labeling approach. Adverse

		developmental outcomes were observed in rabbits during organogenesis and during lactation period in rats occurred at exposures substantially higher than the recommended human dose.
Use in Specific Populations (b) (4)	(b) (4)	FDA recommended deletion (b) (4)
12 Clinical Pharmacology		12.2 Pharmacodynamics: Applicant asked to provide information on exposure-response relationships. Other revisions made to reflect recommendations in Clinical Pharmacology Guidance.
13 Non-clinical Toxicology		Section revised based upon review of carcinogenicity studies and current labeling approaches.
14 Clinical Studies		FDA recommended that the trial names and/or acronyms and NCT #s be added to this section to permit readers to identify the trials. FDA recommended removal (b) (4) FDA recommended removal (b) (4)
16 How Supplied/Storage and Handling		FDA added “Store tablets in original package.” Rationale: Include statement

		that tablets should be stored in original package based (b) (4) NDA submission.
17 Patient Counseling		FDA proposed revision based upon changes to FPI.

The Applicant's submitted proposed Prescribing Information (PI) and Patient Labeling were reviewed for consistency with labeling regulations and guidances; to ensure that the PI is a useful communication tool for healthcare providers; and uses clear, concise language. All disciplines contributed to the PI revisions. Given that labeling negotiations are ongoing, these recommendations should be considered preliminary and may not represent DHP's final recommendations for the Doptelet labeling.

12 Risk Evaluation and Mitigation Strategies (REMS)

No Risk Evaluation and Mitigation Strategy (REMS) is proposed for this application for avatrombopag , i.e., for the treatment of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a procedure.

13 Post-marketing Requirements and Commitments

Four post-marketing pediatric pre-clinical, clinical pharmacology, and clinical studies are required under PREA for this application for avatrombopag, i.e., for the treatment of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a procedure (see section 10 Pediatrics in this review for additional details regarding PMRs for avatrombopag).

14 Division Director (DHOT)

X

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

(This section was derived in part from the reviews of Drs. Laurel Menapace, Yaping Wang, and Andrew Dmytrijuk.)

On September 21, 2017, AkaRx. Inc. submitted NDA 210238 requesting approval of avatrombopag (Doptelet), which is an orally administered thrombopoietin (TPO) receptor (c-MPL) agonist that promotes megakaryocyte production, maturation, and the formation of platelets, for the following indication: "Patients with thrombocytopenia secondary to chronic liver disease undergoing a (b) (4) procedure with associated bleeding risk." This request relied upon the results of 2 identically designed double-blind, placebo-controlled studies: E5501-G000-310 and E5501-G000-311 (Studies 310 and 311 respectively). Slightly in excess of 400 patients (for both trials) were entered who had chronic liver disease (CLD), a platelet count of <50,000/µL, and who were scheduled to undergo an elective procedure that would typically require platelet transfusion support.

The primary endpoint for the trial was the proportion of patients on each arm who did not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure. A secondary efficacy endpoint included the proportion of patients who achieved platelet counts of >50,000/µL. For patients with a low baseline platelet count (<40,000/µL), a daily dose of 60 mg of avatrombopag for 5 consecutive days was used, while if the baseline platelet count was between ≥40,000/µL to <50,000/µL, the dose was 40mg daily for 5 consecutive days.

Efficacy Results for Study 310: In the low baseline platelet count cohort, the proportion of responders was 65.5% (59/90) in the 60 mg avatrombopag group compared to 22.9% (11/48) in the placebo group. The treatment difference in the proportion of responders (60 mg avatrombopag group minus placebo group) was 42.6% (95% CI [27.2%, 58.1%]), which was statistically significant with P <0.0001 by the CMH test (adjusted for bleeding risk associated with scheduled procedures).

In the high baseline platelet count cohort, the proportion of responders was also larger in the 40 mg treatment group: 88.1% (52/59) compared to the placebo group: 38.2% (13/34). The treatment difference (40 mg avatrombopag group minus placebo group) was 49.9% (95% CI [31.6%, 68.2%]), and was statistically significant favoring avatrombopag with P<0.0001 by the CMH test (adjusted for bleeding risk associated with scheduled procedures).

Efficacy Results for Study 311: In the low baseline platelet count cohort (<40,000/µL), the proportion of responders was 68.6% (48/70) in the 60 mg avatrombopag treatment group compared to 34.9% (15/43) in the placebo group. The treatment difference in the proportion of responders (60 mg avatrombopag group minus placebo group) was 33.7% (95% CI [15.8%,

51.6%]), which was statistically significant with P <0.0006 by the CMH test (adjusted for bleeding risk associated with the scheduled procedures).

In the high baseline platelet count cohort (≥40 to <50,000/µL), the proportion of responders was also larger in the 40 mg avatrombopag treatment group, 87.9% (51/58), compared to the placebo group, 33.3% (11/33). The treatment difference (40 mg avatrombopag group minus placebo group) was 54.6% (95% CI [36.5%, 72.7%]), which was statistically significant favoring avatrombopag with P<0.0001 by the CMH test (adjusted for bleeding risk associated with the scheduled procedures).

Safety Results for Studies 310-311: The pooled Study 310 and 311 populations included 435 subjects. A total of 430 subjects were included in the safety population analysis set, defined as those randomized subjects who received at least 1 dose of study drug and had at least 1 post-dose safety assessment. A total of 250 subjects were randomized to the low baseline platelet count cohort whereas 180 subjects were randomized to the high baseline platelet cohort. There were 274 subjects in the combined avatrombopag treatment group (40 mg or 60 mg avatrombopag) and 156 subjects in the combined placebo group, respectively.

Four deaths occurred in the pooled safety population for Studies 310 and 311. There were 3 treatment emergent deaths. One death occurred more than 30 days after the last dose of study drug and was deemed nontreatment-emergent. Of the 3 treatment-emergent deaths, 2 (0.7%) occurred in patients in the combined avatrombopag treatment group and 1 (0.6%) occurred in a subject in the combined placebo group. None of the treatment emergent deaths were assessed as being related to study drug.

No hepatoxicity was identified in avatrombopag treated patients. Furthermore, there was no evidence of increased incidence of clinically significant bleeding was observed in avatrombopag treated patients as compared to placebo.

Regulatory Recommendation of the Supervisory Associate Division Director: This reviewer agrees with the recommendation of the review teams for approval on the basis of a favorable benefit risk ratio.

X

Albert Deisseroth, M.D.
Associate Division Director

18 Office Director (or designated signatory authority)

Recommendation for action: Approval. The risk-benefit profile was assessed by Drs. Deisseroth, Dmytrijuk, and Menapace, who also recommend approval. My signature below represents the approval decision of this application.

APPEARS THIS WAY ON ORIGINAL

19 Appendices

19.1. References

Mitchell O, Feldman DM, Diakow M, Sigal SH. The pathophysiology of thrombocytopenia in chronic liver disease. Hepat Med. 2016 Apr 15;8:39-50. eCollection 2016.

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Aster RH. Pooling of platelets in the spleen: role in the pathogenesis of “hypersplenic” thrombocytopenia. J Clin Invest. 1966;45(5):645–657.

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19.2. Financial Disclosure

Financial disclosure information for the pivotal Phase 3 studies, 310 and 311, is provided below.

Covered Clinical Study (Name and/or Number): Studies 310 and 311

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 297 (Study 310: 135; Study 311 162)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): Does not apply		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Does not apply Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: Does not apply Significant equity interest held by investigator: Does not apply Sponsor of covered study: Does not apply		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) Does not apply		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Figure 9: Attachment 1 to Form 3455

Attachment 1 to Form 3455

List of Clinical investigators in the Eisai-sponsored study (E5501-G000-311) who received Significant Payments of Other Sorts:

Site Number	Investigator	Facility	Number of Subjects Enrolled	Total Disclosure Amount
[redacted]	[redacted]	[redacted]	(b) (6)	$38,441
				$41,499

19.3. Nonclinical Pharmacology/Toxicology

Two-year (104-Week) carcinogenicity studies with avatrombopag were conducted in mice and rats under Special Protocol Assessments using recommendations from the Executive Carcinogenicity Assessment Committee regarding the doses and design of the studies. These studies are reviewed in detail in a separate Pharmacology/Toxicology review. The Executive Carcinogenicity Assessment Committee reviewed and discussed the findings for both the 2-year mouse and rat carcinogenicity studies and concurred that the studies were adequate. The Committee also concurred that there were no drug-related neoplasms in the 2-year mouse carcinogenicity study in either males or females. For the rat study, the Committee concluded that the combined incidence of benign and malignant neuroendocrine cell tumors in the stomach was increased in rats at the 160 mg/kg/day dose in females, and was drug related.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. General Information

Table 57: Listing of clinical pharmacology studies

Study Type	Study Number	Formulation	Study Description
Single Dose Studies	477-CL-001	PFS	Single ascending dose safety PK and PD study in healthy subjects
	501-PK-901	PFS	^{14}C-ADME study in healthy male subjects

Multiple Dose Study	477-CL-002	PFS	Multiple ascending dose safety, PK and PD study in healthy subjects
Effect of Intrinsic Factors on PK and PD	E5501-A001-006	2G	Japanese and Chinese PK, PD and safety bridging study of 10, 40, and 80 mg avatrombopag (fasted) in healthy subjects (completed in US)
	E5501-J081-015	2G	Single dose PK and PD study of avatrombopag in healthy Japanese male subjects (completed in Japan)
	E5501-A001-018	2G	Confirmatory Japanese PK and PD bridging study of 40 and 60 mg avatrombopag (fed) in healthy subjects (completed in US)
Bioavailability and Food Effect	501-PK-902	PFS, 1G	Relative BA study of 1G tablet versus oral suspension formulation and food effect assessment for 1G tablet
	E5501-A001-005	1G, 2G	Relative BA study of 2G tablet versus 1G tablet and food effect assessment for 2G tablet
	E5501-A001-007	2G	Relative BA study for estimation of intra- and inter-subject PK variability for 2 manufacturing lots of 40-mg 2G tablet under fasted state
	E5501-G000-010	2G	Food effect study to evaluate effect of high-fat meal on BA and PK variability of 2G tablet of avatrombopag
	E5501-A001-017	2G	Food effect study to evaluate effect of low-fat meal on BA and PK variability of 2G tablet of avatrombopag
	E5501-G000-012	2G, 3G	Relative BA study of 3G prototype formulations versus 2G tablet
Drug-Drug Interaction Studies	E5501-G000-008	2G	Drug-drug interaction study with strong P-gp inhibitors, verapamil and cyclosporine
	E5501-A001-019	2G	Drug-drug interaction study with CYP2C9 and CYP3A modulators, fluconazole, rifampin, and itraconazole
Thorough QT	E5501-A001-001	1G	Thorough QT study of single 100 mg dose of avatrombopag (1G tablet) in healthy subjects

1G = 1st generation, 2G = 2nd generation, 3G = 3rd generation, PFS = powder for oral suspension, ADME = absorption, distribution, metabolism, and excretion, BA = bioavailability, CYP = cytochrome P450, PD = pharmacodynamic, P-gp = P-glycoprotein, PK = pharmacokinetic.
Source: Clinical Pharmacology Summary, Module 2.7.2

In addition, Studies G000-202 (Part B), -204, -310, and -310 in patients with CLD used the 2G formulation.

Single and Multiple Dose Pharmacokinetics, and Dose Proportionality

Dose proportionality was demonstrated for avatrombopag PK between 10 mg and 80 mg after a single dose in healthy subjects and in patients (Table 58, Table 59, and Table 60). There was a 2-fold accumulation of avatrombopag exposure at steady state (daily dose for 7-days) (Table 58, and Figure 10).

Study A001-006 was a 3-way crossover design study that evaluated the single (10, 40, and 80 mg) and multiple dose (10 mg/day) PK and dose proportionality of avatrombopag (2G formulation) in healthy subjects.

Table 58: Single and multiple dose pharmacokinetics of avatrombopag in healthy subjects in Study-006

	Single-Dose			Dose Proportionality	Multiple Dose
PK Parameter	**10 mg** n=26	**40 mg** n=25	**80 mg** n=25	**Slope (90% CI)**	**10 mg QD x 7 days** (n=26)
$AUC_{0\text{-}inf}$, ng·h/mL	1195 (56%)	4198 (83%)	7562 (106%)	0.9 (0.8, 1.0)	--
$AUC_{0\text{-}t}$, ng·h/mL	1046 (71%)	4051 (86%)	7324 (106%)	0.9 (0.8, 1.0)	--
$AUC_{0\text{-}24}$, ng·h/mL	610 (69%)†				1288 (42) ‡
Accumulation					2.1 (72%)
C_{max}, ng/mL	42 (71%)	166 (84%)	293 (106%)	0.9 (0.8, 1.0)	87 (41%) ‡
C_{min}, ng/mL					31 (45%) ‡
Fluctuation					102 (23%)
Median T_{max}, h (range)	6 (4-8)	5 (4-12)	6 (3-12)		5 (3-8) ‡
T½*, h	18 (4%)	18 (4%)	18 (4%)		17 (3%)
*arithmetic mean, †at Day 1, ‡at Day 7 (steady state) Predose at Days 5-8: slope 0.03 (90% CI: -0.04, 0.10) Source: Study A001-006, Tables 10, 12, and 13					

Figure 10: Predose levels with daily 10 mg dose of avatrombopag for 7 days in healthy subjects in Study A001-006

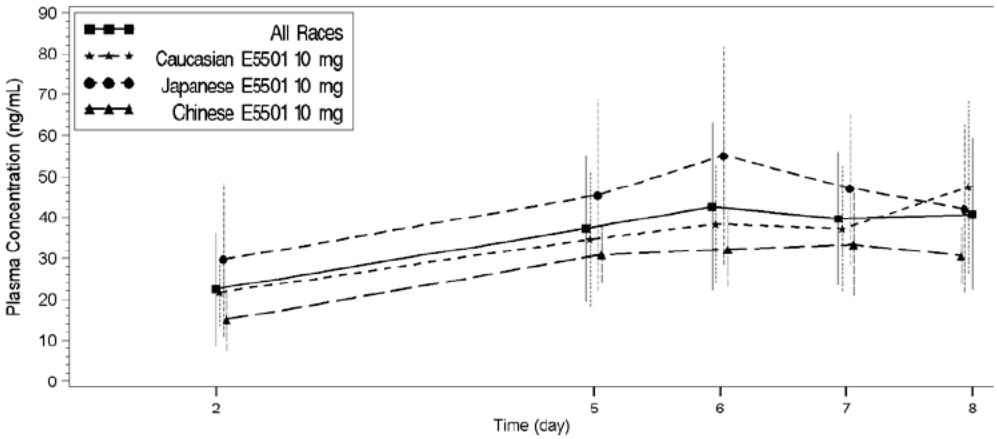


Table 59: Model-derived pharmacokinetic parameters of avatrombopag in patients

PK Parameter	**10 mg** n=23	**20 mg** n=7	**40 mg** n=337	**60 mg** n=194	**80 mg** n=51
AUC, ng·h/mL	1196 (59%)	1644 (91%)	4197 (62%)	5188 (82%)	7582 (85%)
CL/F, L/h	6.8 (14%)	7.4 (23%)	7.0 (15%)	7.4 (21%)	6.9 (20%)
V/F, L/mL	171 (12%)†	280 (8%)	214 (29%)	273 (21%)	288 (26%)
Source: Population PK Report E5501-005R, Table 8-15					

Table 60: Derived multiple dose pharmacokinetics of avatrombopag in patients

PK Parameter	Repeat Dose, Once Daily*	
	40 mg (n=115)	60 mg (n=160)
$AUC_{0\text{-}tau}$, ng·h/mL	3717 (62%)	4820 (85%)
C_{max}, ng/mL	214 (43%)	352 (47%)
Median T_{max}, h (range)	7 (4-16)	6 (4-20)
CL/F, L/h	7.2 (16%)	7.5 (20%)
*Day 5, under Fed conditions Source: Pop PK Report E5501-005R, Table 8-14		

Inter and Intra-subject variability

Inter- and intra-subject variability of avatrombopag under fasted conditions were between 46% to 81%. The variability reduced by 40-70% with either high-fat or low-fat meal (Table 61).

Table 61: Inter- and Intra-subject variability of avatrombopag with a single 40 mg dose

Study	Avatrombopag Dose as 2G Tablet	Food Status	Parameter	Intra-subject Variability, %CV (range)	Inter-subject Variability, %CV (range)
E5501-A001-007	1×40 mg	Fasted	C_{max}	63 – 73	64 – 73
			$AUC_{0\text{-}inf}$	60 – 68	60 – 67
E5501-G000-010	1×40 mg	Fasted	C_{max}	72	46 – 59
			$AUC_{0\text{-}inf}$	75	56 – 58
		Fed (High-fat meal)	C_{max}	33	28 – 31
			$AUC_{0\text{-}inf}$	37	35 – 36
E5501-A001-017	2×20 mg	Fasted	C_{max}	-	79
			$AUC_{0\text{-}inf}$	-	81
		Fed (Low-fat meal)	C_{max}	21 (17-28)*	40 (34, 49)*
			$AUC_{0\text{-}inf}$	32 (26-44)*	46 (39, 56)*
*95% CI					

19.4.2. Absorption, Distribution, and Elimination

Absorption

Avatrombopag is absorbed in the fasted state with a median time to peak concentration (Tmax) of 5 to 7 hour following a single dose of 40 mg (Table 63).

Food Effect

The effect of food on avatrombopag PK was evaluated in the following four, single dose (2x 20 mg) studies in healthy subjects using the 2G tablet formulation:

- Study A001-005: randomized, three period crossover study with a 21-day washout period in 16 healthy subjects (food effect was a secondary objective).

- Study G000-010: randomized (1:1:1:1), open-label, 4-group, 2-period replicate design study in 84 healthy subjects. Subjects in each group (n=21) received 40 mg of one of the two lots of avatrombopag 2G tablet formulation twice in either fasted or fed (high-fat meal) conditions with 5-day washout between periods.
- Study A001-018: randomized, open-label, 5-treatment-period study in healthy Japanese, Chinese, and White subjects who received the 40 mg or 60 mg of avatrombopag 2G tablet in both fed (high-fat meal) and fasted conditions. Periods 1 and 2, used a 2-way crossover design for dose in the fed conditions. Periods 3 and 4 used a 2-way crossover design for dose in the fasted conditions., and Period 5 consisted of single administration of 20 mg avatrombopag in the fed condition. Each period was separated by a washout of at least 28 days.

  A high-calorie, high-fat meal (approximately 918 calories: 59 grams carbohydrate, 59 grams fat and 39 grams protein) was used in Studies -005, -010 and -018, consistent with the recommendations in the Food Effect FDA Guidance for Industry. Food was consumed within 30 minutes and study drug taken within 15 minutes of meal completion.

- Study A001-017: randomized, three period, partial replicate design that included two periods of administration of a 40-mg single dose of avatrombopag 2G tablet with a low-fat meal and one period of administration of avatrombopag after an overnight fast. Treatment Periods 1 and 2 were separated by a 7-day washout interval, and Treatment 2 , Treatment 3, and follow-up were separated by 28-30-day washout.

  A low-fat meal (approximately 500 calories: 3 g fat, 15 g proteins, and 108 g carbohydrates) was used in Study -017. Food was consumed within 30 minutes and study drug taken within 15 minutes of meal completion.

The blood samples for PK were collected over 96 hour period and for PD (platelet count, except for Study G000-10) were collected over 29 days in each period in Studies A001-005, -017, and -018, and G000-010.

Table 62: Point estimates and 90% confidence intervals of pharmacokinetic parameters with a high-fat meal or a low-fat meal versus under a fasted state

Comparison	Geometric Mean Ratio (90% CI)		Median T_{max}
	$AUC_{0\text{-}inf}$ (ng*hr/mL)	C_{max} (ng/mL)	Fed/Fast
Study A001-005 (n=16)			
Fed-Hi vs Fast (40 mg)	1.23 (0.96, 1.59)	1.23 (0.94, 1.62)	1.00
Study G000-010 (n=19-22)			
Fed-Hi vs Fast (40 mg, Lot P01008ZZA)	1.08 (0.89, 1.30)	0.99 (0.82, 1.19)	1.33
Fed-Hi vs Fast (40 mg, Lot P01009ZZA)	1.21 (1.00, 1.47)	1.08 (0.90, 1.30)	1.33
Study A001-018 (n=18-24)			
Fed-Hi vs Fast (Japan, 40 mg)	0.92 (0.76, 1.12)	0.84 (0.69, 1.03)	1.2
Fed-Hi vs Fast (Japan, 60 mg)	1.08 (0.89, 1.32)	0.96 (0.79, 1.18)	1.4
Fed-Hi vs Fast (White, 40 mg)	1.56 (1.26, 1.94)	1.32 (1.07, 1.64)	1.3
Fed-Hi vs Fast (White, 60 mg)	1.80 (1.44, 2.24)	1.44 (1.16, 1.79)	1.4
Study A001-017 (n=34-36)			
Fed-Lo vs Fast (40 mg)	0.96 (0.76, 1.20)	0.93 (0.75, 1.16)	1.0
Fed-Hi: High fat meal, Fed-Std: standard meal, and Fast: fasted state, Japan=Japanese			

Administration of a single 40 mg dose of avatrombopag with a high-fat, high-calorie meal in healthy subjects resulted in ≤ 23% decrease in $AUC_{0\text{-}inf}$ and C_{max} (Table 62), except in the White population in Study -018 which appears to stem from the unusually low avatrombopag exposure in the fasted state in this population (Table 63). The median T_{max} with food was delayed by a median of 0-2 hours as compared to fasted conditions (Table 63). With a high-fat or low-fat meal, the variability in $AUC_{0\text{-}inf}$ and C_{max} is reduced by 40-70% (Table 61). The Applicant recommended administration of DOPTELET with food to reduce the PK variability of avatrombopag. DOPTELET will be recommended to be taken with food.

Table 63: Pharmacokinetic parameters of a single dose of avatrombopag with a high-fat meal or a low-fat meal versus under a fasted state

PK parameter (unit)	AUC_{inf} (ng*hr/mL)	C_{max} (ng/mL)	T_{max}† (hr)	$T_{1/2}$‡ (hr)
Study A001-005 (n=16)*				
Fasted (40 mg)	3670 (88)	140 (83)	6 (4 - 12)	17 (3)
Fed-Hi (40 mg)	4564 (43)	172 (36)	6 (4 - 12)	18 (3)
Study G000-010 (n=19-22)				
Fasted (40 mg, Lot 8ZZA)	4667 (56)	176 (46)	6 (4 - 9)	19 (4)
Fed-Hi (40 mg, Lot 8ZZA)	4773 (36)	166 (28)	8 (4 - 12)	18 (3)
Fasted (40 mg, Lot 9ZZA)	4216 (58)	163 (59)	6 (4.5-10)	19 (4)
Fed-Hi (40 mg, Lot 8ZZA)	4877 (35)	166 (31)	8 (4.5-12))	18 (4)
Study A001-018 (n=18-24)				
Fasted (Japan, 40 mg)	6130 (48)	239 (46)	5 (3 – 12)	17 (11)
Fed-Hi (Japan, 40 mg)	5650 (31)	201 (26)	6 (3 - 12)	16 (13)
Fasted (White, 40 mg)	3360 (52)	118 (60)	6 (4 - 24)	19 (19)
Fed-Hi (White, 40 mg)	5210 (60)	155 (38)	8 (3 - 24)	18 (23)
Fasted (Japan, 60 mg)	8420 (52)	334 (53)	5 (4 - 7)	17 (11)
Fed-Hi (Japan, 60 mg)	9160 (24)	320 (28)	7 (3 - 24)	16 (10)
Fasted (White, 60 mg)	4890 (61)	183 (60)	5 (4 24)	19 (17)
Fed-Hi (White, 60 mg)	8570 (71)	263 (43)	7.5 (3 -24)	18 (22)
Study A001-017 (n=34-36)				
Fasted	4960 (81)	179 (79)	5 (4 – 8)	20 (22)
Fed-Lo (Rep 1)	4590 (50)	162 (47)	5 (4 – 8)	19 (21)
Fed-Lo (Rep 2)	4790 (39)	170 (30)	5 (4 – 8)	20 (23)

* Refer to Appendix 19.4.4 for cross-validation issues
†median (min, max), ‡ arithmetic mean (%CV)
Source: Study A001-005, -018 & -017, and G000-010

Elimination

An open-label, mass balance study (PK-901) was conducted in healthy volunteers (n=6) administered a single oral dose (20 mg) of avatrombopag [^{14}C] oral suspension. PK samples were collected up to 216 hours. For the characterization of metabolite profiles, the determination of radioactivity in blood and plasma, samples. For the determination of avatrombopag in urine, samples were collected at pre-dose, intervals up to 24 hours post dose, and every 24 hours until discharge. The excretion of radioactivity in feces was monitored at predose and every 24 hours until discharge.

The mean erythrocyte transfer ratio (ETR) (%CV) at 4 and 36 hours post-dose were 0.37 (14%) and 0.28 (29%), respectively, indicating that 33% of radioactivity is in erythrocytes and 67% is in the plasma. The erythrocyte/plasma partition coefficient (EPPC) at 4 and 36 hours post-dose were 0.42 (10%) and 0.50 (14%), respectively, indicating that the concentration in erythrocytes is 50% of that in plasma.

Metabolism

A total of 3 metabolites were detected in feces, of which 4-OH-avatrombopag was the major metabolite accounting for approximately 44% of the administered dose. There were no metabolites detected in plasma. Metabolite identification in the urine samples was not feasible due to the low level of radioactivity found in urine.

CYP3A4 and CYP2C9 were the predominant isoforms responsible for the hepatic oxidative metabolism of avatrombopag (Study DMPKA2011-138).

Excretion

High ^{14}C recovery was achieved in this study (94% to 97%). The mass balance of total radioactivity excreted is presented in Table 64. In feces, unchanged avatrombopag accounted for ~33.5% of the administered dose.

Table 64: Distribution of Radioactivity in feces and urine in Study PK-901

	%$Ae_{0\text{-last}}$ in Urine	%$Ae_{0\text{-last}}$ in Feces	Total
N	6.00	6.00	6.00
Median	5.91	88.34	94.45
Mean	6.27	88.44	94.71
CV (%)	19.08	2.02	1.19
Source: Study PK-901, Table 11.4.1.3:1			

19.4.3. In Vivo Drug Interaction Studies

Drug-Drug Interactions

Effects of Other Drugs on Avatrombopag

No management strategy is required for the co-administration of CYP3A and CYP2C9 modulators or P-gp inhibitors.

The effects of itraconazole (a strong CYP3A4 inhibitor), fluconazole (a moderate CYP3A and CYP2C9 inhibitor), rifampin (a strong CYP3A and moderate CYP2C9 inducer), on avatrombopag PK and PD were evaluated in a single dose, randomized, crossover study with a washout period of 28 days in healthy subjects (Study A001-019) under fed conditions.

The effects of cyclosporine (a P-gp inhibitor) and verapamil (a P-gp and moderate CYP3A inhibitor) on avatrombopag PK and PD were evaluated in a single dose, randomized, crossover study with a washout period of 28 days between treatments in healthy subjects (Study G000-008).

PK samples for avatrombopag were adequately collected from pre-dose to 96 hours post-dose, and PD samples were collected over 28 days. The dose and dosing regimen for DOPTELET and the co-administered drugs in the studies and the study results are described in Table 65.

Table 65: Pharmacokinetics & pharmacodynamics of avatrombopag in the presence of co-administered drug

Co-administered Drug	Regimen of Co-administered Drug	DOPTELET Regimen	Geometric Mean Ratio (90% CI)		Mean (%CV)* Combination: DOPTELET Alone	
			$AUC_{0\text{-}inf}$	C_{max}	$AUEC_{0\text{-}28d}$ ($h.10^9/L$)	E_{max} ($10^9/L$)
Strong CYP3A Inhibitor						
itraconazole	200 mg twice daily on Day 1 & 200 mg once daily on Days 2-16	20 mg on Day 7	1.37 (1.10, 1.72)	1.07 (0.86, 1.35)	25100 (72%): 18100 (65%)	307 (27%): 314 (23%)
Moderate CYP3A and CYP2C9 Inhibitor						
Fluconazole	400 mg once daily on Days 1 to 16	20 mg on Day 7	2.16 (1.71, 2.72)	117 (0.96, 1.42)	23300 (61%): 15800 (49%)	307 (21%): 285 (21%)
Moderate CYP2C9 and Strong CYP3A Inducers (n=14-16)						
Rifampin	600 mg once daily on Days 1 to 16	20 mg on Day 7	0.57 (0.47, 0.62)	1.04 (0.88, 1.23)	3460 (297%): 15300 (56%)	307 (14%): 317 (13%)
P-gp Inhibitor						
Cyclosporine	single 400 mg dose	single 20 mg dose	0.83 (0.65, 1.04)	0.66 (0.54, 0.82)	14500 (73%): 17500 (89%)	293 (14%): 310 (19%)
P-gp and Moderate CYP3A Inhibitor						
Verapamil	240 mg once daily on Day 1 to 11	20 mg on Day 7	1.61 (1.21, 2.15)	1.26 (0.96, 1.66)	19800 (77%): 17500 (89%)	316 (16%): 310 (19%)

*arithmetic means. Per sponsor, not transformed due to negative values
Source Study A001-019, Tables 13, 15, 17, and Study G000-008, Table 11

CYP3A and CYP2C9 Modulators and P-gp Inhibitors: Co-administration of strong CYP3A, moderate CYP3A and CYP2C9, and P-gp inhibitors increased avatrombopag exposure by 1.4-fold and 2.2-fold, and a strong CYP3A and moderate CYP2C9 inducer decreased avatrombopag exposure by 40% (Table 65).

PK/PD simulations were conducted to predicted proportion of patients with platelet counts < 50 x 10^9/L, >50 x 10^9/L and < 200 x 10^9/L, and > 200 x 10^9/L for DOPTELET alone, and with concurrent administration of CYP3A and CYP2C9 modulators and P-gp inhibitors for a range of dosing regimens (refer to Appendix 19.4.5 for details). The PK/PD simulations did not show large changes on the proportion of patients with platelet counts < 50 x 10^9/L, >50 x 10^9/L and < 200 x 10^9/L, and > 200 x 10^9/L when DOPTELET was administered concurrently with CYP3A and CYP2C9 modulators and P-gp inhibitors compared to when administered alone as a 5-day regimen (Table 66). Therefore, no dose adjustments are recommended. Although fewer patients are predicted to have platelet counts > 50 x 10^9/L when DOPTELET is administered concurrently with a strong CYP3A and moderate CYP2C9 inducer, 58% of patients are predicted to benefit and minimize platelet transfusion.

Table 66: Predicted pharmacodynamics of avatrombopag with a 5-day dosing of DOPTELET in the presence of co-administered drug

Treatment	Dosing Duration	Percentage of Simulated Patients with Maximum Platelet Counts (x 10^9 cells/mL)		
		< 50	50 < Max Plt < 200	> 200
Avatrobopag alone	5 days	24.8%	73.0 %	2.2 %
+ Strong CYP3A inhibitor	5 days 4 days	20.7% 24.3%	75.8 % 73.6 %	3.5 % 2.1 %
+ Moderate CY3A & CYP2C9 inhibitor	5 days 4 days 3 days ↓ dose by 50% x 5 days	13.9% 16.9% 21.9% 21.9%	77.7% 77.8% 75.4 % 75.6%	8.4 % 5.3% 2.7 % 2.5%
+ 2C9 inhibitor	5 days 4 days	18.4% 21.7%	76.8 % 75.4 %	4.8 % 2.9 %
+ P-gp inhibitor	5 days	25.8%	70.2 %	1.3 %
+ P-gp + Moderate CY3A inhibitor	5 days	22.3%	74.8 %	2.9 %
+ Strong CY3A & Moderate CYP2C9 inducer	5 days	42%	58%	0.2 %

Source: Pharmacometric Review Appendix 19.4.5

Effect of Avatrombopag

On CYP Inhibition: Avatrombopag does not inhibit CYP1A, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A in vitro (Table 67).

Table 67: IC_{50} and calculated R_1 values for avatrombopag inhibition of CYP activities in human liver microsomes

CYP Enzyme	Substrate	Avatrombopag IC_{50} (μM)	Positive Control IC_{50} μM	R_1 value $1+(I_{max,u}/K_i)$
CYP1A2	Phenacetin	> 50	Furafylline (3.6)†, α-Naphthoflavone (<0.02)‡	1.0
CYP2B6	Bupropion	~50	Ticlopidine (0.35†, ~5‡)	1.0
CYP2C8	Amodiaquine†, Paclitaxel‡	`50	Montelukast (0.24†, <0.5‡)	1.0
CYP2C9	Tolbutamide	> 50	Sulfaphenazole (0.25, 3‡)	1.0
CYP2C19	S-Mephenytoin	> 50	*S*-Benzylnirvanol (0.1)†, Ticlopidine (1) ‡	1.0
CYP2D6	Bufuralol	> 50	Quinidine (0.06†, 0.5‡)	1.0
CYP2E1	Chlorzoxazone	> 10	141	1.0
CYP3A	Midazolam Nifedipine Testosterone	> 50 > 10 > 50	Ketoconazole (0.01†, <0.05‡)	1.0

Calculation of avatrombopag R_1 values based on maximal steady-state concentration of 325 ng/mL or 0.5 μM [I_{max}]. Fraction unbound = 4%= 0.04
$R_{1,gut}$ for CYP3A < 14 (Dose/250 mL, Dose=60 mg)
K_i assumed to be $IC_{50}/2$ for competitive inhibition for those CYP enzymes without an experimental K_i value
Source: †DMPKAM2010-001, ‡DMPKT2015-012.

On CYP Induction: In human hepatocytes of 3 donors (Study DMPKT2016-005), 1 to 20 μM avatrombopag showed no increases of CYP1A2 and 2C8 mRNA level. In 1 of the 3 donors, ≥2-fold increase in mRNAs compared to vehicle control and >20% increase of positive controls were observed at 5 μM or 10 μM avatrombopag for CYP2B6, CYP2C9, and CYP3A4. However, no clear dose dependencies were observed for fold inductions over vehicle or positive controls. Also, CYP2C8 activity versus positive controls increased in a concentration dependent manner (0.1, 1, & 5 μM) and CYP2C9 activity over positive control increased at 5 μM in human hepatocyte from all 3 donors (Study DDM2009-001), however, the maximum induction at 5 μM was 30-40% induction of positive control. Nonetheless, the potential for avatrombopag to induce CYP2C8 and CYP2C9 is low, as the maximum observed avatrombopag plasma concentrations in clinical trials were ≤ 0.5 μM.

On Transporters: Avatrombopag has the potential to inhibit BCRP (I_{gut}/IC_{50} = 68) and OAT3 ($I_{max,u}/IC_{50}$ =0.1) at clinically relevant concentrations per the current FDA DDI guidance (2017) (Table 68).

Table 68: IC_{50} and calculated R values for avatrombopag inhibition of transporters

Transporter	Substrate	Avatrombopag IC_{50} (µM)	I_{gut}/IC_{50}	$I_{max,u}/IC_{50}$	1+ $((f_{u,p} \times I_{in,max})/IC_{50})$ [b]
P-gp	Digoxin	>30 *	<12	--	--
BCRP	Prazosin	5.4 *	68	--	--
OCT1	MPP+	2.1†	--	<0.1	--
OCT2	Metformin	>30 ‡	--	<0.1	--
OAT1	PAH	0.7 ‡	--	<0.1	--
OAT3	Estrone 3–sulfate	0.2 ‡	--	0.1	--
MATE1	Metformin	>30 †	--	<0.02	--
MATE2K	ASP	>30 †	--	<0.02	--
OATP1B1	Estrone 3–sulfate	22.1‡	--	--	<1.1
OATP1B3	Estradiol 17ß–glucuronide	2.8 ‡	--	--	<1.1

I_{gut}=Dose/250 mL
[b] $I_{in,max}$ = (Imax + (Fa x Fg x Ka x Dose))/Qh/R_B
Where Imax = 0.5 µM or 0.000325 mg/mL, $f_{u,p}$ = 0.04, Fa=0.5, Fg=1, Ka=5.5/hr or 0.092/min, Dose=60 mg, Qh=25 mL/min/kg =1750 mL/min (@70 kg), and R_B=0.6,
Source: *Study DMPK2011-206, †Study GE-1414-G, ‡Study DMPK2011-20

Substrates of Avatrombopag

Transporters: Avatrombopag is a substrate of P-gp. Greater than 2-fold uptake of avatrombopag was observed in P-gp-expressing cells, and efflux ratio (ER) in the presence of a P-gp inhibitor decreased to <50% of the ER in the absence of inhibitor (Study W-21020375).

Avatrombopag is not a substrate of BCRP, OATP1B1, OATP1B3, OAT1, OAT3, and OCT2. Less than 2-fold uptake of avatrombopag was observed in BCRP-expressing cells (Study W-21020375). In the presence of a BCRP inhibitor, the results were mixed: ER decreased to < 50% of the ER in the absence of inhibitor in Study W-21020375 but was unchanged in Study DMPK2011-206.

Less than 2-fold uptake of avatrombopag was observed in organic anion transporting polypeptide (OATP) B1-, OATPB3-, organic cation transporter (OCT)2-, organic anion transporter (OAT)1-, and OAT3-transfected cells compared to those in the parental cells (DMPK2011-205). The uptake of avatrombopag in the OATP1A2- and OATP2B1-expressing oocytes were comparable to those in the control oocytes (Study GE-1414-G).

Pharmacogenomics

Effect of CYP2C9 polymorphism

In studies G000-008, A001-018, and A001-019 genotyping was conducted for the loss-of-function CYP2C9*2 and *3 alleles. The wild-type *1 allele was defined by the exclusion of the *2 and *3 alleles. Genotype-inferred phenotypes were determined as follows: subjects with two wild-type alleles were categorized as extensive metabolizers (EMs), subjects with one wild-type

and one loss-of-function allele were categorized as intermediate metabolizers (IMs), and subjects with two loss-of-function alleles were categorized as poor metabolizers (PMs).

Pharmacokinetic parameters ($AUC_{0\text{-}inf}$ and C_{max}) were obtained following a single 20 mg dose of avatrombopag in Studies G000-008, A001-018, and A001-019. CYP2C9 genotype-inferred phenotypes and PK parameters from the three studies were pooled to assess the impact of CYP2C9 genetic variation on avatrombopag PK. The pooled dataset contained 94 EMs, 24 IMs, and 2 PMs. Differences in PK parameters were assessed by Dunnett's test with EMs as the control group. The mean $AUC_{0\text{-}INF}$ was significantly higher in CYP2C9 IMs (4088.2±2152.8 h*ng/ml, p=0.002)) and PMs (5919.2±2318.2 h*ng/ml, p=0.014) compared to EMs (2874.6±1358.1 h*ng/ml). C_{max} was not significantly different across CYP2C9 phenotypes.

Reviewer Comment: The Applicant's phenotype assignment based on CYP2C9 genotype is acceptable. The higher exposures observed in CYP2C9 IMs (~1.4-fold) and PMs (~2-fold) compared to EMs are similar to the increase in exposures observed when avatrombopag is administered following administration of itraconazole (a strong inhibitor of CYP3A4/5) or fluconazole (a moderate dual inhibitor of CYP2C9 and CYP3A4/5), respectively. However, the small number of PMs in the analysis limits the confidence in conclusions for this subgroup.

19.4.4. Summary of Bioanalytical Method Validation and In-Study Performance

Total avatrombopag in human plasma (in sodium heparin) was measured using validated bioanalytical methods using liquid chromatography with tandem mass spectrometry (LC/MS/MS). Plasma samples from the clinical pharmacology studies were measured for avatrombopag at 4 bioanalytical sites (Table 69).

- [redacted] validated a LC/MS/MS method with liquid extraction (1-1000 ng/mL: YM-477-P1A/ Report KCM-2005-2133-BIO). This method was used in Studies CL-001 and -002.
- The [redacted] method was transferred to [redacted] (Report 1741), and the extraction was later revised to protein precipitation (PPT) and the assay range narrowed to 0.8-424 ng/mL (STM1884.01/Report 1884) and method was successively revised (Methods STM1884.02 to .05/Reports 1981, 2104 and 2034).
- [redacted] used the [redacted] method albeit at a lower validated range (1-200 ng/mL: BAM AA41274-01/Report AA33298-12). This method was used in Study A001-001.
- [redacted] developed and validated a LC/MS/MS method with an automated PPT extraction (1-500 ng/mL: [redacted] 10035-M01/Report 02509), which underwent successive modifications that were partially validated [redacted] 10035-M02 to M06). Bioanalysis of avatrombopag were conducted at [redacted] for all the clinical pharmacology studies (except A001-005) performed with the 2G formulation and for Studies G000-204, -310, and -311.

Table 69: Performance of avatrombopag bioanalytical methods during validation

Laboratory	Report (range, ng/mL)	QC level	Accuracy		Precision	
			Intra-batch (%RE)	Inter-batch (%RE)	Intra-batch (%CV)	Inter-batch (%CV)
[redacted]	KCM-2005-2133-BIO (1-1000)	LLOQ, QCL, QCM, QCH	–10 to 2.0	–5.0 to –1.1	1.3 to 10.9	3.3 to 7.7

[redacted] (b) (4)	AA33298-12 (1-200)	LLOQ, QCL, QCM, QCH	–12.2 to 2.9	–1.2 to 1.4	1.6 – 6.9	2.7 to 10.7
	1741 * (1-1000)	LLOQ, QCL, QCM, QCH	-0.5 to 17	NR	1.3 to 11	NR
	1884 (0.8-424)	LLOQ, QCL, QCM, QCH	–11.5 to 11	–8.7 to 9	0.9 to 11	2.4 to 7.7
	RPT02509 (1-500)	**Full Validation**				
		QCL, QCM, QCH	–4.3 to 6.50	1.00 to 4.50	2.4 – 12.3	4.6 to 10.2
		IS-D Partial Method Validation (n=6)*				
		QCL, QCM, QCH	–7.7 to 6.6	NR	3.2 to 8.1	NR
		Dual UFLC Systems Partial Method Validation (n=12)				
		QCL, QCM, QCH	-7.5 to 4.0	–4.3 to 3.5	3.5 to 9.7	4.0 to 7.8
		[redacted] (b) (4) **Partial Method Validation (n=5)***				
		QCL, QCM, QCH	3.0 to 6.7	NR	2.2 to 4.2	NR
*based on results from 1 batch						

Stability

Long-term (234 days at -20°C and -70°C), freeze-thaw (6 cycles), bench-top (24 hours at room temperature), extract (163 hours at room temperature) and auto-sampler stability was validated. In addition, dilution integrity was validated.

In-Study Assay Performance:

In-study performance of avatrombopag (in plasma) assays in the clinical pharmacology studies and Studies G000-202, -204, -310 and -311 were evaluated. The study samples were assayed within the validated long-term storage period. The assay accuracy was within 10% of the nominal concentrations and precision was <10% CV (except for a CV of 19% at LLOQ for Study A001-005). Majority (≥ 80%) of the analytical runs were successful and <3% of samples were reassayed in majority of the studies. The incurred sample reanalysis in the studies were within acceptable limits (≥67% of samples within 20% different). The sampling handling conditions in the studies were covered by the conditions under which stability was validated.

Cross-Validation

Cross-validation of the [redacted] (b) (4) 10035-M06 against [redacted] (b) (4) (Method 10023G-M01) and [redacted] (b) (4) (Method 1884) was conducted. Low, mid, and high QC samples were prepared and analyzed by [redacted] (b) (4) and the samples were then sent to [redacted] (b) (4) for the cross-validation test.

Table 70: Cross-laboratory validation of bioanalytical methods for avatrombopag in human plasma

QC Level	Accuracy Intra-lab (%RE)			Precision Intra-batch (%CV)		
	[redacted] (b) (4)					
	(N=6)	(N=6)	(N=6)	(N=6)[a]	(N=6)	(N=6)

Low	0.00	–7.33	–27.3	2.82	4.68	6.57
Middle	3.50	4.50	–16.5	2.40	3.40	3.76
High	1.25	7.00	–12.0	1.91	2.01	5.31

The (b) (4) method did not meet acceptance criteria for accuracy the low- and medium-QC results (Table 70), and all 6 of the blinded low-QC results did not meet the ±20% difference acceptance criteria. The (b) (4) method did not meet the cross-validation limits against the (b) (4) method. Therefore, cross comparison of the results of the studies analyzed at (b) (4) (i.e., Studies A001-001, A001-005, PK-902, and G000-202 (Part A)) with other studies may not be reliable. Nonetheless, sensitivity analysis indicated there is no-clinically meaningful effect of the PK assays used for the different studies in the overall population PK analysis (Refer to Appendix 19.4.5 for details).

19.4.5. Office of Clinical Pharmacology: Pharmacometrics Review

19.4.5.1. EXCUTIVE SUMMARY

19.4.5.1.1 Recommendations

The office of Clinical Pharmacology, Division of Pharmacometrics has reviewed this application and found the proposed PK and PK/PD labeling to be acceptable.

19.4.5.2. APPLICANT'S POPULATION PK AND PK/PD ANALYSIS

19.4.5.2.1 Applicant's Population PK Analysis

19.4.5.2.1.1 Data:

Table 71 outlines the PK data from each study used in the population PK analysis.

Table 71: Summary of Avatrombopag Data for the Population PK Analysis.

Study Number	Study Phase	Formulation	Study Description	No. of Subjects to be Included in Population PK
Phase 1 Studies				
477-CL-001	1	Suspension	Double-blind, placebo-controlled, dose-rising study of safety, PK, and PD of a single oral dose of E5501 in healthy volunteers.	36
477-CL-002	1	Suspension	Double-blind, placebo-controlled, dose-rising study of safety, PK, and PD of multiple oral doses of E5501 suspension in healthy volunteers.	19
501-PK-902	1	Suspension & 1st Generation Tablet	Open-label, randomized, three-way crossover study to evaluate PK, BA, and safety of a single 10-mg dose of E5501 in volunteers as an oral suspension or tablet under fed and fasted conditions.	17
E5501-A001-001	1	1st Generation Tablet	Double-blind, randomized, single, 3-treatment, crossover study performed in healthy adult male and female subjects to assess the effect of E5501 on ventricular repolarization after a single of 100 mg administered orally and compared to placebo.	46
E5501-A001-005	1	1st and 2nd Generation Tablets	Open-label, randomized, 3-treatment crossover BA study of single oral doses of E5501 1G tablet formulation under	16

			fasted conditions and 2G tablet formulation administered under fed and fasted conditions in healthy subjects.	
E5501-A001-006	1	2nd Generation Tablet	Single center, randomized, double-blind, placebo-controlled, single dose, 3-way crossover study to evaluate single dose PK, PD, safety, and tolerability of 10, 40, and 80 mg E5501 followed by a randomized, double blind, placebo-controlled, multiple dose, single active treatment period in healthy Japanese, Chinese, and Caucasian subjects.	41
E5501-A001-007	1	2nd Generation Tablet	Single-center, randomized, open-label, single, 4-way crossover, replicate design study to evaluate relative BA and intra-subject variability of 2 lots of E5501 40 mg 2G formulation.	42
E5501-G000-010	1	2nd Generation Tablet	Single-center, randomized, open-label, 4-group, 2-period, replicate design study to evaluate within- and between-subject variability in exposure of 2 lots of E5501 in fasted and fed conditions.	84
E5501-A001-017	1	2nd Generation Tablet	Randomized, open-label, three-period, partial-replicate design study to evaluate the inter- and intra-subject variability of the avatrombopag TBM formulation administered as single doses of 40 mg to healthy subjects receiving a low-fat meal.	36
E5501-A001-018	1	2nd Generation Tablet	A randomized, open-label, five-treatment-period study to evaluate the single-dose pharmacokinetics and pharmacodynamics of avatrombopag in healthy Japanese and White subjects.	48
E5501-G000-202	2	1st and 2nd Generation Tablets	Randomized, multicenter, placebo controlled, double-blind, parallel-group study to evaluate the efficacy, safety, and population PK of once-daily oral E5501 tablets used up to 7 days in subjects with chronic liver diseases and thrombocytopenia prior to elective surgical or diagnostic procedures.	93
E5501-J081-204	2	2nd Generation Tablets	A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of Once-daily Oral Avatrombopag in Japanese Subjects with Chronic Liver Disease and Thrombocytopenia.	28
E5501-G000-310	3	2nd Generation Tablets	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 elective procedures.	147

E5501-G000-311	3	2nd Generation Tablets	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 elective procedures.	128

(Source: Applicant's population PK, PK/PD Report, Table 6-1)

19.4.5.2.1.2 Applicant's Avatrombopag Population PK Methodology:

"The population PK analysis for avatrombopag was based on pooled data collected from 10 Phase 1 studies in healthy subjects, two Phase 2 and two Phase 3 studies in subjects with chronic liver disease and thrombocytopenia (Studies 202, 204, 310 and 311)."..." All models were developed in NONMEM 7.3. Model building and covariate assessments were conducted using standard methods."

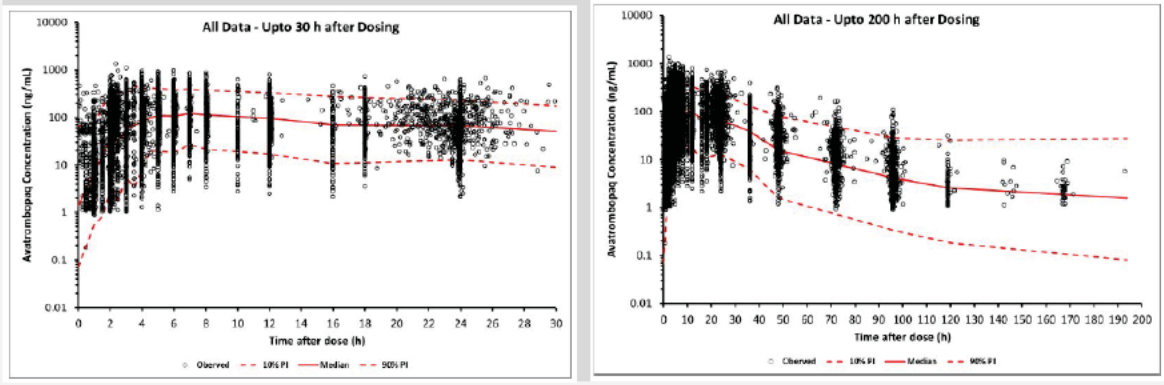
"Based on a graphical analysis of avatrombopag concentration-time profiles, a one-compartment model appeared to adequately describe the concentration-time profile following avatrombopag administration." ... "Separate error models (proportional and combined) were tested covering various cut off times for the absorption and distribution phases separately. Relative bioavailability (F1) to the suspension for 1st generation tablet – lot 56789-101 and other 1st and 2nd generation tablets was also tested. Models testing the effect on food and formulation on Ka were also tested, in addition to the effect of food on F1. Inclusion of inter-occasion variability (IOV) on F1 parameters was also tested." ... "Models ran for all estimation methods with the fitting using the FOCEI method most appropriately describing the avatrombopag concentration-time profiles based on the precision of the parameter estimates and goodness-of-fit-plots." ... "There were 6 statistically significant effects (OFV>6.64 per df) identified by the univariate analysis, including chronic liver disease, body weight, age and albumin on V/F and age and AST on CL/F. These effects were included in the full covariate model for subsequent backward elimination." ... "Following backward deletion the effects of age and AST on CL/F and albumin and age on V/F were removed, therefore the final PK model contained only the covariate effects of CLD subjects and body weight on V/F."

19.4.5.2.1.3 Applicant's Avatrombopag Population PK Results:

"The final NONMEM dataset for avatrombopag population PK analysis included a total of 15515 concentration-time records from 787 subjects, of which 1414 sparse observations were from 396 CLD subjects from Studies 202, 204, 310 and 311. Of the 15515 concentration-time records, 1461 records were obtained following administration of the suspension formulation, 1491 concentration-time records were obtained from the 1st generation tablet formulation, and 12563 concentration-time records were obtained from 2nd generation tablet formulation." ... "There were 522 Caucasians, 59 Black/African Americans, 29 Asians other than Chinese and Japanese, 74 Japanese, 34 Chinese, 29 Korean and 35 other races. There were 524 males and 263 females. The population age and weight ranged from 18 to 86 years (median = 47.0 years) and 38.5 to 175 kg (median = 75.3 kg), respectively. There were 242 viral hepatitis, 45 non-alcoholic steatohepatitis, 49 alcoholic liver and 59 other disease patients."

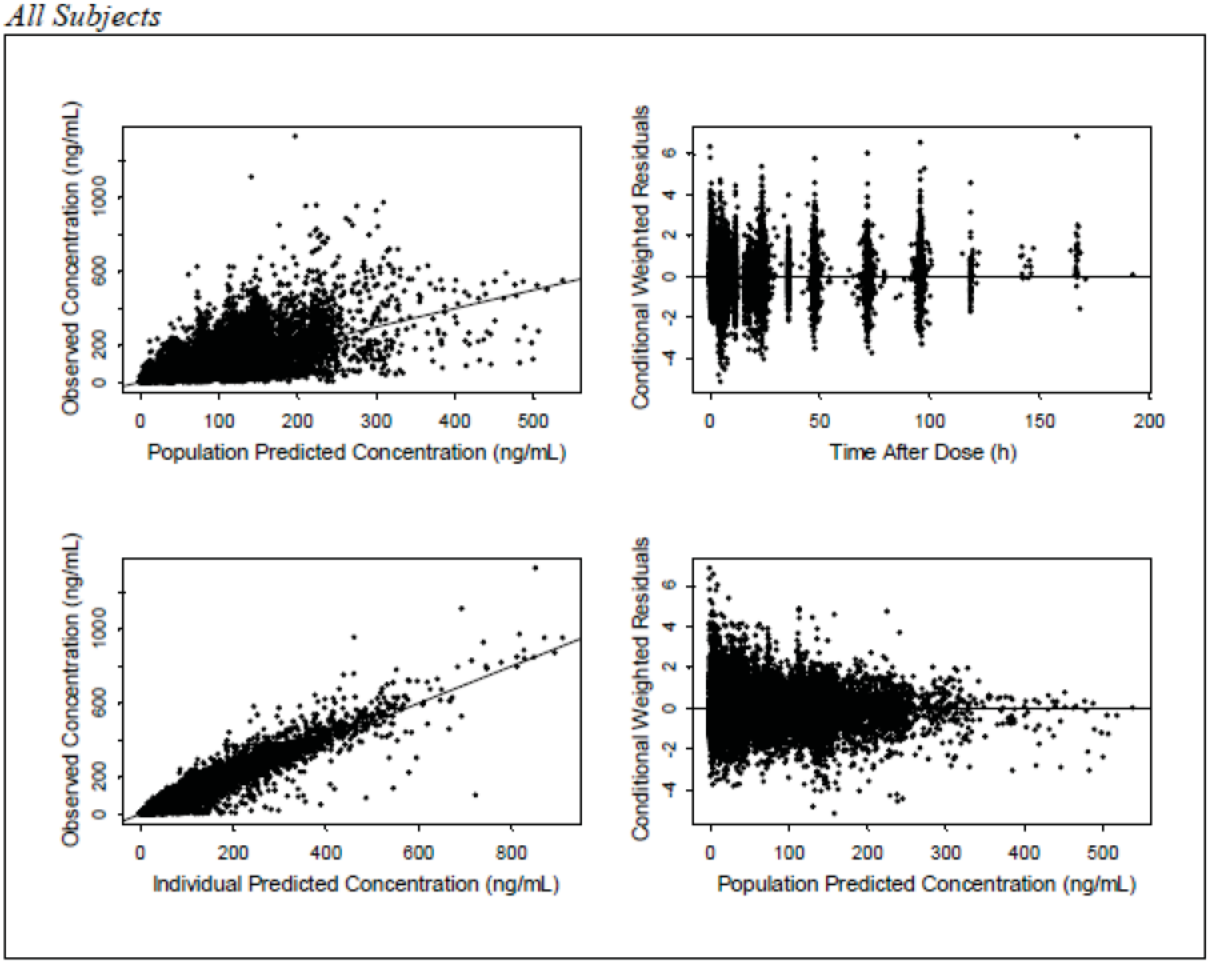
"PK parameters CL/F and V/F were similar for 40 mg and 60 mg doses in CLD subjects, ranging between 5.5 – 16.1 L/h and 143 – 403 L, respectively. Model-derived avatrombopag AUC and Cmax increased approximately proportional between the 40 mg and 60 mg dose levels with geometric means of 3717 and 4820 ng.h/mL, respectively, for AUC and 214 and 352 ng/mL, respectively, for Cmax. For both dose levels median time of Cmax (Tmax) was similar at 6-7 hours." … "Avatrombopag PK was not significantly affected by age (continuous or categorical), race including East Asians, gender, renal function (continuous or categorical), liver function, prothrombin international normalization ratio, or concomitant administration of proton pump inhibitors or H_2-blockers." … "Body weight and chronic liver disease each significantly affected avatrombopag apparent volume of distribution. However, PK simulations demonstrated body weight to have minimal, clinically unimportant effects on exposure to avatrombopag."
"Visual predictive check (20 simulations of PK analysis set) was performed and the 5th, 50th and 95th percentiles were calculated based on estimates from FINAL PK model and plotted together with observed concentrations from all treatments, studies and formulations." … "More than 90% of the observed avatrombopag concentrations are within the 5th and 95th percentiles for all dosing regimens."

Figure 11: Visual Predictive Check up to 30 h and 200 h after Doing of Observed and Predicted Avatrombopag Concentrations in Healthy and Chronic Liver Diseases and Thrombocytopenia Subjects – All Data



(Source: Applicant's Population PK, PK/PD Report, Figure 8-1 and 8-2)

Figure 12: Assessment of Goodness of Fit for the FINAL PK Model – All Data



(Source: Applicant's Population PK, PK/PD Report, Figure 11-5)

Table 72: Parameter Estimates of Final Avatrombopag Population PK Model.

Parameter	Estimate [95% CI]	%RSE [b]
CL/F (L/h)	6.89 [6.64 - 7.14]	1.89
V/F (L)	180 [173 - 187]	2.08
Effect of CLD subjects on V/F (Ratio)	1.65 [1.52 - 1.78]	4.13
Effect of body weight on V/F (Power function)	0.371 [0.226 - 0.516]	19.9
First-order absorption rate constant for suspension - Ka (1/h)	5.50	Fixed
Effect of 1G & 2G tablets on Ka	0.258	Fixed
Zero-order absorption duration - D1 (h)	4.08	Fixed
Lag time in absorption - ALAG (h)	0.389	Fixed
F1 – Bioavailability for 1G and 2G tablet relative to suspension	0.745	Fixed
F1 - Bioavailability for 1G tablet (Lot No. 56789-101) relative to suspension	0.213	Fixed
Inter-subject variability in CL/F (%CV) [a]	28.8	9.19
Inter-subject variability in V/F (%CV) [a]	25.0	11.0
Inter-subject variability in Ka (%CV) [a]	137.0	7.22
Inter-subject variability in D1 (%CV) [a]	21.7	13.1
Inter-subject variability in F1 for 1G and 2G tablet (%CV) [a]	35.9	13.2
Inter-subject variability in F1 for 1G (Lot No. 56789-101) (%CV) [a]	67.7	16.8
Inter-occasion variability for F1 for 1G and 2G tablet (%CV) [a]	41.1	Fixed
Proportional residual variability in avatrombopag concentrations (%CV) [a]	16.9	0.380
Additive residual variability in avatrombopag concentrations (SD in ng/mL)	0.395	7.18
Proportional residual variability in avatrombopag concentrations for TAD ≤ 4 h (%CV) [a]	56.3	1.73
Additive residual variability in avatrombopag concentrations for TAD ≤ 4 h (SD in ng/mL)	0.338	8.77

[a]Coefficient of variation; CI – Confidence Interval. [a] %CV for both inter-subject/patient and proportional residual variability is an approximation taken as the square root of the variance x 100. The approximation is due to the expansion of the exponential function only to first-order. [b] %RSE was calculated as the s.e. divided by the parameter estimate x 100.

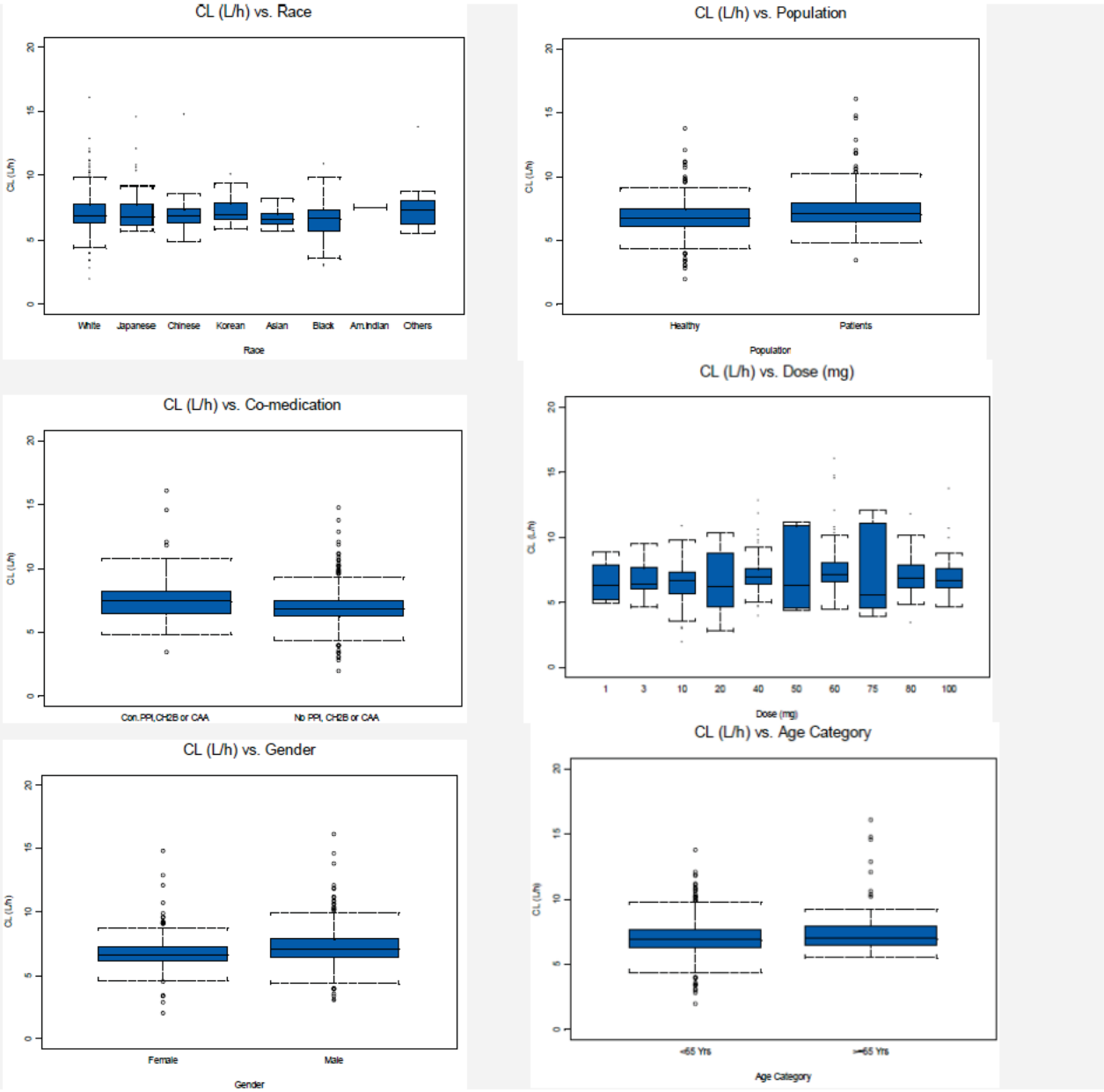
(Source: Applicant's Population PK, PK/PD Report, Table 8-12)

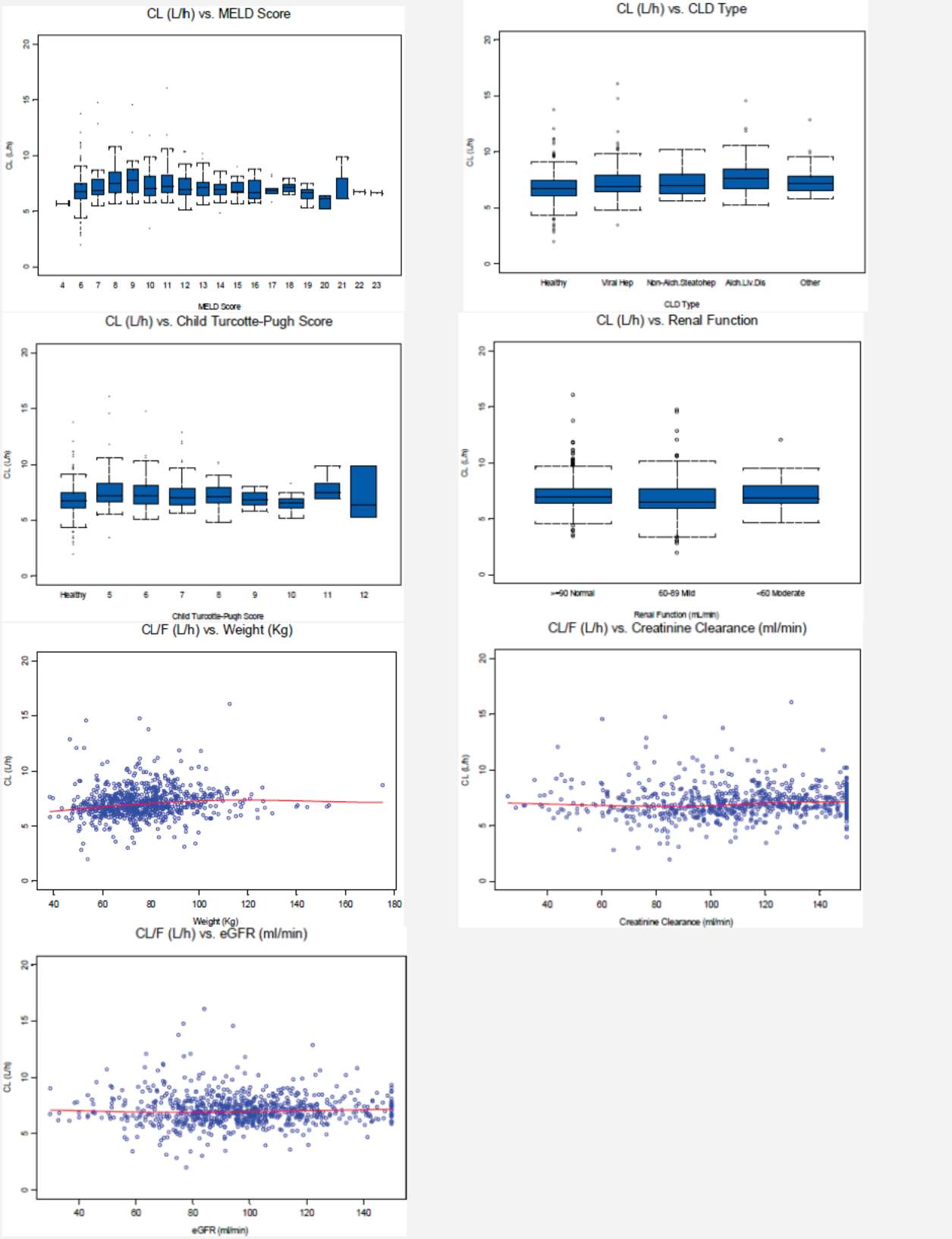
Table 73: Parameter Estimates of Final Avatrombopag Population PK Model in CLD Subjects – Studies 310/311

	Dose(mg)	N	Geometric Mean	SD	Min	Median	Max	Geometric CV%
CL/F (L/h)	40	115	7.24	1.13	5.58	7.05	12.8	15.6
V/F		115	292.1	37.8	198	297.0	401	13.0
AUC (ng.h/mL)		115	3717	2318	726.1	3864	11064	62.4
Cmax (ng/mL)		115	214.3	100.5	77.7	207.6	730.8	42.6
Tmax (h)		115	--	--	4	7	16	--
CL/F (L/h)	60	160	7.46	1.46	5.51	7.36	16.1	19.6
V/F		160	293.9	39.7	143	293.3	403	13.5
AUC (ng.h/mL)		160	4820	4101	788	4932	27242	85.1
Cmax (ng/mL)		160	352.2	194.8	122.9	346.4	1281	47.3
Tmax (h)		160	--	--	4	6	20	--

(Source: Applicant's Population PK, PK/PD Report, Table 8-14)

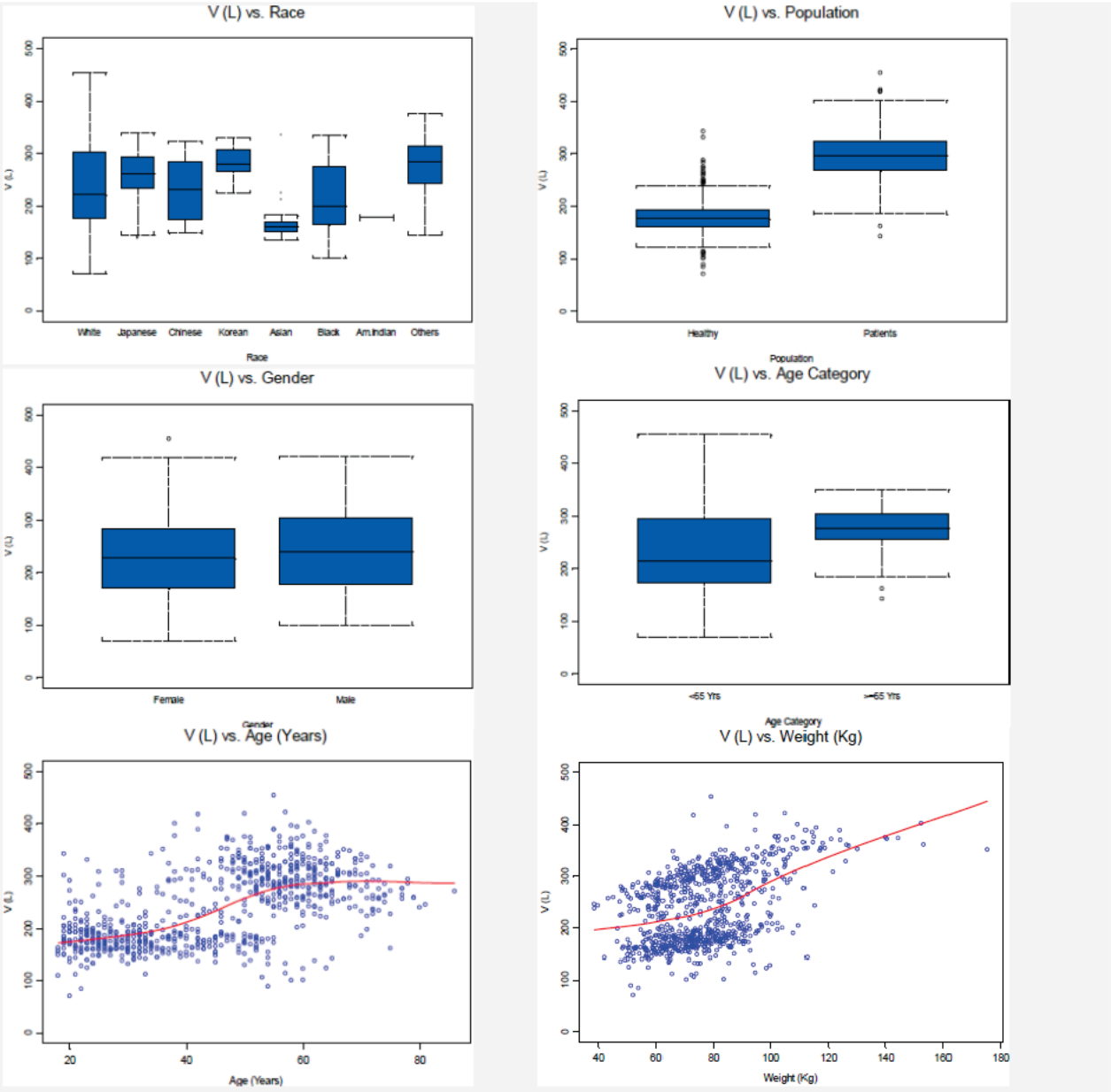
Figure 13: Effect of Covariates on Individual Avatrombopag CL/F





(Source: Applicant's Population PK, PK/PD Report, Figure 8-3)

Figure 14: Effect of Covariates on Individual Avatrombopag V/F



(Source: Applicant's Population PK, PK/PD Report, Figure 8-4)

Reviewer's Comments:

From the population PK perspective, the applicant's VPC simulation and the goodness of fit plots of the final population PK model suggest that the final population PK model appear to fit the data well (Figure 11 and Figure 12). The reviewer agrees with applicant's conclusion that no significant effect on PK was identified for age, race, gender, hepatic function, and renal function (Figure 13 and Figure 14).

19.4.5.2.1.4 Applicant's Sensitivity Analysis for different PK Assays

FDA Information Request: **Your cross-validation results show that the (b) (4) method was not crossvalidated. Bioanalysis for at least 3 studies (A001-005, A001-001, G000-202) were conducted using the (b) (4) method, which constitutes 21% of total subject or patient samples used in population PK analyses (CPMS-E5501-005R). Explain the impact of this observation on the population PK analysis (CPMS-E5501-005R).**

Sponsor Response. To clarify, there were 4 studies (A001-005, A001-001, G000-202 and 501-PK-902) in the population PK analysis dataset for which the (b) (4) method was used. As noted by the reviewers and summarized in Module 2.7.1(Section 2.7.1.3.5.5), the (b) (4) method was not fully cross-validated with other methods. However, the potential impact of the different assays on the population PK analysis was evaluated by assessing different residual variability models for the 2 assays used for bioanalysis of clinical PK samples.

Initially this was examined by re-evaluating the base PK model for the Phase 1 studies by having 2 combined residual variability models (one for TAD ≤ 4 hours and another for TAD > 4 hours) for studies A001-005, A001-001, and 501-PK-902 and 2 combined residual variability models (one for TAD ≤ 4 hours and another for TAD > 4 hours) for the remaining studies in the base PK model of the Phase 1 studies (PKBase14_Phase1_Assay). The objective function value (OFV) for this model was 221.037 point higher (87484.167 vs 87263.13) than that for the base PK model for Phase 1 studies when having only 2 combined residual variability models (one for TAD ≤ 4 hours and another for TAD > 4 hours) common for all data regardless of the assay (PKBase14_Phase1 in Table 8-6 of report CPMS-E5501-005R).

The same approach was performed for the base PK model for all studies by having 2 combined residual variability models (one for TAD ≤ 4 hours and another for TAD > 4 hours) for studies A001-005, A001-001, 501-PK-902 and G000-202 and 2 combined residual variability models (one for TAD ≤ 4 hours and another for TAD >4 hours) for the remaining studies in the base PK model for all studies (PKBase2_All_Assay). The OVF value for this model was 36.246 points lower (99307.944 vs 99344.19) than that for the base PK model for all studies, when having only 2 combined residual variability models (one for TAD ≤ 4 hours and another for TAD > 4 hours) common for all data regardless of the assay.

Applicant's Conclusion:

However, as depicted in Table 74 below, while slight differences were observed in the residual variabilities when accounting for the (b) (4) method, the population parameter estimates for CL/F and V/F and inter-individual variabilities from the 2 models were almost identical. Hence overall, there was minimal impact on either PK parameter estimates or inter-individual variabilities after accounting for the residual variabilities of the different assays.

Table 74: BASE PK Model Estimates of Population PK Parameters of Avatrombopag Comparing Models with Different Residual Variabilities Accounting for Assay Difference

Parameter	Estimate	
	All Data	Excluding Studies 001, 005, 902 and 202
CL/F (L/h)	6.72	6.61
V/F (L)	197	195
First-order absorption rate constant for suspension - Ka (1/h)	5.50 Fixed	5.50 Fixed
Effect of tablet formulation on Ka	0.258 Fixed	0.258 Fixed
Zero-order absorption duration - D1 (h)	4.08 Fixed	4.08 Fixed
Lag time in absorption - ALAG (h)	0.389 Fixed	0.389 Fixed
F1 – Bioavailability for 1G and 2G tablet relative to suspension	0.745	0.745 Fixed
F1 - Bioavailability for 1G tablet (Lot No. 56789-101) relative to suspension	0.213	0.213 Fixed
Inter-subject variability in CL/F (%CV) [a]	29.0	28.9
Inter-subject variability in V/F (%CV) [a]	28.1	27.1
Inter-subject variability in Ka (%CV) [a]	143	143
Inter-subject variability in D1 (%CV) [a]	20.5	19.0
Inter-subject variability in F1 for 1G and 2G tablet (%CV) [a]	39.6	40.0
Inter-subject variability in F1 for 1G (Lot No. 56789-101) (%CV) [a]	61.0	61.0
Inter-occasion variability for F1 for 1G and 2G tablet (%CV) [a]	41.1 Fixed	41.1 Fixed
		Non Pyxant method
Proportional residual variability in avatrombopag concentrations (%CV) [a]	16.9	17.0
Additive residual variability in avatrombopag concentrations (SD in ng/mL)	0.396	0.342
Proportional residual variability in avatrombopag concentrations for TAD ≤ 4 h (%CV) [a]	55.9	57.0
Additive residual variability in avatrombopag concentrations for TAD ≤ 4 h (SD in ng/mL)	0.341	0.207
		Pyxant method
Proportional residual variability in avatrombopag concentrations (%CV) [a]	-	16.8
Additive residual variability in avatrombopag concentrations (SD in ng/mL)	-	0.460
Proportional residual variability in avatrombopag concentrations for TAD ≤ 4 h (%CV) [a]	-	49.5
Additive residual variability in avatrombopag concentrations for TAD ≤ 4 h (SD in ng/mL)	-	0.532

[a] %CV for both inter-subject/patient and proportional residual variability is an approximation taken as the square root of the variance x 100. The approximation is due to the expansion of the exponential function only to first-order.

[b] %RSE was calculated as the s.e. divided by the parameter estimate x 100.

Finally, a similar approach was performed for the final PK model for all studies by having 2 combined residual variability models (one for TAD ≤ 4 hours and another for TAD > 4 hours) for studies A001-005, A001-001, 501-PK-902 and G000-202 and 2 combined residual variability

models (one for TAD ≤ 4 hours and another for TAD > 4 hours) for the remaining studies in the base PK model for all studies (PK_Final_All_Assay). The OVF value for this model was 36.911 point lower (99126 vs 99088.8) than that for the final PK model for all studies when having only 2 combined residual variability models (one for TAD ≤ 4 hours and another for TAD > 4 hours) common for all data regardless of the assay.

Applicant's Conclusion:

Again, as depicted in Table 75 below, while there were slight differences in the residual variabilities when accounting for the (b) (4) method, the population parameter estimates for CL/F and V/F and inter-individual variabilities from the 2 models were nearly identical. Hence overall, there was little impact on either PK parameter estimates or inter-individual variabilities after accounting for the residual variabilities of the different assays.
Overall in conclusion, these analyses indicate there was no impact of the assay methodology on the outcome of the population PK analysis.

Table 75: Final Model Estimates of Population Pharmacokinetics Parameters of Avatrombopag Comparing Models with Different Residual Variabilities Accounting for Assay Difference

Parameter	Estimate [95% CI]	
	All Data	**Excluding Studies 001, 005, 902 and 202**
CL/F (L/h)	6.89	6.89
V/F (L)	180	180
Effect of CLD subjects on V/F (Ratio)	1.65	1.65
Effect of body weight on V/F (Power function)	0.371	0.369
First-order absorption rate constant for suspension - Ka (1/h)	5.50 Fixed	5.50 Fixed
Effect of 1G & 2G tablets on Ka	0.258 Fixed	0.258 Fixed
Zero-order absorption duration - D1 (h)	4.08 Fixed	4.08 Fixed
Lag time in absorption - ALAG (h)	0.389 Fixed	0.389 Fixed
F1 – Bioavailability for 1G and 2G tablet relative to suspension	0.745 Fixed	0.745 Fixed
F1 - Bioavailability for 1G tablet (Lot No. 56789-101) relative to suspension	0.213 Fixed	0.213 Fixed
Inter-subject variability in CL/F (%CV) [a]	28.8	28.8
Inter-subject variability in V/F (%CV) [a]	25.0	25.0
Inter-subject variability in Ka (%CV) [a]	137.0	136
Inter-subject variability in D1 (%CV) [a]	21.7	21.2
Inter-subject variability in F1 for 1G and 2G tablet (%CV) [a]	35.9	35.8
Inter-subject variability in F1 for 1G (Lot No. 56789-101) (%CV) [a]	67.7	68.0
Inter-occasion variability for F1 for 1G and 2G tablet (%CV) [a]	41.1 Fixed	41.1 Fixed
		Non Pyxant method
Proportional residual variability in avatrombopag concentrations (%CV) [a]	16.9	17.0
Additive residual variability in avatrombopag concentrations (SD in ng/mL)	0.395	0.346
Proportional residual variability in avatrombopag concentrations for TAD ≤ 4 h (%CV) [a]	56.3	57.4
Additive residual variability in avatrombopag concentrations for TAD ≤ 4 h (SD in ng/mL)	0.338	0.202
		Pyxant method
Proportional residual variability in avatrombopag concentrations (%CV) [a]		16.8
Additive residual variability in avatrombopag concentrations (SD in ng/mL)		0.451
Proportional residual variability in avatrombopag concentrations for TAD ≤ 4 h (%CV) [a]		49.6
Additive residual variability in avatrombopag concentrations for TAD ≤ 4 h (SD in ng/mL)		0.533

[a]Coefficient of variation; CI – Confidence Interval. [(a)] %CV for both inter-subject/patient and proportional residual variability is an approximation taken as the square root of the variance x 100. The approximation is due to the expansion of the exponential function only to first-order. [(b)] %RSE was calculated as the s.e. divided by the parameter estimate x 100.

(Source: Applicant's Response to Information Request from the Mid-cycle Communication, Dated 1/17/2018)

Reviewer's Comments:

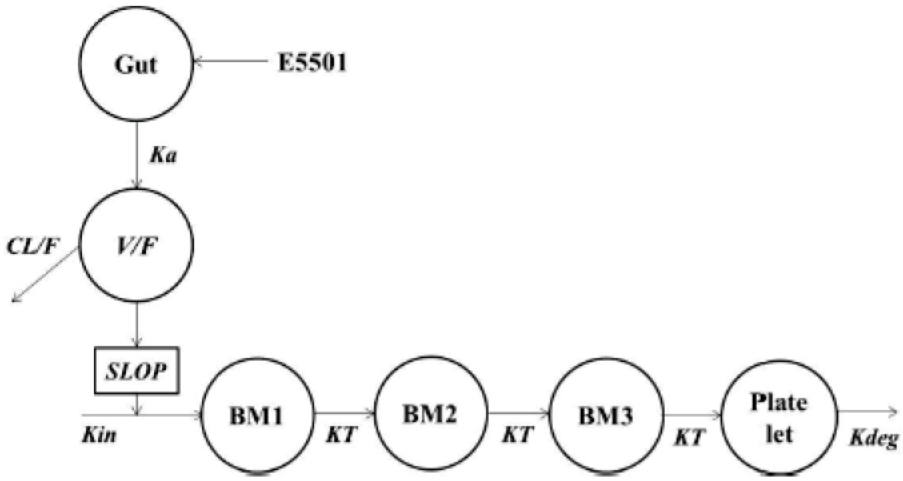
The sensitivity analysis performed by the applicant is acceptable to demonstrate there is no-clinically meaningful effect of different PK assays used for the different study data in the overall population PK analysis.

19.4.5.2.2 Applicant's Population PK/PD Analysis

19.4.5.2.2.1 Applicant's Avatrombopag Population PK/PD Methodology:

"The PK/PD population consisted of 394 subjects of whom 239 Caucasians, 15 Black/African Americans, 3 Asians other than Chinese, Japanese and Korean, 61 Japanese, 17 Chinese, 29 Korean and 25 other races. There were 264 males and 130 females. The population age and weight ranged from 19 to 86 years (median = 58 years) and 38.5 to 175 kg (median = 78.7 kg), respectively. The population platelet count at baseline ranged from 10.0 to 107 $\times 10^9$/L (median = 39.0 $\times 10^9$/L). There were 241 viral hepatitis, 44 non-alcoholic steatohepatitis, 49 alcoholic liver and 59 other disease CLD subjects. There were 86 subjects with hepatocellular carcinoma."
"The final population PK model was used to derive individual post-hoc PK parameters, which were then incorporated into the PK/PD datasets to be used in the subsequent PK/PD analyses. The PK/PD model for the relationship between model-predicted avatrombopag plasma concentration and platelet count was a six-compartment PK/PD lifespan model, with two PK compartments and four PD compartments with a linear slope for the effect of avatrombopag on platelet count, applied to platelet count data in CLD subjects from Studies 202, 204, 310 and 310.
"The PD compartments included one precursor production compartment (BM1), two transit/maturation compartments (BM2 and BM3) and one platelet (blood) compartment (platelet)." … "A proportional error model was compared with either combined proportional and additive error term or additive error term. The model was parameterized for observed baseline platelet count, Slope (linear) for drug effect, Kout and Kin with exponential IIV estimated for all parameters and combined residual error terms for platelet counts were selected as the Base PK/PD model for subsequent univariate analysis."
"The effects of race, TPO, albumin, body weight, HCC and age were tested on slope, body weight and etiology of chronic liver disease on Kout and TPO and body weight on Kin. In addition, the effect of etiology of chronic liver disease was tested on baseline platelet count."

Figure 15: Illustration of Compartments for the Pharmacokinetic/Pharmacodynamic Life-Span model



(Source: Applicant's Population PK, PK/PD Report, Figure 6-1)

19.4.5.2.2 Applicant's Avatrombopag Population PK/PD Results:

"The final NONMEM dataset for avatrombopag population PK/PD analysis included a total of 1877 platelet count-time records from 394 CLD subjects."
"From univariate analysis the effects of East Asian race (Japanese, Chinese & Koreans), TPO, albumin and weight on slope were identified as statistically significant and were included in the full model which was subjected to backward deletion analysis where the effect of body weight on slope was found to be insignificant and removed from the model. Therefore, the final PK/PD model for avatrombopag included the effects of East Asian race (Japanese, Chinese and Korean), TPO and albumin on the drug effect slope parameter. All parameters of the structural model were estimated with excellent precision (%RSE ≤18.4%)." … "A small but significant inverse relationship was identified for drug effect on platelet count with increased albumin and TPO levels. Simulation of the PK/PD model demonstrated that within the range of values of albumin and TPO observed in CLD subjects from Studies 202, 204, 310 and 311 the effect of these covariates on platelet count was minimal and not clinically relevant." … "Neither age, gender, MELD score, CTP score, etiology of chronic liver disease, HCC, splenomegaly nor steroid co-administration had any statistically significant effect on any of the PD parameters to warrant any dose adjustment." … "The estimates of inter-subject variability were estimated with excellent precision (%RSE ≤19.2%). The residual variability in platelet count was estimated with excellent precision with %RSE at ≤8.95%. "
"A lower effect of avatrombopag on platelet levels in Japanese/Chinese/Korean subjects (0.00886 ± 0.00420 mL/ng) compared to other subjects (0.0171 ± 0.0265 mL/ng) was observed. This is also the case when Japanese, Chinese or Korean subjects are assessed separately." …
"While highly variable overall the slope parameter is comparable for different baseline levels of platelet count. Hence, the slope for avatrombopag effect is irrespective of baseline platelet count."

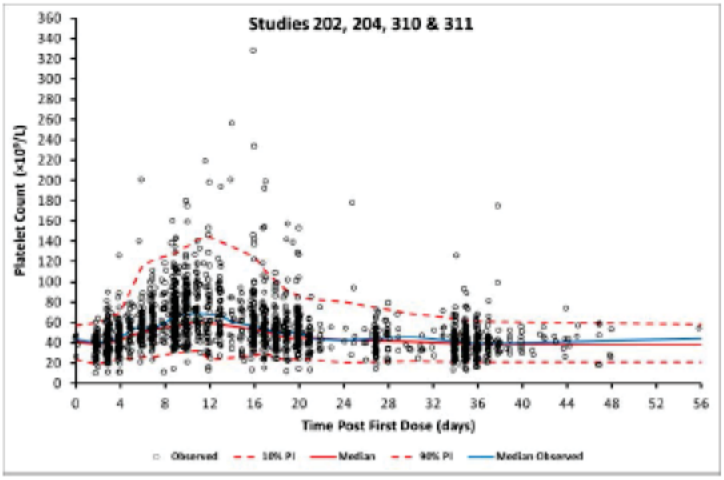
Table 76: Final model estimates of population PK/PD parameters of avatrombopag in subjects with chronic liver diseases and thrombocytopenia.

Parameter	Estimate [95% CI]	%RSE [b]
Slope (mL/ng)	0.0117 [0.0110 – 0.0124]	3.01
Effect of Japanese, Chinese, Korean Race (East Asian) on Slope	0.678 [0.554 – 0.802]	9.35
Effect of TPO on Slope	-0.445 [(-)0.606 – (-)0.284]	18.4
Effect of Albumin on Slope	-0.938 [(-)1.23 – (-)0.644]	16.0
Kin (Gi/L/h)	1.40 [1.29 – 1.51]	4.11
Kout (h^{-1})	0.0160 [0.0153 – 0.0167]	2.09
Inter-subject variability in BASE (%CV) [a]	15.3	6.72
Inter-subject variability in SLOP (%CV) [a]	60.2	6.58
Inter-subject variability in Kin (%CV) [a]	101	19.2
Inter-subject variability in Kout (%CV) [a]	21.2	13.3
Proportional residual variability in platelet count (%CV) [a]	14.0	4.28
Additive residual variability in platelet count (*10^9/L)	3.38	8.95

[a] %CV for both inter-subject/patient and proportional residual variability is an approximation taken as the square root of the variance x 100. The approximation is due to the expansion of the exponential function only to first-order.
[b] %RSE was calculated as the s.e. divided by the parameter estimate x 100.

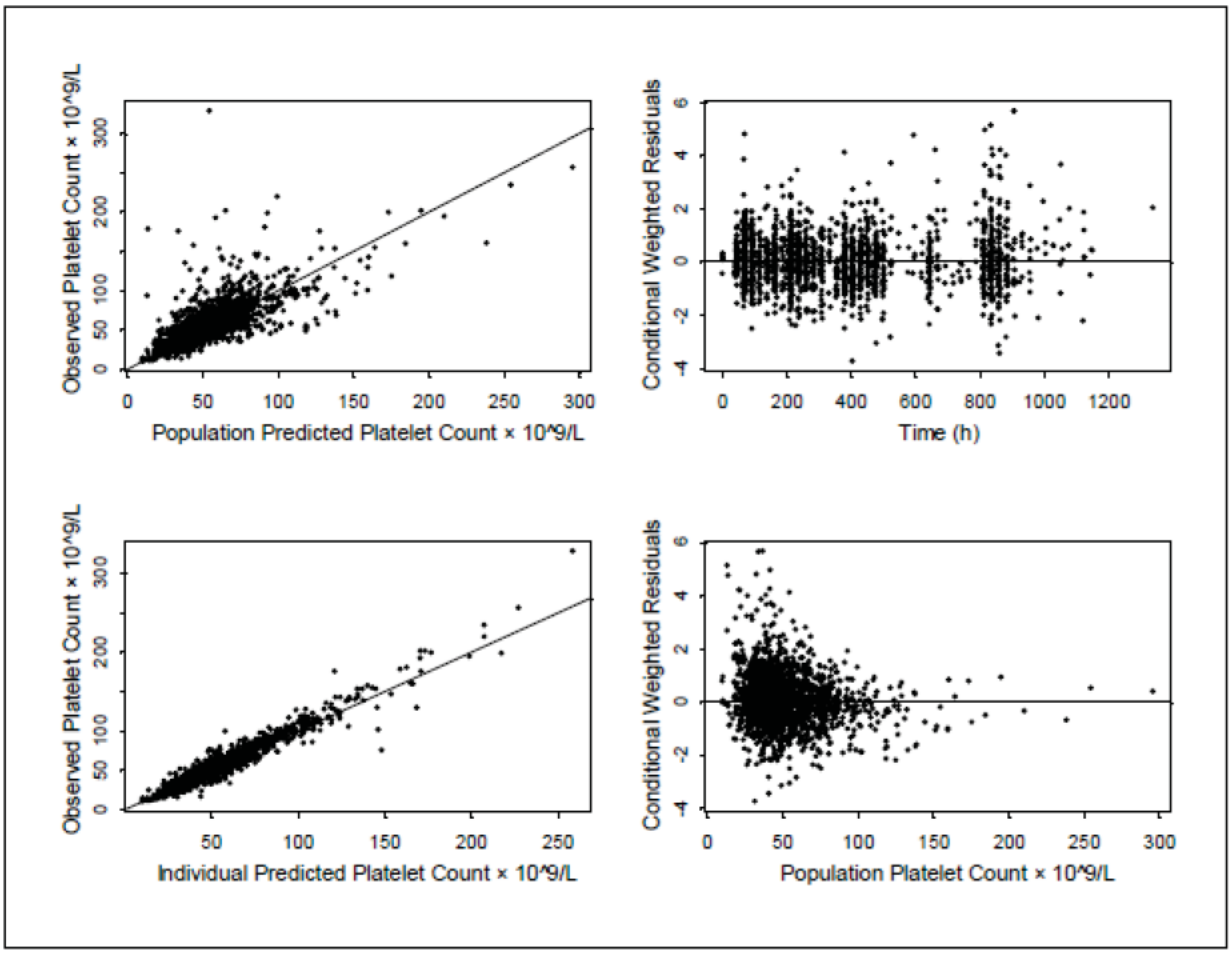
(Source: Applicant's Population PK, PK/PD Report, Table 8-21)

Figure 16: Visual Predictive Check of Observed and Model-Predicted Platelet Count Following in Subjects with Chronic Liver Diseases and Thrombocytopenia in Studies 202, 204, 310 & 311



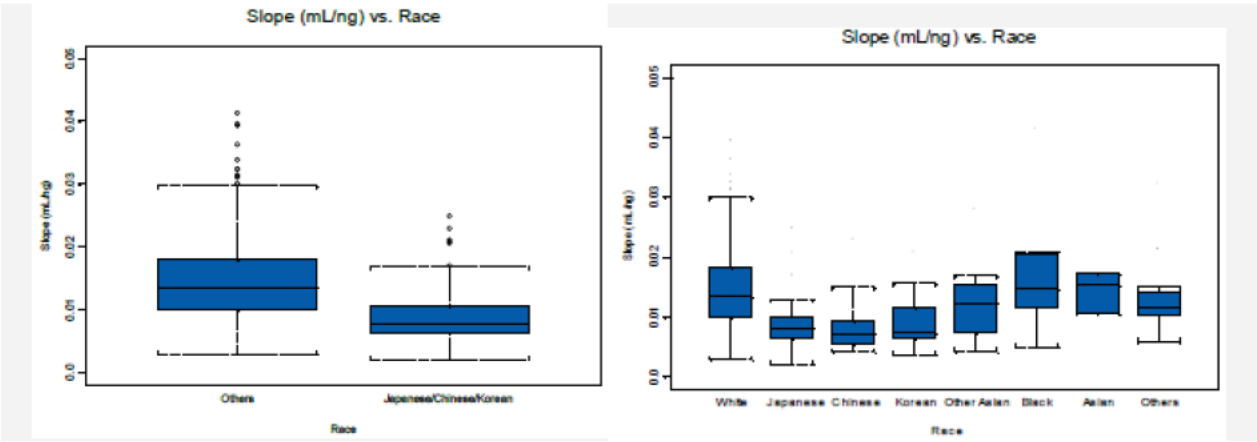
(Source: Applicant's Population PK, PK/PD Report, Figure 8-5)

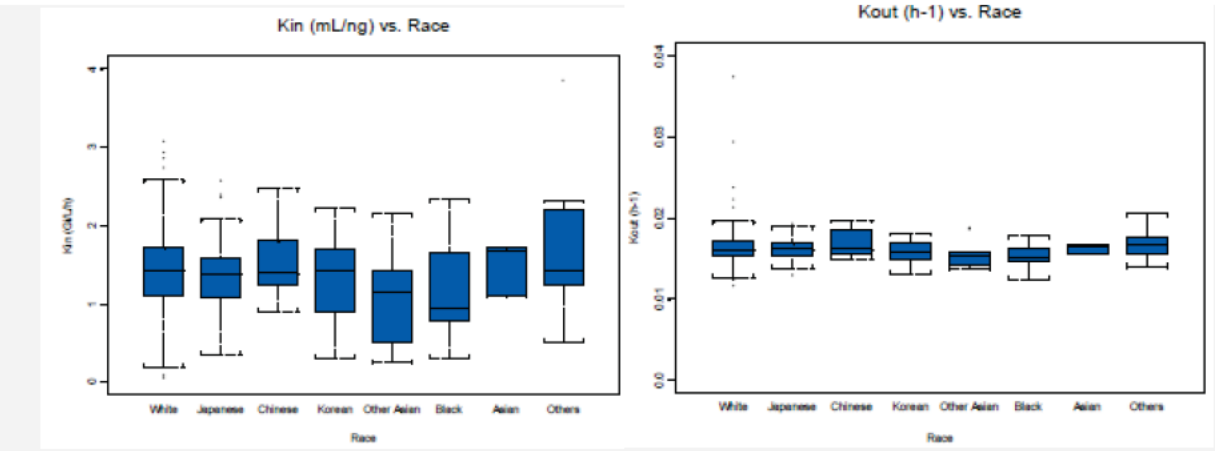
Figure 17: Assessment of Goodness of Fit for the FINAL PK/PD Model



(Source: Applicant's Population PK, PK/PD Report, Figure 11-11)

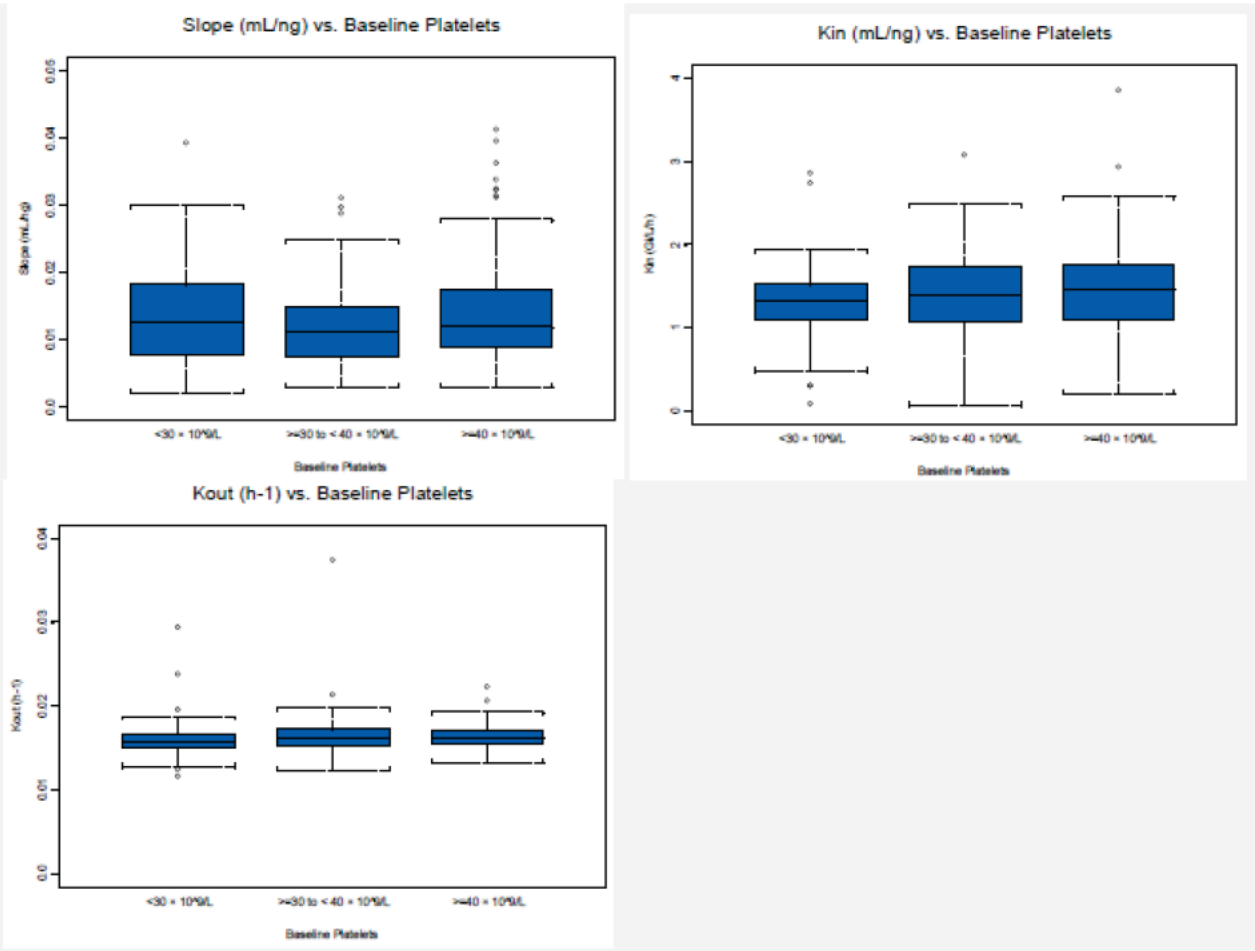
Figure 18: Effect of Race on PK/PD Parameters





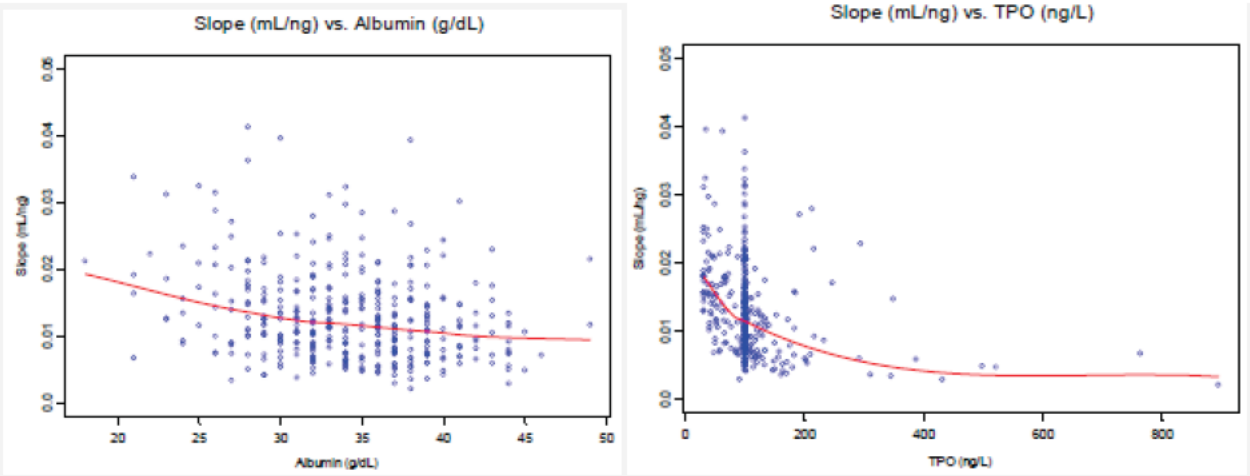
(Source: Applicant's Population PK, PK/PD Report, Figure 8-6)

Figure 19: Effect of Baseline Platelets on PK/PD Parameters



(Source: Applicant's Population PK, PK/PD Report, Figure 8-7)

Figure 20: Effect of Albumin and TPO on PK/PD Drug Effect Parameter



(Source: Applicant's Population PK, PK/PD Report, Figure 8-8 & 8-9)

Reviewer's Comments:

The current sampling scheme of population PK and PK/PD analysis is sufficient to provide an assessment at baseline, rate of onset of drug response, peak and post-dosing platelet counts. Patients numbers appear sufficient to provide distinction in response to drug between East Asians and other ethnicities (107 of the 394 patients were East Asian).The VPC simulation and plots of the effects of covariates on PK/PD parameters suggest that the final population PK/PD models appear to fit the data well (Figure 16, Figure 17, Figure 18, Figure 19, and Figure 20). The linear relationship between drug concentration and platelet count suggests that the platelet production would increase as the concentration of avatrombopag increases, and there is no upper limit for platelet production. It appears reasonable to use the model for interpolation.

19.4.5.3. REVIEWER'S ANALYSIS

19.4.5.3.1 Objectives

Analysis objectives are:
1. Determine whether the population PK and PK/PD model supports the dosing regimen proposed in the label.
2. Determine whether the dose adjustment for concomitant with CYP modulators proposed in the label is reasonable.
3. Determine the reasonable dosing regimen for the repeated dose of avatrombopag if the second procedure is needed.

19.4.5.3.2 Methods

19.4.5.3.2.1 Software

NONMEM 7.3 (Icon, Ellicott City, MD) was used to review the applicant's population pharmacokinetic analysis and performing simulations for concomitant medication scenarios. The statistical software R (www.r-project.org) was used to analyze the NONMEM output table and generate plots. Berkeley Madonna was used to perform the simulations for repeat dosing regimens.

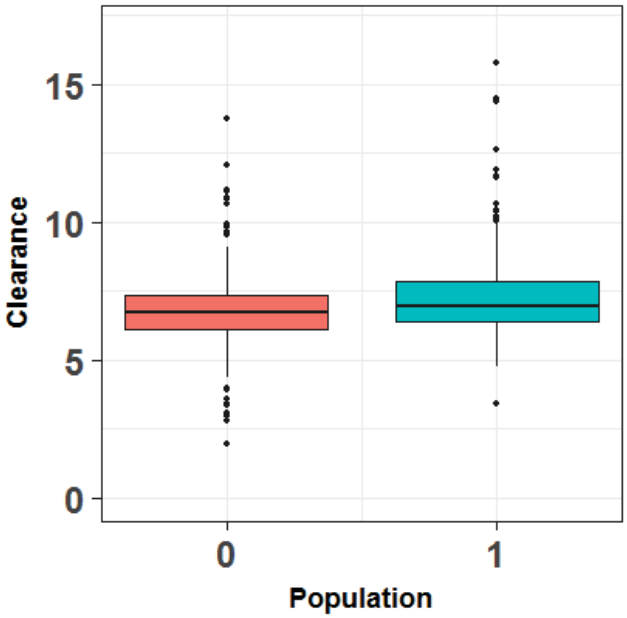
19.4.5.3.2.2 Models

The applicant's base and final population PK and PK/PD model control streams were run with their datasets to examine the effects of each covariate on the parameters clearance and volume of distribution. NONMEM 7.3 was run with the control stream for the final model and the final parameter estimates were compared.
Following verifying the applicant's final population PK/PD model, the PK profiles of avatrombopag from PBPK analysis were used as the input to simulate the platelet count for different concomitant medication scenarios. This helped to determine whether the applicant's proposed dose adjustment for concomitant administration of CYP modulators is reasonable. The FDA reviewer simulated 273 subjects with the same demographic characteristics with those in the applicant's phase 3 clinical studies. Each simulation conducted 200 replicates. The platelet counts for each subject from day 1 to day 38 were simulated. The maximum platelet count for each subject was determined using software R from the NONMEM output table. The proportion of patients with maximum platelet counts < 50 x 10^9/L, 50 to 200 x 10^9/L, and > 200 x 10^9/L were determined.
To help make recommendation for the scenario that the repeat dosing regimen is necessary if the second procedure is needed, the FDA reviewer conducted simulations for different scenarios of repeat dose to evaluate platelet count profile. The simulation was performed using Berkeley Madonna based on the applicant's final PK/PD model for 90th percentile subjects, and the estimates of the parameters of the 90th percentile patients were used as the input. The repeat dosing regimen was simulated to start on Day 13, Day 15 and Day 20, for 4 or 5 consecutive days, respectively. The PK and PD profiles were generated in the plots to evaluate the platelet count profile for the repeat dosing regimen for each scenario.

19.4.5.3.3 Results

The FDA reviewer reran applicant's final population PK and PK/PD models and the analysis parameters were similar with those obtained by the applicant's. The CV% of CL was less than 30%, and the shrinkages of CL and SLOPE were less than 30% as well. The model diagnostics and goodness of fit characteristics support the applicant's proposed avatrombopag dosing regimens in the label. PK characteristics were similar between healthy subjects and target patient population (Figure 21): mean apparent oral clearance (CL/F) was 6.86 (32%) L/hr in healthy subjects and 7.29 (18%) L/hr in patients.

Figure 21: Avatrombopag CL (L/hr) is similar between healthy subjects (6.86 ± 2.20 L/hr) and patients (7.29 ± 1.34 L/hr).



0: Healthy volunteers; 1: CLD patients.

19.4.5.3.3.1 Concomitant medication with p-gp inhibitors

Based on the drug-drug interaction study and PBPK analysis, the AUC of avatrombopag is 20% lower when concomitantly use with the p-gp inhibitor cyclosporine A (CSA) compared with that when dosing avatrombopag alone, while the AUC of avatrombopag is 1.16-fold higher when concomitantly use with p-gp and moderate CYP3A dual inhibitor compared with that when dosing avatrombopag alone. The simulation using the final population PK/PD model and PBPK analysis shows that with concomitant medication with p-gp inhibitor CSA, 5-day regimen of avatrombopag produces similar percentage of patients with the platelet count reaching 50 to 200 x 10^9/L range compared with dosing avatrombopag alone (70.2% vs. 73.0%,Table 77). Thus, the agency agrees with applicant's proposal that no dose adjustment for concomitant use with p-gp inhibitors is needed. A similar result was obtained from the simulation for concomitant use with the p-gp and moderate CYP3A dual inhibitor such as verapamil (74.8% vs. 73.0% avatrombopag alone, Table 77). Thus, the agency agrees with applicant's proposal that no dose adjustment for concomitant use with a p-gp and moderate CYP3A dual inhibitor is needed.

Table 77: The percentage of patients with maximum platelet count in different ranges when concomitantly use with p-gp inhibitors

		Percentage of simulated patients				
	Dose Duration	Plt_{max}<50	50≤Plt_{max}≤200	Plt_{max}>200	Plt_{max}>350	Plt_{max}>400
Avatrombopag alone	5 days	24.8 %	73.0 %	2.2 %	0.2 %	0.1 %
+ p-gp inhibitor	5 days	28.5 %	70.2 %	1.3 %	0.1 %	0.1 %
+ p-gp & Mod. CYP3A	5 days	22.3 %	74.8 %	2.9 %	0.4 %	0.2 %

19.4.5.3.3.2 Concomitant medication with a strong CYP3A and moderate CYP2C9 dual inducer

Based on the drug-drug interaction study and PBPK analysis, the AUC of avatrombopag is 50% lower when concomitantly use with CYP3A and moderate CYP2C9 dual inducer rifampin compared with that when dosing avatrombopag alone. The applicant proposed (b) (4) The reviewer simulated different scenarios for avatrombopag dosing regimens for concomitant use with rifampin. For original avatrombopag dosing regimen (40 mg 5-day QD for high baseline patients, 60 mg 5-day QD for low baseline patients), the percentage of patients with platelet count reaching 50 to 200 x 10^9/L range is significant lower than that obtained from the simulation for dosing avatrombopag alone (57.9 % vs. 73.0 %, Table 78). However, when the dose of avatrombopag is doubled for both high baseline and low baseline patients in the simulation (80 mg 5-day QD for high baseline patients, 120 mg 5-day QD for low baseline patients), the percentage of patients with platelet count reaching 50 to 200 x 10^9/L range is comparable with that of dosing avatrombopag alone (71.1 % vs. 73.0 %, Table 78). When doubling the dosing duration while keeping the dosing amount (40 mg 10-day QD for high baseline patients, 60 mg 10-day QD for low baseline patients, Table 78) in the simulation, the percentage of patients with the maximum platelet count reaching target therapeutic range is significant lower than that when dosing avatrombopag alone. Considering that patients will still benefit at the dosing regimens of 40 mg 5-day QD for high baseline patients, 60 mg 5-day QD for low baseline patients, the Office of Clinical Pharmacology recommends no dose adjustment when concomitantly use with a strong CYP3A and moderate CYP2C9 dual inducer.

Table 78: The percentage of patients with maximum platelet count in different ranges when concomitantly use with a strong CYP3A and moderate CYP2C9 dual inducer

		Percentage of simulated patients				
	Dose Duration	Plt_{max}<50	50≤Plt_{max}≤200	Plt_{max}>200	Plt_{max}>350	Plt_{max}>400
Avatrombopag alone	5 days	24.8 %	73.0 %	2.2 %	0.2 %	0.1 %
Original dose + Rifampin	5 days	41.9 %	57.9 %	0.2 %	0.0 %	0.0 %
Doubled dose + Rifampin	5 days	27.3 %	71.1 %	1.6 %	0.1 %	0.1 %
Original dose + Rifampin	10 days	37.7 %	61.8 %	0.5 %	0.02 %	0.02 %

19.4.5.3.3.3 Concomitant medication with strong CYP3A, CYP2C9 and CYP3A/CYP2C9 dual inhibitors

Based on the drug-drug interaction study and PBPK analysis, the AUC of avatrombopag is 1.4-fold higher when concomitantly use with strong CYP3A inhibitor itraconazole compared with that when dosing avatrombopag alone. The applicant proposed (b) (4) . The reviewer's

simulation result indicates that when concomitantly use with itraconazole for 5 days, the percentage of patients with the platelet counts reaching 50 to 200 x 10^9/L range and higher than 200 x 10^9/L are both only slightly higher than that when dosing avatrombopag alone (Table 79). The Office of Clinical Pharmacology recommends that no dose adjustment is needed when concomitantly use with the strong CYP3A inhibitor itraconazole. Likewise, although the AUC of avatrombopag is 1.5-fold higher when concomitantly use with CYP2C9 inhibitor sulfaphenazole (predicted based on PBPK analysis), and 2.2-fold higher when concomitantly use with moderate CYP3A and CYP2C9 dual inhibitor fluconazole, the percentage of patients with maximum platelet count higher than 200 x 10^9/L was acceptable. Thus, considering avatrombopag is proposed for acute treatment in CLD patients and there appears to be no major safety issue (further details can also be found in the clinical review by Dr. Laurel Menapace), the Office of Clinical Pharmacology recommends that no dose adjustment is needed when concomitantly use with strong CYP3A, CYP2C9 or CYP3A/CYP2C9 dual inhibitors, to reach a satisfied treatment effect and avoid platelet transfusion.

Table 79: The percentage of patients with in different maximum platelet count ranges for multiple drug-drug interaction scenarios.

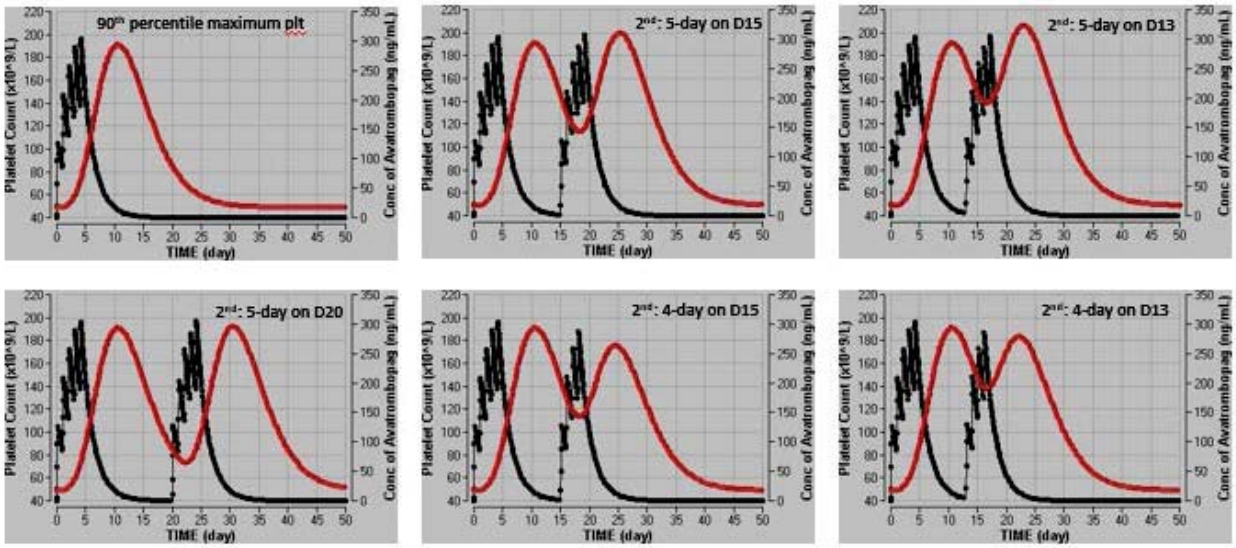
		Percentage of simulated patients				
	Dose Duration	Plt_{max}<50	50≤Plt_{max}≤200	Plt_{max}>200	Plt_{max}>350	Plt_{max}>400
Avatrombopag alone	5 days	24.8 %	73.0 %	2.2 %	0.2 %	0.1 %
+ Strong CYP3A inhibitor	5 days	20.7 %	75.8 %	3.5 %	0.5 %	0.3 %
	4 days	24.3 %	73.6 %	2.1 %	0.2 %	0.1 %
+ Mod. CYP3A & 2C9 inhibitor	5 days	13.9 %	77.7 %	8.4 %	1.6 %	1.0 %
	4 days	16.9 %	77.8 %	5.3 %	0.8 %	0.5 %
	3 days	21.9 %	75.4 %	2.7 %	0.3 %	0.1 %
	↓ Dose x 5 days	21.9 %	75.6 %	2.5 %	0.3 %	0.2 %
+ 2C9 inhibitor	5 days	18.4 %	76.8 %	4.8 %	0.7 %	0.4 %
	4 days	21.7 %	75.4 %	2.9 %	0.4 %	0.2 %

19.4.5.3.3.4 Simulation for repeated dosing regimen for second procedure

The purpose of this simulation was to determine if alterations to the dosing regimen are necessary if a second procedure is needed in a short timeframe after the first procedure as it is likely the patient's platelets will return to less than 50 within about 4 weeks after this acute 5-day regimen. The platelet count reached the maximum after five days after the last dose of the first regimen, and the dropped back to baseline after 30 days. Different scenarios of repeat dosing regimens were simulated and the PK and PD profiles of 90th percentile high baseline patients are shown as Figure 22. The second regimen was simulated to start on day 20, day 15 or day 13 after the first dose of the first regimen, for 5 days or 4 days, respectively. The simulation results indicate that the PD profiles following the 5-day second dosing regimen are generally similar with those following the first dosing regimen (5-day) obtained from the simulations for start date no earlier than day 15. The maximum platelet count following the 5-day second dosing regimen starting on day 13 is slightly higher than that following the first

dosing regimen. Considering that at the studied exposures there appears to be no major safety finding of avatrombopag, the office of clinical pharmacology recommends the same dosing regimen for the repeat dose if the second procedure is needed.

Figure 22: PK and PD profiles of simulations for repeat dosing regimens if the second procedure is needed – 90th percentile high baseline patients.



Black: PK profile after dosing avatrombopag. Red: PD profile after dosing avatrombopag.

19.4.6. Office of Clinical Pharmacology: Physiologically Based Pharmacokinetics Review[1]

1. Executive Summary

1.1 Objectives

The applicant submitted a study report CPMS-E5501-006R entitled ”Development of a Physiologically-Based Pharmacokinetic Model for Avatrombopag and Simulations of Cytochrome P450-Mediated Drug-Drug Interactions”. In this report, the applicant applied physiologically based pharmacokinetic (PBPK) modelling approach to predict in vivo drug-drug interactions (DDIs) between avatrombopag (the victim) and the following compounds (perpetrators):

- Itraconazole: strong CYP3A4 inhibitors
- Fluconazole: moderate CYP3A4 inhibitor and strong CYP2C9 inhibitor
- Rifampicin: strong CYP3A4 inducer and moderate CYP2C9 inducer
- Verapamil: moderate reversible CYP3A4 inhibitor and time dependent inhibitor and strong P-gp inhibitor

[1] CPMS-E5501-006R study report: Application 210238 - Sequence 0000 - CPMS-E5501-006R

On 11/3/2017, the applicant submitted supporting files for the physiologically based pharmacokinetic (PBPK) model development and model performance assessment for CYP3A4 inhibitors (Itraconazole and Ketoconazole), CYP3A4 and CYP2C9 dual inhibitor (Fluconazole), CYP2C9 inhibitor (Sulphaphenazole), CYP3A4 and CYP2C9 inducer (Rifampicin), and CYP3A4 & P-gp inhibitors (Verapamil) (Sequence # 0004).

On 12/13/2017, the applicant submitted additional Simcyp workspace files that supported the development of the PBPK model (Sequence # 0009).

This review evaluates the adequacy of the applicant's PBPK models to predict DDI potential of various CYP modulators on the pharmacokinetics of avatrombopag.

1.2 Background

DOPTELET (avatrombopag) is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in patients with chronic liver disease (CLD) who are scheduled to undergo a procedure. It is an orally dosed tablet with a dosing strength at 20 mg. The proposed dose for avatrombopag is 60 mg QD x 5 days for patients with low baseline platelet ($<40 \times 10^9$/L), 40 mg QD x 5 days for patients with high baseline platelet (≥ 40 and $<50 \times 10^9$/L). Avatrombopag is proposed to be taken with food, as food showed no effect on PK exposure, but decrease PK variability by 50%.

In vitro studies showed that the oxidative metabolism of avatrombopag is mainly mediated by CYP2C9 and CYP3A4. DDI studies with moderate to strong CYP3A4 and CYP2C9 modulators in healthy subjects suggested that CYP2C9 plays the major role relative to CYP3A4 in the oxidative metabolism of avatrombopag. In an open label cross-over study in healthy adult volunteers (Study 019), co-administration of itraconazole, a strong CYP3A4 inhibitor, 200 mg once daily at steady state with a single 20 mg dose of DOPTELET resulted in 7.4% and 37.4% increase in Cmax and $AUC_{(0\text{-inf})}$ of avatrombopag, respectively; co-administration of fluconazole, a moderate dual inhibitor of CYP2C9 and CYP3A4, 400 mg once daily at steady state with a single 20 mg dose DOPTELET resulted in 1.17- and 2.16-fold increase in Cmax and $AUC_{(0\text{-inf})}$ of avatrombopag, respectively; co-administration of rifampin, a strong CYP3A4 and a moderate CYP2C9 inducer 600 mg once daily at steady state, with a single 20 mg dose of DOPTELET resulted in no change in Cmax, but approximately 42.1% decrease in $AUC_{(0\text{-inf})}$ of avatrombopag.

In vitro studies also showed that avatrombopag is a substrate for p-glycoprotein (P-gp) mediated transport. However, DDI studies in healthy subjects showed that strong P-gp inhibitors such as verapamil and cyclosporine (CsA) had mild effects on systemic exposures of avatrombopag. In an open label cross-over study in healthy adult volunteers (Study 008), co-administration of verapamil, a P-gp and CYP3A4 inhibitor, 240 mg once daily at steady state, with a single 20 mg dose of DOPTELET resulted in 26% and 61% increase in plasma avatrombopag Cmax and $AUC_{(0\text{-inf})}$, respectively; co-administration of a single 20 mg dose of DOPTELET with a single 400 mg dose of cyclosporine, a strong P-gp inhibitor, did not have clinically important effect on avatrombopag Cmax or $AUC_{(0\text{-inf})}$. Based on in vitro studies, no

other transporters (OATP1B1, OATP1B3, OCT2, OAT1, and OAT3) are expected to play a significant role in the disposition of avatrombopag.

The applicant applied a PBPK modelling approach to predict in vivo DDIs between avatrombopag and CYP3A4 and CYP2C9 inhibitors and inducers. The predicted clearance values from PBPK analysis were used as the model inputs of a population pharmacokinetic (PK) and pharmacodynamic (PD) analysis to simulate the platelet counts. Based on the simulated platelet counts, the applicant proposed the following labeling claim:

(b) (4)

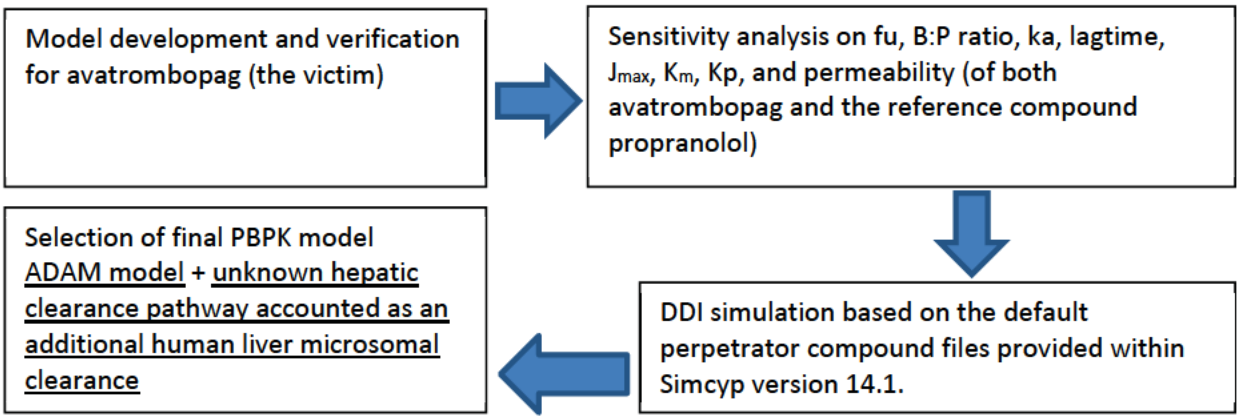
This review evaluates the ability of the applicant's PBPK models to 1) describe the PK profiles for avatrombopag; and 2) predict DDI potential of CYP3A4 and CYP2C9 inhibitors and inducers on the pharmacokinetics of avatrombopag.

2. Model Development

2.1 Modeling Development Overview

The models were developed in Simcyp (version 14.1; Simcyp Ltd., a Certara Company, Sheffield, United Kingdom). A flow chart of modeling strategy is summarized below by the reviewer (Figure 23). The applicant's modeling strategy is appropriate.

Figure 23: Summary of applicant's PBPK model building strategy



2.2 Modeling Development

Two different absorption models were explored: an empirical first order absorption model with lagtime, and a mechanistic advanced dissolution, absorption, and metabolism (ADAM) model, where dissolution was modeled with input from the dissolution profile of avatrombopag in fed

state simulated intestinal fluid (FeSSIF). Volume of distribution was modeled using tissue partition coefficients from a quantitative tissue distribution study in rats. Clearance input was optimized with Simcyp's built-in retrograde calculator, using clearance values from two clinical avatrombopag studies and the fractional contributions (fm) of CYP2C9 and CYP3A4 determined from in vitro metabolism studies. Three different clearance models were tested, where an unassigned metabolic clearance pathway (identified in the human mass balance study) was either added to the fm value assigned to CYP3A4 or CYP2C9, or simply entered as an additional clearance from human liver microsomes (HLM) in Simcyp. A diagram for the final mass balance of avatrombopag used to develop the PBPK models are shown below in Figure 24.

Figure 24: A diagram for the final mass balance of avatrombopag used to develop the PBPK models

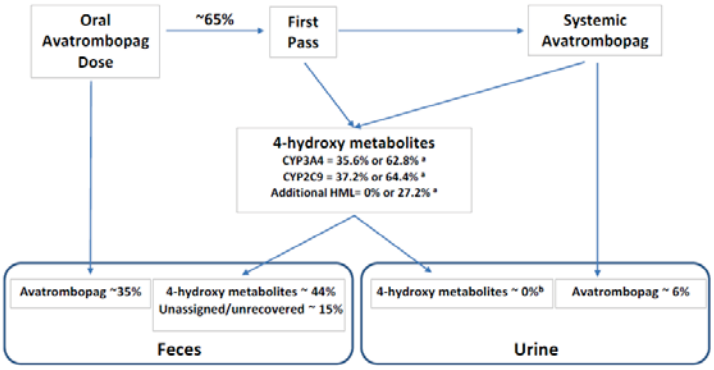


Figure obtained from study report CPMS-E5501-006R Figure 1.

PBPK simulations were performed following a single 20 mg or 40 mg oral dose administered with 250 mL water under either fasted or fed conditions, in accordance to the respective clinical study design. The performance of all 6 PBPK model candidates in characterizing avatrombopag PK under either fasted or fed conditions is summarized in Table 80.

Table 80: Fold-differences between observed and predicted geometric mean avatrombopag exposures

	Dose (mg)	Study	1st-order absorption with lag time			ADAM		
			CM1[a]	CM 2 [a]	CM 3 [a]	CM1[a]	CM 2 [a]	**CM 3** [a]
Cmax Ratio observed-vs-predicted	20 Fasted	008	1.42	1.38	1.36	1.42	1.41	**1.41**
	20 Fed	019	1.39	1.38	1.36	1.43	1.43	**1.43**
	40 Fasted	017	1.31	1.27	1.26	1.30	1.29	**1.30**
	40 Fed	017	1.20	1.17	1.16	1.22	1.21	**1.22**
AUC Ratio observed-vs-predicted	20 Fasted	008	1.65	1.60	1.59	0.92	0.91	**0.93**
	20 Fed	019	1.68	1.62	1.64	0.97	0.96	**1.00**
	40 Fasted	017	1.63	1.58	1.58	0.91	0.90	**0.92**
	40 Fed	017	1.51	1.47	1.46	0.88	0.88	**0.90**

Values obtained from study report CPMS-E5501-006R Table 9 and 10.
[a]Three clearance models were proposed by assigning the additional hepatic clearance to CYP3A pathway -> CM1 model; CYP2C9 pathway -> CM2 model; additional liver intrinsic clearance ->CM3 model

For predicting drug-drug interactions, the inhibitor/ inducer dosing for PBPK simulation started on simulation Day 1 and continued for the whole duration of the simulation. A single 20 mg oral dose of avatrombopag was administered with 250 mL of water under fed conditions on simulation Day 8. All inhibitor and inducer compound files used for the simulations were the default compound files provided within Simcyp version 14.1. The final PBPK model parameters are summarized in Appendix 1. Using the developed PBPK models, DDI simulations of avatrombopag were performed with CYP inhibitors itraconazole, ketoconazole, fluconazole, verapamil, sulphaphenazole, and with the CYP inducer rifampicin. All 6 developed PBPK models adequately predicted the pharmacokinetic profiles of avatrombopag in three clinical studies. The performance of all 6 PBPK model candidates is summarized in Table 81.

Table 81: Observed and predicted AUC ratios for DDI simulations of 20 mg avatrombopag with itraconazole, fluconazole, verapamil, and rifampicin

Dose (mg)	Study	Observations	1st-order absorption with lag time			ADAM		
			CM1[a]	CM 2 [a]	CM 3 [a]	CM1[a]	CM 2 [a]	**CM 3** [a]
Itraconazole 200 mg QD	019	1.37	1.73	1.34	1.33	1.59	1.28	**1.27**
Fluconazole 400 mf QD	019	2.20	3.34	3.32	2.16	3.03	3.06	**2.04**
Rifampicin 600 mg QD	019	0.57	0.23	0.35	0.36	0.31	0.43	**0.44**
Verapamil 240 mg QD	008	1.61	1.44	1.23	1.22	1.32	1.17	**1.16**
Ketoconazole 200 mg BID	N/A	N/A	2.17	1.53	1.50	2.00	1.46	**1.42**
Sulphaphenazole 2000 mg QD	N/A	N/A	1.52	2.24	1.51	1.50	2.17	**1.47**

Values obtained from study report CPMS-E5501-006R Table 11, 12 and 13.
[a]Three clearance models were proposed by assigning the additional hepatic clearance to CYP3A pathway -> CM1 model; CYP2C9 pathway -> CM2 model; additional liver intrinsic clearance ->CM3 model

The applicant stated that both the 1st-order absorption with lag time and the mechanistic ADAM models described well the absorption phase of the PK profile. The prediction errors for the exposures were less than 2-fold for all models, with the ADAM absorption models providing the closest predictions of mean avatrombopag AUC. Of the 3 clearance models tested, the model where the unassigned metabolic clearance was entered as an additional human liver microsomal clearance (CM3) produced the best AUCR predictions, while the model where the unassigned metabolic clearance was added to the total fraction of metabolism of CYP3A4

(CM1), was the least successful, as it predicted an AUCR for the rifampicin DDI that was outside the lower limit of the acceptable prediction range.

The applicant proposed the final PBPK model to be the model with a ADAM absorption model and assumed an additional hepatic clearance (CM3). FDA reviewers agreed with the sponsor's justification on model selection, as the selected final PBPK model appears to provide a more mechanistically driven oral absorption model and have a better predicted DDI compared to observed data (Table 81). Unless otherwise stated, the simulation results evaluated in the rest of the review is based on the applicant's final PBPK model.

2.3 Modeling Verification

The developed avatrombopag model was verified by comparing the simulated and observed PK data in health subjects following a single dose of avatrombopag in both fed and fasted condition (study E5501-A001-017 and E5501-A001-019, Table 80), and observed DDI from three clinical studies (E5501-G000-008 and E5501-A001-019, Table 81). Table 82 summarized the design of the clinical studies and simulation protocol used in model verification and application.

Table 82: Trial design for clinical and simulated DDI studies

Study	Substrate	Dose Regimen	Perpetrator	Dose Regimen	Note
A001-017	avatrombopag	40 mg single dose	N/A	N/A	Single PK under fasted/fed condition
A001-019	avatrombopag	20 mg single dose	N/A	N/A	Single PK under fed condition
G000-008	avatrombopag	20 mg single dose	N/A	N/A	Single PK under fasted condition
G000-008	avatrombopag	20 mg single dose on Day 7	Verapamil	240 mg QD on Day 1 to 11	Clinical DDI under fasted condition
A001-019, Part A-DDI	avatrombopag	20 mg single dose on Day 7	Fluconazole	400 mg QD on Day 1 to 16	Clinical DDI under fed condition
A001-019, Part B-DDI	avatrombopag	20 mg single dose on Day 7	Itraconazole	200 mg BID on Day 1, 200 QD on Day 2 to 16	Clinical DDI under fed condition
A001-019, Part C-DDI	avatrombopag	20 mg single dose on Day 7	Rifampin	600 mg QD on Day 1 to 16	Clinical DDI under fed condition
Simulation	avatrombopag	20 mg single dose on Day 8	ketoconazole	200 mg BID from day 1 to 17	PBPK prediction

Simulation	avatrombopag	20 mg single dose on Day 8	sulphaphenazole	2000 mg QD from day 1 to 17	PBPK prediction

Reviewer found that the submitted PBPK models cannot reproduce the simulation outputs (such as e5501-unassigned-addl-cl-foitraconazole-ddi.wks vs. ddi-e5501-20-mg-itra-200-mg-qd-fo-unass-add-cl.xlsx). On December 7th, 2017, an information request was sent to the applicant. The applicant submitted additional Simcyp workspace files models to reproduce the simulation outputs used in the final PBPK report.

2.4 Modeling Application

Applicant used the final PBPK to predict PK of avatrombopag under either fasted or fed conditions (Table 80), and DDI between avatrombopag and CYP3A4 and CYP2C9 inhibitor fluconazole, CYP3A4 inhibitors itraconazole and ketoconazole, CYP2C9 inhibitor sulphaphenazole, CYP3A4 and P-gp inhibitor verapamil, and CYP3A4/CYP2C9 inducer rifampicin (Table 81).

Based on applicant's final model, the reviewer performed additional PBPK simulations to explore the impact of CYP2C9 polymorphism on avatrombopag PK. Virtual populations of CYP2C9 extensive metabolizers (EMs), CYP2C9 intermediate metabolizers (IMs) and CYP2C9 poor metabolizers (PMs) were established by modifying CYP2C9 enzyme abundance values and demographic frequency section in the default Sim-Healthy Volunteers population file. Liver and gut CYP2C9 enzyme abundance of CYP2C9 in CYP2C9 IMs and PMs are assumed to be 50% and 0% of that in CYP2C9 EMs (Table 83). In demographic section, CYP2C9 phenotype frequency setting for EM/IM/PM/UM in CYP2C9 EMs, IMs, and PMs was 1/0/0/0, 0/0/0/1 and 0/0/1/0, respectively.

Table 83: PBPK model setting for CYP2C9 EMs, IMs and PMs

Demographic	EM		PM		IM		UM	
	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)
Liver	73	54	0	0	36.5	100	0	0
Gut	12.9	60	0	0	6.5	100	0	0

The predicted clearance values from the final PBPK model were used in the simulations for platelet count under DDI conditions.

3. Question Based Review

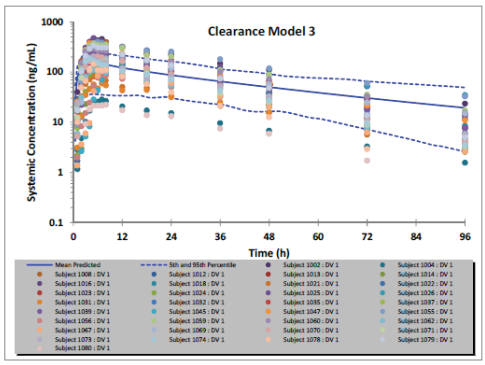
When using PBPK modeling to predict the interaction potential of avatrombopag as a substrate for both CYP2C9 and CYP3A4, the following questions were considered:

a. Can the PBPK model of avatrombopag (the investigational product) describe the available clinical PK data using different dosing regimens?

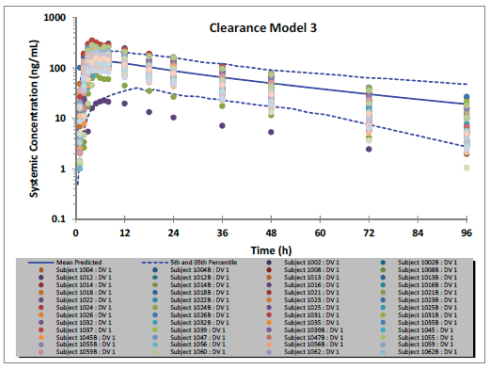
Yes, the proposed final avatrombopag model (a full PBPK model with mechanistic oral absorption (ADAM) and an additional hepatic clearance (CM3)) reasonably described the plasma concentrations of avatrombopag at dose levels ranging from 20 mg to 40 mg (Figure 25).

Figure 25: Predicted and observed plasma concentration versus time profiles of avatrombopag after a single 20 mg or 40 mg oral dose in healthy volunteers under fasted or fed conditions

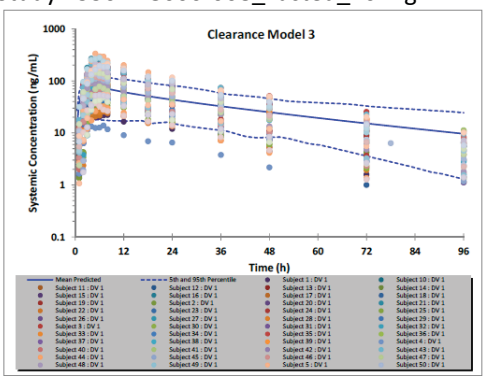
Study E5501-A001-017_Fasted_40 mg



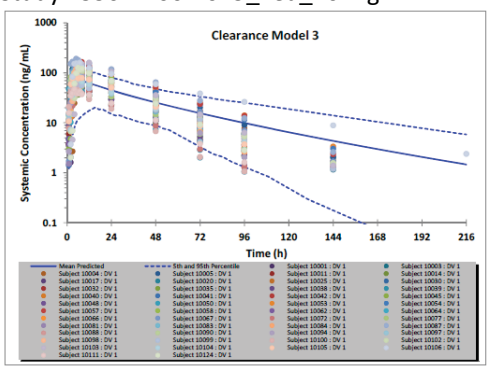
Study E5501-A001-017_Fed_40 mg



Study E5501- G000-008_Fasted_20 mg



Study E5501-A001-019_Fed_20 mg



*Data was obtained from study report CPMS-E5501-006R Figure 2-5

The simulated mean C_{max} and AUC_t at both dose levels were in good agreement with the respective observed values (Table 80). The fold differences between the observed vs. predict C_{max} values ranged from 1.22 to 1.43, that between the observed vs. predict AUC_t values ranged from 0.90 to 1.00.

b. Can the proposed PBPK model be used to predict the DDIs between avatrombopag and CYP3A4 and CYP2C9 inhibitors?

Yes. The final PBPK model reasonably predicted the clinical DDI results with verapamil, itraconazole, fluconazole, and rifampicin in studies E5501-G000-008 and E5501-A001-019 (Table 81). The PBPK model was also used to predict metabolic DDI of avatrombopag with ketoconazole (strong CYP3A inhibitor) and sulphaphenazole (CYP2C9 inhibitor). The predicted

AUCR of avatrombopag with ketoconazole 200 mg BID is 1.42. The predicted AUCR of avatrombopag with sulphaphenazole 2000 mg QD is 1.47.

P-gp mediated uptake was included in the submitted PBPK model for avatrombopag. Sensitivity analysis on J_{max} and K_m values for P-gp transport in the intestine indicated that the predicted avatrombopag C_{max}, AUC, and t_{max} are not very sensitive to changes in these parameters within the boundaries of the values, which agrees with what observed clinically. DDI studies in healthy subjects showed that strong P-gp inhibitors such as verapamil and cyclosporine (CsA) had mild effects on systemic exposures of avatrombopag. On the other hand, the applicant's PBPK model didn't evaluate the P-gp inhibition potential of verapamil, which was treated as a time dependent inhibitor for CYP3A4 and CYP3A5 in the applicant submitted model using Simcyp V14.1 default setting for verapamil.

c. Can the proposed PBPK model be used to predict the impact of CYP2C9 polymorphism on avatrombopag PK?

Based on additional simulations, the derived AUC ratios of avatrombopag in CYP2C9 IMs and PMs between CYP2C9 IMs/PMs and EMs are similar to those observed clinically in the healthy subjects (Table 84).

Table 84: Predicted and observed AUC ratios of avatrombopag in CYP2C9 IMs and PMs compared to CYP2C9 EMs following a single 20 mg oral dose

AUCR	PBPK Predictions	Observations*
IMs/EMs	1.20	1.4
PMs/EMs	1.49	2.2[#]

[*]Values derived based on pooled data from studies A001-017, A001-019 and G000-008.
[#]N = 2 for observed PM data.

The PBPK analyses were also conducted to evaluate the impact of CYP2C9 polymorphism on avatrombopag DDI (Table 85). The model predicted that in CYP2C9 EMs and PMs, co-administration of itraconazole, a strong CYP3A4 inhibitor 200 mg once daily at steady state with a single 20 mg dose of avatrombopag led to increases in avatrombopag AUC by 1.27 and 2.09-fold, respectively, relative to those predicted in EMs with a single dose of 20 mg avatrombopag alone. The simulation results suggested that the magnitude of the increases in AUC of avatrombopag in CYP2C9 PMs when co-administered with a strong CYP3A4 inhibitor itraconazole (a 2.09-fold increase, Table 79) would be similar to those observed in CYP2C9 EMs when co-administered with fluconazole (a 2.20-fold increase, Table 81), a CYP3A4 and CYP2C9 dual inhibitor.

Table 85: Predicted AUC ratios of avatrombopag in CYP2C9 IMs and PMs after co-administration of itraconazole

	Cmax ratios	AUC ratios

IMs + itraconazole/EMs	1.12	1.59
PMs+ itraconazole/EMs	1.18	2.09

*PK of avatrombopag following a single dose of 20 mg avatrombopag with/without a repeated administration of itraconazole 200 mg QD for 7 days

2. Conclusion

The submitted avatrombopag PBPK models are adequate to predict the PK profiles of avatrombopag in healthy subjects under various DDI scenarios. The model was verified with the observed DDI effects between single dose of avatrombopag and itraconazole (strong CYP3A4 inhibitor), fluconazole (CYP3A4 and CYP2C9 dual inhibitor), and CYP3A4 and CYP2C9 inducer (rifampicin). The simulation results predicted 1.42- and 1.47-fold increase in avatrombopag AUC when the drug is co-administered with ketoconazole (strong CYP3A4 inhibitor) and sulphaphenazole (strong CYP2C9 inhibitor), respectively. Consistent with clinical observed DDI, the model predicted a 2.04-fold increase in avatrombopag AUC after co-administration of fluconazole, a dual CYP3A and CYP2C9 inhibitor. The PBPK model was also used to evaluate the impact of CYP2C9 polymorphism on avatrombopag PK. The model predicted that in CYP2C9 EMs and PMs, co-administration of itraconazole 200 mg once daily at steady state with a single 20 mg dose of avatrombopag led to increases in avatrombopag AUC by 1.27 and 2.09-fold, respectively, relative to those predicted in EMs with a single dose of 20 mg avatrombopag alone. The avatrombopag PBPK models are determined to be adequate to predict the DDI effects on the PK of avatrombopag and consequent development of dose recommendations with concomitant administration of CYP3A and/or CYP2C9 modulators.

Appendix 1

Table 6. Physiological, Physico-Chemical, In vitro Input Parameters, and General Assumptions Utilized for Simcyp Model Development of Avatrombopag

Parameter	Input Value/Option	Comment/Reference
MW	649.65	GIB 2016
Compound type	Ampholyte	See section 4.1.1.1
$LogP_{o:w}$	3.8	Measured LogD at 37°C in absence of buffer (See section 4.1.1.1)
pKa1 pKa2	2.8 8.4	Calculated using Marvin View v. 5.4.0.1
B:P ratio	0.57	AE-7539-G
fu	0.036	ME03171
Main plasma binding protein	Albumin	Assumed
Absorption models	- First order absorption with lagtime; - ADAM	See section 4.1.3 for details
fa	0.65	Based on calculations from human ADME study 501-PK-901. For first-order absorption model only. See section 4.1.3.1 for details.
ka	1.23	For first-order absorption model only. See section 4.1.3.1 for details
lagtime	1.82	For first-order absorption model only. See section 4.1.3.1 for details
Q_{gut}	5.87 L/h	Predicted by Simcyp; for first-order absorption model only. See section 4.1.3.1 for details
Fg	1.0	Assumption
fu_{gut}	1.0	Assumption. See section 4.1.1.1 for details.
Permeability (P_{eff}) Apparent permeability (P_{app}): Avatrombopag Propranolol	0.982×10^{-4} cm/s 3.89×10^{-5} cm/s 36.0×10^{-6} cm/s	Predicted P_{eff}, based on in vitro permeability in LLC-PK1 (DMPKA2011-206). Assumed to be the default value given in Simcyp
Formulation	Solid; IR tablet	Only for ADAM model. See section 4.1.2.1 for details
Dissolution	Dissolution profile in pH 6.8 and FeSSIF	Only for ADAM model. See section 4.1.2.1 for details and input values
V_{ss} (L/kg) Tissue Kps values: Kp scalar	2.50 User input 1.0	Predicted value in Simcyp using the full PBPK with user input Kp Kp values calculated based on data from study No. 501-ME-034. See Table 3. Default value

Parameter	Input Value/Option	Comment/Reference
Intrinsic clearance input: fm (%)	Recombinant Enzyme Kinetics	CL_{int} obtain with Simcyp's retrograde calculator from a mean CL/F of 8.2 L/h. See section 4.1.5 for details.
CYP3A4:	35.6 or 62.8	Depending on CL model used; see section 4.1.5.2.
CYP2C9:	37.2 or 64.4	Depending on CL model used; see section 4.1.5.2.
CL_{int} (µL/min/pmol protein)		
CYP3A4:	0.094 or 0.166	Depending on CL model used; see section 4.1.5.3.
CYP2C9:	0.185 or 0.319	Depending on CL model used; see section 4.1.5.3.
Additional HLM clearance (L/h)	9.85	Only for Clearance Model 3. Calculated by retrograde calculator based on results of human mass-balance study 501-PK-901. See section 4.1.5.3 for details.
fu_{mic}	1.0	Fixed to 1.0 since input of CL_{int} was obtained from retrograde calculation
Active uptake into hepatocytes	1.0	Default value in Simcyp
CL_{ren} (L/h)	0.181	Calculated from human mass balance study 501-PK-901. See section 4.1.5.1
Intestinal transport (P-gP) J_{max} (pmol/min) K_m (µmol/L)	 1.76 1.68	Values obtained from analysis of data from study No. BMD-517. Used only for model with ADAM absorption See section 4.1.2.3. OBS: Non-saturable colon option enabled
Metabolic interactions	None	
Transporter interactions (K_i):		Same Ki values used for intestinal, liver, and kidney transporters, when applicable
P-gp (µmol/L)	15	DMPKA2011-206. See section 14.1.6.2.
MRP2 (µmol/L)	3.35	DMPKA2011-206. See section 14.1.6.2.
BCRP (µmol/L)	2.7	DMPKA2011-206. See section 14.1.6.2.
OATP1B1 (µmol/L)	11.05	DMPKA2011-205. See section 14.1.6.2.
OATP1B3 (µmol/L)	1.4	DMPKA2011-205. See section 14.1.6.2.
OCT2 (µmol/L)	15	DMPKA2011-205. See section 14.1.6.2.
OAT1 (µmol/L)	0.35	DMPKA2011-205. See section 14.1.6.2.
OAT2 (µmol/L)	0.1	DMPKA2011-205. See section 14.1.6.2.

19.4.7. QT-IRT Review

(DARRTS 11/03/2017)

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: May 17, 2018

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Kelly Miller, RPM
DHP

Subject: QT-IRT Consult to NDA 210238

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 09/27/2017 regarding the advice on sponsor's proposed QT-related labeling. The QT-IRT reviewed the following materials:

- Previous QT-IRT reviews for IND [redacted] (b) (4);
- Sponsor's proposed label submitted to NDA 210238; and
- Summary of clinical pharmacology, Integrated summary of safety [ISS, ISS Appendix 1], Study reports for Phase 3 studies [Study 310, Study 311], Population PK and PK/PD report submitted to NDA 210238.

The sponsor's proposed labeling is as follows:

12.2 Pharmacodynamics
Cardiac Electrophysiology

[redacted] (b) (4)

(b) (4)

1. QT-IRT Responses to the Division

The sponsor's ECG assessments from the submitted studies (mainly, TQT study E5501-A001-001 submitted to IND (b) (4) and the Phase 3 studies 310 and 311 submitted to NDA 210238) are not adequate to exclude small mean QTc effects (10 ms) at the mean C_{max} corresponding to the proposed therapeutic dosing regimens (40 and 60 mg QD for 5 days). However, the data suggest that no large mean QTc effects (>20 ms) are anticipated with the proposed therapeutic dosing regimens for this acute treatment (5 days). If the benefit-risk warrants excluding the small mean QTc effects (10 ms), the division may recommend a TQT study.

With the currently available information/data, the following is QT-IRT's proposed labeling language, which is a suggestion only. We defer final labeling decision to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4) QTc prolongation effects (>20 ms) are anticipated with the highest recommended therapeutic dosing regimen.

Our conclusion above is based on the following information:

- The predicted geometric mean C_{max} on the last day of dosing in the Phase 3 Studies 310 and 311 is 214 ng/mL and 352 ng/mL for 40 mg QD and 60 mg QD dosing, respectively.[2]
- The highest clinically relevant exposure scenario for the drug is co-administration of verapamil, a strong P-gp and a moderate CYP3A4/5 inhibitor (240 mg QD at steady state), which results in 26% and 61% increase in C_{max} and $AUC_{0\text{-}inf}$ for a single 20 mg dose of avatrombopag.[3] Thus, the highest clinically relevant mean exposures for the highest proposed therapeutic dosing of 60 mg QD (for 5 days) would be ≥443 ng/mL (352*1.26).
- The ECG assessments in this development program (including the TQT study and the two Phase 3 studies) do not provide adequate coverage for the highest clinically relevant exposure (443 ng/mL) as well as for the therapeutic exposure (352 ng/mL).
  - The on-treatment post-baseline ECG measurements in Phase 3 studies 310 and 311 were done pre-dose (C_{trough}) on Day 4 (±1).[4] The observed geometric mean plasma concentration at this C_{trough} are 107 ng/mL (min-max range= 15 - 374) and 137 ng/mL (min-max range= 16 - 673) for 40 mg QD and 60 mg QD dosing, respectively.[5]
  - The TQT study was conducted with a single 100 mg dose of 1st generation tablet, which had geometric mean Cmax of 106 ng/mL (arithmetic mean of 125 ng/mL).[6] Even though the dose level is higher in this study, the 1st generation tablet used in the study had lower bioavailability and thus lower exposures than the 2nd generation tablet, which is the to-be-marketed formulation.

[2] Results from the sponsor's Pop-PK analysis shown in Table 6 Appendix below.
[3] Information from sponsor's proposed label.
[4] ECG assessment schedule shown in Table 7 in Appendix below.
[5] Reviewer's analysis of PK data for Studies 310 and 311.
[6] Previous QT-IRT review for IND (b) (4)

- A linear regression analysis for data from pooled Phase 3 Studies 310 and 311 did not show a statistically significant slope for the relationship between drug concentration and ΔQTcF or ΔΔQTcF. Although there were limitations in this data (e.g., just 1 post-baseline on-treatment ECG assessment in each subject and inadequate exposure coverage for anticipated C_{max}), the upper bound of 90% CI of predicted effect at 352 ng/mL and 443 ng/mL plasma concentrations with the concentration-ΔQTcF relationship were 6.1 ms and 8.4 ms, respectively. Based on this and the preclinical information, we can conclude that no large mean QTc effects (>20 ms) are anticipated with the proposed therapeutic dosing regimens (Refer to ICH E14 Q&A (R3), Section 6.1: *"In the absence of a positive control, […] if the upper bound of the two-sided 90% confidence interval around the estimated maximal effect on QTc is less than 10 ms, it is unlikely to have an actual mean effect as large as 20 ms.").*

2. BACKGROUND

Product Information

DOPTELET (avatrombopag) is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a procedure. The proposed dose and duration are as follows:

Platelet Count ($x10^9$/L)	Once Daily Dose	Duration
<40	60 mg	5 days
≥40 to <50	40 mg	5 days

Preclinical cardiovascular safety

E5501(avatrombopag) had no significant effect on cardiovascular function measured in vitro on isolated guinea pig papillary muscles or in vivo in dogs. Inhibition of hERG current occurred in a dose-dependent manner with an IC_{50} of 1.4 mol/L.

Source: IB, January 15, 2010

Previous interactions with the sponsor

QT-IRT had previously reviewed a TQT study report and found no significant QTc prolongation for a single dose of 100 mg for the first generation (1G) tablet.[6] The TQT study was a single supratherapeutic dose study. The study did not identify a positive relationship for concentration-QTc. However, based on the Highlights of Clinical Pharmacology, there was insufficient information to determine whether the tested dose provides sufficient coverage for the maximum therapeutic exposure and supratherapeutic exposure.

In the next interaction, the sponsor provided more information based on their Phase 1/ 2 studies and the QT-IRT provided the following feedback:[7]

[7] Previous QT-IRT review for IND (b) (4)

Sponsor's proposal: *Eisai has received the Division's recommendations (FDA Correspondence, October 20, 2010) on the E5501-A001-001 study. In response to the FDA's comments, Eisai feels that all the preclinical and clinical data collected to date indicate that E5501 does not have any impact on QTc interval up to the exposures equivalent to the highest proposed dose (40 mg) for the Phase 3 program.*

QT-IRT's response: *Yes, we agree. Preclinical and clinical studies do not show a QTc signal with E5501. The updated information suggests that it is unlikely that higher E5501 systemic exposures than those observed in the thorough QT study will prolong the QTc interval. We advise you to collect routine ECGs as clinically indicated in ongoing and future clinical trials.*

3. SPONSOR'S RESULTS

Summary of safety from pooled data from the two Phase 3 studies (310 and 311)

The safety of DOPTELET was evaluated in two randomized, double-blind, placebo-controlled trials, in which 430 patients with chronic liver disease and thrombocytopenia received either DOPTELET (n=274) or placebo (n=156) daily for 5 days, and had 1 post-dose safety assessment. Patients were divided into two groups based on their platelet count at Baseline:

- Low Baseline Platelet Count Cohort (< 40 X 10^9/L) who received DOPTELET 60 mg once daily for 5 days
- High Baseline Platelet Count Cohort (≥40 to <50 X 10^9/ L) who received DOPTELET 40 mg once daily for 5 days

For the Low Baseline Platelet Count Cohort, the incidence of serious adverse events was 7% (11/159) in the 60 mg DOPTELET treatment group and 13% (12/91) in the matching placebo treatment group. For the High Baseline Platelet Count Cohort, the incidence of serious adverse events was 8% (9/115) in the 40 mg group.

There were 3 TEAEs of death reported during the course of the Phase 3 studies, 2 (0.7%) in the combined avatrombopag treatment group and 1 (0.6%) in the combined placebo treatment group; none of the deaths were assessed as related to study drug by the investigators. All treatment-emergent deaths were in the High Baseline Platelet Count Cohort and occurred more than 30 days after the last dose of study drug.

Summary of QTc assessments in pooled data from the two Phase 3 studies (310 and 311)

The descriptive statistics and categorical analyses for QTc effects are listed in the following tables:

Table 1: Descriptive Summary of ΔQTcF

Baseline Platelet Count	Treatment	Visit	N	Mean ΔQTcF (SD)
<40 x 10^9/L	Placebo	Study Day 4	89	0.9 (17.9)
	Avatrombopag 60 mg	Study Day 4	156	1.9 (18.3)
>=40 to <50 x 10^9/L	Placebo	Study Day 4	64	0.4 (17.9)
	Avatrombopag 40 mg	Study Day 4	113	-1.5 (16.1)

Table 2: Categorical Analysis for QTcF

Baseline Platelet Count	Treatment	N	QTcF>=450 n (n/N %)	QTcF>=500 n (n/N %)
<40 x 10^9/L	Placebo	90	39 (43.3 %)	0
	Avatrombopag 60 mg	158	58 (36.7 %)	1 (0.6 %)
>=40 to <50 x 10^9/L	Placebo	65	21 (32.3 %)	1 (1.5 %)
	Avatrombopag 40 mg	115	40 (34.8 %)	0

Table 3: Categorical Analysis for ΔQTcF

Baseline Platelet Count	Treatment	N	30 =< ΔQTcF<=60 n (n/N %)	ΔQTcF>60 n (n/N %)
<40 x 10^9/L	Placebo	90	10 (11.1 %)	0
	Avatrombopag 60 mg	158	11 (7.0 %)	2 (1.3 %)
>=40 to <50 x 10^9/L	Placebo	65	9 (13.8 %)	0
	Avatrombopag 40 mg	115	7 (6.1 %)	0

Source: Adapted from data submitted in ISS Appendix 1, page 3247, 3252, 3253 of 7683

Summary of population PK-ddQTcF analysis

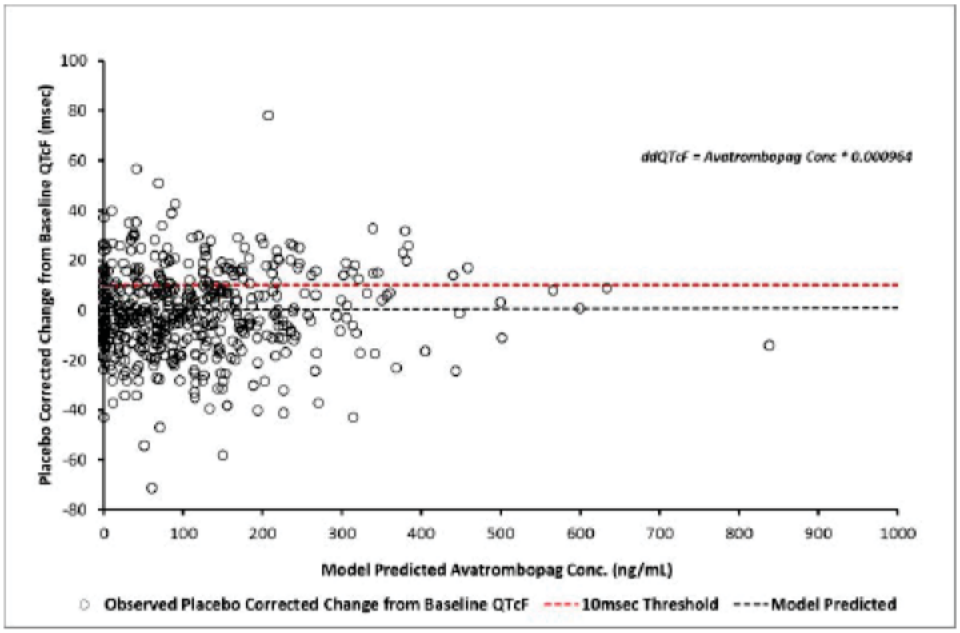
The relationship between model-predicted avatrombopag concentration and *dd*QTcF following avatrombopag administration to CLD subjects in Studies 202, 204, 310 and 311 was best assessed using a linear relationship, where the slope of the relationship was estimated.

*ddQTcF = Avatrombopag Conc. (ng/mL) * Slope*

The model included an additive error model for estimation of residual variability. Inter-individual variability on slope was not estimable and a model with an intercept did not converge successfully.

The population estimate of slope was 0.000964 [-0.00870 - 0.0106] msec/ng/mL, and was estimated with poor precision, with %RSE of 511%. The 95% CI for the slope parameter includes zero, which indicates no change in *dd*QTcF with increasing avatrombopag concentration. IIV for slope parameter could not be determined. Residual variability in *dd*QTcF was 17.4 msec. Observed and model predicted relationship for avatrombopag concentrations and *dd*QTcF are presented below which demonstrates the absence of any exposure-effect relationship. Since IIV on the slope parameter could not be determined model predicted 90% prediction intervals of the *dd*QTcF vs. time from avatrombopag administration could not be determined.

Table 4: Observed and Model Predicted Relationship between Avatrombopag Concentration and ddQTcF in CLD Subjects – Studies 202, 204, 310 and 311



4. REVIEWER'S ANALYSIS

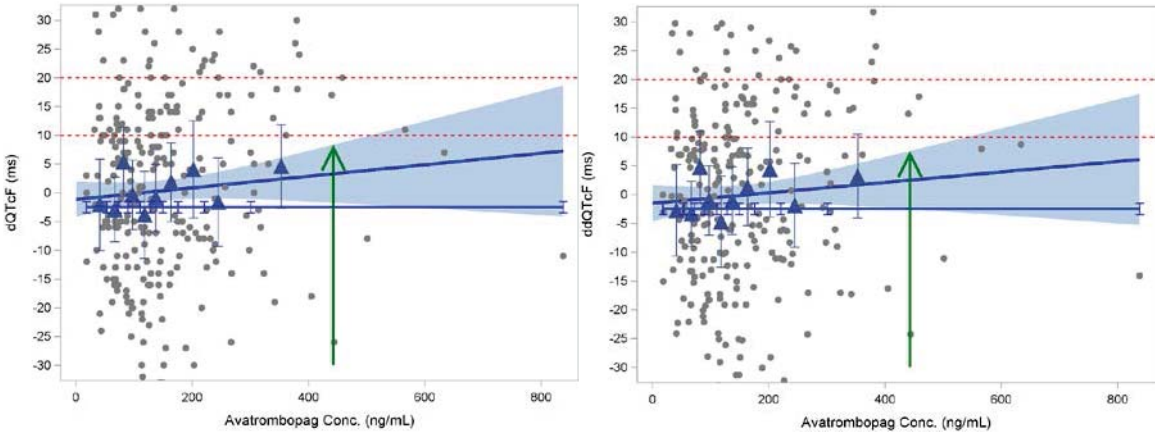
Pooled data from Phase 3 studies 310 and 311 (placebo-controlled studies) in patients were used for reviewer's analysis. These studies had the relevant therapeutic dosing at which ECGs were assessed, had large sample size and the trial design were similar for appropriateness of pooling. Other studies including a TQT study had lower exposures and were not poolable because of differences in design. These two studies had ECG measurements at baseline and at just one on-treatment post-baseline timepoint (pre-dose (C_{trough}) on Day 4 (±1)). The details of design, sample size, and dosing in the two studies for this pooled data have been described in Section 3 above.

Because there was just one on-treatment post-baseline QTc measurement per individual, a usual linear mixed effects model with a random effect on slope/intercept could not be used for this analysis. Instead, a simple linear regression analysis was used for evaluating the relationship between drug concentration and ΔQTcF or ΔΔQTcF. ΔΔQTcF was calculated by subtracting mean placebo response for the placebo control arm from the baseline corrected QTcF for each subject in the treatment arm. Both the analyses did not show a statistically significant positive slope for the relationship.

With concentration-ΔQTcF analysis, the predicted effect (mean [90% CI]) at 352 ng/mL and 443 ng/mL plasma concentrations were 2.4 [-1.3, 6.1] ms and 3.3 [-1.8, 8.4] ms, respectively.

With concentration-ΔΔQTcF analysis, the predicted effect (mean [90%CI]) at 352 ng/mL and 443 ng/mL plasma concentrations were 1.7 [-2.0, 5.4] ms and 2.5 [-2.6, 7.6] ms, respectively.

Table 5: Relationship between Avatrombopag Concentration and ΔQTcF or ΔΔQTcF – Pooled data from Studies 310 and 311



Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

5. APPENDIX

Table 6: Summary of Individual Pharmacokinetic Parameters for Avatrombopag in CLD Subjects – Studies 310/311

	Dose(mg)	N	Geometric Mean	SD	Min	Median	Max	Geometric CV%
CL/F (L/h)	40	115	7.24	1.13	5.58	7.05	12.8	15.6
V/F		115	292.1	37.8	198	297.0	401	13.0
AUC (ng.h/mL)		115	3717	2318	726.1	3864	11064	62.4
Cmax (ng/mL)		115	214.3	100.5	77.7	207.6	730.8	42.6
Tmax (h)		115	--	--	4	7	16	--
CL/F (L/h)	60	160	7.46	1.46	5.51	7.36	16.1	19.6
V/F		160	293.9	39.7	143	293.3	403	13.5
AUC (ng.h/mL)		160	4820	4101	788	4932	27242	85.1
Cmax (ng/mL)		160	352.2	194.8	122.9	346.4	1281	47.3
Tmax (h)		160	--	--	4	6	20	--

Source: Population PK/PD study report, Table 8-14, page 57 of 384

Table 7: Schedule of assessments in Phase 3 Study 311 (Similar ECG/PK assessments in Study 310)

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
continued						
PK blood sampling		X[p]	X[p,q]			

p: On Visit 2 (Day 1), 1 PK sample was to be collected between 2 to 6 hours after dosing.
q: On Visit 3 (Day 4 ±1), 2 PK samples were to be collected: predose (within 2 hours prior to dosing) and between 2 to 6 hours after dosing.
Source: CSR for Study 311, Table 3, page 66-68 of 1599

19.5. Additional Clinical Outcome Assessment Analyses

No additional clinical outcome assessment analyses were performed for this application for avatrombopag.

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/s/

WAN LEE
05/18/2018

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BRIAN P BOOTH on behalf of NAM ATIQUR RAHMAN
05/18/2018

YAPING WANG

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: April 25, 2018

From: Albert Deisseroth, M.D., Ph.D.
Supervisory Associate Division Director, DHP

Subject: NDA 210238 Avatrombopag
Received September 21, 2017

The Division Director summary review is complete and has been added to the NDA 210238 Multidisciplinary Review and Evaluation. This reviewer (Supervisory Associate Division Director, DHP) agrees with the recommendation of the review team for regular approval of this application.

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/s/

ALBERT B DEISSEROTH
04/25/2018

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: April 23, 2018

From: Andrew Dmytrijuk, M.D.
Acting Cross Disciplinary Team Leader (CDTL)

Subject: NDA 210238 Avatrombopag
Supporting Document 1
Letter date September 21, 2017 (Received September 21, 2017)

The Cross Disciplinary Team Leader (CDTL) review is complete and has been added to the NDA 210238 Multidisciplinary Review and Evaluation. My recommendation for this application is regular approval.

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/s/

ANDREW DMYTRIJUK
04/23/2018

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CARCINOGENICITY STUDIES

NDA/BLA #:	NDA 210,238 (SDN-1 (eCTD SN-0000))
Drug Name:	Doptelet (avatrombopag)
Indication(s):	Treatment of Thrombocytopenia
Applicant:	Eisai Inc.
Date(s):	September 21, 2017 (Submitted/Received)
Study Reviewed:	A 104-Week Oral (Gavage) Carcinogenicity Study of AKR-501 (E5501) in Mice; A 104-Week Oral (Gavage) Carcinogenicity Study of AKR-501 (E5501) in Rats
Biometrics Division:	Division of Biometrics VI
Primary Reviewer:	Eiji Ishida, MS
Concurring Reviewers:	Karl Lin, PhD, Team Leader
Medical Division:	Division of Hematology, Oncology, Toxicology (DHOT)
Reviewing Pharmacologist:	Brenda Gehrke, PhD
Keywords:	Carcinogenicity, Dose response, Mortality

Table of Contents

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1 SUMMARY

The objective of the submitted studies: (b) (4).152.09 and (b) (4)152.10 was to evaluate the carcinogenic potential of E5501 in mice and rats, respectively, following 104-week oral administration and to determine systemic exposure. The former was a mouse study (abbreviated to Study 152.09), and the latter was a rat study (abbreviated to Study 152.10).

The reviewer analyzes the dose-response relationship of tumor incidence and mortality (including tumor-related mortality). The analyses of tumor data consist of analyses for dose-response relationships in tumor incidence for five daily doses 0, 0, 20, 60 and 160 mg/kg in mice (0, 0, 20, 50 and 160 mg/kg in rats) and pairwise comparisons in tumor incidence between each of the treated groups 20, 60 and 160 mg/kg/day in mice (0, 20, 50 and 160 mg/kg/day in rats) and the combined two control groups (0 mg/kg/day).

Statistical Conclusion: The reviewer's survival analysis results are comparable with the Sponsor's findings that the High dose (160 mg/kg) increased the mortality for female rats and mice when compared to the other dose groups and the control group. The statistical analyses for the dose response relationship (trend) and pairwise comparisons of each dose to the control group in the frequencies of Sponsor recorded tumor types were also found comparable with the Sponsor's neoplastic findings. Specifically, (1) In female rats, Neuroendocrine cell tumor (benign), Stomach, is found statistically significant for trend if it is considered as a rare tumor; (2) a combined tumor type, #Neuroendocrine cell tumor (benign/malignant), Stomach, that includes both benign and malignant cases is also found statistically significant for trend, whether it is a rare tumor or a common tumor; (3) Neuroendocrine cell tumor (benign), Stomach, is found statistically significant for High dose if it is a rare tumor; (4) A combined tumor type, #Neuroendocrine cell tumor (benign/malignant), Stomach, that includes both benign and malignant is also found statistically significant for the high dose in the pairwise comparison with the control group, whether it is a rare tumor or a common tumor; and (5) Adenocarcinoma (Mammary gland), is found statistically significant for Low dose if it is a rare tumor. (6) In female mice, Alveolar/bronchiolar adenoma (Lung) is found statistically significant for Med dose, whether it is a rare tumor or a common tumor.

2 BACKGROUND

The Sponsor filed a new drug application[1] on September 21, 2017 of Doptelet®(Avatrombopag) for a treatment of thrombocytopenia in patients with chronic liver disease (CLD). This NDA submission includes two carcinogenicity studies, Study 152.09 (mouse study) and Study 152.10 (rat study). The study reports are titled 'A 104-WEEK ORAL (GAVAGE) CARCINOGENICITY STUDY OF AKR-501 (E5501) IN MICE', and 'A 104-WEEK ORAL (GAVAGE) CARCINOGENICITY STUDY OF AKR-501 (E5501) IN RATS', respectively. The former was started on May 7, 2008 and completed on December 5, 2012, and the latter was started on April 15, 2008 and completed on November 2, 2012.

[1] The submission was made under NDA210238 (eCTD#0000/SD#1).

This statistical reviewer evaluates the two carcinogenicity studies submitted under the NDA.

2.1 Main Study Design Elements

In Study 152.09, the test article, E5501, was administered orally by gavage once a day to CD-1 mice (62 – 64 animals/sex/group main study), for 101 – 105 weeks at daily doses of 20, 60, or 160 mg/kg. Terminal Necropsy was planned to be performed in Week 104 - 105 for male mice and in Week 101 - 103 (all animals not on the 20 and 160 mg/kg dose groups) and in Week 101 - 102 (the 20 and 160 mg/kg dose groups) for female mice.

In the main cohort of Study 152.10, the test article, E5501, was administered orally by gavage once a day to Sprague Dawley rats (60 animals/sex/group main study), for 82-99 weeks at daily doses of 20, 50, 160 mg/kg. Both studies included two control groups that received an equivalent volume of control article/vehicle (0.5% methylcellulose in water). Terminal Necropsy was planned to be performed in Week 99 for male rats and in Week 103 (all animals not on the 160 mg/kg dose group) and in Week 91 (the 160 mg/kg dose group) for female rats.

2.2 Submitted Data and Reports

The submission includes two reports of one mouse study and one rat study, respectively titled "A 104-Week Oral (Gavage) Carcinogenicity Study of AKR-501 (E5501) in Mice" and "A 104-Week Oral (Gavage) Carcinogenicity Study of AKR-501 (E5501) in Rats."

The reports were submitted in eCTD SN 0000 on September 21, 2017, and are located at the FDA server:

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On January 16, 2018, two "tumor.xpt" datasets were submitted in eCTD SN-0015, as a response to Information Request letter, which was sent to the Sponsor on December 22, 2017. They are located at the FDA server:

\\CDSESUB1\evsprod\NDA210238\0015\m4\datasets

2.3 Statistical Method to Evaluate Carcinogenicity

2.3.1 Survival Analysis

In the reviewer's analysis of survival data of the rat and mouse carcinogenicity studies, the survival distributions of animals in all treatment groups are estimated using the Kaplan-Meier product limit method. For control, low, mid, and high dose groups, a dose response relationship is tested using the likelihood ratio test, and the homogeneity of survival distributions is tested using the log-rank test. The term "dose response relationship" refers to a linear component of treatment effect, and not necessarily a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

2.3.2 Tumor Data Analysis

Poly-k test: A dose response relationship and pairwise comparisons of each of the three dose groups to the control group are statistically tested for each of the tumor types of interest via the poly-k method,[2] which uses a fractional weighting scheme for animals that were not at the full risk of tumor development. The reported number as labeled *weighted (mortality adjusted) total number of animals* in the poly-k analysis tables represents the risk set obtained by discounting (weighting fractionally) the risk of every animal if it dies before the terminal sacrifice without having the tumor type being tested. If there are no animals that had no tumor and die before the terminal sacrifice, or if all animals die before terminal sacrifice but develop the tumor type being tested, then the size of the risk set equals the number of randomized animals.
The poly-k test is an extension of Cochran-Armitage (CA) test. The CA test assumes that all animals are at an equal risk of the development of the tumor type being tested, regardless of the time of their death, while the poly-k test assigns a discounted risk of the tumor development to an animal that dies before the terminal sacrifice without having had the tumor type, by applying an appropriate polynomial weight. The weighting scheme of the poly-k method is based on an idea that an animal that dies before the terminal sacrifice without developing the tumor type was under a smaller onset risk of the tumor type. An animal may live till the end of a study period or die before the end of a study period, i.e., the time of the terminal sacrifice. If an animal dies before the terminal sacrifice without having had the tumor of interest, the risk of a tumor onset is considered having been reduced because of its shorter exposure duration. In this review, a polynomial weight of k=3 is used.

Multiple testing adjustment: For the adjustment of multiple testing of dose response relationship alone, the FDA guidance for the carcinogenicity study design and data analysis suggests the use of test levels α=0.005 for a common tumor and α =0.025 for a rare tumor for a submission with two two-year studies in two species. A rare tumor is defined as one in which the published spontaneous tumor rate or the incidence rate of the tumor type in the concurrent control group is less than 1%. For multiple pairwise comparisons of individual treated groups with control alone, the FDA guidance suggests the use of test levels α=0.01 for a common tumor and α=0.05 for a rare tumor. The use of the recommended test levels of significance will result in an overall false positive rate of approximately 10% for both submissions with two or one species. It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman (1998). In this work the authors investigated the use of this rule for Peto analysis. In a later work Rahman and Lin (2008) showed that this rule for multiple testing for dose response relationship is also suitable for poly-k tests.

3 STATISTICAL EVALUATION

3.1 Rat Study

Study (b) (4).152.10, a carcinogenicity study in rats, assessed the carcinogenic potential of E5501 in male and female Crl:CD®(SD)IGS BR rats. The test article, E5501, was administered orally by gavage once a day to Crl:CD®(SD)IGS BR rats (60/sex/group main study), for 82-99

[2] The details of this method are found in the following articles: Bailer and Portier (1988) and Bieler and Williams (1993).

weeks at daily doses of 20, 50, 160 mg/kg. The study included two control groups that received an equivalent volume of control article/vehicle (0.5% methylcellulose in water).

Table 1 and Table 2 (male/female rats) list all organs recorded in the submitted dataset. The listed organs were those that were examined in the Sponsor's submitted data. This reviewer calculated the number of animals *examined and found usable* from the submitted tumor data. In some organs, no tumors were found. As an example, no tumors were found in *Cecum* (Male Rats). In male rats, 10 out of 35 organs[3] were such cases. In female rats, 9 out of 27 organs[4] were such cases. In these cases, trend and pairwise comparison tests may be meaningless to conduct. This reviewer performed analyses on the rest of these organs, 25 organs for male rats and 18 organs for female rats.

Table 1: Frequency of Tumors (#Examined Animals) in Organs (Male Rats)

Organ	[#Tumors]/[#Animals Examined] BY ORGAN]	0 mg	20 mg	50 mg	160 mg
Adrenals	33/300	10 (120)	15 (60)	2 (60)	6 (60)
Brain	9/298	1 (120)	3 (60)	3 (59)	2 (59)
Cavity	3/300	2 (120)	1 (60)	0 (60)	0 (60)
Cecum	0/299	0 (119)	0 (60)	0 (60)	0 (60)
Diaphragm	0/299	0 (120)	0 (60)	0 (59)	0 (60)
Epididymides	1/300	0 (120)	0 (60)	0 (60)	1 (60)
Esophagus	1/300	1 (120)	0 (60)	0 (60)	0 (60)
Eyelid	0/299	0 (120)	0 (60)	0 (60)	0 (59)
Heart	0/299	0 (120)	0 (59)	0 (60)	0 (60)
Hematopoietic and lymphatic organs	14/300	4 (120)	5 (60)	1 (60)	4 (60)
Jejunum	1/300	0 (120)	0 (60)	0 (60)	1 (60)
Kidneys	4/300	2 (120)	1 (60)	0 (60)	1 (60)
Lacrimal glands	0/296	0 (118)	0 (59)	0 (59)	0 (60)
Liver	8/300	2 (120)	3 (60)	1 (60)	2 (60)
Lung	2/299	1 (120)	0 (59)	1 (60)	0 (60)
Mammary gland	4/300	2 (120)	0 (60)	2 (60)	0 (60)
Mesenteric lymph node	1/300	0 (120)	0 (60)	0 (60)	1 (60)
Optic nerves	0/299	0 (120)	0 (60)	0 (59)	0 (60)
Pancreas	29/300	12 (120)	6 (60)	6 (60)	5 (60)
Parathyroids	5/294	2 (119)	1 (58)	0 (58)	2 (59)
Pituitary	175/297	69 (119)	43 (59)	35 (59)	28 (60)

[3] The submitted data (male rats) has records for 35 organs.
[4] The submitted data (female rats) has records for 27 organs.

Organ	[#Tumors]/[#Animals Examined] BY ORGAN]	0 mg	20 mg	50 mg	160 mg
Preputial/Clitoral glands	2/300	0 (120)	1 (60)	1 (60)	0 (60)
Prostate	0/299	0 (120)	0 (59)	0 (60)	0 (60)
Rib	1/300	1 (120)	0 (60)	0 (60)	0 (60)
Seminal vesicles	0/299	0 (120)	0 (59)	0 (60)	0 (60)
Skin	49/300	20 (120)	15 (60)	6 (60)	8 (60)
Spleen	0/297	0 (120)	0 (59)	0 (60)	0 (58)
Stomach	4/300	0 (120)	0 (60)	1 (60)	3 (60)
Testes	6/300	4 (120)	0 (60)	1 (60)	1 (60)
Thymus	0/261	0 (106)	0 (55)	0 (45)	0 (55)
Thyroids	39/299	15 (120)	10 (59)	7 (60)	7 (60)
Tongue	1/298	0 (119)	0 (59)	1 (60)	0 (60)
Trachea	1/298	0 (120)	0 (59)	1 (59)	0 (60)
Urinary bladder	2/298	1 (120)	0 (59)	1 (60)	0 (59)
Zymbal glands	2/300	0 (120)	2 (60)	0 (60)	0 (60)

Note: The reviewer analyzes reported tumors of the organs in bold in ORGAN column. The frequency of tumors does not always match that of animals, as an animal can have more than one tumor within an organ. The numbers reported in parentheses for each dose group are the counts of examined animals.

Table 2: Frequency of Tumors (#Examined Animals) in Organ (Female Rats)

Organ	[#Tumors]/[#Animals Examined] BY ORGAN]	0 mg	20 mg	50 mg	160 mg
Adrenals	23/300	7 (120)	6 (60)	5 (60)	5 (60)
Bone	0/299	0 (120)	0 (60)	0 (59)	0 (60)
Bone marrow	0/299	0 (120)	0 (60)	0 (59)	0 (60)
Brain	1/299	1 (120)	0 (59)	0 (60)	0 (60)
Diaphragm	0/297	0 (119)	0 (59)	0 (60)	0 (59)
Eyes	1/300	0 (120)	0 (60)	0 (60)	1 (60)
Hematopoietic and lymphatic organs	5/300	2 (120)	0 (60)	2 (60)	1 (60)
Jejunum	1/300	1 (120)	0 (60)	0 (60)	0 (60)
Lacrimal glands	0/296	0 (118)	0 (58)	0 (60)	0 (60)
Mammary gland	221/298	80 (120)	50 (59)	56 (60)	35 (59)
Mesentery	1/300	1 (120)	0 (60)	0 (60)	0 (60)
Omentum	1/300	0 (120)	1 (60)	0 (60)	0 (60)
Optic nerves	0/299	0 (120)	0 (60)	0 (59)	0 (60)
Ovaries	1/300	0 (120)	0 (60)	0 (60)	1 (60)

Organ	[#Tumors]/[#Animals Examined] BY ORGAN]	0 mg	20 mg	50 mg	160 mg
Pancreas	4/300	1 (120)	0 (60)	2 (60)	1 (60)
Parathyroids	3/297	2 (120)	0 (58)	0 (59)	1 (60)
Pituitary	240/299	103 (119)	50 (60)	46 (60)	41 (60)
Skin	9/298	2 (120)	0 (59)	6 (60)	1 (59)
Spleen	0/298	0 (120)	0 (59)	0 (60)	0 (59)
Stomach	5/300	1 (120)	0 (60)	0 (60)	4 (60)
Submaxillary lymph node	0/298	0 (119)	0 (59)	0 (60)	0 (60)
Thymus	5/275	3 (111)	1 (56)	1 (52)	0 (56)
Thyroids	21/300	10 (120)	6 (60)	3 (60)	2 (60)
Urinary bladder	0/299	0 (119)	0 (60)	0 (60)	0 (60)
Uterus	23/299	10 (119)	8 (60)	1 (60)	4 (60)
Vagina	0/299	0 (119)	0 (60)	0 (60)	0 (60)
Zymbal glands	2/300	1 (120)	0 (60)	1 (60)	0 (60)

Note: The reviewer analyzes reported tumors of the organs in bold in ORGAN column. The frequency of tumors does not always match that of animals, as an animal can have more than one tumor within an organ. The numbers reported in parentheses for each dose group are the counts of examined animals.

The submitted dataset of male rats for example contains 522 entered rows and 397 reported tumors in 35 organs out of the 522 rows. The poly-k analysis results for the 397 reported tumors are provided in Section 5.2 (Table 15). This reviewer merged and combined some of the reported tumors to perform additional poly-k analyses in Section 5.3 (Table 19).

The submitted dataset of female rats for example contains 639 entered rows and 567 reported tumors in 27 organs out of the 639 rows. The poly-k analysis results for the 397 reported tumors are provided in Section 5.2 (Table 16). This reviewer merged and combined the reported tumors to perform additional poly-k analyses in Section 5.3 (Table 20).

3.1.1 Survival Analysis

The Sponsor's final report has the following statement[5]: *The lower survival rate in 160 mg/kg females was attributed to the increased incidence of deaths due to chronic nephropathy*. This reviewer's survival analysis confirms this statement in the analyses shown below.

Note: The Sponsor explains in Section 6.1.3 Cause of Death and Moribund Sacrifice of the final report: "Neoplastic lesions did not affect the incidence of deaths/moribundity," and "Increased severity of spontaneous chronic nephropathy affected the incidence of deaths/moribundity in the females given 160 mg/kg. However, a sufficient number of high dose females were dosed through 82 weeks and, necropsied at Week 91 to allow for evaluation of the carcinogenic potential of E5501 in this dose group".

Reviewer's Survival Analysis

The Kaplan-Meier curves for survival rates are given in Figures 1 and 2 of Section 5.1 for male and female rats, respectively. The intercurrent mortality data are given in Table 3 and Table 5 for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survival are given in Table 4 and Table 6 for male and female rats, respectively.

Findings: As seen from Table 3 and Table 5, the numbers (proportions) of death before terminal sacrifice was 74 (61.67%), 30 (50%), 32 (53.33%), and 37 (61.67%) in male rats and 76 (63.33%), 41 (68.33%), 44 (73.33%), and 60 (100%) in female rats in the Control, Low dose, Med dose, and High dose groups, respectively. Female rats of the 160 mg/kg dose died at a faster rate of 100% in comparison to all other dose groups. As for male rats, as seen in Table 4, the statistical tests did not show a statistically significant dose response relationship in mortality across Control and treated groups for male rats (p= 0.6596). In female rats, as seen in Table 6, however, a statistically significant dose response relationship in mortality across Control and treated groups was shown (p<.001) at the significance level of 5%. Similarly, the pairwise comparisons did not show a statistically significant mortality between Control and High dose for male rats (p=0.9399), but in female rats, the pairwise comparisons between Control and High dose showed a statistically significant mortality difference (p<.001) at the significance level of 5% (two-sided).

Table 3: Intercurrent Mortality Rate in Male Rats

	0 mg|kg|day Control (n=50)		20 mg|kg|day Low (n=50)		50 mg|kg|day Med (n=50)		160 mg|kg|day High (n=50)	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 49	16	13.33	3	5.00	8	13.33	6	10.00
50 - 63	4	16.67	1	6.67	6	23.33	1	11.67
64 - 75	10	25.00	8	20.00	5	31.67	7	23.33
76 - 98	44	61.67	18	50.00	13	53.33	23	61.67
Ter. Sac.	46	38.33	30	50.00	28	46.67	23	38.33

Note: Cum. %: Cumulative Percent except for Terminal sacrifice; No. of Death: Number of Deaths

[5] Refer to Text Table 10 of the final report (page 58), also to Histopathology Report (Appendix 4 of the final report).

Table 4: Tests for Dose Response and Homogeneity of Survival in Male Rats

Test	0, 20,50,160 mg|kg|day (Control, Low, Mid, High)	0 vs. 20 mg|kg|day (Control vs. Low)	0 vs 50 mg|kg|day (Control vs. Med)	0 vs. 160 mg|kg|day (Control vs. High)
	p values			
Dose Response (Likelihood Ratio)	0.6596	0.0860	0.4465	0.9399
Homogeneity (Log Rank)	0.3379	0.0889	0.4468	0.9393

Table 5: Intercurrent Mortality Rate in Female Rats

	0 mg|kg|day Control (n=50)		20 mg|kg|day Low (n=50)		50 mg|kg|day Med (n=50)		160 mg|kg|day High (n=50)	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	7	5.83	4	6.67	5	8.33	5	8.33
53 - 74	13	16.67	9	21.67	13	30.00	23	46.67
75 - 91	31	42.50	16	48.33	17	58.33	32	100.00
92 - 102	25	63.33	12	68.33	9	73.33	-	-
Ter. Sac.	44	36.67	19	31.67	16	26.67	-	-

Note: Cum. %: Cumulative Percent except for Terminal sacrifice; No. of Death: Number of Deaths. Terminal Sacrifice was performed in Week 92 for the 160 mg/kg group, but in Week 103 for the other groups.

Table 6: Tests for Dose Response and Homogeneity of Survival in Female Rats

Test	0, 20,50,160 mg|kg|day (Control, Low, Mid, High)	0 vs. 20 mg|kg|day (Control vs. Low)	0 vs 50 mg|kg|day (Control vs. Med)	0 vs. 160 mg|kg|day (Control vs. High)
	p values			
Dose Response (Likelihood Ratio)	<.0001	0.3944	0.0780	<.0001
Homogeneity (Log Rank)	<.0001	0.3839	0.0689	<.0001

3.1.2 Tumor Data Analysis

Table 15 and Table 16 display the numbers of tumor-bearing animals and examined animals with the size of mortality adjusted risk set for tumors by dose group for each sex. They also list p values for trend and pairwise comparison tests based on poly-k analysis. Table 19 and Table 20 display merged/combined tumor types in individual organs for male and female rats, respectively. Table 7 is an extract from Table 15 (male rats) and Table 8 is an extract from Table 16 and Table 20 (female rats). In this section, tumor types whose p value of either the poly-k trend test or pairwise tests is less than 0.05 are all provided.

The results match those reported by the Sponsor (Text Table 22 (page 66 of the final report)), in which the Sponsor explained "This low level of endocrine tumor induction at the high dose is an

expected finding likely related to the higher incidence of focal endocrine cell hyperplasia at this dose[6]."

Table 7: Findings from tumor data analysis for Male Rats

Organ	Tumor	Control (0 mg)	Low Dose (20 mg)	Med Dose (50 mg)	High Dose (160 mg)
		Observed Proportion #Animals with Tumor/Total Number of Examined Animals (Poly-3 Mortality Adjusted Total Number of Animals)			
		P value			
		Trend test	Pairwise Comparison with Control		
Stomach	#Neuroendocrine cell tumor, benign/malignant	0/120 (82) 0.0370	0/60 (47)	0/60 (41)	2/60 (41) 0.1093

Note: The p values are reported in the second row of each cell. The p value reported in the control column is for Trend test, and the other three p values are for pairwise comparison of each indicated dose group to the control group. If no tumor is found in a dose group, its pairwise comparison is not possible to conduct, and thus the p value is not obtainable. The numerator indicates the number of animals that had a tumor of interest, and the denominator the number of animals examined (and found useful). The number inside of ( ) indicates the weighted (mortality adjusted) total number of animals for the poly-k analysis. A tumor with # is a combined event.

Table 8: Findings from tumor data analysis for Female Rats

Organ	Tumor	Control (0 mg)	Low Dose (20 mg)	Med Dose (50 mg)	High Dose (160 mg)
		Observed Proportion #Animals with Tumor/Total Number of Examined Animals (Poly-3 Mortality Adjusted Total Number of Animals)			
		P value			
		Trend test	Pairwise Comparison with Control		
Stomach	Neuroendocrine cell tumor, benign	0/120 (85) 0.0065	0/60 (40)	0/60 (36)	3/60 (38) 0.0210
	Neuroendocrine cell tumor, malignant	0/120 (85) 0.1869	0/60 (40)	0/60 (36)	1/60 (37) 0.2761
Stomach	#Neuroendocrine cell tumor, benign/malignant	0/120 (85) 0.0012	0/60 (40)	0/60 (36)	4/60 (38) 0.0056
Mammary gland	Adenocarcinoma	28/120 (93) 0.7442	22/59 (45) 0.0255	19/60 (43) 0.0799	11/59 (40) 0.5751

Note: The p values are reported in the second row of each cell. The p value reported in the control column is for Trend test, and the other three p values are for pairwise comparison of each indicated dose group to the control group. If no tumor is found in a dose group, its pairwise comparison is not possible to conduct, and thus the p value is not obtainable. The numerator indicates the number of animals that had a tumor of interest, and the denominator the number of animals examined (and found useful). The number inside of ( ) indicates the weighted (mortality adjusted) total number of animals for the poly-k analysis. A tumor with # is a combined event.

Reviewer's findings: The findings described below are in accordance with the multiplicity adjustment specified in the FDA guidance for the carcinogenicity study design and data analysis (see Section 2.2.2 of this review).

[6] It refers to the 160 mg/kg dose.

Male rats (Table 7)

Dose response relationship

No tumor types tested showed statistically significant trend in tumor incidence.

Pairwise comparisons:

No tumor types tested showed statistically significant pairwise increases in incidence rate in treated groups when compared with the combined control group.

Female rats (Table 8)

Dose response relationship

Neuroendocrine cell tumor (benign), Stomach, is found statistically significant for trend if it is considered as a rare tumor, because the p values (0.0065) are <0.025 but not <0.005. A combined tumor type, #Neuroendocrine cell tumor (benign/malignant), Stomach, that includes both benign and malignant is also found statistically significant for trend (p value=0.0012<0.005), whether it is a rare tumor or a common tumor.

No other tumor types tested showed statistically significant trend in tumor incidence.

Pairwise comparisons:

Neuroendocrine cell tumor (benign), Stomach, is found statistically significant for High dose if it is a rare tumor, because the p value (0.021) is <0.05, but not <0.01. A combined tumor type, #Neuroendocrine cell tumor (benign/malignant), Stomach, that includes both benign and malignant is also found statistically significant for the high dose in the pairwise comparison with the control group (p value=0.0056 <0.01), whether it is a rare tumor or a common tumor.

Adenocarcinoma (Mammary gland), is found statistically significant for Low dose if it is a rare tumor, because the p value (0.0225) is <0.05, but not <0.01.

No other tumor types tested showed statistically significant pairwise increases in incidence rate in treated groups when compared with the control group.

3.2 Mouse Study

Study (b) (4) 152.09, a carcinogenicity study in mice, assessed the carcinogenic potential of E5501 in male and female CD-1 mice (62 – 64 animals/sex/group main study). The test article, E5501, was administered orally by gavage once a day to CD-1 mice, for 101 - 105 weeks at daily doses of 20, 60, 160 mg/kg. The study included two control groups that received an equivalent volume of control article/vehicle (0.5% methylcellulose in water). Terminal Necropsy was planned to be performed in Week 104 - 105 for male mice and in Week 101 - 103 (all animals not on the 20 and 160 mg/kg dose groups) and in Week 101 - 102 (the 20 and 160 mg/kg dose groups) for female mice.

Table 9 and Table 10 (male/female mice) list all organs recorded in the submitted dataset. The listed organs were those that were examined in the Sponsor's submitted data. This reviewer calculated the number of animals *examined and found usable* from the submitted tumor data. In some organs, no tumors were found. As an example, no tumors were found in *Brain* (Male

Mice). In male mice, 21 out of 44 organs[7] were such cases. In female mice, 16 out of 38 organs[8] were such cases. In these cases, trend and pairwise comparison tests may be meaningless to conduct. This reviewer performed analyses on the rest of these organs, 23 organs for male mice and 22 organs for female mice.

Table 9: Frequency of Tumors (#Examined Animals) in Organ (Male Mice)

Organ	[#Tumors]/[#Animals Examined] BY ORGAN]	0 mg	20 mg	60 mg	160 mg
Adrenals	8/316	3 (128)	3 (62)	0 (64)	2 (62)
Aorta	0/317	0 (128)	0 (62)	0 (64)	0 (63)
Brain	0/316	0 (127)	0 (63)	0 (63)	0 (63)
Cavity	2/318	1 (128)	0 (63)	0 (64)	1 (63)
Cecum	0/317	0 (128)	0 (62)	0 (64)	0 (63)
Colon	1/317	0 (128)	0 (62)	0 (64)	1 (63)
Diaphragm	0/317	0 (128)	0 (62)	0 (64)	0 (63)
Duodenum	0/317	0 (128)	0 (62)	0 (64)	0 (63)
Epididymides	2/314	1 (126)	0 (62)	1 (64)	0 (62)
Esophagus	0/313	0 (126)	0 (61)	0 (64)	0 (62)
Gallbladder	1/311	0 (128)	1 (60)	0 (62)	0 (61)
Harderian glands	7/318	5 (128)	0 (63)	0 (64)	2 (63)
Heart	0/317	0 (128)	0 (62)	0 (64)	0 (63)
Hematopoietic and lymphatic organs	27/318	15 (128)	4 (63)	4 (64)	4 (63)
Ileum	0/316	0 (127)	0 (62)	0 (64)	0 (63)
Jejunum	1/317	0 (128)	0 (62)	1 (64)	0 (63)
Joint	1/318	1 (128)	0 (63)	0 (64)	0 (63)
Kidneys	7/317	3 (128)	1 (62)	2 (64)	1 (63)
Lacrimal glands	0/298	0 (123)	0 (59)	0 (61)	0 (55)
Liver	38/317	18 (128)	7 (62)	8 (64)	5 (63)
Lung	91/317	47 (128)	10 (62)	16 (64)	18 (63)
Mesenteric lymph node	4/303	1 (123)	1 (59)	1 (61)	1 (60)
Optic nerves	0/301	0 (119)	0 (61)	0 (58)	0 (63)
Pancreas	1/316	1 (128)	0 (62)	0 (63)	0 (63)
Parathyroids	2/302	1 (121)	0 (60)	1 (61)	0 (60)
Pituitary	9/307	5 (122)	2 (60)	1 (62)	1 (63)

[7] The submitted data (male mice) has records for 44 organs.
[8] The submitted data (female mice) has records for 38 organs.

Organ	[#Tumors]/[#Animals Examined] BY ORGAN]	0 mg	20 mg	60 mg	160 mg
Prostate	0/314	0 (126)	0 (61)	0 (64)	0 (63)
Rectum	0/317	0 (128)	0 (62)	0 (64)	0 (63)
Sciatic nerve	0/317	0 (128)	0 (62)	0 (64)	0 (63)
Seminal vesicles	1/314	0 (126)	0 (61)	1 (64)	0 (63)
Skeletal muscle	1/317	0 (128)	0 (62)	1 (64)	0 (63)
Skin	5/317	3 (128)	1 (62)	0 (64)	1 (63)
Spinal cord	0/316	0 (127)	0 (62)	0 (64)	0 (63)
Spleen	8/316	3 (127)	3 (62)	1 (64)	1 (63)
Stomach	7/317	2 (128)	3 (62)	0 (64)	2 (63)
Sublingual glands	0/314	0 (127)	0 (61)	0 (63)	0 (63)
Submaxillary glands	0/316	0 (127)	0 (62)	0 (64)	0 (63)
Submaxillary lymph node	0/305	0 (124)	0 (60)	0 (62)	0 (59)
Testes	7/318	6 (128)	0 (63)	1 (64)	0 (63)
Thymus	0/253	0 (101)	0 (53)	0 (50)	0 (49)
Thyroids	1/316	0 (128)	0 (62)	0 (64)	1 (62)
Tongue	0/317	0 (128)	0 (62)	0 (64)	0 (63)
Trachea	0/299	0 (121)	0 (59)	0 (59)	0 (60)
Urinary bladder	0/317	0 (128)	0 (62)	0 (64)	0 (63)

Note: The reviewer analyzes reported tumors of the organs in bold in ORGAN column. The frequency of tumors does not always match that of animals, as an animal can have more than one tumor within an organ. The numbers reported in parentheses for each dose group are the counts of examined animals.

Table 10: Frequency of Tumors (#Examined Animals) in Organ (Female Mice)

Organ	[#Tumors]/[#Animals Examined] BY ORGAN]	0 mg	20 mg	60 mg	160 mg
Abdomen	4/313	2 (125)	0 (63)	2 (63)	0 (62)
Adrenals	12/311	4 (124)	3 (63)	5 (63)	0 (61)
Aorta	0/311	0 (125)	0 (63)	0 (62)	0 (61)
Cavity	1/313	0 (125)	0 (63)	1 (63)	0 (62)
Cecum	1/312	0 (125)	1 (62)	0 (63)	0 (62)
Colon	0/312	0 (125)	0 (62)	0 (63)	0 (62)
Diaphragm	0/311	0 (124)	0 (63)	0 (63)	0 (61)
Duodenum	0/312	0 (125)	0 (62)	0 (63)	0 (62)
Esophagus	0/311	0 (124)	0 (62)	0 (63)	0 (62)

Organ	[#Tumors]/[#Animals Examined] BY ORGAN]	0 mg	20 mg	60 mg	160 mg
Gallbladder	0/310	0 (124)	0 (62)	0 (62)	0 (62)
Harderian glands	2/313	0 (125)	1 (63)	1 (63)	0 (62)
Heart	1/313	0 (125)	0 (63)	1 (63)	0 (62)
Hematopoietic and lymphatic organs	85/313	33 (125)	21 (63)	16 (63)	15 (62)
Ileum	0/312	0 (125)	0 (62)	0 (63)	0 (62)
Jejunum	0/312	0 (125)	0 (62)	0 (63)	0 (62)
Kidneys	1/313	0 (125)	0 (63)	0 (63)	1 (62)
Lacrimal glands	0/281	0 (112)	0 (52)	0 (60)	0 (57)
Liver	8/313	4 (125)	0 (63)	3 (63)	1 (62)
Lung	32/313	13 (125)	4 (63)	11 (63)	4 (62)
Mammary gland	5/294	0 (119)	3 (57)	1 (60)	1 (58)
Mesenteric lymph node	4/308	1 (123)	1 (62)	1 (63)	1 (60)
Optic nerves	0/296	0 (119)	0 (60)	0 (59)	0 (58)
Ovaries	15/312	6 (124)	2 (63)	4 (63)	3 (62)
Pancreas	3/312	3 (125)	0 (62)	0 (63)	0 (62)
Parathyroids	0/296	0 (117)	0 (61)	0 (59)	0 (59)
Pituitary	13/298	5 (116)	2 (60)	3 (62)	3 (60)
Sciatic nerve	0/307	0 (123)	0 (63)	0 (60)	0 (61)
Skin	3/313	2 (125)	0 (63)	0 (63)	1 (62)
Spleen	6/312	4 (125)	1 (63)	1 (62)	0 (62)
Stomach	7/312	3 (125)	1 (62)	2 (63)	1 (62)
Sublingual glands	0/312	0 (125)	0 (62)	0 (63)	0 (62)
Submaxillary lymph node	0/306	0 (122)	0 (62)	0 (62)	0 (60)
Thymus	3/259	1 (105)	1 (53)	1 (57)	0 (44)
Thyroids	3/309	0 (123)	2 (62)	0 (63)	1 (61)
Trachea	0/300	0 (119)	0 (61)	0 (61)	0 (59)
Urinary bladder	0/311	0 (124)	0 (62)	0 (63)	0 (62)
Uterus	39/311	14 (123)	9 (63)	13 (63)	3 (62)
Vagina	1/310	0 (123)	0 (62)	1 (63)	0 (62)

Note: The reviewer analyzes reported tumors of the organs in bold in ORGAN column. The frequency of tumors does not always match that of animals, as an animal can have more than one tumor within an organ. The numbers reported in parentheses for each dose group are the counts of examined animals.

The submitted dataset of male mice for example contains 562 entered rows and 232 reported tumors in 44 organs out of the 562 rows. The poly-k analysis results for the 232 reported tumors are provided in Section 5.2 (Table 17). This reviewer merged and combined some of the reported tumors to perform additional poly-k analyses in Section 5.3 (Table 21).

The submitted dataset of female mice for example contains 538 entered rows and 249 reported tumors in 38 organs out of the 538 rows. The poly-k analysis results for the 249 reported tumors are provided in Section 5.2 (Table 18). This reviewer merged and combined the reported tumors to perform additional poly-k analyses in Section 5.3 (Table 22).

3.2.1 Survival Analysis

The Sponsor's final report[9] has the following statement: *Decreased survival was seen in the 160 mg/kg females*. This reviewer's survival analysis confirms this statement in the analyses shown below.

Note: The Sponsor explains in Section 6.1.3 Cause of Death and Moribund Sacrifice of the final report: "Neoplastic lesions did not affect the incidence of deaths/moribundity", and "Increased severity of chronic nephropathy affected the incidence of deaths/moribundity in females given 160 mg/kg. However, a sufficient number of high dose females were dosed for more than 100 weeks to enable evaluation of the carcinogenic potential of E5501 in this dose group."

Reviewer's Survival Analysis

The Kaplan-Meier curves for survival rates are given in Figures 3 and 4 of Section 5.1 for male and female mice, respectively. The intercurrent mortality data are given in Table 11 and Table 13 for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survival are given in Table 12 and Table 14 for male and female rats, respectively.

Findings: As seen from Table 11 and Table 13, the numbers (proportions) of death before terminal sacrifice was 59 (46.09%), 31 (49.21%), 31 (48.44%), and 33 (52.38%) in male mice and 80 (72%), 50 (79.37%), 41 (65.08%), and 54 (87.1%) in female mice in the Control, Low dose, Medium dose, and High dose groups, respectively. Female mice of the 160 mg/kg dose at a faster rate of 87.1% in comparison to all other dose groups. This has been confirmed by the statistical tests. As for male mice, as seen in Table 12, the statistical tests did not show a statistically significant dose response relationship in mortality across Control and treated groups for male rats (p= .5146). In female mice, as seen in Table 14, however, a statistically significant dose response relationship in mortality across Control and treated groups was shown (p=.0454) at the significance level of 5%. Similarly, the pairwise comparisons did not show a statistically significant mortality between Control and High dose for male rats (p=.4842), but in female mice, the pairwise comparisons between Control and High dose showed a statistically significant mortality difference (p=.0288) at the significance level of 5% (two-sided).

[9] Refer to Text Table 13 (page 65) of the final study report.

Table 11: Intercurrent Mortality Rate in Male Mice

	0 mg|kg|day		20 mg|kg|day		60 mg|kg|day		160 mg|kg|day	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	10	7.81	4	6.35	5	7.81	2	3.17
53 - 78	19	22.66	13	26.98	8	20.31	12	22.22
79 - 90	18	36.72	5	34.92	8	32.81	10	38.10
91 - 103	12	46.09	9	49.21	10	48.44	9	52.38
Ter. Sac.	69	53.91	32	50.79	33	51.56	30	47.62

Note: Cum. %: Cumulative Percent except for Terminal sacrifice; No. of Death: Number of Deaths

Table 12: Tests for Dose Response and Homogeneity of Survival in Male Mice

	0, 20,60,160 mg|kg|day (Control, Low, Mid, High)	0 vs. 20 mg|kg|day (Control vs. Low)	0 vs 60 mg|kg|day (Control vs. Med)	0 vs. 160 mg|kg|day (Control vs. High)
Test	p values			
Dose Response (Likelihood Ratio)	0.5146	0.8727	0.9765	0.4842
Homogeneity (Log Rank)	0.9077	0.8717	0.9764	0.4776

Table 13: Intercurrent Mortality Rate in Female Mice

	0 mg|kg|day		20 mg|kg|day		60 mg|kg|day		160 mg|kg|day	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	15	12.00	5	7.94	8	12.70	14	22.58
53 - 76	22	29.60	12	26.98	6	22.22	13	43.55
77 - 89	21	46.40	11	44.44	5	30.16	11	61.29
90 - 100	17	60.00	15	68.25	13	50.79	9	75.81
Ter. Sac.	50	40.00	20	31.75	31	49.21	15	24.19

Note: Cum. %: Cumulative Percent except for Terminal sacrifice; No. of Death: Number of Deaths

Table 14: Tests for Dose Response and Homogeneity of Survival in Female Mice

	0, 20,60,160 mg|kg|day (Control, Low, Mid, High)	0 vs. 20 mg|kg|day (Control vs. Low)	0 vs 60 mg|kg|day (Control vs. Med)	0 vs. 160 mg|kg|day (Control vs. High)
Test	p values			
Dose Response (Likelihood Ratio)	0.0454	0.5828	0.2344	0.0288
Homogeneity (Log Rank)	0.0175	0.5777	0.2369	0.0237

3.2.2 Tumor Data Analysis

Table 17 and Table 18 display the numbers of tumor-bearing animals and examined animals with the size of mortality adjusted risk set for tumors by dose group for each sex. They also list p values for trend and pairwise comparison tests based on poly-k analysis. Table 21 and Table 22 display merged/combined tumor types in individual organs for male and female mice, respectively.
For Alveolar/bronchiolar adenoma, Lung (female mice), the p value of pairwise test for Med dose vs the control group was 0.0050 (<0.05). Also for Adenocaricinoma, pars distalis, Pituitary (female mice), the p value for trend test was 0.0419 (< 0.05). No other tumor types had the raw p values less than 0.05 in either trend test or pairwise comparison tests.

The results match those reported by the Sponsor (Text Table 22 (page 66 of the final report)), in which the Sponsor explained "This low level of endocrine tumor induction at the high dose is an expected finding likely related to the higher incidence of focal endocrine cell hyperplasia at this dose[10]."

Reviewer's findings: The findings described below are in accordance with the multiplicity adjustment specified in the FDA guidance for the carcinogenicity study design and data analysis (see Section 2.2.2 of this review).

Male mice

Dose response relationship

No tumor types tested showed statistically significant trend in tumor incidence.

Pairwise comparisons:

No tumor types tested showed statistically significant pairwise increases in incidence rate in treated groups when compared with the combined control group.

Female mice

Dose response relationship

No tumor types tested showed statistically significant trend in tumor incidence.

Pairwise comparisons:

Alveolar/bronchiolar adenoma, Lung, is found statistically significant for Med dose, whether it is a rare tumor or a common tumor, because the p value (0.0050) is <0.01. No other tumor types tested showed statistically significant pairwise increases in incidence rate in treated groups when compared with the combined control group.

[10] It refers to the 160 mg/kg dose.

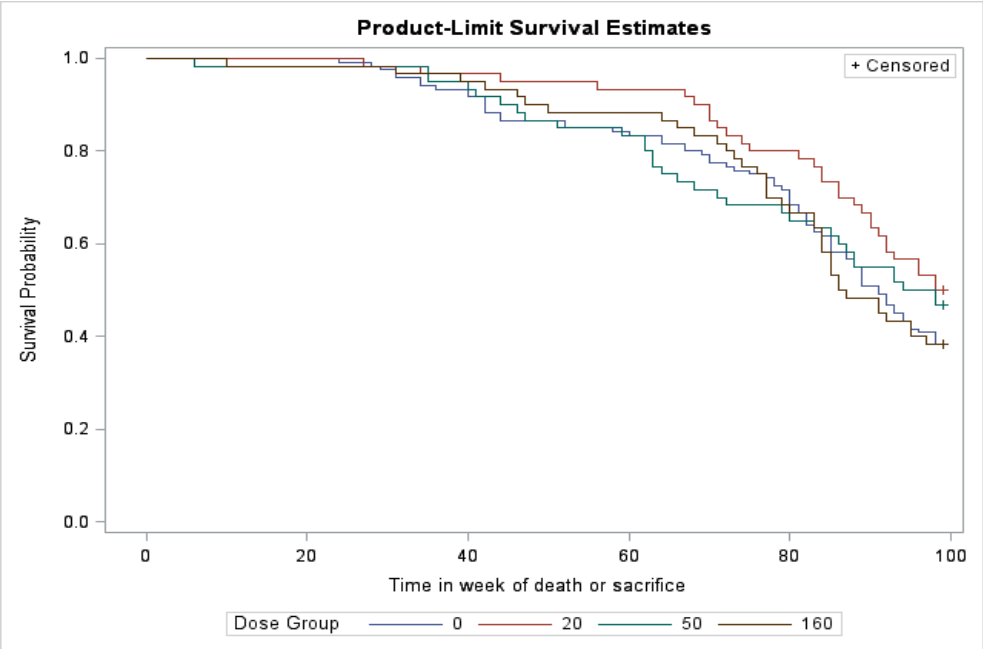
4 CONCLUSIONS

The reviewer's survival analysis results are comparable with the Sponsor's findings that the High dose (160 mg/kg) increased the mortality for female rats and mice when compared to the other dose groups and the control group. The statistical analyses for the dose response relationship (trend) and pairwise comparisons of each dose to the control group in the frequencies of Sponsor recorded tumor types were also found comparable with the Sponsor's neoplastic findings. Specifically, (1) In female rats, Neuroendocrine cell tumor (benign), Stomach, is found statistically significant for trend if it is considered as a rare tumor; (2) a combined tumor type, #Neuroendocrine cell tumor (benign/malignant), Stomach, that includes both benign and malignant cases is also found statistically significant for trend, whether it is a rare tumor or a common tumor; (3) Neuroendocrine cell tumor (benign), Stomach, is found statistically significant for High dose if it is a rare tumor; (4) A combined tumor type, #Neuroendocrine cell tumor (benign/malignant), Stomach, that includes both benign and malignant is also found statistically significant for the high dose in the pairwise comparison with the control group, whether it is a rare tumor or a common tumor; and (5) Adenocarcinoma (Mammary gland), is found statistically significant for Low dose if it is a rare tumor. (6) In female mice, Alveolar/bronchiolar adenoma (Lung) is found statistically significant for Med dose, whether it is a rare tumor or a common tumor.

5 APPENDICES

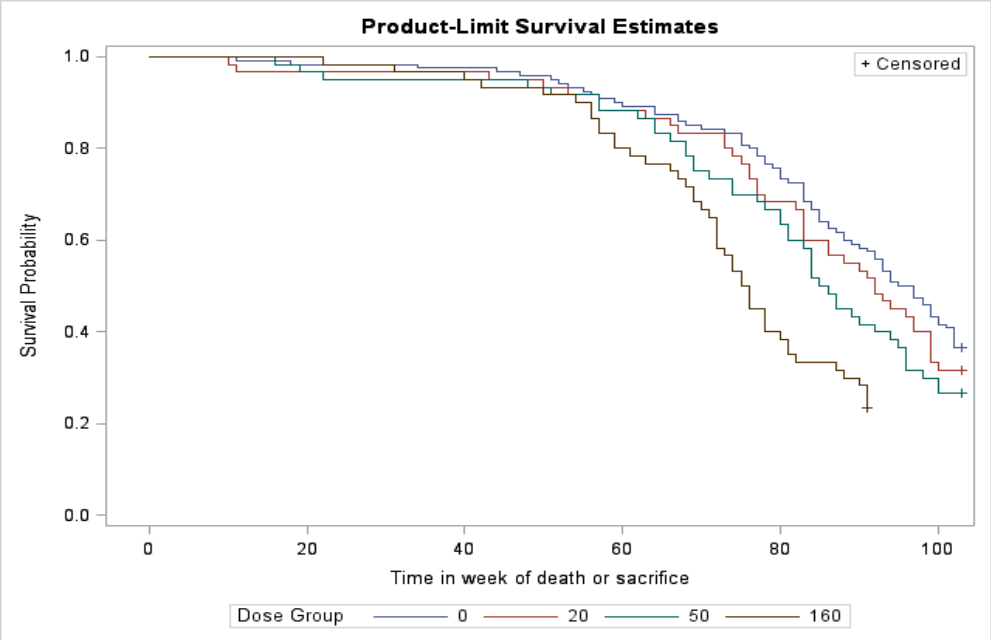
5.1 Kaplan-Meier Plots by Dose Group

Figure 1: Kaplan-Meier Survival Functions for Male Rats



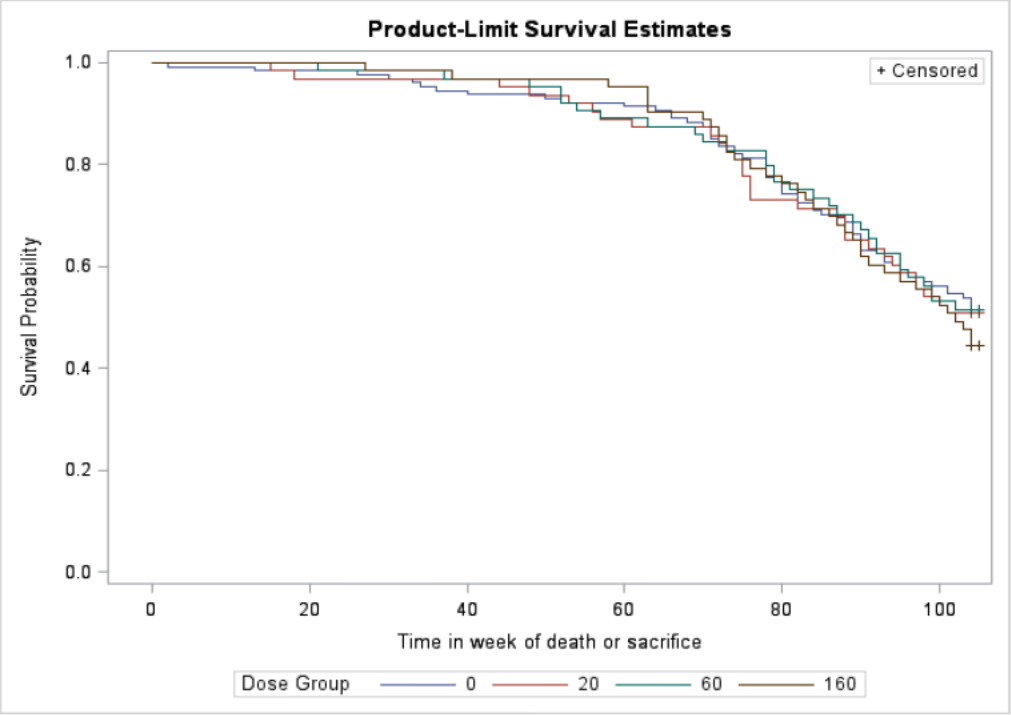
Note: The unit for the dose groups is mg/kg/day.

Figure 2: Kaplan-Meier Survival Functions for Female Rats



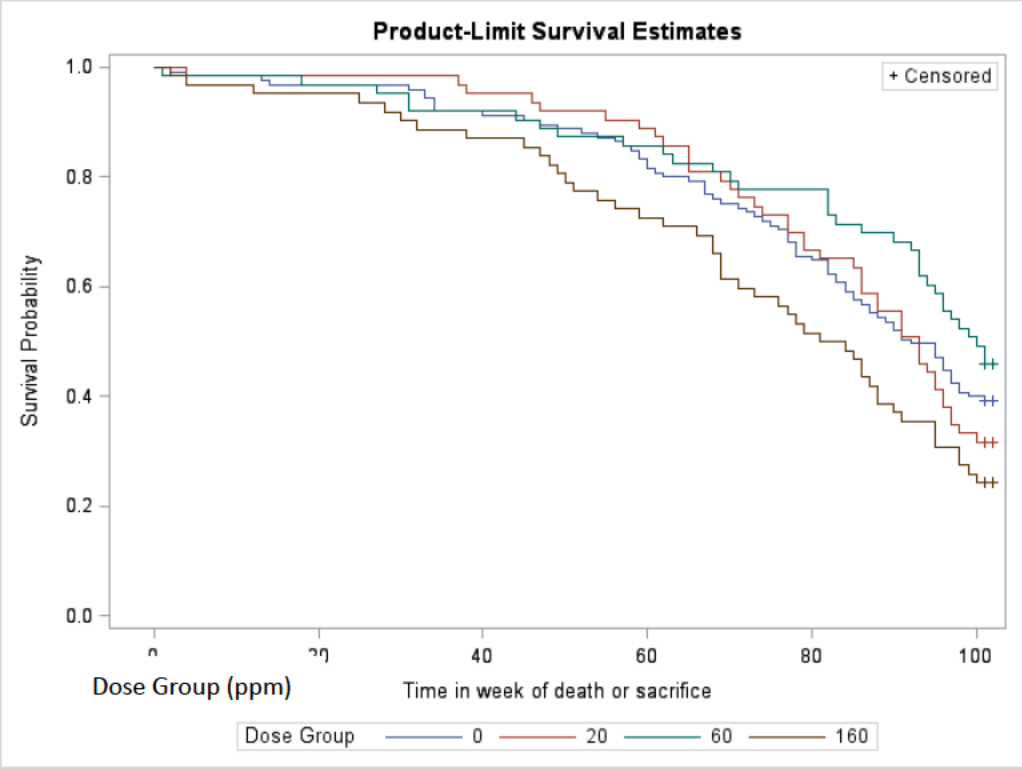
Note: The unit for the dose groups is mg/kg/day.

Figure 3: Kaplan-Meier Survival Functions for Male Mice



Note: The unit for the dose groups is mg/kg/day.

Figure 4: Kaplan-Meier Survival Functions for Female Mice



Note: The unit for the dose groups is mg/kg/day.

5.2 Poly-3 Analysis Results for Sponsor Tumor Findings by Dose Group

The following tables provide Poly-3 analyses (Trend and Pairwise Tests) for *neoplastic findings recorded by the Sponsor*. The analysis was not performed either for an organ in which no tumor was found or for an organ for which at least one of the dose groups had no examined animals.

Table 15: P-values for Poly-3 Trend Test and Pairwise Comparisons with Control [Reported Tumors] (Male Rats)

Organ	Tumor	Control (0 mg)	Low Dose (20 mg)	Med Dose (50 mg)	High Dose (160 mg)
		Observed Proportion			
		#Animals with Tumor/Total Number of Examined Animals			
		(Poly-3 Mortality Adjusted Total Number of Animals)			
		P value			
		Trend test	Pairwise Comparison with Control		
Adrenals	Cortical adenoma	1/120 (82) 1.0000	0/60 (47) 1.0000	0/60 (41) 1.0000	0/60 (41) 1.0000
	Cortical carcinoma	0/120 (82) 0.3915	0/60 (47)	1/60 (42) 0.3387	0/60 (41)
	Malignant pheochromocytoma	2/120 (82) 0.2930	2/60 (47) 0.4631	0/60 (41) 1.0000	2/60 (41) 0.4074
	Pheochromocytoma	7/120 (83) 0.7456	13/60 (48) 0.0052	1/60 (41) 0.9642	4/60 (42) 0.5394
Brain	Astrocytoma	1/120 (82) 0.1302	1/60 (47) 0.5977	1/59 (41) 0.5574	2/59 (41) 0.2574
	Granular cell tumor	0/120 (82) 0.3857	0/60 (47)	1/59 (41) 0.3333	0/59 (40)
	Malignant reticulosis	0/120 (82) 0.6095	1/60 (47) 0.3643	0/59 (41)	0/59 (40)
	Meningeal sarcoma	0/120 (82) 0.6114	1/60 (48) 0.3692	0/59 (41)	0/59 (40)
	Oligodendroglioma	0/120 (82) 0.3857	0/60 (47)	1/59 (41) 0.3333	0/59 (40)
Cavity	Malignant mesothelioma	2/120 (82) 0.9434	1/60 (48) 0.7525	0/60 (41) 1.0000	0/60 (41) 1.0000
Epididymides	Leiomyosarcoma	0/120 (82) 0.1943	0/60 (47)	0/60 (41)	1/60 (41) 0.3333
Esophagus	Squamous cell carcinoma	1/120 (82) 1.0000	0/60 (47) 1.0000	0/60 (41) 1.0000	0/60 (41) 1.0000

Hematopoietic and lymphatic organs	Histiocytic sarcoma	4/120 (82) 0.5968	4/60 (48) 0.3319	1/60 (41) 0.8737	2/60 (42) 0.6650
	Malignant lymphoma	0/120 (82) 0.0557	1/60 (47) 0.3643	0/60 (41)	2/60 (42) 0.1129
Jejunum	Adenocarcinoma	0/120 (82) 0.1943	0/60 (47)	0/60 (41)	1/60 (41) 0.3333
Kidneys	Adenoma	1/120 (82) 1.0000	0/60 (47) 1.0000	0/60 (41) 1.0000	0/60 (41) 1.0000
	Lipoma	1/120 (82) 0.8501	1/60 (47) 0.5977	0/60 (41) 1.0000	0/60 (41) 1.0000
	Renal mesenchymal tumor	0/120 (82) 0.1943	0/60 (47)	0/60 (41)	1/60 (41) 0.3333
Liver	Hepatocellular adenoma	0/120 (82) 0.6114	1/60 (47) 0.3643	0/60 (41)	0/60 (41)
	Hepatocellular carcinoma	2/120 (82) 0.2833	2/60 (47) 0.4631	1/60 (41) 0.7074	2/60 (41) 0.4074
Lung	Adenoma, bronchiolo-alveolar	1/120 (82) 1.0000	0/59 (46) 1.0000	0/60 (41) 1.0000	0/60 (41) 1.0000
	Carcinoma, bronchiolo-alveolar	0/120 (82) 0.3905	0/59 (46)	1/60 (41) 0.3333	0/60 (41)
Mammary gland	Adenocarcinoma	0/120 (82) 0.3886	0/60 (47)	1/60 (41) 0.3333	0/60 (41)
	Adenoma	2/120 (82) 0.7841	0/60 (47) 1.0000	1/60 (41) 0.7074	0/60 (41) 1.0000
Mesenteric lymph node	Hemangioma	0/120 (82) 0.1943	0/60 (47)	0/60 (41)	1/60 (41) 0.3333
Pancreas	Acinar cell adenoma	1/120 (82) 0.2595	0/60 (47) 1.0000	1/60 (41) 0.5574	1/60 (41) 0.5574
	Islet-cell adenoma	11/120 (83) 0.7124	6/60 (47) 0.6299	5/60 (41) 0.6657	4/60 (41) 0.8011
Parathyroids	Adenoma	2/119 (81) 0.2296	1/58 (45) 0.7379	0/58 (39) 1.0000	2/59 (40) 0.4024
Pituitary	Adenocarcinoma, pars distalis	4/119 (81) 0.5114	3/59 (47) 0.5088	4/59 (42) 0.2700	2/60 (41) 0.6598
	Adenoma, pars distalis	65/119 (94) 0.9828	40/59 (52) 0.2103	31/59 (45) 0.5930	26/60 (48) 0.9735
Preputial/Clitoral glands	Squamous cell carcinoma	0/120 (82) 0.6114	1/60 (47) 0.3643	0/60 (41)	0/60 (41)

	Squamous cell papilloma	0/120 (82) 0.3886	0/60 (47)	1/60 (41) 0.3333	0/60 (41)
Rib	Osteochondroma	1/120 (82) 1.0000	0/60 (47) 1.0000	0/60 (41) 1.0000	0/60 (41) 1.0000
Skin	Basal cell adenoma	0/120 (82) 0.6114	1/60 (47) 0.3643	0/60 (41)	0/60 (41)
	Basal cell carcinoma	0/120 (82) 0.6114	1/60 (47) 0.3643	0/60 (41)	0/60 (41)
	Fibroma	4/120 (82) 0.7478	1/60 (47) 0.9009	0/60 (41) 1.0000	1/60 (42) 0.8788
	Fibrosarcoma	2/120 (82) 0.5365	1/60 (48) 0.7525	0/60 (41) 1.0000	1/60 (41) 0.7074
	Hemangioma	0/120 (82) 0.1943	0/60 (47)	0/60 (41)	1/60 (41) 0.3333
	Hemangiosarcoma	0/120 (82) 0.3915	0/60 (47)	1/60 (42) 0.3387	0/60 (41)
	Keratoacanthoma	8/120 (83) 0.3502	5/60 (48) 0.5544	4/60 (41) 0.6071	5/60 (42) 0.4566
	Leiomyoma	0/120 (82) 0.6114	1/60 (47) 0.3643	0/60 (41)	0/60 (41)
	Lipoma	3/120 (82) 0.9670	2/60 (47) 0.6022	0/60 (41) 1.0000	0/60 (41) 1.0000
	Schwannoma	1/120 (82) 1.0000	0/60 (47) 1.0000	0/60 (41) 1.0000	0/60 (41) 1.0000
	Sebaceous cell adenoma	0/120 (82) 0.6114	1/60 (47) 0.3643	0/60 (41)	0/60 (41)
	Squamous cell carcinoma	1/120 (82) 0.8501	1/60 (47) 0.5977	0/60 (41) 1.0000	0/60 (41) 1.0000
	Squamous cell papilloma	0/120 (82) 0.3886	0/60 (47)	1/60 (41) 0.3333	0/60 (41)
	Trichoepithelioma	1/120 (82) 0.8501	1/60 (47) 0.5977	0/60 (41) 1.0000	0/60 (41) 1.0000
Stomach	Neuroendocrine cell tumor, benign	0/120 (82) 0.1943	0/60 (47)	0/60 (41)	1/60 (41) 0.3333
	Neuroendocrine cell tumor, malignant	0/120 (82) 0.1943	0/60 (47)	0/60 (41)	1/60 (41) 0.3333
	Squamous cell carcinoma	0/120 (82) 0.1129	0/60 (47)	1/60 (41) 0.3333	1/60 (41) 0.3333

Testes	Interstitial cell adenoma	4/120 (82) 0.6642	0/60 (47) 1.0000	1/60 (41) 0.8737	1/60 (41) 0.8737
Thyroids	C-cell adenoma	12/120 (83) 0.7222	4/59 (46) 0.8932	4/60 (41) 0.8462	4/60 (41) 0.8462
	C-cell carcinoma	1/120 (82) 0.6861	1/59 (46) 0.5914	1/60 (41) 0.5574	0/60 (41) 1.0000
	Follicular cell adenoma	1/120 (82) 0.1004	3/59 (47) 0.1370	1/60 (41) 0.5574	3/60 (42) 0.1123
	Follicular cell carcinoma	1/120 (82) 0.7389	2/59 (46) 0.2931	1/60 (41) 0.5574	0/60 (41) 1.0000
Tongue	Granular cell tumor	0/119 (81) 0.3923	0/59 (46)	1/60 (41) 0.3361	0/60 (41)
Trachea	Granular cell tumor	0/120 (82) 0.3905	0/59 (46)	1/59 (41) 0.3333	0/60 (41)
Urinary bladder	Papilloma	0/120 (82) 0.3876	0/59 (46)	1/60 (41) 0.3333	0/59 (40)
	Transitional cell carcinoma	1/120 (82) 1.0000	0/59 (46) 1.0000	0/60 (41) 1.0000	0/59 (40) 1.0000
Zymbal glands	Carcinoma	0/120 (82) 0.6755	2/60 (48) 0.1345	0/60 (41)	0/60 (41)

Note: The p values are reported in the second row of each cell. The p value reported in the control column is for Trend test, and the other three p values are for pairwise comparison of each indicated dose group to the control group. If no tumor is found in a dose group, its pairwise comparison is not possible to conduct, and thus the p value is not obtainable. The numerator indicates the number of animals that had a tumor of interest, and the denominator the number of animals examined (and found useful). The number inside of ( ) indicates the weighted (mortality adjusted) total number of animals for the poly-k analysis.

Table 16: P-values for Poly-3 Trend Test and Pairwise Comparisons with Control [Reported Tumors]

(Female Rats)

Organ	Tumor	Control (0 mg)	Low Dose (20 mg)	Med Dose (50 mg)	High Dose (160 mg)
		Observed Proportion			
		#Animals with Tumor/Total Number of Examined Animals			
		(Poly-3 Mortality Adjusted Total Number of Animals)			
		P value			
		Trend test	Pairwise Comparison with Control		
Adrenals	Cortical adenoma	3/120 (85) 0.1941	3/60 (41) 0.3010	3/60 (37) 0.2579	3/60 (37) 0.2087
	Cortical carcinoma	2/120 (85) 0.2084	1/60 (40) 0.6892	0/60 (36) 1.0000	2/60 (37) 0.3053
	Malignant pheochromocytoma	0/120 (85) 0.5707	1/60 (40) 0.3200	0/60 (36)	0/60 (37)
	Pheochromocytoma	2/120 (85) 0.7349	1/60 (40) 0.6892	2/60 (37) 0.3534	0/60 (37) 1.0000
Brain	Granular cell tumor	1/120 (85) 1.0000	0/59 (39) 1.0000	0/60 (36) 1.0000	0/60 (37) 1.0000
Eyes	Squamous cell carcinoma	0/120 (85) 0.1869	0/60 (40)	0/60 (36)	1/60 (37) 0.2761
Hematopoietic and lymphatic organs	Histiocytic sarcoma	1/120 (85) 0.5317	0/60 (40) 1.0000	2/60 (36) 0.2107	0/60 (37) 1.0000
	Malignant lymphoma	1/120 (86) 0.3381	0/60 (40) 1.0000	0/60 (36) 1.0000	1/60 (37) 0.4745
Jejunum	Leiomyoma	1/120 (85) 1.0000	0/60 (40) 1.0000	0/60 (36) 1.0000	0/60 (37) 1.0000
Mammary gland	Adenocarcinoma	28/120 (93) 0.7442	22/59 (45) 0.0255	19/60 (43) 0.0799	11/59 (40) 0.5751
	Adenoma	7/120 (87) 0.2573	2/59 (40) 0.8392	7/60 (39) 0.0946	4/59 (38) 0.3617
	Fibroadenoma	45/120 (92) 0.6080	26/59 (45) 0.2140	30/60 (46) 0.0508	20/59 (42) 0.4392
Mesentery	Hemangiosarcoma	1/120 (85) 1.0000	0/60 (40) 1.0000	0/60 (36) 1.0000	0/60 (37) 1.0000
Omentum	Liposarcoma	0/120 (85) 0.5707	1/60 (40) 0.3200	0/60 (36)	0/60 (37)
Ovaries	Sertoli's cell tumor	0/120 (85) 0.1869	0/60 (40)	0/60 (36)	1/60 (37) 0.2761

Pancreas	Acinar cell adenoma	0/120 (85) 0.1869	0/60 (40)	0/60 (36)	1/60 (37) 0.2761
	Islet-cell adenoma	1/120 (85) 0.5327	0/60 (40) 1.0000	2/60 (37) 0.2181	0/60 (37) 1.0000
Parathyroids	Adenoma	2/120 (85) 0.4700	0/58 (38) 1.0000	0/59 (35) 1.0000	1/60 (37) 0.6240
Pituitary	Adenocarcinoma, pars distalis	19/119 (90) 0.8125	5/60 (41) 0.9328	9/60 (40) 0.5144	5/60 (39) 0.8693
	Adenoma, pars distalis	84/119 (108) 0.8509	45/60 (54) 0.2705	37/60 (49) 0.7011	36/60 (50) 0.7570
Skin	Fibroma	0/120 (85) 0.4622	0/59 (39)	3/60 (37) 0.0263	0/59 (36)
	Keratoacanthoma	0/120 (85) 0.3674	0/59 (39)	2/60 (38) 0.0937	0/59 (36)
	Lipoma	2/120 (85) 0.3850	0/59 (39) 1.0000	1/60 (36) 0.6570	1/59 (37) 0.6240
Stomach	Neuroendocrine cell tumor, benign	0/120 (85) 0.0065	0/60 (40)	0/60 (36)	3/60 (38) 0.0210
	Neuroendocrine cell tumor, malignant	0/120 (85) 0.1869	0/60 (40)	0/60 (36)	1/60 (37) 0.2761
	Squamous cell papilloma	1/120 (86) 1.0000	0/60 (40) 1.0000	0/60 (36) 1.0000	0/60 (37) 1.0000
Thymus	Thymoma	3/111 (79) 0.8712	1/56 (37) 0.7902	1/52 (32) 0.7491	0/56 (34) 1.0000
Thyroids	C-cell adenoma	6/120 (86) 0.6582	3/60 (40) 0.5887	1/60 (36) 0.9198	2/60 (37) 0.6978
	C-cell carcinoma	0/120 (85) 0.3687	0/60 (40)	1/60 (36) 0.2975	0/60 (37)
	Follicular cell adenoma	4/120 (86) 0.9373	3/60 (40) 0.3919	1/60 (37) 0.8388	0/60 (37) 1.0000
Uterus	Endometrial adenocarcinoma	0/119 (84) 0.5736	1/60 (40) 0.3226	0/60 (36)	0/60 (37)
	Endometrial adenoma	0/119 (84) 0.1878	0/60 (40)	0/60 (36)	1/60 (37) 0.2782
	Endometrial stromal polyp	7/119 (84) 0.6416	5/60 (40) 0.3324	0/60 (36) 1.0000	3/60 (39) 0.5935
	Endometrial stromal sarcoma	1/119 (84) 0.6554	1/60 (40) 0.5429	1/60 (37) 0.5198	0/60 (37) 1.0000

	Granular cell tumor	1/119 (84) 1.0000	0/60 (40) 1.0000	0/60 (36) 1.0000	0/60 (37) 1.0000
	Squamous cell carcinoma	0/119 (84) 0.5736	1/60 (40) 0.3226	0/60 (36)	0/60 (37)
	Yolk sac tumor	1/119 (84) 1.0000	0/60 (40) 1.0000	0/60 (36) 1.0000	0/60 (37) 1.0000
Zymbal glands	Carcinoma	1/120 (85) 0.6026	0/60 (40) 1.0000	1/60 (36) 0.5083	0/60 (37) 1.0000

Note: The p values are reported in the second row of each cell. The p value reported in the control column is for Trend test, and the other three p values are for pairwise comparison of each indicated dose group to the control group. If no tumor is found in a dose group, its pairwise comparison is not possible to conduct, and thus the p value is not obtainable. The numerator indicates the number of animals that had a tumor of interest, and the denominator the number of animals examined (and found useful). The number inside of ( ) indicates the weighted (mortality adjusted) total number of animals for the poly-k analysis.

Table 17: P-values for Poly-3 Trend Test and Pairwise Comparisons with Control [Reported Tumors] (Male Mice)

Organ	Tumor	Control (0 mg)	Low Dose (20 mg)	Med Dose (60 mg)	High Dose (160 mg)
		Observed Proportion			
		#Animals with Tumor/Total Number of Examined Animals			
		(Poly-3 Mortality Adjusted Total Number of Animals)			
		P value			
		Trend test	Pairwise Comparison with Control		
Adrenals	Cortical adenoma	1/128 (96) 1.0000	0/62 (46) 1.0000	0/64 (48) 1.0000	0/62 (46) 1.0000
	Hemangioma	1/128 (96) 1.0000	0/62 (46) 1.0000	0/64 (48) 1.0000	0/62 (46) 1.0000
	Pheochromocytoma	0/128 (96) 0.5932	1/62 (46) 0.3239	0/64 (48)	0/62 (46)
	Subcapsular cell adenoma	1/128 (96) 0.1955	2/62 (47) 0.2515	0/64 (48) 1.0000	2/62 (46) 0.2452
Cavity	Malignant mesothelioma	1/128 (96) 0.3580	0/63 (46) 1.0000	0/64 (48) 1.0000	1/63 (47) 0.5509
Colon	Adenocarcinoma	0/128 (96) 0.1983	0/62 (46)	0/64 (48)	1/63 (47) 0.3287
Epididymides	Malignant schwannoma	0/126 (94) 0.4017	0/62 (46)	1/64 (48) 0.3380	0/62 (46)
	Schwannoma	1/126 (95) 1.0000	0/62 (46) 1.0000	0/64 (48) 1.0000	0/62 (46) 1.0000
Gallbladder	Papillary adenoma	0/128 (96) 0.5862	1/60 (45) 0.3191	0/62 (46)	0/61 (45)
Harderian glands	Adenocarcinoma	2/128 (96) 0.5006	0/63 (46) 1.0000	0/64 (48) 1.0000	1/63 (48) 0.7068
	Adenoma	3/128 (97) 0.6172	0/63 (46) 1.0000	0/64 (48) 1.0000	1/63 (47) 0.7983
Hematopoietic and lymphatic organs	Histiocytic sarcoma	7/128 (99) 0.9751	0/63 (46) 1.0000	2/64 (48) 0.8554	0/63 (47) 1.0000
	Malignant lymphoma	8/128 (98) 0.5430	4/63 (48) 0.6002	2/64 (49) 0.9040	4/63 (49) 0.6138
Jejunum	Adenocarcinoma	0/128 (96) 0.4034	0/62 (46)	1/64 (49) 0.3379	0/63 (47)
Joint	Synovial sarcoma	1/128 (96) 1.0000	0/63 (46) 1.0000	0/64 (48) 1.0000	0/63 (47) 1.0000
Kidneys	Adenocarcinoma	1/128 (96) 1.0000	0/62 (46) 1.0000	0/64 (48) 1.0000	0/63 (47) 1.0000

	Adenoma	2/128 (96) 0.7040	0/62 (46) 1.0000	2/64 (48) 0.4074	0/63 (47) 1.0000
	Hemangiosarcoma	0/128 (96) 0.1966	1/62 (46) 0.3239	0/64 (48)	1/63 (47) 0.3287
Liver	Cholangioma	2/128 (96) 1.0000	0/62 (46) 1.0000	0/64 (48) 1.0000	0/63 (47) 1.0000
	Hemangioma	0/128 (96) 0.4773	1/62 (46) 0.3239	1/64 (48) 0.3333	0/63 (47)
	Hemangiosarcoma	5/128 (97) 0.5520	3/62 (46) 0.5052	6/64 (50) 0.1236	2/63 (48) 0.7389
	Hepatoblastoma	1/128 (96) 1.0000	0/62 (46) 1.0000	0/64 (48) 1.0000	0/63 (47) 1.0000
	Hepatocellular adenoma	7/128 (96) 0.6229	2/62 (46) 0.8519	0/64 (48) 1.0000	3/63 (49) 0.7201
	Hepatocellular carcinoma	3/128 (96) 0.9008	1/62 (47) 0.8011	1/64 (48) 0.8066	0/63 (47) 1.0000
Lung	Alveolar/bronchiolar adenoma	24/128 (99) 0.6681	4/62 (47) 0.9957	7/64 (49) 0.9501	9/63 (48) 0.8309
	Alveolar/bronchiolar carcinoma	23/128 (98) 0.6794	6/62 (47) 0.9619	9/64 (50) 0.8352	9/63 (49) 0.8202
Mesenteric lymph node	Hemangioma	1/123 (93) 0.3364	1/59 (44) 0.5408	1/61 (46) 0.5540	1/60 (45) 0.5474
Pancreas	Islet-cell adenoma	1/128 (96) 1.0000	0/62 (46) 1.0000	0/63 (47) 1.0000	0/63 (47) 1.0000
Parathyroids	Adenoma	1/121 (93) 0.6431	0/60 (44) 1.0000	1/61 (47) 0.5603	0/60 (45) 1.0000
Pituitary	Adenocarcinoma, pars distalis	4/122 (95) 0.9481	1/60 (45) 0.8610	1/62 (48) 0.8752	0/63 (47) 1.0000
	Adenoma, pars distalis	1/122 (93) 0.4046	1/60 (45) 0.5474	0/62 (47) 1.0000	1/63 (47) 0.5603
Seminal vesicles	Adenocarcinoma	0/126 (95) 0.4043	0/61 (45)	1/64 (48) 0.3357	0/63 (47)
Skeletal muscle	Rhabdomyosarcoma	0/128 (96) 0.4008	0/62 (46)	1/64 (48) 0.3333	0/63 (47)
Skin	Basal cell tumor	1/128 (96) 1.0000	0/62 (46) 1.0000	0/64 (48) 1.0000	0/63 (47) 1.0000
	Keratoacanthoma	0/128 (96) 0.1983	0/62 (46)	0/64 (48)	1/63 (47) 0.3287
	Liposarcoma	0/128 (96) 0.5949	1/62 (46) 0.3239	0/64 (48)	0/63 (47)

	Papilloma	1/128 (96) 1.0000	0/62 (46) 1.0000	0/64 (48) 1.0000	0/63 (47) 1.0000
	Squamous cell carcinoma	1/128 (96) 1.0000	0/62 (46) 1.0000	0/64 (48) 1.0000	0/63 (47) 1.0000
Spleen	Hemangioma	1/127 (96) 0.8369	1/62 (46) 0.5445	0/64 (48) 1.0000	0/63 (47) 1.0000
	Hemangiosarcoma	2/127 (96) 0.5568	2/62 (46) 0.3905	1/64 (48) 0.7068	1/63 (47) 0.7006
Stomach	Neuroendocrine cell tumor, malignant	0/128 (96) 0.1983	0/62 (46)	0/64 (48)	1/63 (47) 0.3287
	Squamous cell carcinoma, forestomach	1/128 (96) 0.8390	2/62 (47) 0.2515	0/64 (48) 1.0000	0/63 (47) 1.0000
	Squamous cell papilloma	1/128 (96) 0.3964	1/62 (46) 0.5445	0/64 (48) 1.0000	1/63 (47) 0.5509
Testes	Hemangioma	1/128 (96) 1.0000	0/63 (46) 1.0000	0/64 (48) 1.0000	0/63 (47) 1.0000
	Interstitial cell adenoma	5/128 (96) 0.9689	0/63 (46) 1.0000	1/64 (48) 0.9168	0/63 (47) 1.0000
Thyroids	Follicular cell adenoma	0/128 (96) 0.1949	0/62 (46)	0/64 (48)	1/62 (46) 0.3239

Note: The p values are reported in the second row of each cell. The p value reported in the control column is for Trend test, and the other three p values are for pairwise comparison of each indicated dose group to the control group. If no tumor is found in a dose group, its pairwise comparison is not possible to conduct, and thus the p value is not obtainable. The numerator indicates the number of animals that had a tumor of interest, and the denominator the number of animals examined (and found useful). The number inside of ( ) indicates the weighted (mortality adjusted) total number of animals for the poly-k analysis.

Table 18: P-values for Poly-3 Trend Test and Pairwise Comparisons with Control [Reported Tumors] (Female Mice)

Organ	Tumor	Control (0 mg)	Low Dose (20 mg)	Med Dose (60 mg)	High Dose (160 mg)
		Observed Proportion			
		#Animals with Tumor/Total Number of Examined Animals			
		(Poly-3 Mortality Adjusted Total Number of Animals)			
		P value			
		Trend test	Pairwise Comparison with Control		
Abdomen	Hemangioma	0/125 (82) 0.3951	0/63 (42)	1/63 (47) 0.3643	0/62 (34)
	Hemangiosarcoma	1/125 (83) 1.0000	0/63 (42) 1.0000	0/63 (47) 1.0000	0/62 (34) 1.0000
	Malignant schwannoma	0/125 (82) 0.3951	0/63 (42)	1/63 (47) 0.3643	0/62 (34)
	Osteosarcoma	1/125 (83) 1.0000	0/63 (42) 1.0000	0/63 (47) 1.0000	0/62 (34) 1.0000
Adrenals	Cortical adenoma	0/124 (82) 0.3502	0/63 (42)	2/63 (47) 0.1309	0/61 (33)
	Subcapsular cell adenoma	2/124 (82) 0.7695	3/63 (42) 0.2139	3/63 (47) 0.2544	0/61 (33) 1.0000
	Subcapsular cell carcinoma	2/124 (82) 1.0000	0/63 (42) 1.0000	0/63 (47) 1.0000	0/61 (33) 1.0000
Cavity	Malignant mesothelioma	0/125 (82) 0.3951	0/63 (42)	1/63 (47) 0.3643	0/62 (34)
Cecum	Leiomyoma	0/125 (82) 0.6019	1/62 (43) 0.3440	0/63 (47)	0/62 (34)
Harderian glands	Adenocarcinoma	0/125 (82) 0.3951	0/63 (42)	1/63 (47) 0.3643	0/62 (34)
	Adenoma	0/125 (82) 0.6000	1/63 (42) 0.3387	0/63 (47)	0/62 (34)
Heart	Schwannoma	0/125 (82) 0.3951	0/63 (42)	1/63 (47) 0.3643	0/62 (34)
Hematopoietic and lymphatic organs	Histiocytic sarcoma	7/125 (85) 0.4751	4/63 (43) 0.5391	4/63 (47) 0.5973	3/62 (34) 0.5853
	Malignant lymphoma	25/125 (91) 0.4878	17/63 (46) 0.1732	12/63 (49) 0.7176	12/62 (39) 0.4280
	Malignant mast cell tumor	1/125 (83) 1.0000	0/63 (42) 1.0000	0/63 (47) 1.0000	0/62 (34) 1.0000

Kidneys	Adenoma	0/125 (82) 0.1659	0/63 (42)	0/63 (47)	1/62 (34) 0.2931
Liver	Hemangioma	1/125 (82) 0.5275	0/63 (42) 1.0000	2/63 (47) 0.3000	0/62 (34) 1.0000
	Hemangiosarcoma	3/125 (83) 0.8816	0/63 (42) 1.0000	1/63 (47) 0.8382	0/62 (34) 1.0000
	Hepatocellular adenoma	0/125 (82) 0.1659	0/63 (42)	0/63 (47)	1/62 (34) 0.2931
Lung	Alveolar/bronchiolar adenoma	3/125 (83) 0.1044	2/63 (42) 0.5471	9/63 (47) 0.0050	3/62 (35) 0.2452
	Alveolar/bronchiolar carcinoma	10/125 (85) 0.9597	2/63 (43) 0.9558	2/63 (47) 0.9675	1/62 (34) 0.9798
Mammary gland	Adenocarcinoma	0/119 (79) 0.6676	3/57 (40) 0.0361	1/60 (45) 0.3629	0/58 (32)
	Adenoma	0/119 (79) 0.1641	0/57 (39)	0/60 (45)	1/58 (32) 0.2883
Mesenteric lymph node	Hemangioma	1/123 (81) 0.3012	1/62 (43) 0.5751	1/63 (47) 0.6014	1/60 (34) 0.5057
Ovaries	Cystadenocarcinoma	1/124 (82) 1.0000	0/63 (42) 1.0000	0/63 (47) 1.0000	0/62 (34) 1.0000
	Cystadenoma	4/124 (83) 0.1591	1/63 (42) 0.8762	3/63 (47) 0.4957	3/62 (34) 0.3291
	Hemangioma	1/124 (81) 0.8435	1/63 (42) 0.5682	0/63 (47) 1.0000	0/62 (34) 1.0000
	Leiomyosarcoma	0/124 (81) 0.3971	0/63 (42)	1/63 (47) 0.3672	0/62 (34)
Pancreas	Islet-cell adenoma	2/125 (83) 1.0000	0/62 (42) 1.0000	0/63 (47) 1.0000	0/62 (34) 1.0000
	Squamous cell carcinoma	1/125 (83) 1.0000	0/62 (42) 1.0000	0/63 (47) 1.0000	0/62 (34) 1.0000
Pituitary	Adenocarcinoma, pars distalis	0/116 (79) 0.0419	1/60 (40) 0.3361	0/62 (46)	2/60 (34) 0.0887
	Adenoma, pars distalis	4/116 (79) 0.5992	1/60 (39) 0.8712	3/62 (46) 0.5108	1/60 (33) 0.8320
	Adenoma, pars intermedia	1/116 (79) 1.0000	0/60 (39) 1.0000	0/62 (46) 1.0000	0/60 (33) 1.0000
Skin	Hemangioma	1/125 (83) 1.0000	0/63 (42) 1.0000	0/63 (47) 1.0000	0/62 (34) 1.0000

	Liposarcoma	0/125 (82) 0.1659	0/63 (42)	0/63 (47)	1/62 (34) 0.2931
	Papilloma	1/125 (83) 1.0000	0/63 (42) 1.0000	0/63 (47) 1.0000	0/62 (34) 1.0000
Spleen	Hemangioma	2/125 (83) 0.7835	0/63 (42) 1.0000	1/62 (46) 0.7371	0/62 (34) 1.0000
	Hemangiosarcoma	2/125 (82) 0.9365	1/63 (42) 0.7144	0/62 (46) 1.0000	0/62 (34) 1.0000
Stomach	Neuroendocrine cell tumor, malignant	0/125 (82) 0.3951	0/62 (42)	1/63 (47) 0.3643	0/62 (34)
	Squamous cell carcinoma, forestomach	0/125 (82) 0.6000	1/62 (42) 0.3387	0/63 (47)	0/62 (34)
	Squamous cell papilloma	3/125 (82) 0.5146	0/62 (42) 1.0000	1/63 (47) 0.8411	1/62 (34) 0.7557
Thymus	Hemangioma	0/105 (70) 0.3989	0/53 (37)	1/57 (45) 0.3913	0/44 (26)
	Hemangiosarcoma	1/105 (70) 1.0000	0/53 (37) 1.0000	0/57 (45) 1.0000	0/44 (26) 1.0000
	Thymoma	0/105 (70) 0.6067	1/53 (37) 0.3458	0/57 (45)	0/44 (26)
Thyroids	Follicular cell adenoma	0/123 (82) 0.2587	2/62 (42) 0.1129	0/63 (47)	1/61 (34) 0.2931
Uterus	Endometrial adenocarcinoma	0/123 (82) 0.5546	2/63 (43) 0.1165	1/63 (47) 0.3643	0/62 (34)
	Endometrial stromal polyp	10/123 (84) 0.9448	7/63 (44) 0.3530	6/63 (47) 0.5450	1/62 (34) 0.9806
	Endometrial stromal sarcoma	2/123 (82) 0.7889	0/63 (42) 1.0000	1/63 (47) 0.7466	0/62 (34) 1.0000
	Fibroma	1/123 (82) 1.0000	0/63 (42) 1.0000	0/63 (47) 1.0000	0/62 (34) 1.0000
	Granular cell tumor	0/123 (82) 0.1659	0/63 (42)	0/63 (47)	1/62 (34) 0.2931
	Leiomyoma	0/123 (82) 0.1107	0/63 (42)	3/63 (47) 0.0464	1/62 (34) 0.2931
	Leiomyosarcoma	1/123 (82) 0.6353	0/63 (42) 1.0000	1/63 (47) 0.5977	0/62 (34) 1.0000
	Yolk sac tumor	0/123 (82) 0.3951	0/63 (42)	1/63 (47) 0.3643	0/62 (34)

Vagina	Squamous cell carcinoma	0/123 (82) 0.3971	0/62 (41)	1/63 (47) 0.3643	0/62 (34)

Note: The p values are reported in the second row of each cell. The p value reported in the control column is for Trend test, and the other three p values are for pairwise comparison of each indicated dose group to the control group. If no tumor is found in a dose group, its pairwise comparison is not possible to conduct, and thus the p value is not obtainable. The numerator indicates the number of animals that had a tumor of interest, and the denominator the number of animals examined (and found useful). The number inside of ( ) indicates the weighted (mortality adjusted) total number of animals for the poly-k analysis.

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5.3 Poly-3 Analysis Review Results for Merged/Combined Tumor Findings by Dose Group

The following tables provide Poly-3 analyses (Trend and Pairwise Tests) for *neoplastic events for review, which are merged and/or combined by the reviewer*. The analysis was not performed either for an organ in which no tumor was found or for an organ for which at least one of the dose groups had no examined animals.

Table 19: P-values for Poly-3 Trend Test and Pairwise Comparisons with Control [Merged/Combined Tumor Records] (Male Rats)

Organ	Tumor	Control (0 mg)	Low Dose (20 mg)	Med Dose (50 mg)	High Dose (160 mg)
		Observed Proportion			
		#Animals with Tumor/Total Number of Examined Animals			
		(Poly-3 Mortality Adjusted Total Number of Animals)			
		P value			
		Trend test	Pairwise Comparison with Control		
All sites	#Hemangioma/Hemangiosarcoma	0/120 (82) 0.1137	0/60 (47)	1/60 (42) 0.3387	1/60 (41) 0.3333
	#Lipomas/Liposarcomas	4/120 (82) 0.9808	3/60 (47) 0.5022	0/60 (41) 1.0000	0/60 (41) 1.0000
Liver	#Hemangioma/Hemangiosarcoma	2/120 (82) 0.3331	3/60 (48) 0.2624	1/60 (41) 0.7074	2/60 (41) 0.4074
Lung	#Adenoma/Carcinoma, bronchiolo-alveolar	1/120 (82) 0.6274	0/60 (47) 1.0000	1/60 (41) 0.5574	0/60 (41) 1.0000
Mammary gland	#Adenoma/Adenocarcinoma	2/120 (82) 0.6926	0/60 (47) 1.0000	2/60 (41) 0.4074	0/60 (41) 1.0000
Pancreas	#Adenoma	12/120 (83) 0.6291	6/60 (47) 0.6977	6/60 (41) 0.5881	5/60 (42) 0.7437
Skin	#Adenoma/Carcinoma, Basal cell	0/120 (82) 0.6761	2/60 (47) 0.1309	0/60 (41)	0/60 (41)
	#Papilomas/Carcinomas/Keratoacanthomas, Squamous cell	9/120 (83) 0.4479	6/60 (48) 0.4911	5/60 (42) 0.5381	5/60 (42) 0.5381
Stomach	#Neuroendocrine cell tumor, benign/malignant	0/120 (82) 0.0370	0/60 (47)	0/60 (41)	2/60 (41) 0.1093
Thyroids	#Adenoma/Carcinoma, C-cell	13/120 (83) 0.7823	5/60 (48) 0.8661	5/60 (42) 0.7958	4/60 (41) 0.8827
	#Adenoma/Carcinoma, Follicular-cell	2/120 (82) 0.2520	5/60 (48) 0.0641	2/60 (41) 0.4074	3/60 (42) 0.2139

Note: The p values are reported in the second row of each cell. The p value reported in the control column is for Trend test, and the other three p values are for pairwise comparison of each indicated dose group to the control group. If no tumor is found in a dose group, its pairwise comparison is not possible to conduct, and thus the p value is not obtainable. The numerator indicates the number of animals that had a tumor of interest, and the denominator the number of animals examined (and found useful). The number inside of ( ) indicates the weighted (mortality adjusted) total number of animals for the poly-k analysis.

Table 20: P-values for Poly-3 Trend Test and Pairwise Comparisons with Control [Merged/Combined Tumor Records] (Female Rats)

Organ	Tumor	Control (0 mg)	Low Dose (20 mg)	Med Dose (50 mg)	High Dose (160 mg)
		Observed Proportion			
		#Animals with Tumor/Total Number of Examined Animals			
		(Poly-3 Mortality Adjusted Total Number of Animals)			
		P value			
		Trend test	Pairwise Comparison with Control		
All sites	#Lipomas/Liposarcomas	2/120 (85)	1/60 (40)	1/60 (36)	1/60 (37)
		0.4469	0.6892	0.6570	0.6240
Stomach	#Neuroendocrine cell tumor, benign/malignant	0/120 (85)	0/60 (40)	0/60 (36)	4/60 (38)
		0.0012			0.0056
Thyroids	#Adenoma/Carcinoma, C-cell	6/120 (86)	3/60 (40)	2/60 (36)	2/60 (37)
		0.6366	0.5887	0.7440	0.6978
Uterus	#Endometrial Adenoma/Adenocarcinoma	0/120 (85)	1/60 (40)	0/60 (36)	1/60 (37)
		0.1783	0.3200		0.2761
	#Endometrial Stromal Polyp/Sarcoma	8/120 (85)	6/60 (41)	1/60 (37)	3/60 (39)
		0.7197	0.2781	0.9662	0.6613

Note: The p values are reported in the second row of each cell. The p value reported in the control column is for Trend test, and the other three p values are for pairwise comparison of each indicated dose group to the control group. If no tumor is found in a dose group, its pairwise comparison is not possible to conduct, and thus the p value is not obtainable. The numerator indicates the number of animals that had a tumor of interest, and the denominator the number of animals examined (and found useful). The number inside of ( ) indicates the weighted (mortality adjusted) total number of animals for the poly-k analysis.

Table 21: P-values for Poly-3 Trend Test and Pairwise Comparisons with Control [Merged/Combined Tumor Records] (Male Mice)

Organ	Tumor	Control (0 mg)	Low Dose (20 mg)	Med Dose (60 mg)	High Dose (160 mg)
		Observed Proportion			
		#Animals with Tumor/Total Number of Examined Animals			
		(Poly-3 Mortality Adjusted Total Number of Animals)			
		P value			
		Trend test	Pairwise Comparison with Control		
All sites	#Hemangioma/Hemangiosarcoma	10/128 (98)	9/63 (48)	9/64 (51)	4/63 (48)
		0.7066	0.1202	0.1508	0.7391
Harderian glands	#Adenoma/Adenocarcinoma	5/128 (97)	0/63 (46)	0/64 (48)	2/63 (48)
		0.5340	1.0000	1.0000	0.7389
Liver	#Hepatocellular Adenoma/Carcinoma	9/128 (97)	3/63 (47)	1/64 (48)	3/63 (49)
		0.7765	0.8168	0.9847	0.8344

Organ	Tumor	Control (0 mg)	Low Dose (20 mg)	Med Dose (60 mg)	High Dose (160 mg)
		Observed Proportion			
		#Animals with Tumor/Total Number of Examined Animals			
		(Poly-3 Mortality Adjusted Total Number of Animals)			
		P value			
		Trend test	Pairwise Comparison with Control		
Lung	#Alveolar-bronchiolar Adenoma/Carcinoma	45/128 (102)	10/63 (48)	16/64 (51)	18/63 (50)
		0.6921	0.9987	0.9558	0.8710
Skin	#Squamous cell Carcinoma/Keratoacanthoma/Papilloma	2/128 (97)	0/63 (46)	0/64 (48)	1/63 (47)
		0.4926	1.0000	1.0000	0.6975
Stomach	#Neuroendocrine cell tumor, benign/malignant	0/128 (96)	0/63 (46)	0/64 (48)	1/63 (47)
		0.1983			0.3287

Note: The p values are reported in the second row of each cell. The p value reported in the control column is for Trend test, and the other three p values are for pairwise comparison of each indicated dose group to the control group. If no tumor is found in a dose group, its pairwise comparison is not possible to conduct, and thus the p value is not obtainable. The numerator indicates the number of animals that had a tumor of interest, and the denominator the number of animals examined (and found useful). The number inside of ( ) indicates the weighted (mortality adjusted) total number of animals for the poly-k analysis.

Table 22: P-values for Poly-3 Trend Test and Pairwise Comparisons with Control [Merged/Combined Tumor Records] (Female Mice)

Organ	Tumor	Control (0 mg)	Low Dose (20 mg)	Med Dose (60 mg)	High Dose (160 mg)
		Observed Proportion			
		#Animals with Tumor/Total Number of Examined Animals			
		(Poly-3 Mortality Adjusted Total Number of Animals)			
		P value			
		Trend test	Pairwise Comparison with Control		
All sites	#Hemangioma/Hemangiosarcoma	12/125 (84)	3/63 (43)	6/63 (48)	1/62 (34)
		0.9510	0.9386	0.7043	0.9910
Uterus	#Endometrial stromal Polyp/Sarcoma	12/125 (84)	7/63 (44)	7/63 (47)	1/62 (34)
		0.9643	0.4986	0.5580	0.9910
	#Leiomyoma/Leiomyosarcoma	1/125 (82)	0/63 (42)	4/63 (47)	1/62 (34)
		0.1899	1.0000	0.0587	0.5021

Note: The p values are reported in the second row of each cell. The p value reported in the control column is for Trend test, and the other three p values are for pairwise comparison of each indicated dose group to the control group. If no tumor is found in a dose group, its pairwise comparison is not possible to conduct, and thus the p value is not obtainable. The numerator indicates the number of animals that had a tumor of interest, and the denominator the number of animals examined (and found useful). The number inside of ( ) indicates the weighted (mortality adjusted) total number of animals for the poly-k analysis.

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/s/

EIJI ISHIDA
03/01/2018

KARL K LIN
03/01/2018
Concur with review

Executive Carcinogenicity Assessment Committee Cover Sheet for Final Carcinogenicity Study Reports

P/T Reviewer(s): Brenda J Gehrke, PhD
Supervisor/TL: Christopher M Sheth, PhD
Division(s): Division of Hematology Oncology Toxicology for Division of Hematology Products

IND/NDA: IND (b) (4), IND (b) (4), IND 76680, NDA 210238
Sponsor/Applicant: Eisai Inc./Dova Pharmaceuticals Inc.
Drug Name(s): Avatrombopag (Doptelet)
Drug Code#: E5501, AKR-501, YM477, YM-301477
CAS#: 677007-74-8

Indication(s): Thrombocytopenia in patients with chronic liver disease undergoing an (b) (4) procedure, (b) (4)

Pharmacological/Chemical Classification: Thrombopoietin receptor agonist
Mutagenic/Genotoxic (y/n/equivocal/na; assay): No; in vitro bacterial reverse mutation (Ames) assay, in vitro chromosomal aberration assay in human lymphocytes, and in vivo micronucleus test in rats conducted

Rat Carcinogenicity Study

Study Duration (weeks): Scheduled for 104 weeks; animals were terminated early with males euthanized during Week 99 and females euthanized during Weeks 91 (high dose) and 103
Study site: (b) (4)
Carcinogenicity Study Report Date: November 2, 2012
Date of first dose: April 30, 2008
Rat Strain: Sprague-Dawley (Crl:CD(SD)IGS BR)
Route: Oral gavage
Vehicle: 0.5% methylcellulose in water
Dosing Comments: Dosing was discontinued early with a dosing period of 82 weeks in females at 160 mg/kg/day, 96 weeks in females at 50 mg/kg/day, and 98 or 99 weeks in the other groups.

Doses and numbers of animals:

Dose (mg/kg/day)	Male	Female
Control (vehicle)	60	60
Control (vehicle)	60	60
Low: 20 mg/kg/day	60	60
Mid: 50 mg/kg/day	60	60
High: 160 mg/kg/day	60	60

Basis for Doses Selected: Based on the MTD of 160 mg/kg/day in 13-week repeat-dose study in rats

Prior FDA execCAC Dose Concurrence?: DARRTS says No Agreement for SPA; IND (b) (4); Applicant/Sponsor followed the dose recommendations of execCAC

Rat Carcinogenicity Conclusion: Negative in males; Positive in females

Rat Tumor Findings (details):

Findings from tumor data analysis for female rats

Organ	Tumor	Control 0 mg/kg/day	20 mg/kg/day	50 mg/kg/day	160 mg/kg/day
		# Animals with tumor/total # of examined animals (Poly-3 mortality adjusted total # of animals)			
		P value			
		Trend test	Pairwise Comparison with Control		
Stomach	Neuroendocrine cell tumor, benign	0/120 (85) 0.0065	0/60 (40)	0/60 (36)	3/60 (38) 0.0210
	Neuroendocrine cell tumor, benign and malignant combined	0/120 (85) 0.0012	0/60 (40)	0/60 (36)	4/60 (38) 0.0056

Rat Study Comments:

- Survival was significantly decreased in females treated with 160 mg/kg/day avatrombopag compared to controls. The decrease in survival was attributed to increases in the incidence and severity of chronic nephropathy.
- Body weights were lower in females treated with 160 mg/kg/day compared to the control groups with mean weights 15% lower than control group 1 at Week 91.
- Non-neoplastic findings included changes in the stomach (degeneration of glandular epithelium, atrophy of glandular mucosa, regenerative hyperplasia, intraluminal deposits, and neuroendocrine cell hyperplasia) at 50 and 160 mg/kg/day and increased incidences and severity of chronic nephropathy in the kidneys at 160 mg/kg/day in males and at 50 and 160 mg/kg/day in females.

Mouse Carcinogenicity Study:

Study Duration (weeks): Scheduled for 104 weeks; females were terminated early with euthanization during Weeks 101-103
Study site: (b) (4)
Carcinogenicity Study Report Date: December 5, 2012
Date of first dose: May 28, 2008 for main study and hematology males and all toxicokinetics animals and May 29, 2008 for main study and hematology females
Mouse Strain: CD-1
Route: Oral gavage
Vehicle: 0.5% methylcellulose in water
Dosing Comments: Dosing was discontinued early in females with a dosing period of 101-102 weeks

Doses and numbers of animals:

Dose (mg/kg/day)	Male	Female
Control (vehicle)	64	62
Control (vehicle)	64	63
Low: 20 mg/kg/day	63	63
Mid: 60 mg/kg/day	64	63
High: 160 mg/kg/day	63	62

Basis for Doses Selected: Based on the MTD of 160 mg/kg/day in 13-week repeat-dose study in mice

Prior FDA execCAC Dose Concurrence?: DARRTS says Agreement for SPA; IND (b) (4); Applicant/Sponsor followed the dose recommendations of execCAC

Mouse Carcinogenicity Conclusion: Negative in males and females

Mouse Tumor Findings (details): Malignant neuroendocrine cell tumors in stomach observed in one male at 160 mg/kg/day and one female at 60 mg/kg/day; not statistically significant.

Mouse Study Comments:

- Survival was significantly decreased in females treated with 160 mg/kg/day avatrombopag compared to controls. The decrease in survival was attributed to increases in the incidence and severity of chronic nephropathy.
- Non-neoplastic findings included hyperplasia of the mucosa in the stomach and increased incidences and severity of chronic nephropathy in the kidneys in males at 160 mg/kg/day and females at 60 and 160 mg/kg/day.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	210238
Supporting document/s:	1
Applicant's letter date:	September 21, 2017
CDER stamp date:	September 21, 2017
Product:	Avatrombopag (Doptelet)
Indication:	Treatment of thrombocytopenia (b) (4) in adult patients with chronic liver disease who are scheduled to undergo a procedure
Applicant:	Eisai Inc./Dova Pharmaceuticals Inc.
Review Division:	Division of Hematology Oncology Toxicology (for Division of Hematology Products)
Reviewer:	Brenda J Gehrke, PhD
Supervisor/Team Leader:	Christopher M Sheth, PhD
Division Director:	John Leighton, PhD Ann Farrell, MD (DHP)
Project Manager:	Wan Lee, PharmD

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA number 210238 are owned by Eisai Inc./Dova Pharmaceuticals Inc. or are data for which Eisai Inc./Dova Pharmaceuticals Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 210238 that Eisai Inc./Dova Pharmaceuticals Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 210238.

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1 Executive Summary

1.1 Introduction

Avatrombopag is an orally administered thrombopoietin (TPO) receptor agonist that does not compete with TPO for binding to the TPO receptor that stimulates proliferation and differentiation of megakaryocytes from bone marrow progenitor cells, resulting in an increased production of platelets. (b) (4) (b) (4) NDA 210238 has been submitted for the indication of treatment of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a procedure. Two-year carcinogenicity studies with avatrombopag have been conducted in mice and rats, and are reviewed in detail in this review. The comprehensive nonclinical review for avatrombopag with the review of the pharmacology, pharmacokinetics, and toxicology studies has been added to the Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for additional details.

1.2 Brief Discussion of Nonclinical Findings

In the 2-year (104-Week) carcinogenicity studies conducted in mice and rats, avatrombopag was administered by oral gavage once daily at a dose volume of 10 mL/kg. CD-1 mice were administered doses of 0, 20, 60, or 160 mg/kg/day and Sprague-Dawley rats were administered doses of 0, 20, 50, or 160 mg/kg/day. Discontinuation of dosing and early termination of animals occurred in both studies. In the mouse study, females were dosed for 101-102 weeks and were necropsied during Weeks 101-103, but males were dosed for the entire study (104-105 weeks). In the rat study, the dosing period was 82 weeks in females at 160 mg/kg/day, 96 weeks in females at 50 mg/kg/day, and 98 or 99 weeks in the other groups. All rats were also terminated early with surviving males necropsied during Week 99 and surviving females necropsied during Weeks 91 (160 mg/kg/day) and 103 (all other female groups). Survival was significantly decreased in females treated with 160 mg/kg/day avatrombopag compared to controls in both species and the decreases in survival were attributed to increases in the incidence and severity of chronic nephropathy in the kidneys. Body weights were lower in female rats treated with 160 mg/kg/day compared to the control groups with mean weights 15% lower than the first control group at necropsy on Week 91. The toxicokinetics of avatrombopag were evaluated in both species and exposures to avatrombopag (C_{max} and AUC_{0-24}) increased with an increase in dose. Exposures were greater in males than females in mice and greater in females than males in rats. Avatrombopag-related non-neoplastic microscopic findings included changes in the stomach and increased incidences and severity of chronic nephropathy in the kidneys in both species. Findings in the stomach included hyperplasia of the mucosa in mice and degeneration of glandular epithelium, atrophy of glandular mucosa, regenerative hyperplasia, intraluminal deposits, and neuroendocrine cell hyperplasia in rats.

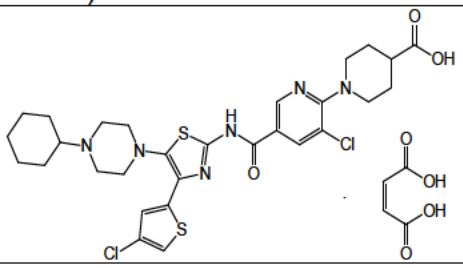
Avatrombopag induced malignant neuroendocrine tumors in the stomach in one male at 160 mg/kg/day and 1 female at 60 mg/kg/day in mice and induced benign and

malignant neuroendocrine tumors in the stomach at 160 mg/kg/day in rats. Benign and malignant neuroendocrine cell tumors in the stomach were not observed in the concurrent controls (<1%); therefore, they are considered rare tumors. Based on the FDA criteria for a positive carcinogenicity response, the single incidences of malignant neuroendocrine cell tumors observed in mice and the incidences of benign and malignant neuroendocrine cell tumors observed in male rats at 160 mg/kg/day were not statistically significant. In female rats, the incidences of benign neuroendocrine cell tumors and benign and malignant neuroendocrine cell tumors combined in the stomach were statistically significant for both the trend test and the pairwise comparison to controls.

The Executive Carcinogenicity Assessment Committee reviewed and discussed the findings for both the 2-year mouse and rat carcinogenicity studies. The Committee concurred that there were no drug-related neoplasms in the 2-year mouse carcinogenicity study in either males or females. For the rat study, the Committee concluded that the combined incidence of benign and malignant neuroendocrine cell tumors in the stomach was increased in rats at the 160 mg/kg/day dose in females, and was drug related.

2 Drug Information

2.1 Drug

CAS Registry Number	677007-74-8
Generic Name	Avatrombopag maleate
Code Names	E5501, AKR-501, ER-875039-12, YM477, YM-301477
Chemical Name	4-piperidinecarboxylic acid, 1-[3-chloro-5-[[[4-(4-chloro-2-thienyl)-5-(4-cyclohexyl-1-piperazinyl)-2-thiazolyl]amino]carbonyl]-2-pyridinyl]-,(2Z)-2-butenedioate (1:1)
Molecular Formula/ Molecular Weight	$C_{29}H_{34}Cl_2N_6O_3S_2 \cdot C_4H_4O_4$ / 765.73 g/mol (649.65 g/mol free base)
Structure or Biochemical Description	
Pharmacologic Class	Thrombopoietin receptor agonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND [redacted] (b) (4)
IND [redacted] (b) (4)

IND 76680 (Thrombocytopenia in patients with chronic liver disease undergoing an (b) (4) procedure (b) (4))

2.3 Drug Formulation

Avatrombopag is provided as an immediate-release 20 mg oral tablet. Each tablet contains 20 mg avatrombopag (equivalent to 23.6 mg of avatrombopag maleate) and the following inactive ingredients: lactose monohydrate, colloidal silicon dioxide, crospovidone, magnesium stearate, and microcrystalline cellulose. The coating film contains polyvinyl alcohol, talc, polyethylene glycol, titanium dioxide, and ferric oxide yellow.

2.6 Proposed Clinical Population and Dosing Regimen

The proposed indication of avatrombopag is for the treatment of thrombocytopenia (b) (4) in adult patients with chronic liver disease who are scheduled to undergo a procedure. Avatrombopag will be administered as a tablet with food once daily for 5 consecutive days with treatment beginning 10 to 13 days prior to a scheduled procedure. The recommended dose is 60 mg for patients with a platelet count <40 x 10^9/L and 40 mg for patients with a platelet count of ≥40 x 10^9/L to <50 x 10^9/L.

8 Carcinogenicity

Study title: A 104-Week Oral (Gavage) Carcinogenicity Study of AKR-501 (E5501) in Mice

Study no.:	(b) (4) 152-09
Study report location:	eCTD Module 4.2.3.4.1.
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 7, 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Avatrombopag (E5501), lot # K4770302, Purity: 98-99%
CAC concurrence:	Agreement; IND (b) (4)

Key Study Findings

- Survival was significantly decreased in females treated with 160 mg/kg/day avatrombopag compared to controls. The decrease in survival was attributed to increases in the incidence and severity of chronic nephropathy.
- Avatrombopag induced malignant neuroendocrine tumors in the stomach in one male at 160 mg/kg/day and 1 female at 60 mg/kg/day.
- Non-neoplastic findings included hyperplasia of the mucosa in the stomach and increased incidences and severity of chronic nephropathy in the kidneys in males at 160 mg/kg/day and females at 60 and 160 mg/kg/day.

Adequacy of Carcinogenicity Study

- DARRTS indicates that there was agreement for the Special Protocol Assessment for the 2-year carcinogenicity study in mice and the Applicant/Sponsor appears to have followed the recommendations of the Executive CAC committee including testing doses of 20, 60, and 160 mg/kg/day and following the guidance regarding when to conduct histological examination in all groups.
- According to the study report, dosing was discontinued early in females with a dosing period of 101-102 weeks and females were necropsied during Weeks 101-103 when the 160 mg/kg/day group was reduced to 15 animals. The Applicant/Sponsor contacted the FDA for guidance and appears to have followed the recommendations of the Executive CAC committee.

Appropriateness of Test Models

- The study evaluated three doses of avatrombopag and had two control groups treated with the vehicle. The highest dose chosen was the MTD in the 13-week repeat-dose study in mice.
- Histopathology was evaluated for all animals in all main study groups. The study report provided sufficient histopathology data from the designated organs and tissues to evaluate both the non-neoplastic and neoplastic effects. Additionally, data on survival, clinical signs, body weights, food consumption, and hematology were provided.
- The toxicokinetics of avatrombopag were evaluated in satellite animals during Weeks 13 and 26 of dosing. Exposures to avatrombopag (C_{max} and AUC_{0-24}) increased with an increase in dose.
- Based on pharmacology data, the mouse is not a relevant species; there are no available relevant species for toxicology studies. Hematology data indicate that the expected pharmacological effect of an increase in platelets was not observed in mice in this study.

Evaluation of Tumor Findings

A statistical review of the neoplastic results of the 2-year (104-week) mouse carcinogenicity study for avatrombopag was conducted by Eiji Ishida of the Division of Biometrics 6 in the Office of Biostatistics.

Based on the lack of the neoplasm in the concurrent controls (<1%), malignant neuroendocrine cell tumor in the stomach is considered a rare tumor; however, the single incidences of malignant neuroendocrine cell tumors observed in a male at 160 mg/kg/day and a female at 60 mg/kg/day were not statistically significant.

Methods

Doses:	0, 20, 60, or 160 mg/kg/day
Frequency of dosing:	Once daily for 101-105 weeks[a]
Dose volume:	10 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% methylcellulose in water

Basis of dose selection:	Executive CAC recommended the doses based on the results of 13-week repeat-dose study in mice; mortality observed at 320 mg/kg/day and 160 mg/kg/day considered maximum tolerated dose
Species/Strain:	Mouse/CD-1
Number/Sex/Group:	62-64[b]/sex/group
Age:	8 weeks at initiation of dosing
Animal housing:	Individually housed
Paradigm for dietary restriction:	Food and water available *ad libitum*
Dual control employed:	Yes; 2 control groups dosed with vehicle
Interim sacrifice:	No
Satellite groups:	Toxicokinetics: 38-40[b]/sex/group; 20, 60, and 160 mg/kg/day Hematology: 30-33[b]/sex/group Pre-dose health screen: 10/sex for control group 1 only; hematology and gross pathology conducted

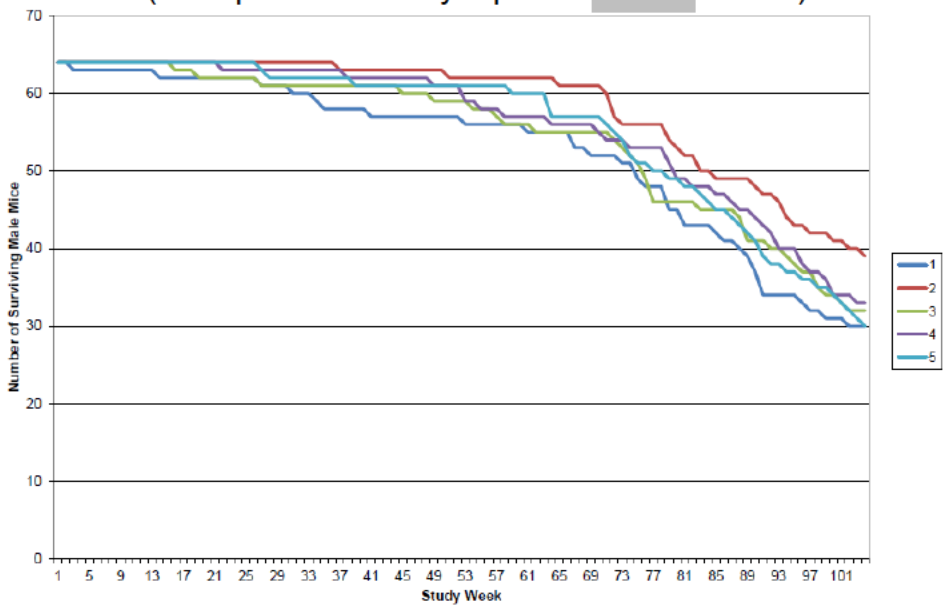
[a] Females dosed for 101-102 weeks. Dosing of females was discontinued when the 160 mg/kg/day group was reduced to 20 animals, and females were necropsied during Weeks 101-103 when the 160 mg/kg/day group was reduced to 15 animals. Males were dosed for 104-105 weeks.

[b]Due to early deaths, the 5/sex/group satellite animals that were originally intended to be culled following Week 4 were reassigned to the main study, hematology, or toxicokinetic groups.

Observations and Results

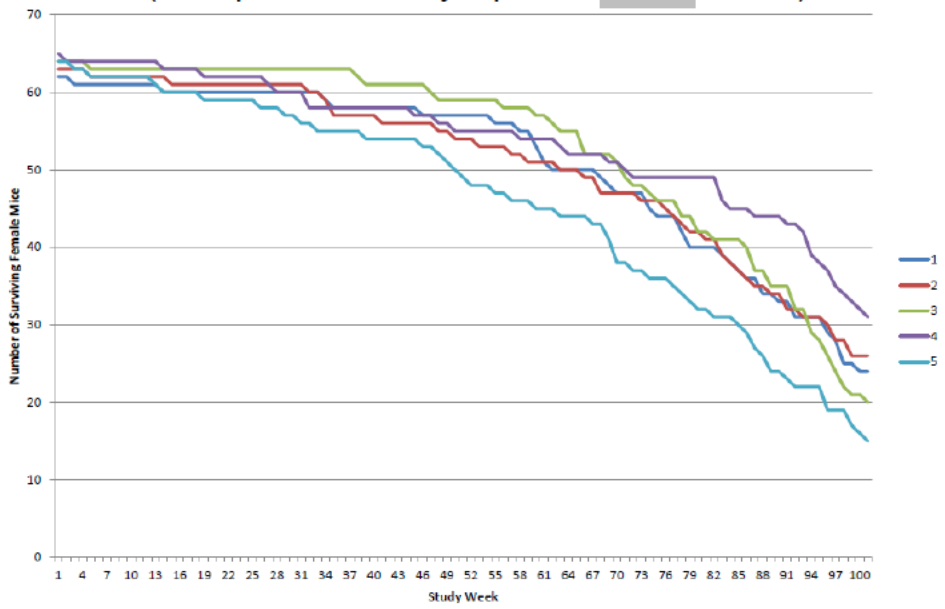
Mortality

Figure 1: Survival in male mice through Week 104
(excerpted from study report for (b) (4) 152-09)



Groups: 1 and 2= 0 mg/kg/day 3= 20 mg/kg/day 4= 60 mg/kg/day 5=160 mg/kg/day

Figure 2: Survival in female mice through Week 101
(excerpted from study report for (b) (4) 152-09)



Groups: 1 and 2= 0 mg/kg/day 3= 20 mg/kg/day 4= 60 mg/kg/day 5=160 mg/kg/day

Table 1: Survival rate in carcinogenicity study in mice

Dose (mg/kg/day)	Males					Females				
	0 Control	0 Control	20	60	160	0 Control	0 Control	20	60	160
Animals initially in study	64	64	63	64	63	62	63	63	63	62
No. of animals at scheduled necropsy for group[a]	29	37	32	33	28	23	26	20	29	15*
Survival rate (%)	45	58	51	52	44	37	41	32	46	24

*p<0.05, significantly different from control groups 1 and 2
[a] Number of males alive at Week 104 (Day 727), number of females alive at Week 101 (Day 705)

Table 2: Cause of death/moribundity in carcinogenicity study in mice

Dose (mg/kg/day)	Males					Females				
	0 Control	0 Control	20	60	160	0 Control	0 Control	20	60	160
Animals initially in study	64	64	63	64	63	62	63	63	63	62
No. of death/moribundity	35	27	31	31	35	39	37	43	34	47
Hematopoietic tumor	7	5	2	2	3	9	12	16	9	9
Other neoplastic lesion	9	12	9	13	7	6	6	6	7	4
Chronic nephropathy	2	1	1	0	5	8	2	4	5	13
Other non-neoplastic lesion	10	7	16	9	15	11	10	17	10	13
Accidental/gavage error	1	1	2	2	1	2	1	0	1	5
Undetermined	6	1	1	5	4	3	6	0	2	3

Clinical Signs

Unremarkable

Body Weights

Unremarkable

Food Consumption

Unremarkable

Hematology

Blood samples for hematology assessment were collected from hematology satellite animals during Weeks 26 and 52 and prior to the scheduled necropsy (Week 102 in females; Week 105 in males) and from main study animals prior to the scheduled necropsy (Week 102 in females; Week 105 in males).

Unremarkable

Gross Pathology

Table 3: Macroscopic findings for scheduled necropsies in carcinogenicity study in mice

Macroscopic findings		No. of animals affected									
		Males					Females				
Dose (mg/kg/day)		0	0	20	60	160	0	0	20	60	160
Number of animals examined		29	37	32	33	28	23	26	20	29	15
Organ	Finding										
Kidney	Cyst	3	0	2	4	5	0	0	0	0	0
	Discoloration	0	0	0	0	2	0	0	1	0	0

Table 4: Macroscopic findings for unscheduled necropsies in carcinogenicity study in mice

Macroscopic findings		No. of animals affected									
		Males					**Females**				
Dose (mg/kg/day)		0	0	20	60	160	0	0	20	60	160
Number of animals examined		35	27	31	31	35	39	37	43	34	47
Organ	Finding										
Kidney	Cyst	1	1	1	0	3	0	0	0	0	2
	Discoloration	3	6	4	5	10	6	3	10	8	18
	Rough surface	0	0	0	0	1	0	1	2	0	3

Histopathology

Peer Review: Yes

Neoplastic

Table 5: Neoplastic findings in carcinogenicity study in mice

Neoplastic microscopic findings		**Males**					**Females**				
Dose (mg/kg/day)		0	0	20	60	160	0	0	20	60	160
Number of animals examined		64	64	63	64	63	62	63	63	63	62
Organ and Finding											
Stomach											
Neuroendocrine cell tumor, malignant	No. animals affected	0	0	0	0	1	0	0	0	1	0
	P value	Trend: 0.1983		-	-	Pairwise: 0.3287	Trend: 0.3951		-	Pairwise: 0.3643	-

- =no statistical comparison conducted
Pairwise comparisons made with control groups combined

Non-Neoplastic

- Avatrombopag-related microscopic findings included hyperplasia of the mucosa in the stomach and increased incidences and severity of chronic nephropathy in the kidneys in males at 160 mg/kg/day and females at 60 and 160 mg/kg/day. See table below.
- The increased severity of chronic nephropathy resulted in exacerbation of other changes in tissues and organs sensitive to renal malfunction including atrial thrombosis in the heart and alveolar hemorrhage, edema, and foamy cell accumulation in the lung.

Table 6: Non-neoplastic findings in carcinogenicity study in mice

Non-neoplastic microscopic findings			No. of animals affected									
			Males					**Females**				
Dose (mg/kg/day)			0	0	20	60	160	0	0	20	60	160
Number of animals examined			64	64	63	64	63	62	63	63	63	62
Organ	Finding											
Stomach	Hyperplasia, mucosa	Total	5	10	7	6	43	3	4	4	13	44
		Slight	5	6	4	4	7	3	3	2	5	16
		Moderate	0	3	3	1	4	0	1	2	7	17
		Marked	0	1	0	1	32	0	0	0	1	11
Kidneys	Chronic nephropathy	Total	24	33	28	32	35	17	9	21	26	33
		Slight	17	29	24	29	22	6	4	11	14	10
		Moderate	5	3	3	2	5	2	3	2	7	4
		Marked	1	0	1	1	5	7	1	4	2	6
		End stage	1	1	0	0	3	2	1	4	3	13

Toxicokinetics

The toxicokinetics of avatrombopag were evaluated in toxicokinetics animals during Weeks 13 and 26 of dosing with samples collected pre-dose and 1, 2, 4, 8, and 24 hours after dosing.

- Exposures to avatrombopag (C_{max} and AUC_{0-24}) increased with an increase in dose.
- Exposures were greater in males than in females.
- Exposures were higher on Week 26 than on Week 13 for the lowest dose of 20 mg/kg/day only, indicating slight accumulation only at the low dose and possible saturation of absorption at the mid and high doses with repeated administration.

Table 7: Toxicokinetics of avatrombopag in carcinogenicity study in mice

Week	Dose level (mg/kg/day)	Sex	T_{max} (hours)	C_{max} (ng/mL)	AUC_{0-24} (hr·ng/mL)
13	20	Female	2	6000	34800
		Male	1	6470	53900
	60	Female	4	15200	127000
		Male	4	14900	180000
	160	Female	4	19700	247000
		Male	4	28000	343000
26	20	Female	2	7400	62900
		Male	4	8940	66100
	60	Female	2	9470	135000
		Male	4	12700	135000
	160	Female	4	16400	249000
		Male	2	23600	315000

Study title: A 104-Week Oral (Gavage) Carcinogenicity Study of AKR-501 (E5501) in Rats

Study no.:	(b) (4) 152-10
Study report location:	eCTD Module 4.2.3.4.1.
Conducting laboratory and location:	(b) (4)
Date of study initiation:	April 15, 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Avatrombopag (E5501), lot # K4770302, Purity: 98-99%
CAC concurrence:	No agreement; IND (b) (4)

Key Study Findings

- Survival was significantly decreased in females treated with 160 mg/kg/day avatrombopag compared to controls. The decrease in survival was attributed to increases in the incidence and severity of chronic nephropathy.

- Body weights were lower in females treated with 160 mg/kg/day compared to the control groups with mean weights 15% lower than control group 1 at Week 91.
- Avatrombopag induced benign and malignant neuroendocrine tumors in the stomach at 160 mg/kg/day.
- Non-neoplastic findings included changes in the stomach (degeneration of glandular epithelium, atrophy of glandular mucosa, regenerative hyperplasia, intraluminal deposits, and neuroendocrine cell hyperplasia) at 50 and 160 mg/kg/day and increased incidences and severity of chronic nephropathy in the kidneys at 160 mg/kg/day in males and at 50 and 160 mg/kg/day in females.

Adequacy of Carcinogenicity Study

- DARRTS indicates that there was no agreement for the Special Protocol Assessment for the 2-year carcinogenicity study in rats; however, the Applicant/Sponsor appears to have followed the recommendations of the Executive CAC committee including testing doses of 20, 50, and 160 mg/kg/day and following the guidance regarding when to conduct histological examination in all groups.
- Dosing was discontinued early with a dosing period of 82 weeks in females at 160 mg/kg/day, 96 weeks in females at 50 mg/kg/day, and 98 or 99 weeks in the other groups. Animals were also terminated early with the surviving males euthanized during Week 99 and the surviving females euthanized during Week 91 (160 mg/kg/day) and 103 (all other female groups). The Applicant/Sponsor contacted the FDA for guidance and the Executive CAC committee concurred with the discontinuation of dosing and early termination of the groups.

Appropriateness of Test Models

- The study evaluated three doses of avatrombopag and had two control groups treated with the vehicle. The highest dose chosen was the MTD in the 13-week repeat-dose study in rats.
- Histopathology was evaluated for all animals in all main study groups. The study report provided sufficient histopathology data from the designated organs and tissues to evaluate both the non-neoplastic and neoplastic effects. Additionally, data on survival, clinical signs, body weights, food consumption, and hematology were provided.
- The toxicokinetics of avatrombopag were evaluated in satellite animals during Weeks 26 and 52 of dosing. Exposures to avatrombopag (C_{max} and AUC_{0-24}) increased with an increase in dose.
- Based on pharmacology data, the rat is not a relevant species; there are no available relevant species for toxicology studies. Hematology data indicate that the expected pharmacological effect of an increase in platelets was not observed in rats in this study.

Evaluation of Tumor Findings

A statistical review of the neoplastic results of the 2-year (104-week) rat carcinogenicity study for avatrombopag was conducted by Eiji Ishida of the Division of Biometrics 6 in the Office of Biostatistics.

- Based on the lack of the neoplasms in the concurrent controls (<1%), benign and malignant neuroendocrine cell tumors in the stomach are considered rare tumors.
- **Males:** The incidences of benign and malignant neuroendocrine cell tumors observed in males at 160 mg/kg/day were not statistically significant.
- **Females:**
  - Benign neuroendocrine cell tumors were observed in 3/60 (5%) females at 160 mg/kg/day. As a rare tumor, both the trend test (p=0.0065) and the pairwise comparison to the controls (p=0.0210) were statistically significant.
  - Benign and malignant neuroendocrine cell tumors combined were observed in 4/60 (7%) females at 160 mg/kg/day. Both the trend test (p=0.0012) and the pairwise comparison to the controls (p=0.0056) were statistically significant.

Methods

Doses:	0, 20, 50, or 160 mg/kg/day
Frequency of dosing:	Once daily for 82-99 weeks*
Dose volume:	10 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% methylcellulose in water
Basis of dose selection:	Executive CAC recommended the doses based on the results of 13-week repeat-dose study in rats; mortality observed at 320 mg/kg/day and 160 mg/kg/day considered maximum tolerated dose
Species/Strain:	Rat/Sprague-Dawley (Crl:CD(SD)IGS BR)
Number/Sex/Group:	60/sex/group
Age:	7 weeks at initiation of dosing
Animal housing:	Individually housed
Paradigm for dietary restriction:	Food and water available *ad libitum*
Dual control employed:	Yes; 2 control groups dosed with vehicle
Interim sacrifice:	No
Satellite groups:	Toxicokinetics: 12/sex/group; 20, 50, and 160 mg/kg/day Culled: 5/sex/group; 0, 20, 50, and 160 mg/kg/day; allowed for potential procedural errors; one animal found dead (SSAN 137) and one euthanized *in extremis* (SSAN 304) during the first 4 weeks were considered culled animals; remaining animals euthanized at end of 4-week period

Pre-dose health screen: 10/sex for control group 1 only; hematology and gross pathology conducted

* Dosing was discontinued for a group when the dose group size was reduced to 20 or fewer animals. Dosing was discontinued for all animals of a given sex (including control groups) when the number of animals in all avatrombopag-treated groups of that sex was reduced to 20 or fewer.

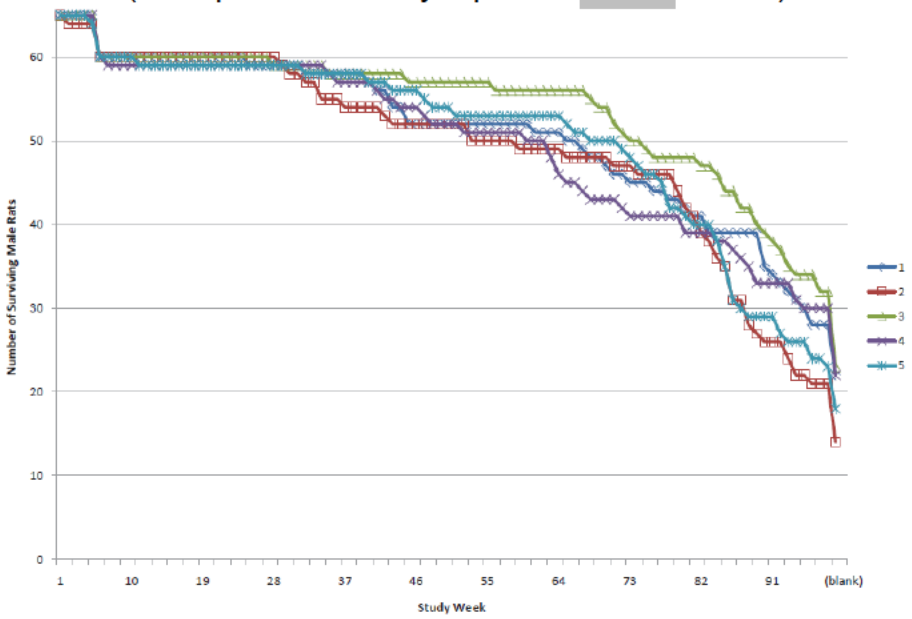
Table 8: Duration of dosing and week of necropsy in carcinogenicity study in rats

Dose mg/kg/day	Males					Females				
	0 Control	0 Control	20	50	160	0 Control	0 Control	20	50	160
No. of weeks of dosing	99	98	99	99	99	99	99	99	96	82
Week of terminal necropsy of group	99	99	99	99	99	103	103	103	103	91

Observations and Results

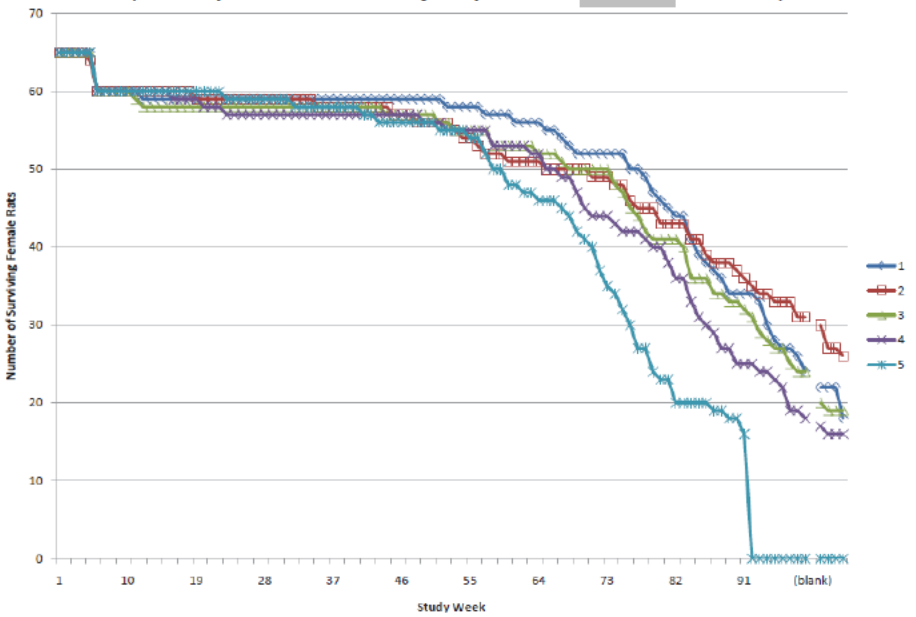
Mortality

Figure 3: Survival in male rats through Week 99
(excerpted from study report for (b) (4) 152-10)



Groups: 1 and 2= 0 mg/kg/day 3= 20 mg/kg/day 4= 50 mg/kg/day 5=160 mg/kg/day

Figure 4: Survival in female rats through Week 99
(excerpted from study report for (b) (4) 152-10)



Groups: 1 and 2= 0 mg/kg/day 3= 20 mg/kg/day 4= 50 mg/kg/day 5=160 mg/kg/day

Table 9: Survival rate in carcinogenicity study in rats

Dose (mg/kg/day)	Males					Females				
	0 Control	0 Control	20	50	160	0 Control	0 Control	20	50	160
Animals initially in study	60	60	60	60	60	60	60	60	60	60
No. of animals at scheduled necropsy for group	28	20	31	28	23	18	26	19	16	14*
Survival rate (%)	47	33	52	47	38	30	43	32	27	23

*p<0.0001, significantly different from control groups 1 and 2

Table 10: Cause of death/moribundity in carcinogenicity study in rats

Dose (mg/kg/day)	Males					Females				
	0 Control	0 Control	20	50	160	0 Control	0 Control	20	50	160
Animals initially in study	60	60	60	60	60	60	60	60	60	60
No. of death/moribundity	32	42	30	32	37	42	34	41	44	46
Neoplastic lesion	15	20	21	12	15	40	30	37	39	25
Chronic nephropathy	0	2	1	0	4	0	0	0	0	14
Other non-neoplastic lesion	8	7	4	11	5	1	1	1	3	2
Accidental/gavage error	5	6	1	6	10	1	2	3	2	4
Undetermined	4	7	3	3	3	0	1	0	0	1

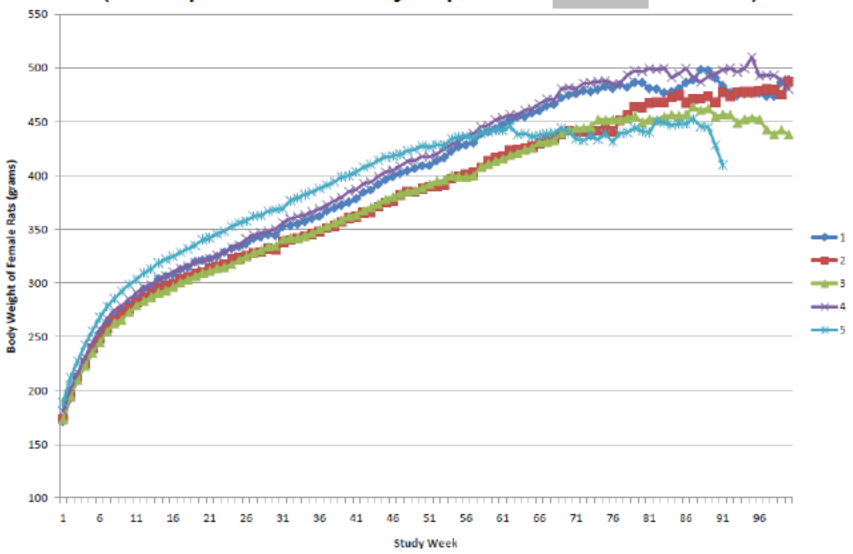
Clinical Signs

- Increased incidences of eyelid closure, hunched posture, lack of turgor, piloerection, abnormal color of feces, and sunken and swollen head (ear, nose, eye, and mouth) were observed in females at 160 mg/kg/day. These findings were likely due to declining clinical condition/health associated mostly with chronic nephropathy.

Body Weights

- The mean body weights of females treated with 160 mg/kg/day were lower compared to the control groups starting around Day 487 (↓7%); mean body weight was 15% lower than control group 1 on Day 634 (Week 91).

Figure 5: Mean body weight of female rats through Week 103
(excerpted from study report for (b) (4) 152-10)



Groups: 1 and 2= 0 mg/kg/day 3= 20 mg/kg/day 4= 50 mg/kg/day 5=160 mg/kg/day

Food Consumption

Unremarkable

Hematology

Blood samples for hematology assessment were collected from a limited number of main study animals (14 or 15/sex/group) during Week 51 and prior to scheduled necropsy.

- Platelet count was decreased in both males (↓23%) and females (↓29%; statistically significant) treated with 160 mg/kg/day compared to controls during Week 51, but this effect was not observed at later time points.
- Importantly, the expected pharmacological effect of an increase in platelets was not observed in rats in this study.

Gross Pathology

Table 11: Macroscopic findings for scheduled necropsies in carcinogenicity study in rats

Macroscopic findings		No. of animals affected									
		Males					Females				
Dose (mg/kg/day)		0	0	20	50	160	0	0	20	50	160
Number of animals examined		28	18	30	28	23	18	26	19	16	14
Organ	Finding										
Kidney	Cyst	0	1	0	1	0	0	0	1	1	1
	Rough surface	0	0	0	1	0	0	0	0	0	3

Table 12: Macroscopic findings for unscheduled necropsies in carcinogenicity study in rats

Macroscopic findings		No. of animals affected									
		Males					Females				
Dose (mg/kg/day)		0	0	20	50	160	0	0	20	50	160
Number of animals examined		32	42	30	32	37	42	34	41	44	46
Organ	Finding										
General condition	Thin	0	0	0	1	5	0	0	1	0	0
Kidney	Cyst	0	0	0	1	0	0	0	0	0	1
	Discoloration	0	2	1	1	2	1	1	1	1	14
	Enlargement	0	2	1	0	5	0	0	0	0	2
	Rough surface	0	4	2	0	1	0	0	0	0	14

Histopathology

Peer Review: Yes

Neoplastic

Table 13: Neoplastic findings in carcinogenicity study in rats

Neoplastic microscopic findings		Males					Females				
Dose (mg/kg/day)		0	0	20	50	160	0	0	20	50	160
Number of animals examined		60	60	60	60	60	60	60	60	60	60
Organ and Finding											
Stomach											
Neuroendocrine cell tumor, benign	No. animals affected (%)	0	0	0	0	1	0	0	0	0	3 (5%)
	P value	-		-	-	-	Trend: 0.0065		-	-	Pairwise: 0.0210
Neuroendocrine cell tumor, malignant	No. animals affected	0	0	0	0	1	0	0	0	0	1
	P value	-		-	-	-	Trend: 0.1869		-	-	Pairwise: 0.2761
Neuroendocrine cell tumor, benign and malignant combined	No. animals affected (%)	0	0	0	0	2 (3%)	0	0	0	0	4 (7%)
	P value	Trend: 0.0370		-	-	Pairwise: 0.1093	Trend: 0.0012		-	-	Pairwise: 0.0056

- =no statistical comparison conducted
Pairwise comparisons made with control groups combined

Non-Neoplastic

- Avatrombopag-related microscopic findings included gastric changes in the stomach at 50 and 160 mg/kg/day; the findings were similar to those reported in previous toxicology studies of avatrombopag. An additional change observed in this study was neuroendocrine cell hyperplasia. See table below.
- Increased incidences and severity of chronic nephropathy in the kidneys were observed in animals treated with avatrombopag, particularly males at 160 mg/kg/day and females at 50 and 160 mg/kg/day. See table below.
- The increased severity of chronic nephropathy resulted in exacerbation of other changes in tissues and organs sensitive to renal malfunction including diffuse hyperplasia in the parathyroid, fibrous osteodystrophy in the bone, arteritis/thrombosis in various organs and tissues, brain malacia secondary to arteritis, mineralization in the heart, aorta, and tongue, and cardiomyopathy in the heart.

Table 14: Non-neoplastic findings in carcinogenicity study in rats

Non-neoplastic microscopic findings	No. of animals affected

			Males					Females				
Dose (mg/kg/day)			0	0	20	50	160	0	0	20	50	160
Number of animals examined			60	60	60	60	60	60	60	60	60	60
Organ	Finding											
Stomach	Degeneration of glandular epithelium	Slight	0	0	0	5	8	0	0	0	7	15
	Atrophy of glandular mucosa	Total	13	11	7	18	40	6	5	5	26	47
		Slight	13	11	7	15	20	6	5	5	23	31
		Moderate	0	0	0	3	17	0	0	0	3	13
		Marked	0	0	0	0	3	0	0	0	0	3
	Regenerative hyperplasia of glandular epithelium	Slight	0	0	0	3	4	0	0	0	4	10
	Intraluminal deposits, glandular	Total	0	0	0	17	56	0	0	0	54	55
		Slight	0	0	0	12	50	0	0	0	49	48
		Moderate	0	0	0	5	6	0	0	0	5	7
	Neuroendocrine cell hyperplasia, diffuse	Slight	3	2	4	7	7	10	10	12	11	4
	Neuroendocrine cell hyperplasia, focal	Total	0	0	0	10	19	0	0	0	9	40
		Slight	0	0	0	7	13	0	0	0	3	31
		Moderate	0	0	0	3	6	0	0	0	6	7
		Marked	0	0	0	0	0	0	0	0	0	2
Kidneys	Chronic nephropathy	Total	27	30	32	36	46	7	6	14	16	49
		Slight	13	18	23	23	24	6	5	13	12	15
		Moderate	9	5	7	9	13	1	1	0	1	11
		Marked	4	7	2	4	8	0	0	1	3	8
		End stage	1	0	0	0	1	0	0	0	0	15

Toxicokinetics

The toxicokinetics of avatrombopag were evaluated in toxicokinetics animals during Weeks 26 and 52 of dosing with samples collected pre-dose and 1, 2, 4, 8, and 24 hours after dosing.

- Exposures to avatrombopag (C_{max} and AUC_{0-24}) increased with an increase in dose and were consistently greater in females than in males.
- Exposures were slightly higher on Week 52 than on Week 26, indicating some accumulation of the drug.

Table 15: Toxicokinetics of avatrombopag in carcinogenicity study in rats

Week	Dose level (mg/kg/day)	Sex	T_{max} (hours)	C_{max} (ng/mL)	AUC_{0-24} (hr·ng/mL)
26	20	Female	4	5120	62800
		Male	4	2890	44900
	50	Female	4	12300	150000
		Male	4	6560	75900
	160	Female	8	24300	426000
		Male	8	11400	182000
52	20	Female	8	5800	93300
		Male	4	4400	54400
	50	Female	2	16900	230000
		Male	4	8080	119000
	160	Female	4	33600	565000
		Male	4	18300	287000

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/s/

BRENDA J GEHRKE
02/28/2018

CHRISTOPHER M SHETH
02/28/2018

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 21, 2018

APPLICATION/DRUG: NDA 210238 avatrombopaq (DOPTELET)

FROM: Yaping Wang, PhD, Primary Statistical Reviewer

THROUGH: Yuan-Li Shen, PhD, Statistical Team Leader

Avatrombopag is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure. The primary statistical review for NDA 210238 is complete and has been added to the NDA/BLA Multi-Disciplinary Review and Evaluation, which will be uploaded to DARRTS when finalized. Refer to the Multi-Disciplinary Review and Evaluation for additional details. There are no statistical issues that would prevent approval of this application. My recommendation for this application is approval

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/s/

YAPING WANG
02/21/2018

YUAN L SHEN
02/22/2018

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 21, 2018

APPLICATION/DRUG: NDA 210238 Avatrombopag (DOPTELET)

FROM: *Laurel A. Menapace, MD, Clinical Reviewer*

THROUGH: *Andrew Dmytrijuk, MD, Clinical Team Leader*

SUBJECT: Primary Clinical Review Memo

Please see my clinical review in the Multi-Disciplinary Review document. My regulatory recommendation is approval.

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/s/

LAUREL A MENAPACE
02/21/2018

ANDREW DMYTRIJUK
02/22/2018

Office of Clinical Pharmacology Memo	
NDA	210238
Link to EDR	\\CDSESUB1\evsprod\NDA210238\
Submission Date	September 21, 2017
Submission Type	NME (Priority)
Brand Name	DOPTELET
Generic Name	Avatrombopag
Dosage Form and Strength	20 mg tablets
Route of Administration	Oral
Proposed Indication	Treatment of thrombocytopenia in patients with chronic liver disease (CLD) who are scheduled to undergo a procedure
Applicant	Eisai, Inc.
Associated INDs	076680
OCP Review Team	Sriram Subramaniam, Ph.D., Olanrewaju Okusanya, Pharm.D., M.S., Ruojing Li, Ph.D., Justin Earp, Ph.D., Xiling Jiang, Ph.D., Yuching Yang, Ph.D., Robert Schuck, Pharm.D., Christian Grimstein, Ph.D.
OCP Final Signatory	NAM Atiqur Rahman, Ph.D. (Division Director)

The Office of Clinical Pharmacology (OCP) review is complete and has been added to the Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for details. The proposed DOPTELET dosing regimen of 60 mg daily for 5 consecutive days for patients with baseline platelet counts $<40 \times 10^9$ /L and 40 mg daily for 5 consecutive days for patients with baseline platelet count of 40×10^9 /L and $< 50 \times 10^9$/L are acceptable and are supported by the efficacy and safety results. From a Clinical Pharmacology standpoint, the NDA is approvable provided the Applicant and the FDA reach an agreement regarding the labeling language.

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/s/

SRIRAM SUBRAMANIAM
02/21/2018

OLANREWAJU OKUSANYA
02/21/2018
I concur with the recommendation.OOO

RUOJING LI
02/21/2018

XILING JIANG
02/21/2018

ROBERT N SCHUCK
02/21/2018

YUCHING N YANG
02/21/2018

JUSTIN C EARP
02/22/2018

CHRISTIAN GRIMSTEIN
02/22/2018

NAM ATIQUR RAHMAN
02/22/2018

MEMORANDUM

Date: February 20, 2018
From: Brenda J. Gehrke, PhD
Nonclinical Reviewer
Division of Hematology Oncology Toxicology (DHOT)
for Division of Hematology Products (DHP)
Through: Christopher M. Sheth, PhD
Nonclinical Supervisor
To: NDA 210238 Avatrombopag
Re: Nonclinical Review

Avatrombopag is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure. The nonclinical review is complete and has been added to the Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for additional details. There are no nonclinical issues that would prevent approval of this application.

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/s/

BRENDA J GEHRKE
02/20/2018

CHRISTOPHER M SHETH
02/20/2018
I concur with the primary review