CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210923Orig1s000

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	New Drug Application (NDA)
Application Number(s)	210923
Priority or Standard	Priority
Submit Date(s)	December 26, 2017
Received Date(s)	December 26, 2017
PDUFA Goal Date	August 26, 2018
Division/Office	DHP/OHOP
Review Completion Date	July 27, 2018
Established Name	Lusutrombopag
(Proposed) Trade Name	Mulpleta®
Pharmacologic Class	Thrombopoietin receptor agonist
Code name	B02BX07
Applicant	Shionogi, Inc.
Formulation(s)	Tablets
Dosing Regimen	One 3-mg tablet taken orally once daily with or without food for 7 days
Applicant Proposed Indication(s)/Population(s)	Treatment of thrombocytopenia in patients with chronic liver disease who are at increased risk for bleeding associated with invasive procedures
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure

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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
DMPP=Division of Medical Policy Programs
DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
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
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
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
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
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Lusutrombopag (S-888711, MULPLETA®) is an orally administered, active, small-molecule thrombopoietin (TPO) receptor agonist that interacts with the transmembrane domain of human TPO receptors expressed on megakaryocytes to induce the proliferation and differentiation of megakaryocytic progenitor cells from hematopoietic stem cells and megakaryocyte maturation. It is assigned to the pharmacotherapeutic group (ATC Code) B02BX07 (other systemic hemostatics).

Lusutrombopag 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.

Lusutrombopag is provided in a 3-mg oral tablet formulation to be taken with or without food. Dosing should begin 8-14 days prior to scheduled procedure. The recommended dosage is 3-mg once daily for 7 days. Patients should undergo their procedure 2-8 days after last dose.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness for lusutrombopag in patients with chronic liver disease with thrombocytopenia scheduled to undergo a procedure. This conclusion was based on the results from two randomized, multicenter, double-blind, placebo-controlled trials (L-PLUS1 and L-PLUS2). In L-PLUS1, a greater proportion of patients who received lusutrombopag did not require a platelet transfusion prior to the primary procedure compared to the placebo treatment group. Likewise, in Study L-PLUS2, a similar higher proportion of patients did not require platelet transfusion prior to procedure as well as rescue therapy from bleeding from randomization through 7 days after the primary procedure compared to the placebo treatment group. In both studies, the proportion of responders, defined as patients who had platelet counts ≥ 50,000/µL with an increase of ≥ 20,000/µL from baseline, was significantly higher in the lusutrombopag treatment groups compared to the placebo treatment groups.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Thrombocytopenia is a common hematological toxicity among patients with chronic liver disease (CLD) with a reported incidence of over 70%. The low platelet count in patients with CLD who require a procedure is a serious condition due to the increased risk of bleeding during or after diagnostic and therapeutic procedures. Historically, the main treatment for thrombocytopenia in patients with CLD is platelet transfusions or avoidance of medical interventions. Patients with CLD with thrombocytopenia often require multiple platelet transfusions prior to a procedure and adequate responses to a platelet transfusion are frequently not attained due to alloimmunization or splenic sequestration *(Dahal, Upadhyay et al. 2017)*. The risks of using platelet transfusions include infections, transfusion reactions, volume overload, and alloimmunization with specific concern for platelet refractoriness in 50% of patients who need repeated platelet transfusions *(Peck-Radosavljevic 2017)*. Other methods such as splenic artery embolization, transjugular intrahepatic portosystemic shunts (TIPS) or splenectomy are associated with significant risks that make them not optimal procedures for the proposed population. There is one approved treatment of thrombocytopenia in patients with CLD who are scheduled to undergo a procedure, avatrombopag.

Two similar, double-blind, placebo-controlled studies (L-PLUS1 and L-PLUS2) demonstrated that lusutrombopag was superior to placebo based on the proportion of patients who did not require a platelet transfusion or receive any rescue procedure for bleeding after randomization and up to 7 days following a procedure. The patient populations were similar in both studies and included patients with chronic liver disease who were undergoing an invasive procedure and had a platelet count less than 50 x 10^9/L. Patients were randomized 1:1 to receive 3 mg of lusutrombopag or placebo once daily for up to 7 days. Randomization was stratified by liver ablation/coagulation or other procedures and the platelet count at screening/baseline. In L-PLUS1, 57% of patients underwent procedures other than liver ablation/coagulation and 43% underwent liver ablation/coagulation. In L-PLUS2, 98% of patients underwent procedures other than liver ablation/coagulation and 2% underwent liver ablation/coagulation. The primary efficacy endpoint in L-PLUS1 was the proportion of patients not requiring platelet transfusion prior to invasive procedure. The primary efficacy endpoint in L-PLUS2 was the proportion of patients not requiring platelet transfusion prior to invasive procedure and no rescue therapy for bleeding (i.e. platelet preparations, other blood preparations, including red blood cells and plasma, volume expanders) from randomization through 7 days after invasive procedure.

Lusutrombopag treatment demonstrated a statistically significant increase in the proportion of patients who did not require a platelet transfusion or who received rescue therapy. In both the L-PLUS1 and L-PLUS2 trials, responders were defined as patients who had a platelet count of $\geq 50 \times 10^9$/L with an increase of $\geq 20 \times 10^9$/L from baseline. In L-PLUS1, the proportion of patients who did not require a platelet transfusion was 78% (95% CI: 63%, 88%) in the lusutrombopag treatment group and 13% (95% CI: 4.7%, 25%) in the placebo treatment group ($p<0.0001$). In the L-PLUS2 study, the proportion of patients in the lusutrombopag treatment arm not requiring platelet transfusion prior to invasive procedure or rescue therapy for bleeding was 65% (95% CI: 55%, 74%) compared to 29% (95% CI: 21%,39%) in the placebo treatment group ($p<0.001$). The median (quartiles Q1, Q3) duration of platelet count increase to at least 50×10^9/L was 22 (17, 27) days in lusutrombopag-treated patients without platelet transfusion and 1.8 (0.0, 8.3) days in placebo-treated patients with platelet transfusion in L-PLUS1 and 19 (13, 28) days in lusutrombopag-treated patients without platelet transfusion and 0.0 (0.0, 5.0) days in placebo-treated patients with platelet transfusion in L-PLUS2.

In general, lusutrombopag was well tolerated. Safety results were presented from pooled data from L-PLUS1, L-PLUS2, and study MO626. In all three studies, patients with chronic liver disease and thrombocytopenia were treated at a dose of 3 mg daily for up to 7 days prior to a scheduled procedure. The majority of patients in both trials experienced at least one TEAE (76% on lusutrombopag arm and 83% on placebo arm). Headache was the most common treatment emergent adverse event (occurring in at least 3%) for lusutrombopag treatment group. The incidence of serious adverse events was 5% in the lusutrombopag treatment group and 7% in the placebo group. The most common serious adverse event reported with lusutrombopag was portal vein thrombosis.

Thromboembolic events were a pre-defined adverse event of special interest (AESI) given previous experience with other TPO receptor agonists. In the thromboembolic category, treatment emergent AESIs were reported in 6 patients (1.8%) in the lusutrombopag arm and 4 patients (1.2%) in the placebo group. Portal vein thrombosis was reported in 1% (2 of 171) of lusutrombopag-treated patients and 1% (2 of 170) of placebo-treated patients in 3 randomized, double-blind trials and was identified post-procedure in protocol-specified imaging. The thromboses were not associated with a marked increase in platelet count. The product label adequately addresses the risk of using this product in patients with CLD and thrombocytopenia.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Thrombocytopenia is a common hematological abnormality in patients with CLD with incidence of up to 70%. • Thrombocytopenia in patients with CLD is associated with increased risk of bleeding secondary to procedures. • Severe thrombocytopenia can negatively impact the ability to provide routine care to patients with CLD by interfering with the ability to perform diagnostic and therapeutic procedures in patients with CLD.	Thrombocytopenia in patients with CLD who require a procedure is a serious condition due to the increases risk of bleeding.
Current Treatment Options	• Platelet transfusions have historically been the mainstay of treatment for thrombocytopenia in CLD patients undergoing procedures. • Platelet refractoriness remains significant risk and challenge in the management of this population. Other interventions include splenectomy, splenic artery embolization and transjugular intrahepatic portosystemic shunt (TIPS), however these procedures convey significant risks and are not optimal treatment options for this population. • Avatrombopag, a TPO agonist, was approved in 2018 for the treatment of patients with thrombocytopenia with CLD.	The treatment armamentarium will be enhanced with an additional therapeutic option for the treatment of patients with liver disease and of thrombocytopenia undergoing procedures.
Benefit	• Two similar, double-blind, placebo-controlled studies were conducted in patients with CLD and thrombocytopenia. • In both the L-PLUS1 and L-PLUS2 trials, responders were defined as patients who had a platelet count of $\geq 50 \times 10^9$/L with an increase of $\geq 20 \times 10^9$/L from baseline. • In the L-PLUS1 trial (n=97), the proportion of subjects in the lusutrombopag treatment group (n=49) who did not receive preprocedural platelet transfusion was 78% (95% CI: 63%,88%)	Lusutrombopag treatment demonstrated an effective elevation in platelet counts prior to a scheduled procedure and reduced the need for platelet transfusions compared to placebo. In addition, the proportion of patients who received lusutrombopag and did not require a rescue procedure for bleeding

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	compared to 13%(95% CI: 4.7%,25%) in the placebo group(n=48) with a p-value < 0.0001. • In the L-PLUS2 trial(n=215), for the lusutrombopag group (n= 108) the proportion of subjects who did not receive a transfusion before the primary invasive procedure and no rescue therapy for bleeding from randomization through 7 days after the primary invasive procedure was 64.8%(95% CI: 55%, 74%) compared to the 29%(95% CI: 21%,39%) in the placebo group (n=107) with a p-value < 0.0001. • The median (quartiles Q1, Q3) duration of platelet count increase to at least $50X10^9$/L was 22 (17, 27) days in lusutrombopag-treated patients without platelet transfusion and 1.8 (0.0, 8.3) days in placebo-treated patients with platelet transfusion in L PLUS1 and 19 (13, 28) days in lusutrombopag-treated patients without platelet transfusion and 0.0 (0.0, 5.0) days in placebo-treated patients with platelet transfusion in L-PLUS2.	was less than in the patients treated with placebo.
Risk and Risk Management	• Lusutrombopag was generally well tolerated. • The most common adverse event in the safety population was headache (4.69%). • Serious adverse events were primarily post-procedural, general disorders, and administration site events. • Serious adverse events such as thrombotic or thromboembolic events, procedural pain, hyper/hypotension, fever, and hemorrhage and increase in transaminases occurred after an invasive procedure were performed. The maximum platelet count at the time of the thrombotic event did not reach over 200,000/µL. • Among the four deaths reported in the safety population, all occurred at least two weeks from the date of the last study drug administration. None of the deaths were secondary to a	In patients with CLD, the safety profile of lusutrombopag was comparable to placebo. The product label adequately addresses the risk of using this product in patients with CLD and thrombocytopenia.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	thromboembolic event.	

1.4. Patient Experience Data

Table 2 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	N/A
	☐ 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.)	N/A
	☐ Patient-focused drug development or other stakeholder meeting summary reports	N/A
	☐ Observational survey studies designed to capture patient experience data	N/A
	☐ Natural history studies	N/A
	☐ Patient preference studies (e.g., submitted studies or scientific publications)	N/A
	☐ Other: (Please specify)	N/A

x	Patient experience data that was not submitted in the application, but was considered in this review.

Patient experience data and related information required by the 21st Century Cures Act were not submitted as part of this application.

Tanya Wroblewski, MD
Cross-Disciplinary Team Leader

2 Therapeutic Context

Appears this way on original

2.1. [redacted]

Thrombocytopenia (defined at a platelet count of < 150,000/µL) is a common hematological complication in patients with chronic liver disease. Those patients with severe thrombocytopenia have platelet levels below 50,000/µL. This threshold is considered as the level below which performing invasive maneuvers (e.g. liver biopsy). The prevalence and severity of thrombocytopenia varies due to severity of underlying liver condition in this patient population. In patients with chronic hepatitis with thrombocytopenia, it is about 6%; however, those patients with cirrhosis, it occurs in 78% of patients. A correlation has even been shown between bleeding during therapeutic procedures (not diagnostic procedures with lower gauge needles). This becomes more problematic in cirrhotic patients where bleeding complications are most likely to occur when platelet counts are ≤50,000/µL, along with other features like, Child-Pugh Stage C classification and/or the diagnosis of alcoholic liver cirrhosis. In sub-analysis of diagnostic procedures among this population, the number of bleeding events was 16 (0.6%) out of 2740 liver biopsies. The main risk factor for bleeding was a platelet count at ≤60,000/µL (5% rate), with virtually no risk at >150,000/µL and very little risk at >60,000/µL *(Peck-Radosavljevic 2017)*. Thrombocytopenia (defined as <50 000/µL) is a major risk factor and predictor for bleeding with medical interventions, such as surgical procedures and antiviral therapy. The seriousness of this condition and the overall impact this condition has in delaying required diagnostic and therapeutic procedures increases the demand for transfusion products.

The pathophysiology of thrombocytopenia is multifactorial. The known mechanisms associated with thrombocytopenia in patients with CLD include decreased thrombopoietin levels, portal hypertension, hypersplenism, cirrhosis, hepatocellular cancer, chemotherapy, viral suppression, antiviral therapy, and anti-platelet antibodies. One complication of CLD and cirrhosis is hepatocellular carcinoma which has the third highest death rate among malignancies in the world. Hepatocellular carcinoma and other etiologies of CLD can cause an excessive deposition of fibrin which in the context of chronic liver injury replaces liver tissue with an extracellular matrix (ECM) which gradually impacts hepatic function. The parenchymal, non-parenchymal hepatic cells, and hepatic stellate cells (HSCs) along with platelets work collectively to prevent myofibrosis within the ECM. This symbiosis in the environment of normal platelet production is impeded with any liver insult *(Kurokawa, 2017)*.

Recent efforts have led to trying to understand the importance of the pathophysiology in the regulation of thrombopoiesis. Those important regulators of platelet production include interleukin (IL)-3, -6, -11, steel factor and thrombopoietin (TPO). TPO is the prominent thrombopoietic hormone that is primarily synthesized in the hepatocytes. Decreased TPO

production in patients with various degrees of CLD related to HCV infection has been linked to decreased hepatocellular functioning mass which is not reflected in hepatic function blood tests. Evidence has demonstrated that thrombocytopenia in patients who underwent liver transplantation showed a rise in TPO levels and peripheral platelet counts due to the restoration of functional liver cell mass *(Giannini E, 2003)*.

Thrombopoietins (C-MPL ligands) have been recently developed based on their ability to bind and activate the TPO receptor, c-mpl. The second-generation TPO mimetics are currently used to treat thrombocytopenia associated with conditions like immune thrombocytopenia (ITP), severe aplastic anemia (SAA) and hepatitis C virus-associated chronic liver disease without introducing the risk of antibody formation to endogenous TPO which has occurred among the first generation TPO mimetics. The efficacy of repeated lusutrombopag is its action to selectively bind the human TPO receptor and activate signal transduction promoting proliferation and differentiation of bone marrow progenitor cells into megakaryocytes.

2.2. Analysis of Current Treatment Options

Treatment options for clinically relevant thrombocytopenia have historically consisted off platelet transfusions. However, platelet transfusions, the most effective option, can become refractory after multiple platelet transfusions due to human leukocyte antigen alloimmunization. Other treatment options include splenic artery embolization, splenectomy, and transjugular intrahepatic portosystemic stent shunting. While these treatment options often effectively increased the platelet count, costs and risks are substantial.

Eltrombopag and romiplostim are approved TPO mimetics for the management of thrombocytopenia but not for the treatment of thrombocytopenia in chronic liver disease patients undergoing invasive procedures. The arbitrary assignment of a platelet count of 200,000/µL is based upon the thrombotic events associated with the use of eltrombopag (PROMACTA®), which was approved for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy in November 2008. Post-hoc analysis revealed that eight patients had thrombotic events (10 events); five had the event when the platelet count was higher than 200,000/µL (the maximum platelet count achieved during the study). Six patients in the eltrombopag group (7 events) and 2 patients (3 events) in the placebo group (odds ratio with eltrombopag, 3.04; 95% CI, 0.62, 14.82) presented with symptomatic portal-vein or splanchnic-vein thromboses. None of the events occurred during therapy and the median time to onset was 8.5 days (range, 1 to 38) after the last dose. None of the 8 patients who had thrombotic events had received both eltrombopag and a platelet transfusion or any blood-product use. In addition, 5 of the 8 patients with a thrombotic event had evidence of cancer. These safety concerns led to the termination of the Phase 3 trial by the independent data and safety monitoring committee in this population of patients *(Afdhal, N. H. et al. 2008)*.

Recently, avatrombopag (DOPTELET®), a TPO agonist, was approved on May 21, 2018, for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure in the United States.

Table 3: Summary of Treatment Armamentarium Relevant to Thrombocytopenia in Chronic Liver Disease

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments (e.g., subpopulation not addressed
FDA Approved Treatments [Thrombopoietin Receptor Agonist]						
DOPTELET® (avatrombopag)	Treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure	2018	40 or 60 mg orally once daily for five days (depending on baseline platelet count)	Two clinical trials* where 67-93% patients achieved target platelet count ≥ 50K on the day of procedure ($p < 0.0001$)	Pyrexia, fatigue, headache, nausea, abdominal pain, and peripheral edema	

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Lusutrombopag (MULPLETA®) is a new molecular entity and not currently marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

IND 104047 was submitted to the Agency on January 8, 2009, to provide for the clinical investigation of lusutrombopag (S-888711) (b) (4)

On October 9, 2014, an End-of-Phase 2 meeting was held to discuss Shionogi's global development plan to investigate lusutrombopag as treatment for thrombocytopenia in adults with chronic liver disease (CLD) who are undergoing elective invasive procedures. The Agency acknowledged the Applicant's proposal to conduct a multicenter, randomized, double-blind, placebo-controlled trial in a total of 200 subjects with a primary endpoint of the proportion of subjects who require no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding for 7 days following that procedure.

An Agreed Initial Pediatric Study Plan – Agreement letter was issued on June 5, 2015, in which the Agency agreed with the Applicant's request for a full waiver of the pediatric assessment requirement for lusutrombopag for the treatment of thrombocytopenia in patients 0 through 17 years of age with CLD to reduce the need for platelet transfusions associated with elective invasive procedures. The basis for the Applicant's request was that due to the small number of pediatric patients estimated to have CLD and thrombocytopenia, it would be impossible or highly impractical to conduct safety and efficacy trials in such patients undergoing elective invasive procedures.

On March 6, 2017, the Agency granted Fast Track designation to lusutrombopag for the treatment of thrombocytopenia in patients with chronic liver disease who are at increased risk for bleeding associated with elective invasive procedures.

A Pre-NDA meeting was scheduled for May 12, 2017, to discuss the content of the Applicant's planned NDA application and meeting preliminary comments were provided to the Applicant on May 9, 2017. The Agency advised the Sponsor that there was no identified specific safety concern; however, the need for a REMS for lusutrombopag would be made during the review of the NDA.

The Applicant was granted rolling submission and review of their planned NDA. Three separate submissions comprising the original NDA were received on August 29, September 27, and December 26, 2017, respectively. The Applicant requested priority review, which was granted by the Agency at the time of filing on February 14, 2018.

3.3. Foreign Regulatory Actions and Marketing History

A marketing application was submitted to the Ministry of Health, Labour and Welfare (MHLW) in Japan on 17 December 2014 for lusutrombopag as treatment for thrombocytopenia in patients with CLD who are undergoing elective invasive procedures. The MHLW was approved on 28 September 2015 and has been marketed for this indication in Japan since 01 December 2015. The number of patients exposed to lusutrombopag is estimated to be (b) (4)

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

4.1. Office of Scientific Investigations (OSI)

An OSI audit was requested. Site inspections included review of: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, correspondence, and informed consent documents. CRFs were compared with source data to assess that the primary study endpoint was verifiable at the study site. Study M0634, was conducted internationally with the highest enrollment at sites in Poland and Italy. Site 8EC in Italy was chosen because of the following reasons:

1. Four patients were discontinued from the study drug due to an increase in the platelet count.
2. Adverse event of thrombosis of the hepatic portal vein.
3. Ineligibility due to the exclusion criteria.

Study MO634 was conducted in the US and Site 8GJ in California was identified for a site inspection. Most US sites had low enrollment numbers whereas Site 8GJ enrolled six patients.

Table 4: Site Inspection Results

Site	Principal Investigator	Site Number/Enrollment	Inspection Dates	Findings
IRCCS Ospedale Casa Sollievo della SC Sofferenza Gastroenterologia ed Endoscopia Digestiva Viale Cappuccini 1 San Giovanni Rotondo FG Italy 71013	Angelo Iacobellis, MD	8EC/10	16-20 April 2018	VAI (Voluntary Action Indicated) • Gastrointestinal endoscopy not performed within 180 days prior to randomization for 7 of the 10 patients enrolled with planned invasive procedures other than endoscopic treatment of gastroesophageal varices • At screening or (b) (6), Subject (b) (6) had been on cardioaspirin since (b) (6). The subject was directed after the planned procedure to take 100 mg cardioaspirin daily • Subject (b) (6) (age 51) at screening was documented to have been in menopause for one year. No documentation was available for confirmation. No pregnancy test was performed at screening or at any time of study. • Subject (b) (6) has a platelet count of 48,000/µL on Day 12. A platelet transfusion was not given prior to the planned invasive procedure on Day 13.

Site	Principal Investigator	Site Number/Enrollment	Inspection Dates	Findings
				• Across ten patients, there were 14 missed visits requiring platelet counts attributed to subject noncompliance • Delinquent reporting of visits requiring platelet counts on 5 patients and dosing in one patients • Assessment for portal vein thrombosis 3-10 days post invasive procedure were not completed on 2 patients and completed 12 days' post procedure on one subject. *Dr. Iacobellis responded to the inspection findings adequately, in a letter dated May 10, 2018.* *The above regulatory deficiencies observed did not have a substantial clinical impact on the integrity of the study data.*
Inland Empire Liver Foundation 2006 North Riverside Ave Suite A Rialto California United States 92377	Zeid Kayali, MD	8GJ/6	21-25 May 2018	NAI (No Action Indicated)
Kitasato University East Hospital 2-1-1 Asamizodai, Minami-ku Sagamihara-City Kanagawa, Japan	Hisashi Hidaka, MD	2CH/6	7-10 May 2018	NAI (No Action Indicated)
Shionogi, Inc. 300 Campus Drive Florham Park, NJ 07932		Study 1304M0631 Study 1423M0634	5-12 May 2018	NAI (No Action Indicated)

Reviewer's Comment: As per OSI overall assessment of findings and recommendations (final letter 8 June 2018 by Anthony Orencia, MD, FACP):
"Three clinical sites (Drs. Hidaka, Iacobellis and Kayali) were selected by the Division of Hematology Products (DHP) for inspection in support of BLA 761036 S-013. The sponsor (Shionogi, Inc.) was also inspected. The study data from these clinical sites, as reported by the sponsor to the NDA, are considered to be reliable in support of the requested indication.
The preliminary regulatory classification for Drs. Hidaka and Kayali is No Action Indicated (NAI).
The final regulatory classification for Dr. Iacobellis is Voluntary Action Indicated (VAI). The final regulatory classification for the sponsor is NAI."

4.2. Product Quality

Dr. Sherita McLamore (Chemistry Reviewer in the Office of Product Quality [OPQ]) concluded in her final review (on final signature date 30 May 2018) for NDA 210923 that that all review issues were adequately addressed and potential risks to patient safety, product efficacy, and product quality was appropriately mitigated. OPQ recommends approval of the application for lusutrombopag submitted under NDA 210923. Clinical Microbiology

Dr. Sherita McLamore (OPQ) has stated in her final review (final signature date 30 May 2018) that no microbiology testing was required for this application for lusutrombopag.

4.3. Devices and Companion Diagnostic Issues

A companion device or diagnostic was not included in this application.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Lusutrombopag (also known as RSC-888711 and S-888711) is a thrombopoietin (TPO) receptor agonist that acts on the transmembrane domain of TPO receptors expressed on megakaryocytes. The interaction of lusutrombopag with the TPO receptor induces JAK/STAT and RAS-MAPK pathway signaling leading to proliferation and differentiation of megakaryocytes and ultimately resulting in the production of platelets. The applicant hypothesizes that the production of platelets induced by lusutrombopag will be an effective treatment of thrombocytopenia in patients with chronic liver disease. The established pharmacological class for lusutrombopag is thrombopoietin receptor agonist.

Multiple pharmacology studies were conducted as proof of principle and to further characterize the mechanism of action of lusutrombopag. In in vitro studies, incubation of lusutrombopag with TPO receptor expressing cells (Ba/F3-hMpl) resulted in proliferative activity with an EC_{50} of 84.0 nM. Proliferation was also induced by the lusutrombopag metabolites lusutrombopag-deshexyl and -5-keto but to a much lesser extent with EC_{50} values of approximately 35 and 0.56 µM, respectively. The observed proliferative effect of lusutrombopag is thought to be induced by the activation of the JAK/STAT and MAPK signaling pathways as evidenced by increased phosphorylation of JAK2, STAT3, STAT5, and p44/42 MAPK proteins. Similar protein phosphorylation was observed following incubation of TPO receptor expressing cells with human recombinant TPO.

Primary pharmacology studies were also conducted in vivo using a human TPO receptor knock-in mouse model (TPOR-Ki/Shi) that was developed by the applicant. In multiple studies, administration of lusutrombopag at doses from 0.3 to 10 mg/kg resulted in statistically significant and dose dependent increases in platelet counts when compared to vehicle control. The platelet increase induced by administration of lusutrombopag at 0.3, 1, and 3-mg/kg/day for 6 weeks in the TPOR-Ki/Shi model reached a peak level follow by a plateau that occurred in a dose-dependent manner with maximum platelet production reached at Day 8, 29, and 36 in the low, mid, and high dose groups, respectively.

In safety pharmacology studies, no consistent effects of toxicological significance were observed.

At low doses (< 30 mg/kg), exposure to lusutrombopag was generally dose proportional. As doses increased, exposure to lusutrombopag was either similar to or less than levels at lower doses. The reduced exposure at higher dose levels is believed to be due to the difference in the solubility of lusutrombopag in the dosing formulation and a reduction in ration of surface-active substance.

The repeat-dose toxicity studies for lusutrombopag were conducted in the rat and dog. A 6-month repeat-dose study was conducted in Crl:CD(SD) rats at doses of 2, 20 or 100 mg/kg/day. Significant increases in prothrombin time (PT) and activated partial thromboplastin time (APTT) occurred that remained elevated through recovery. Additionally, dose-dependent increases in multiple electrolytes and a severe decrease of the corpus luteum was reported. The primary organ of toxicity was the kidney. A dose-dependent and statistically significant increase in organ weight was reported that was accompanied by slight to moderate histopathology findings and an increase in protein positive urine.

A 9-month repeat-dose study was conducted in Beagle dogs at doses of 3, 10, or 100 mg/kg/day. In dogs, lusutrombopag was generally well tolerated. Notable findings were limited to an increase in ALT levels at the mid and high dose groups and moderate to marked atrophy of the thymus. Potential liver toxicity also occurred in a 3-month study conducted in dogs evidenced by increased transaminase levels and hepatocyte atrophy and focal necrosis, however, the clinical chemistry and histopathological findings did not occur in the same animals.

Lusutrombopag was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay and not clastogenic in the in vitro human lymphocyte chromosomal aberration assay, and were not genotoxic in an in vivo mouse bone marrow micronucleus assay. In 104-week carcinogenicity studies conducted in rats and mice, lusutrombopag did not result in any tumor findings that met the threshold for statistical significance in either sex or species.

In a fertility and early embryonic development study in rats, administration of lusutrombopag did not have any effects of toxicological concern on reproductive function.

In an embryo-fetal development study in rats, lusutrombopag was orally administered during organogenesis at doses of 4, 12.5, 40, and 80 mg/kg/day. Low body weight and a decrease in the number of ossified sternebrae were noted in fetuses at doses of 80 mg/kg/day (approximately 251 times the AUC observed in patients at the recommended clinical dose of 3-mg once daily). Minor skeletal variations (supernumerary ribs) were observed at doses as low as 4-mg/kg/day (approximately 23 times the AUC observed in patients at the recommended clinical dose of 3-mg once daily). A whole-body autoradiography study in pregnant rats demonstrated radioactivity was present in the placenta with levels peaking at 8 hr post-dose, and fetal tissue radioactivity peaked at 24 hr post-dose, suggesting placental transfer had occurred.

In a pre- and postnatal development study at oral doses of 1, 4, 12.5, and 40 mg/kg/day, there were adverse effects of lusutrombopag on postnatal development at a dose of 40 mg/kg/day (approximately 230 times the AUC observed in patients at the recommended clinical dose of 3-mg once daily), including prolongation of the gestation period in dams, low viability before weaning, delayed postnatal growth (such as delayed negative geotaxis, delayed eyelid opening, or low pup body weight), abnormal clinical signs (such as prominent annular rings on the tail

after weaning), low fertility index, a low number of corpora lutea or implantations, and an increased pre-implantation loss rate. The incidence of short thoracolumbar supernumerary ribs on postnatal Day 4 of F1 pups was high at doses of 12.5 mg/kg/day or more (approximately 89 times the AUC observed in patients at the recommended clinical dose of 3-mg once daily). Excretion of radioactivity into milk after single oral administration of [^{14}C]-lusutrombopag in nursing rats peaked at 12 hr post-dose.

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

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Primary pharmacology

Table 5 Summary of Primary Pharmacology Studies

Study No.	Study title	Findings
EB-063-N	Effect of RSC-888711 on Megakaryocyte Colony Formation from Human Bone Marrow derived CD34+ Cells	A MegaCult -C kit was used to assess RSC-888711 activity on megakaryocyte colony formation. After 12 days of incubation with RSC-888711, the number of megakaryocyte colony forming units were increased with an EC_{50} of 0.31 µM.
EB-121-N	Proliferative Effect of S-888711 on Ba/F3 Cells Expressing Human TPO Receptor	Incubation of human TPO receptor expressing Ba/F3-hMpl cells with RSC-888711 for 3 days resulted in increased proliferation with an EC_{50} of 84.0 nM
EB-122-N	Study for Signal Transduction of S-888711 in Ba/F3 Cells Expressing Human TPO Receptor	Incubation of Ba/F3-hMpl cells with RSC-8887111 for 15 minutes induced phosphorylation of JAK2, STAT3, STAT5 and p44/42 MAPK. The same pathways were activated by incubation with human recombinant TPO.
EB-158-N	Proliferative Effect of S-888711 on Cytokine Dependent Cells	Incubation of RSC-888711 with cell lines expressing EPO, G-CSF, IL-3 and GM-CSF receptors did not result in proliferation.
EB-189-N	Proliferative Effect of S-888711 Metabolites on Ba/F3 Cells Expressing Human TPO Receptor	Incubation of Ba/F3-hMpl cells with the RSC-888711 metabolites RSC-8887111-deshexyl and -5-keto resulted in proliferative activity with EC_{50} values of approximately 35 and .56 µM, respectively.
EB-042-N	Effect of RSC-888711 on Platelet Production in Human TPO Receptor Knock-in Mice	RSC-888711 was administered to TPOR-Ki/Shi mice, a chimeric TPO knock-in mouse model, at 0.3, 1, 3, and 10 mg/kg. Administration of RSC-888711 resulted in a statistically significant dose-dependent increase in platelet count when compared to vehicle control.

EB-131-N	Effect of S-888711 on Platelet Production for Six-Week Administration in TPORKi/Shi Mice)	RSC-888711 was administered to TPOR-Ki/Shi mice, at 0.3, 1, and 3-mg/kg/day for six weeks. Administration of RSC-888711 resulted in a statistically significant dose-dependent increase in platelet count when compared to vehicle control that reached maximum platelet production on days 8, 29, and 36 for the low, mid and high-dose groups, respectively.

Secondary Pharmacology

In study EF-275-N, the pharmacological activity of lusutrombopag was assessed in 11 enzyme assays and 30 receptor binding assay. In total, 5 enzyme assays had inhibition greater than 50% at 10 µM. There were no significant effects observed in the receptor binding assays. The calculated IC_{50} values for the 5 targets are tabulated below.

Table 6 Enzyme Inhibition Profiling of Lusutrombopag

Assay Name	Species	IC_{50} (µM)
Cyclooxygenase COX-1	Human	16.2
Cyclooxygenase COX-2	Human	4.08
Phosphodiesterase PDE1	Bovine	1.36
Adrenergic α2C	Human	2.75
Leukotriene, BLT (LTB4)	Human	2.78

Safety Pharmacology

Neurological Effects: (Study No. SF-071-L, GLP-compliant) Male Sprague- Dawley rats were treated with a single oral dose of 0, 40, 200 or 1000 mg/kg of lusutrombopag. At doses ≥ 40 mg/kg, slight effects were observed that included cage licking, increased rearing and a decrease in fecal pellets.

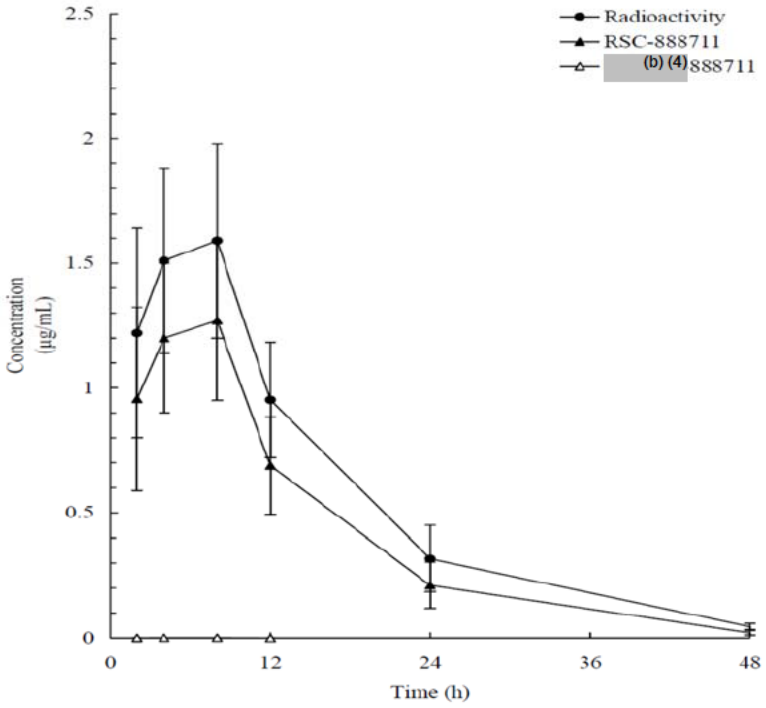
Cardiovascular Effects: (Study No. SF-073-L, GLP-compliant) Dogs were treated with single oral doses of 0, 100, 300, or 500 mg/kg of lusutrombopag. Blood pressure, heart rate, electrocardiograms (ECG) parameters and analysis of arrhythmia were examined at 1 hour before administration and, 1, 2, 4, 8, and 24 hours after administration. Blood samples were collected 1, 2, 4, 8, and 24 hours after dosing. No toxicologically significant effects were observed.

Effects on hERG Channel: (Study No. SF-075-L, GLP-compliant) lusutrombopag solutions at 0.1, 1 and 10 µM resulted in tail peak current changes from pre-application of 17.0, 29.0 and 38.3%, respectively, showing significant difference from that of the vehicle control (DMSO), which had a change of 3.7%. IC_{50} was estimated to be 70.04 µmol/L.

Pulmonary Effects: (Study No. SF-072-L, GLP-compliant) Male Sprague- Dawley rats were treated with a single oral dose of 0, 40, 200, or 1000 mg/kg lusutrombopag and respiration rate and tidal volume were measured at 1, 2, 4, and 8 hours post-dose. No toxicologically significant effects were observed.

5.4. ADME/PK

Table 7 ADME and Toxicokinetic Summary

Type of Study	Major Findings
Absorption	
PF-037-N: Plasma Concentration Following Single Oral Administration of [^{14}C]-RSC-888711 in Rats	After a single oral administration of [^{14}C]-RSC-888711 to rats at 3-mg/kg, the maximum concentration of radioactivity and RSC-888711 in plasma were reached at 7 hours. RSC-888711 accounted for more than 73% of radioactivity, making it the predominant component. The (b) (4) of RSC-888711 was present at similar levels in plasma as the test substance.  (Excerpted from Sponsor's submission)
Distribution	
PF-138-N: Quantitative Whole-body Autoradiography Following Repeated Oral Administration of [^{14}C]-S-888711 in Rats	Distribution was relatively similar between multiple studies. Radioactivity concentration in plasma 4 hours after the last dose (Day 14) was 2.16 µg equiv/g. The tissues with the highest concentrations of radioactivity above the level measured in plasma are tabulated below.

	<table><tr><th>Tissue</th><th>Radioactivity (µg equiv/g)</th></tr><tr><td>Liver</td><td>9.84</td></tr><tr><td>Non-fundic stomach</td><td>7.11</td></tr><tr><td>Adrenal cortex</td><td>7.52</td></tr><tr><td>Adrenal medulla</td><td>4.27</td></tr><tr><td>Small intestine</td><td>3.92</td></tr><tr><td>Large intestine</td><td>2.85</td></tr></table>
PB-226-N: Excretion into Milk of Radioactivity after Single Oral Administration of [^{14}C]-S-888711 in Nursing Rats	<table><tr><th colspan="3">Lusutrombopag</th></tr><tr><th></th><th colspan="2">Concentration (µg eq./mL)</th></tr><tr><th>Time (hr)</th><th>Plasma</th><th>Milk</th></tr><tr><td>2</td><td>1.94 ± 0.56</td><td>1.07 ± 0.31</td></tr><tr><td>4</td><td>2.12 ± 0.61</td><td>2.38 ± 0.88</td></tr><tr><td>8</td><td>2.09 ± 0.26</td><td>4.19 ± 1.03</td></tr><tr><td>12</td><td>1.8 ± 0.39</td><td>4.87 ± 1.30</td></tr><tr><td>24</td><td>0.58 ± 0.14</td><td>2.44 ± 0.72</td></tr><tr><td>48</td><td>0.076 ± 0.024</td><td>0.492 ± 0.342</td></tr></table>
PB-227-N: Quantitative Whole-Body Autoradiography after Single Oral Administration of [^{14}C]-S-888711 in Pregnant Rats	After single oral administration of [^{14}C]- lusutrombopag at 3-mg/kg in pregnant rats, radioactivity in the placenta reached maximum levels (2649 ng eq. of lusutrombopag/g) at 8 hr post-dose. Fetal tissue contained highest radioactivity levels at 24 hr post-dose. These results indicate that drug-derived radioactivity was transferred to fetus via placenta.
Metabolism	
Study numbers: PF-228-N; PB-229-N; PF-035-N; PF-100-N	Radioactivity after a single oral administration of [^{14}C]-lusutrombopag was measured in the plasma of multiple species from 2 to 24 hours post-dose. Approximate percentages of identified metabolites are tabulated below. <table><tr><th colspan="5">Lusutrombopag metabolites (approx. % of total radioactivity)</th></tr><tr><th>Metabolite</th><th>Mice</th><th>Rats</th><th>Rabbits</th><th>Dogs</th></tr><tr><td>Unchanged</td><td>70-80</td><td>70-80</td><td>90</td><td>80</td></tr><tr><td>Acyl-glucuronide</td><td>7.7-15.9</td><td>-</td><td>-</td><td>-</td></tr><tr><td>Deshexyl</td><td>1.8-2.0</td><td>-</td><td>0.4-0.6</td><td>-</td></tr><tr><td>β-oxidated carboxylic acid</td><td>-</td><td>ND-1.1</td><td>0.2-0.3</td><td>0.4-1.6</td></tr><tr><td>5-keto</td><td>1.7-1.8</td><td>1.8-5.0</td><td>1.8-3.5</td><td>3.7-4.4</td></tr></table> ND – not detected; "-" – not reported

Excretion

PF-034-N: Urinary, Fecal and Biliary Excretion Following Single Oral Administration of [^{14}C]-RSC-888711 in Rats

Biliary secretion of lusutrombopag into the intestines and excretion through feces is the primary route of elimination.

Cumulative recovery of radioactivity					
Bile duct	**Bile**	**Urine**	**Feces**	**Carcass**	**Total**
Intact	-	0.5%	95.9%	0.8%	96.5%
Cannulated	23.7%	0.2%	70.6%	2.0%	100.8%

"-" – not reported

TK data from general toxicology studies

TB-046-L: One-Month Oral Toxicity Study of RSC-888711 in Rats

Lusutrombopag				
Day	**Dose (mg/kg/day)**	**Sex**	**C_{max} (ug/mL)**	**AUC_{0-24} (ng*hr/mL)**
1	8	M	6.0	88.2
		F	7.6	124.8
	40	M	30.1	461.4
		F	40.7	501.7
	200	M	51.9	960.9
		F	75.7	1452.1
	1000	M	34.9	610.2
		F	40.9	767.0
30	8	M	7.4	93.1
		F	11.9	196.5
	40	M	30.9	446.9
		F	47.8	838.6
	200	M	56.6	968.8
		F	123.3	2695.7
	1000	M	28.4	447.8
		F	49.4	952.0

TB-047-L: One-Month Oral Toxicity Study of RSC-888711 in Dogs

Lusutrombopag				
Day	**Dose (mg/kg/day)**	**Sex**	**C_{max} (ug/mL)**	**AUC_{0-24} (ng*hr/mL)**
1	3	M	5.4	44.0
		F	5.5	43.9
	10	M	15.9	129.8
		F	10.9	103.7
	30	M	16.8	172.7

			F	13.3	127.9
		300	M	11.4	116.4
			F	9.0	114.4
	30	3	M	4.8	38.1
			F	4.7	41.0
		10	M	16.1	138.5
			F	14.7	136.4
		30	M	21.5	200.7
			F	16.0	148.1
		300	M	17.1	219.6
			F	14.1	179.8

TF-127-L: Six-Month Oral Toxicity Study of S-888711 in Rats

Lusutrombopag				
Day	**Dose (mg/kg/day)**	**Sex**	**C_{max} (ug/mL)**	**AUC_{0-24} (ng*hr/mL)**
1	2	M	1.7	21.9
		F	2.7	39.2
	20	M	21.5	321
		F	26.8	423
	100	M	31.5	483
		F	38.5	691
91	2	M	4.7	48.5
		F	6.0	80.7
	20	M	22.0	301
		F	46.7	803
	100	M	28.4	435
		F	64.9	1110
182	2	M	3.3	35.7
		F	6.2	77.6
	20	M	24.3	391
		F	70.8	993
	100	M	28.6	441
		F	84.4	1550

TF-163-L: Nine-Month Oral Toxicity Study of S-888711 in Dogs

Lusutrombopag				
Day	**Dose (mg/kg/day)**	**Sex**	**C_{max} (ug/mL)**	**AUC_{0-24} (ng*hr/mL)**
1	3	M	0.31	3.8
		F	0.39	5.5

	10	M	1.1	15
		F	1.4	18
	100	M	7.4	97
		F	8.0	123
182	3	M	0.47	5.2
		F	0.56	6.8
	10	M	1.8	23
		F	1.2	15
	100	M	10.9	137
		F	7.4	106
273	3	M	0.38	4.3
		F	0.35	4.2
	10	M	1.4	20
		F	1.3	14
	100	M	8.0	107
		F	7.0	108

TK data from reproductive toxicology studies

TF-106-L: Oral Study for Effects of RSC-888711 on Embryo-Fetal Development in Rats

Rat

Lusutrombopag				
Gestation Day	**Dose (mg/kg/day)**	**C_{max} (ug/mL)**	**AUC_{0-24} (ng*hr/mL)**	**Tmax (hr)**
7	4	3.69	64.1	6.0
	12.5	13.1	244	6.7
	40	33.5	631	8.0
	80	36.0	687	8.0
17	4	6.78	124	8.0
	12.5	21.9	392	6.7
	40	62.7	1228	8.0
	80	52.6	1045	3.7

TF-107-L: Oral Study for Effects of RSC-888711 on Embryo-Fetal Development in Rabbits

Rabbit

Lusutrombopag				
Gestation Day	**Dose (mg/kg/day)**	**C_{max} (ug/mL)**	**AUC_{0-24} (ng*hr/mL)**	**Tmax (hr)**
6	100	8.24	140	6.7
	300	17.6	332	13.3
	1000	23.6	440	12.0
18	100	8.10	149	2.7
	300	30.5	662	3.3

		1000	38.0	588	2.0

TK data from Carcinogenicity studies

TF-219-L: Carcinogenicity Study (Gavage) of S-888711 in Mice for 104 Weeks

Mouse

Lusutrombopag				
Week	**Dose (mg/kg/day)**	**Sex**	**C_{max} (ug/mL)**	**AUC_{0-24} (ng*hr/mL)**
13	2	M	1.9	24.1
		F	0.42	5.4
	6	M	4.2	53
		F	2.3	31
	20	M	14.2	177
		F	13.6	168
26	2	M	1.2	15.3
		F	0.63	8.6
	6	M	6.5	83
		F	2.4	28
	20	M	18.7	227
		F	9.6	124

TF-218-L: Carcinogenicity Study (Gavage) of S-888711 in Rats for 104 Weeks

Rat

Lusutrombopag				
Week	**Dose (mg/kg/day)**	**Sex**	**C_{max} (ug/mL)**	**AUC_{0-24} (ng*hr/mL)**
13	2	M	1.6	21.5
	6	M	3.4	46.0
	20	M	8.4	110
	0.5	F	0.7	12.1
	1	F	1.7	31.0
	2	F	3.0	53.3
26	2	M	1.1	17.3
	6	M	3.9	56.1
	20	M	9.8	135
	0.5	F	0.98	18.4
	1	F	2.4	44.7
	2	F	4.7	83.4

5.5. Toxicology

5.5.1. General Toxicology

The repeat-dose toxicity studies for lusutrombopag were conducted in the rat and dog. A 6-month repeat-dose study was conducted in Crl:CD(SD) rats at doses of 2, 20 or 100 mg/kg/day. The high dose in the rat study was selected based on a preliminary 1-month study (TB-046-L) that had a NOAEL of 8 mg/kg/day and a dose-dependent increase in exposure up to 200 mg/kg/day. The low and mid dose groups were set to establish a dose dependent relationship. A 9-month repeat-dose study was conducted in Beagle dogs at doses of 3, 10, or 100 mg/kg/day. The high dose in the dog study was based on a preliminary 3-month study (TB-126-L) that had histopathological evidence of toxicity to the intestine and adrenal gland at the mid dose of 80 mg/kg/day. The low and mid dose were selected to establish a dose-dependent relationship. Findings from the repeat-dose toxicity studies are reviewed below.

Study title/ number: Six-Month Oral Toxicity Study of S-888711 in Rats/ TF-127-L

Key Study Findings

- In male rats, PT and APTT were significantly increased in the high dose group when compared to controls. The degree of change was less after recovery but remained statistically significant.
- Administration of lusutrombopag resulted in small but dose-dependent and statistically significant increases in multiple electrolytes.
- The primary target organ of toxicity was the kidney. A dose-dependent and statistically significant increase in organ weight was reported that was accompanied by slight to moderate histopathology findings and an increase in protein positive urine.
- A severe decrease of the corpus luteum was reported in female rats that occurred in a dose-dependent manner.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
<u>Methods</u>	
Dose and frequency of dosing:	2, 20, or 100 mg/kg/day
Route of administration:	Oral gavage
Formulation/Vehicle:	Polyethylene glycol 400 with 5 w/w% polyoxyethylene sorbitan monooleate (PEG/Tw 80)
Species/Strain:	Crl:CD(SD) rats
Number/Sex/Group:	12/sex/group

Age:	6 weeks
Satellite groups/ unique design:	4-week recovery of 8/sex/group (control and high dose) and TK treatment groups of 6/sex/group
Deviation from study protocol affecting interpretation of results:	None

Table 8 Observation and Results of Lusutrombopag in Crl:CD(SD) Rats at 6 months

<table>
<tr><th>Parameters</th><th>Major findings</th></tr>
<tr><td>Mortality</td><td>One animal from the low dose group died on day 179 with no abnormal clinical signs. Pathological examination revealed hemorrhage that was likely due to a dosing error. No other unscheduled deaths occurred during the study.</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>Unremarkable</td></tr>
<tr><td>Hematology</td><td>
<table>
<tr><th></th><th colspan="4">Male</th><th colspan="4">Female</th></tr>
<tr><td>Dose (mg/kg/day)</td><td>0</td><td>2</td><td>20</td><td>100</td><td>0</td><td>2</td><td>20</td><td>100</td></tr>
<tr><td>PT (s)</td><td>11.7</td><td>13.8</td><td>14.9</td><td>17.6</td><td>7</td><td>6.9</td><td>6.9</td><td>6.9</td></tr>
<tr><td>APTT (s)</td><td>20</td><td>21</td><td>21</td><td>23</td><td>17.8</td><td>18</td><td>17.5</td><td>17.2</td></tr>
<tr><td colspan="9">Recovery (+4 weeks)</td></tr>
<tr><td>PT (s)</td><td>9.3</td><td>-</td><td>-</td><td>12.6</td><td>7</td><td>-</td><td>-</td><td>6.9</td></tr>
<tr><td>APTT (s)</td><td>18.7</td><td>-</td><td>-</td><td>20.2</td><td>18.3</td><td>-</td><td>-</td><td>17.4</td></tr>
</table>
Bold = p < 0.05"-" – not reported
</td></tr>
<tr><td>Clinical Chemistry</td><td>Small but statistically significant changes were observed in inorganic phosphorous (IP), sodium (Na) and chloride (Cl) that did not persist through recovery.
<table>
<tr><th colspan="7">Clinical chemistry (% change from control)</th></tr>
<tr><th></th><th colspan="3">Male</th><th colspan="3">Female</th></tr>
<tr><td>Dose (mg/kg/day)</td><td>2</td><td>20</td><td>100</td><td>2</td><td>20</td><td>100</td></tr>
<tr><td>IP</td><td>7.97</td><td>4.17</td><td>11.41</td><td>0.36</td><td>-3.20</td><td>0.18</td></tr>
<tr><td>Na</td><td>0.55</td><td>1.11</td><td>1.25</td><td>-0.21</td><td>0.56</td><td>1.32</td></tr>
<tr><td>Cl</td><td>0.00</td><td>1.53</td><td>1.53</td><td>-1.12</td><td>-0.75</td><td>-1.40</td></tr>
<tr><td colspan="7">Recovery (+4 weeks)</td></tr>
<tr><td>IP</td><td>-</td><td>-</td><td>0.55</td><td>-</td><td>-</td><td>-2.49</td></tr>
<tr><td>Na</td><td>-</td><td>-</td><td>0.56</td><td>-</td><td>-</td><td>0.28</td></tr>
<tr><td>Cl</td><td>-</td><td>-</td><td>0.38</td><td>-</td><td>-</td><td>0.47</td></tr>
</table>
Bold = p < 0.05"-" – not reported
</td></tr>
<tr><td>Urinalysis</td><td>
<table>
<tr><th></th><th colspan="4">Male</th><th colspan="4">Female</th></tr>
<tr><td>Dose (mg/kg)</td><td>0</td><td>2</td><td>20</td><td>100</td><td>0</td><td>2</td><td>20</td><td>100</td></tr>
<tr><td>No. of animals</td><td>10</td><td>10</td><td>10</td><td>10</td><td>10</td><td>10</td><td>10</td><td>10</td></tr>
<tr><td>Protein positive</td><td colspan="8"></td></tr>
</table>
</td></tr>
</table>

	Week 13								
	negative	0	0	0	0	3	3	1	0
	trace	5	3	0	0	5	4	1	0
	slight	4	7	3	5	2	3	5	1
	moderate	1	0	6	5	0	0	3	5
	considerable	0	0	1	0	0	0	0	3
	severe	0	0	0	0	0	0	0	1
	Week 26								
	negative	0	0	0	0	0	1	0	0
	trace	0	0	0	0	1	2	3	0
	slight	7	6	4	3	8	5	6	3
	moderate	1	2	5	3	0	2	1	3
	considerable	2	2	1	4	1	0	0	2
	severe	0	0	0	0	0	0	0	2
	Recovery (+4 weeks, n = 6))								
		0	-	-	0	1	-	-	0
	trace	0	-	-	0	2	-	-	1
	slight	1	-	-	3	1	-	-	3
	moderate	3	-	-	2	0	-	-	1
	considerable	2	-	-	1	2	-	-	0
	severe	0	-	-	0	0	-	-	1

"-" – not reported

Gross Pathology

	Male				Female			
Dose (mg/kg)	**0**	**2**	**20**	**100**	**0**	**2**	**20**	**100**
No. of animals	**12**	**11**	**12**	**12**	**12**	**12**	**12**	**12**
Liver								
Enlargment	0	0	0	2	0	0	0	0
Adrenal								
Brownish change, bilateral	0	0	0	2	0	0	0	6
Dark brownish spot, unilateral	0	0	0	0	0	0	0	1
Ovary								
Light brownish change, bilateral	-	-	-	-	0	0	2	8

"-" – not reported

Organ Weights

	Male				Female			
Dose (mg/kg/day)	**0**	**2**	**20**	**100**	**0**	**2**	**20**	**100**
Lung	0.24	0.26	0.26	0.25	0.37	0.37	0.37	0.38
Heart	0.24	0.25	0.25	0.25	0.31	0.30	0.32	0.33
Kidney (Left)	0.30	0.31	0.31	0.31	0.34	0.35	0.37	**0.42**
Kidney (Right)	0.31	0.32	0.31	0.32	0.36	0.36	**0.39**	**0.44**
Liver	2.85	2.72	2.60	2.82	2.60	2.71	**2.90**	**2.96**

	Ovary (Right, 10^{-3})	-	-	-	-	12.7	10.2	10.2	**8.8**
	Recovery (+4 weeks)								
	Lung	0.24	-	-	**0.26**	0.34	-	-	0.36
	Heart	0.24	-	-	**0.26**	0.29	-	-	**0.34**
	Kidney (Left)	0.29	-	-	0.31	0.32	-	-	0.37
	Kidney (Right)	0.29	-	-	**0.32**	0.33	-	-	0.37
	Liver	2.53	-	-	2.61	2.63	-	-	2.74
	Ovary (Right, 10^{-3})	-	-	-	-	9.8	-	-	11.4

Bold = $p < 0.05$; "-" – not reported

Histopathology
Adequate battery: Yes

	Male				Female			
Dose (mg/kg)	**0**	**2**	**20**	**100**	**0**	**2**	**20**	**100**
No. of animals	**12**	**11**	**12**	**12**	**12**	**12**	**12**	**12**
Kidney								
Cast, hyaline								
slight	5	7	5	9	1	1	2	4
moderate	0	0	0	0	0	0	0	2
Mineralization, glomerulus								
slight	0	0	1	3	0	0	10	10
moderate	0	0	0	0	0	0	0	2
Regeneration, tubule								
slight	7	6	9	10	1	2	1	6
moderate	0	0	0	1	0	0	0	2
Vacuolation, glomerulus								
slight	0	0	1	5	0	0	12	2
moderate	0	0	0	0	0	0	0	10
Adrenals								
Decrease, lipid, zona fasciulata cell								
slight	0	0	10	12	0	0	12	7
moderate	0	0	0	0	0	0	0	5
Ovaries								
Decrease, corpus luteum								
slight	-	-	-	-	0	1	0	0
moderate	-	-	-	-	3	1	0	2
severe	-	-	-	-	0	3	3	6
Cystic follicle								
slight	-	-	-	-	3	1	1	3
moderate	-	-	-	-	0	4	4	5

"-" – not reported

Study title/ number: Nine-Month Oral Toxicity Study of S-888711 in Dogs/ TF-163-L
Key Study Findings

- An increase in ALT levels was observed in the mid and high dose groups that reached statistical significance in females.
- Moderate to marked atrophy of the thymus was observed in males of the low and mid dose groups, respectively.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 3, 10 or 100 mg/kg/day
Route of administration: Oral gavage
Formulation/Vehicle: Vehicle: 0.5 w/v% methylcellulose (MC) solution
Species/Strain: Beagle dog
Number/Sex/Group: 4/sex/group
Age: 6 to 8 months old
Satellite groups/ unique design: 4-week recovery for control and high dose groups: 3/sex/group

Deviation from study protocol affecting interpretation of results: None

Table 9 Observation and Results of Lusutrombopag in Dogs at Nine Months

Parameters	Major findings
Mortality	No unscheduled deaths were considered test article related.
Clinical Signs	Unremarkable
Body Weights	Unremarkable
Ophthalmoscopy	Unremarkable
Hematology	Unremarkable
Clinical Chemistry	A statistically significant increase in ALT was observed in high dose females that did not persist through recovery.
Urinalysis	Unremarkable

ALT levels (% change from control)

	Male			Female		
Dose (mg/kg/day)	**3**	**10**	**100**	**3**	**10**	**100**
Week 13	-27.4	-7.4	45.5	-13.5	-17.0	**42.5**
Week 26	-19.7	34.1	36.7	-7.3	-1.1	46.6
Week 39	-11.0	4.3	17.6	3.5	59.2	**59.5**
Recovery (+4 weeks)						
Week 43	-	-	0.9	-	-	-8.8

Bold – $p < 0.05$"-" – not reported

Gross Pathology	Unremarkable
Organ Weights	Unremarkable
Histopathology **Adequate battery:**	Yes

	Male				Female			
Dose (mg/kg)	**0**	**3**	**10**	**100**	**0**	**3**	**10**	**100**
No. of animals	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
Gallbladder								
Vacuolation, mucosal epithelium								
very slight	0	0	2	0	0	0	0	1
slight	0	0	0	4	0	0	0	3
Thymus								
Atrophy								
very slight	2	1	2	2	1		2	2
slight	1	2	1	2	3	3	1	2
moderate	0	1	0	0	0	0	0	0
marked	0	0	1	0	0	0	0	0
Thyroid								
Mononuclear cell infiltration								
slight	0	0	0	1	0	0	1	1
moderate	0	0	1	0	0	1	0	0

LD: low dose; MD: mid dose; HD: high dose.
-: indicates reduction in parameters compared to control.

General toxicology; additional studies
Study title/ number: One-month oral toxicity study of RSC-888711 in rats/ TB-046-L

RSC-888711 was administered to Crl:CD(SD) rats at doses of 8, 40, 200 or 1000 mg/kg/day for 28 days with a 4-week recovery period. Primary toxicities occurred at doses ≥ 40 mg/kg and were to epidermal tissue, kidney, and included coagulopathy. Specifically, toxicities included epidermal thickening, hyperkeratosis of the skin and forestomach, hypertrophy of the adrenal gland fasciculate zone, lymphocyte depletion the thymus cortex, cytoplasmic vacuolation of epithelial tissue of the Bowman's capsule in the kidney. The coagulopathy was characterized by prolongations of PT and APTT. Some changes in hematology were seen revolving around RBC decreases.

Study title/ number: Three-Month Oral Toxicity Study of S-888711 in Dogs/ TB-126-L

RSC-8887111 was administered to Beagle dogs at doses of 10, 80 or 600 mg/kg/day for 3 months with a 1-month recovery period. Primary toxicities occurred at doses ≥ 80 mg/kg and included lipid-like vacuoles in the duodenum and jejunum, decreases in lipids of cortical cells in the adrenals, and increases in cholesterol, transaminases and creatine kinase. Additionally,

hepatocyte hypertrophy and focal necrosis was observed but did not correspond to elevated transaminases.

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: Reverse Mutation Test of RSC-888711 with Bacteria/ TB-060-L

Key Study Findings:

- Compound was negative for mutagenicity in all strains at concentrations from 5 to 5000 µg/plate with and without S9 metabolic activation.

GLP compliance: Yes
Test system: TA98, TA100, TA1535, TA1537, and WP2 uvrA up to 5000 ug/plate; +/- S9
Study is valid: Yes

In Vitro Assays in Mammalian Cells

Study title/ number: Chromosomal Aberration Test of RSC-888711 in Cultured Chinese Hamster Lung Cells/ TF-061-L

Key Study Findings:

- Growth inhibition of lusutrombopag was tested with a dose range of 2.44 to 5000 µg/mL to determine appropriate concentrations for the cytogenetic test. Lusutrombopag was tested at concentrations from approximately 10 to 75 µg/mL without S9 and 20 to 150 µg/mL with S9, which corresponded to dose levels 2 times the ID_{50}. Lusutrombopag was negative for the induction of structural and numerical chromosome aberrations with and without S9 metabolic activation.

GLP compliance: Yes
Test system: Human peripheral blood lymphocytes up to 150 µg/mL ± rat S9.
Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/ number: Micronucleus Test of RSC-888711 with Mouse Bone Marrow Cells / TF-062-L

Key Study Findings:

- Lusutrombopag did not induce a biologically significant increase in the number of micronucleated polychromatic erythrocytes in bone marrow of male and female ICR mice at doses of 500, 1000, and 2000 mg/kg/day. Lusutrombopag did not demonstrate evidence of clastogenic activity and was concluded to be negative in the mouse micronucleus test.

GLP compliance: Yes
Test system: Cells of the bone marrow from the femur (5 per sex per treatment) of mice (ICR) were assessed for micronuclei in 2000 polychromic erythrocytes 24 hours after the oral administration of two daily doses at 0, 500, 1000, or 2000 mg/kg of lusutrombopag.
Study is valid: Yes

5.5.3. Carcinogenicity

The carcinogenic potential of lusutrombopag was investigated in 104-week studies conducted in CD-1 mice and Sprague-Dawley rats. In mice, lusutrombopag was administered at doses of 2, 6 or 20 mg/kg/day. In rats, lusutrombopag was administered at doses of 2, 6, or 20 mg/kg/day in males and 0.5, 1 or 2-mg/kg/day in females. The studies were conducted under a special protocol agreement (SPA) with concurrence from the executive carcinogenicity advisory committee (ECAC). Neither the survival analyses nor the tumor findings achieved statistical significance in either sex or species. Non-neoplastic findings were limited to increased incidence in granulosa cell hyperplasia in the ovaries of female rats.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Study title/ number: Oral Study for Effects of S-888711 on Fertility and Early Embryonic Development to Implantation in Rats/ TF-153-L

Key Study Findings

- Administration of lusutrombopag did not have any effects of toxicological concern on reproductive function.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
Methods	
Dose and frequency of dosing:	4, 20, or 100 mg/kg/day
Route of administration:	Oral gavage
Formulation/Vehicle:	Polyethylene glycol 400 solution containing Tween 80 at 5 w/w%
Species/Strain:	Sprague-Dawley rats; Crl:CD(SD)
Number/Sex/Group:	20/sex/group
Satellite groups:	None
Study design:	(1) Treated animals were mated with treated animals. 1 male rat was coupled with 1 female rat in the cohabitation phase. (2) Male rats: Test article was administered daily starting 28 days before cohabitation and continued through the cohabitation period until Day 63-66.

(3) Female rats: Test article was administered daily starting 14 days before cohabitation and continued through Gestation Day 7 (GD 7).
(4) Cohabitation period consisted of a maximum of 14 days.
(6) Female rats were sacrificed on GD 13 and offspring removed by Caesarean section.

Deviation from study protocol affecting interpretation of results: No

Table 10 Observations and Results of FEED Study in Rats

Parameters	Major findings
Mortality	No unscheduled deaths occurred during the study.
Clinical Signs	Exfoliation of the limbs occurred in the HD group for both sexes and the MD group for females.
Body Weights	Unremarkable
Necropsy findings	No effects of toxicological concern regarding reproductive function were observed. A decrease in progressive sperm rate and straight line velocity was observed in HD males but values remained within the range of historical controls. Failure to conceive occurred in 1 female in the control group and 2 females in the HD group. Fertility index for the HD group was within the range of historical controls.

Embryo-Fetal Development

Study title/ number: Oral Study for Effects of RSC-888711 on Embryo-Fetal Development in Rats / TF-106-L

Key Study Findings

- Maternal toxicity was observed was observed at doses ≥ 40 mg/kg.
- A significant decrease in fetal weights occurred in the high dose group (80 mg/kg)
- A trend of increased skeletal variations in the offspring occurred in all dose groups and reached statistical significance at doses ≥ 12.5 mg/kg.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 4, 12.5, 40, or 80 mg/kg/day
Route of administration: Oral gavage
Formulation/Vehicle: Polyethylene glycol 400 solution containing Tween 80 at 5 w/w%

Species/Strain:	Female Crl:CD (SD) rats
Number/Sex/Group:	20/F/group
Satellite groups:	Toxicokinetics 5/F/group
Study design:	(1) Females which had copulated were grouped on Day 0 of pregnancy (2) Animals were dosed twice daily from GD 7 – GD 17 (3) On GD 20, main study females were sacrificed and the fetuses removed by Caesarean section.
Deviation from study protocol affecting interpretation of results:	No

Table 11 Observations and Results of EFD Study in Rats

<table>
<tr><th>Parameters</th><th>Major findings</th></tr>
<tr><td>Mortality</td><td>No unscheduled deaths occurred during the study.</td></tr>
<tr><td>Clinical Signs</td><td>Unremarkable</td></tr>
<tr><td>Body Weights</td><td>A significant decrease in maternal body weight gain was observed in the HD and mid-HD group that corresponded to decreased body weight gain and food consumption. Fetal body weights were also significantly decreased in the HD group with no significant changes in placental weight when compared to the control. The gravid uterus weights and body weights without uterus were not reported.
<table>
<tr><th colspan="5">Body weight (% relative to control)</th></tr>
<tr><th>Dose (mg/kg/day)</th><th>4</th><th>12.5</th><th>40</th><th>80</th></tr>
<tr><td>Body weight gain</td><td>93%</td><td>93%</td><td>81%</td><td>78%</td></tr>
<tr><td>Body weight</td><td>99%</td><td>99%</td><td>95%</td><td>94%</td></tr>
<tr><td>Food consumption</td><td>99%</td><td>98%</td><td>89%</td><td>84%</td></tr>
</table></td></tr>
<tr><td>Necropsy findings Cesarean Section Data</td><td>
<table>
<tr><th colspan="6">Litter data (mean)</th></tr>
<tr><th>Dose (mg/kg/day)</th><th>0</th><th>4</th><th>12.5</th><th>40</th><th>80</th></tr>
<tr><td>Corpora lutea</td><td>15.0</td><td>14.8</td><td>15.1</td><td>14.6</td><td>15.2</td></tr>
<tr><td>Implantation sites</td><td>14.5</td><td>14.1</td><td>13.9</td><td>13.7</td><td>14.0</td></tr>
<tr><td>Live fetuses</td><td>14.0</td><td>13.6</td><td>12.8*</td><td>12.8</td><td>13.2</td></tr>
<tr><td>Total fetuses</td><td>279</td><td>271</td><td>255</td><td>255</td><td>251</td></tr>
<tr><td>Pre-implantation loss (%)</td><td>2.9</td><td>4.9</td><td>7.5</td><td>6.4</td><td>7.5</td></tr>
<tr><td>Post-implantation loss (%)</td><td>3.7</td><td>4.0</td><td>7.8</td><td>6.5</td><td>5.9</td></tr>
</table>
*p < 0.05
</td></tr>
</table>

Necropsy findings Offspring

Fetal weights (%relative to control)				
Dose (mg/kg/day)	4	12.5	40	80
Male	99%	99%	98%	93%*
Female	100%	98%	98%	93%*

Visceral abnormalities (%)					
Dose (mg/kg/day)	0	4	12.5	40	80
Short brachiocephalic artery					
Fetal incidence	0%	0%	1%	2%	3%
Litter incidence	0%	0%	5%	10%	16%

Skeletal variations (%)					
Dose (mg/kg/day)	0	4	12.5	40	80
Short supernumerary rib					
Fetal incidence	8%	30%	38%**	79%**	89%**
Litter incidence	40%	60%	85%	95%	100%
Cervical rib					
Fetal incidence	1%	2%	2%	10%	13%*
Litter incidence	10%	50%	10%	30%	47%

*p < 0.05; **p < 0.01

Degree of ossification (mean)					
Dose (mg/kg/day)	0	4	12.5	40	80
Degree of ossification					
No. of sternebrae	5.7	5.7	5.8	5.4	5.1**
Other bones	-	-	-	-	-

**p < 0.01

LD: low dose; MD: mid dose; HD: high dose

Study title/ number: Oral Study for Effects of RSC-888711 on Embryo-Fetal Development in Rabbits/ TF-107-L

Key Study Findings

- A slight decrease in total fetuses and a slight increase in preimplantation loss were reported but values remained within historical controls.
- A statistically significant increase in short supernumerary rib occurred in the mid-dose group (300 mg/kg).

Conducting laboratory and location: (b) (4)

(b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	100, 300, or 1000 mg/kg/day
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5 w/v% methylcellulose aqueous solution containing Tween 80 at 0.1 w/v%
Species/Strain:	Kbl: JW rabbits
Number/Sex/Group:	20/F/group
Satellite groups:	None
Study design:	(1) Females which had copulated were grouped on Day 0 of pregnancy (2) Animals were dosed twice daily from GD 6 – GD 18 (3) On GD 28, main study females were sacrificed and the fetuses removed by Caesarean section.
Deviation from study protocol affecting interpretation of results:	No

Table 12 Observations and Results of EFD Study in Rabbits

Parameters	Major findings
Mortality	No unscheduled deaths occurred during the study.
Clinical Signs	Unremarkable
Body Weights	Unremarkable
Necropsy findings Cesarean Section Data	

Litter data (mean)				
Dose (mg/kg/day)	**0**	**100**	**300**	**1000**
Corpora lutea	9.5	9.5	9.6	9.1
Implantation sites	8.7	8.6	8.8	7.8
Live fetuses	8.0	8.2	8.2	7.2
Total fetuses	152	147	139	136
Pre-implantation loss (%)	10.1	10.1	9.8	15.1
Post-implantation loss (%)	7.9	4.2	6.4	8.4

Necropsy findings Offspring	

Skeletal variations (%)				
Dose (mg/kg/day)	**0**	**100**	**300**	**1000**

	Full supernumerary rib				
	Fetal incidence	2%	6%	6%	8%
	Litter incidence	16%	39%	41%	26%
	Short supernumerary rib				
	Fetal incidence	8%	11%	24%*	10%
	Litter incidence	47%	50%	77%	47%

*p < 0.05

LD: low dose; MD: mid dose; HD: high dose

Prenatal and Postnatal Development

Study title/ number: Oral Study for Effects of S-888711 on Pre- and Postnatal Development, Including Maternal Function, in Rats/ TF-252-L

Key Study Findings

- Maternal toxicity was observed was observed in the high dose group (40 mg/kg).
- Developmental toxicities in the F1 generation occurred in the high dose group and included pup death, low body weight, low negative geotaxis scores, low rate of eyelid opening, and a reduced viability index.
- The F1 generation had retarded sexual maturation with a trend of decreases fertility in both males and females in the high dose groups.
- A statistically significant increase in the occurrence of short supernumerary rib in the F1 generation was observed at doses ≥ 12.5 mg/kg but did not persist through animal maturation.

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

Methods

Dose and frequency of dosing:	1, 4, 12.5, or 40 mg/kg/day
Route of administration:	Oral gavage
Formulation/Vehicle:	Polyethylene glycol 400 solution containing 5 w/w% Tween 80
Species/Strain:	Crl:CD(SD) Rats
Number/Sex/Group:	23/F/group
Satellite groups:	None
Study design:	(1) F0 generation rats were dosed daily from GD 7 – Day of Lactation (DL) 20 and sacrificed on Day 21 after delivery. (2) F1 generation pups were not directly administered lusutrombopag or vehicle.

	(3) F1 generation pups designated for histopathology or not selected for further evaluation were sacrificed on Day 21 after birth. (4) F1 generation dams were sacrificed on GD 15. (5) F2 embryos, number of postimplantation losses and their condition (classified as implantation site, placental remnant, or embryonic death) were recorded.
Deviation from study protocol affecting interpretation of results:	No

Table 13 Observation and Results of PPND Study in Rats

<table>
<tr><th>Generation</th><th>Major Findings</th></tr>
<tr><td>F0 Dams</td><td>A female in the HD group died on GD 23. The dam had opacity of the eyeball, small thymus and spleen, undeveloped mammary glands, and a fetus lodged in the uterine cervix. The death was attributed to difficult parturition and potentially substance related.
<table>
<tr><th colspan="5">F0 Generation (% relative to control)</th></tr>
<tr><th>Dose (mg/kg/day)</th><th>1</th><th>4</th><th>12.5</th><th>40</th></tr>
<tr><td colspan="5">Bodyweight</td></tr>
<tr><td>GD 20</td><td>99%</td><td>98%</td><td>96%*</td><td>91%**</td></tr>
<tr><td>DL 21</td><td>101%</td><td>99%</td><td>98%</td><td>97%</td></tr>
<tr><td colspan="5">Bodyweight gain</td></tr>
<tr><td>GD 20</td><td>101%</td><td>97%</td><td>93%</td><td>79%**</td></tr>
<tr><td>DL 21</td><td>151%</td><td>164%</td><td>143%</td><td>216%**</td></tr>
<tr><td colspan="5">Food consumption</td></tr>
<tr><td>GD 20</td><td>101%</td><td>99%</td><td>96%</td><td>92%*</td></tr>
<tr><td>DL 20</td><td>97%</td><td>98%</td><td>95%</td><td>91%*</td></tr>
</table>
</td></tr>
<tr><td>F1 Generation</td><td>There were 2 deaths in the HD group on Days 23 and 29 after birth. Animals had small thymus, markedly low body weight, decreased spontaneous activity, rough fur and/or soft stool.

In the HD group, animals presented the low negative geotaxis scores and low completion rate of eyelid opening on Day 14 after birth. Prominent annular rings</td></tr>
</table>

were also observed on the tail but did not persist through maturation.

Pup Viability (%)					
Dose (mg/kg/day)	0	1	4	12.5	40
Pups delivered (mean)	14.2	14.1	13.9	13.8	12.9
Viability index[a]	96.7	91.6	97.7	90.4	85.9
Lactation index[b]	97.8	94.9	99.5	100	99.4

[a]Number of live pups on day 4 postpartum/number of liveborn pups on day 1 postpartum

[b]Number of live pups on day 21 (weaning) postpartum/number of live pups on day 4 postpartum

Bodyweight (g, mean)					
Dose (mg/kg/day)	0	1	4	12.5	40
Males					
Day 0	6.63	6.40	6.70	6.54	6.44
Day 21	61.72	57.76	59.48	57.66	53.50**
Females					
Day 0	6.31	5.99	6.32	6.15	6.00
Day 21	60.06	55.34*	57.13	55.48*	52.17**

*p < 0.05; **p < 0.01

Necropsy observations (%)					
Dose (mg/kg/day)	0	1	4	12.5	40
Supernumerary rib[a]					
Litter incidence	4.7	3.7	10.7	32.3**	78.2**
Pup incidence	13.0	15.8	31.8	76.2	94.4

[a]not present in any mature animals; **p < 0.01

Sexual maturation (mean)					
Dose (mg/kg/day)	0	1	4	12.5	40
Preputial separation (Day 45)	82.6	66.7	69.6	57.1	55
Fertile males (%)	95.5	95.0	100	100	88.9
Vaginal patency (Day 35)	82.6	85.7	91.3	81.0	76.2
Fertile females (%)	84.0	84.0	84.6	80.8	65.4
Pre-implantation loss (%)	5.6	6.4	6.0	4.6	18.2

F2 Generation	Unremarkable

5.5.5. Other Toxicology Studies

Not Applicable

Brian Cholewa, PhD	Christopher Sheth, PhD
Primary Reviewer	Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

Lusutrombopag is a small molecule thrombopoietin (TPO) receptor agonist that binds to the transmembrane domain of the human TPO receptors to stimulate megakaryocyte proliferation and differentiation, which results in increased platelet production. Lusutrombopag is proposed for the treatment of thrombocytopenia in adult patients with chronic liver disease (CLD) who are scheduled to undergo a procedure.

The safety and efficacy of MULPLETA® were evaluated in two randomized, double-blind, placebo-controlled trials (L-PLUS1 and L-PLUS2). Patients with chronic liver disease who were undergoing an invasive procedure and had a platelet count less than 50,000/μL were eligible to participate. The primary endpoint was the proportion of patients who did not require platelet transfusion prior to the invasive procedure or rescue therapy for bleeding from randomization through 7 days after the invasive procedure. In L-PLUS1, the proportion of patients meeting the primary endpoint was 76% in the MULPLETA® arm compared to 13% in the placebo arm (p-value < 0.0001). In L-PLUS2, the proportion of patients meeting the primary endpoint was 65% in the MULPLETA® arm compared to 29 % in the placebo arm (p-value < 0.0001).

A dose of 3-mg was selected based on a significantly lower rate of transfusion and a longer duration of platelet count > 50,000/μL compared to lower doses (0.25 to 2-mg). A higher dose of 4-mg was not selected due to a concern of increased incidences of thrombotic events.
No dose adjustment is required for patients with mild or moderate hepatic impairment, as Trials L-PLUS1and L-PLUS2 were conducted in patients with Child-Pugh Class A and B liver disease. Data were limited in patients with Child-Pugh Class C.

No dose adjustment is required for patients with renal impairment. The results of a mass balance study demonstrated that renal clearance accounted for 1% of lusutrombopag elimination. Based on population pharmacokinetic-pharmacodynamic (PK/PD) analysis, no dose adjustment is required based on renal function, age, sex, race/ethnicity, or body weight.
No dose adjustment is required based on drug-food interactions. A high-fat, high-calorie meal did not affect lusutrombopag exposure. Similarly, no dose adjustment is required based on drug-drug interactions. Lusutrombopag is metabolized by CYP4 enzymes, including CYP4A11. Based on *in vitro* screening studies, lusutrombopag is not likely to inhibit CYP enzymes and transporter systems. Lusutrombopag is a substrate of P-gp and BCRP, and its exposure increased with the co-administration of cyclosporine, albeit not to a clinically relevant extent. Co-administration of calcium carbonate with lusutrombopag did not affect its exposure, suggesting that it is not subject to interactions with antacids.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Mechanism of Action: Lusutrombopag is a thrombopoietin (TPO) receptor agonist
Absorption: The median time to maximum plasma concentration after a 3-mg dose is 4 hours. Food reduces AUC and C_{max} by approximately 9%.
Distribution: Lusutrombopag has a volume of distribution of 39.5 liters. The *in vitro* plasma protein binding of lusutrombopag is greater than 99.9%. Lusutrombopag does not distribute into red blood cells.
Metabolism: Lusutrombopag is primarily metabolized by ω-oxidation followed by β-oxidation of O-hexyl group. Lusutrombopag is metabolized by CYP4 enzymes, including CYP4A11.
Elimination: Approximately 83% of the administered radioactive lusutrombopag was excreted in feces and approximately 1% was excreted in urine. Terminal half-life was approximately 27 hours.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended dosing is one 3-mg tablet once daily taken orally with or without food for 7 days. Administration of MULPLETA® should be initiated 8-14 days prior to a scheduled procedure.

Therapeutic Individualization

No adjustments are proposed based on intrinsic or extrinsic factors.

No clinically significant differences in the pharmacokinetics of lusutrombopag were observed based on age or race/ethnicity. Though lusutrombopag exposure tends to decrease with increasing body weight, differences in exposure are not considered clinically relevant.
Safety and efficacy trials were conducted in patients with Child-Pugh Classes A and B liver disease, and data in patients with Child-Pugh Class C disease were limited. The mean observed lusutrombopag exposure decreased by 20% to 30% in patients (n=5) with severe (Child-Pugh Class C) hepatic impairment compared to patients with Child-Pugh Class A and Class B liver disease.

Renal clearance has minimal contribution to lusutrombopag elimination. Population pharmacokinetic analysis did not find a clinically meaningful effect of mild and moderate renal impairment on the pharmacokinetics of lusutrombopag. Data in patients with severe renal impairment are limited.

Food intake did not affect lusutrombopag exposure to a clinically relevant extent. Additionally, drug interactions with concomitant medications are unlikely based on the unique metabolic pathway of lusutrombopag, *in vitro* screening studies, and clinical DDI studies.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

PHARMACOLOGY	
Mechanism of Action	Lusutrombopag is a small molecule TPO receptor agonist that acts on the transmembrane domain of human TPO receptors expressed on megakaryocytes to induce the proliferation and differentiation of megakaryocytic progenitor cells from hematopoietic stem cells and megakaryocyte maturation.
Active Moiety	Lusutrombopag
QT Prolongation	In a thorough QT/QTc study with 6 mg lusutrombopag (2 times the recommended dose) and 24-mg (8 times the recommended dose), lusutrombopag did not have an effect on the QTc interval compared with placebo. Additionally, no correlation was found between plasma lusutrombopag concentration and ΔΔQTcF.
GENERAL INFORMATION	
Molecular Weight	591.54 g/mol
Formulation Development	A 1-mg tablet formulation was used in the dose finding study (M0626) in CLD patients. A 4-mg tablet formulation was used for the food effect study; the 4-mg tablet formulation was bioequivalent to the 1-mg formulation. A 3-mg tablet formulation was used in Study M0631 (registration trial in Japanese patients). The 4-mg formulation and the 3-mg formulation (b) (4). A manufacturing site change to produce the 3-mg tablet used in Study M0634 (global registration trial) and the to-be-marketed formulation was bridged using *in vitro* release similarity.
Bioanalysis	Lusutrombopag was measured using a validated LC/MS/MS method. A summary of the method validation report is included in Appendix 4.1.
Dose Proportionality	The PK of lusutrombopag exhibited dose-proportional increase in AUC and C_{max} after single doses ranging from 0.25 mg to 50 mg in healthy volunteers. Additionally, AUC and C_{max} exhibited dose proportional increase in AUC and C_{max} on Day 7 or Day 14 of continuous once daily dosing in the dose range of 0.5 to 2-mg in healthy volunteers.

	In thrombocytopenic subjects with CLD, the steady-state AUC and C_{max} lusutrombopag increased in a dose-proportional manner in the dose range of 0.25 to 4-mg.
Accumulation	The steady-state plasma concentration of lusutrombopag appeared to be achieved on Day 5. The accumulation of C_{max} and AUC_{0-24h} values on Day 7 or Day 14 relative to Day 1 was approximately 2-fold.
Variability	Pharmacokinetic data obtained from the dose escalation studies M0611 and M0613 demonstrated that lusutrombopag exhibited moderate variability. The %CV for AUC and C_{max} were typically below 25% when administered as a single doses or multiple doses. Based on the population PK modeling estimates, the interindividual variability in apparent clearance and volume of distribution were 30% and 32%, respectively.
ABSORPTION	
Absolute Bioavailability	The absolute bioavailability of lusutrombopag has not been characterized.
T_{max}	In patients with CLD, the peak lusutrombopag concentration was observed 6 to 8 hours after oral administration.
Food Effect	A high-fat and high-calorie meal resulted in a small decrease in AUC (9.1%) and C_{max} (8.5%) relative to AUC and C_{max} in the fasted state.
Substrate Transporter Systems	Lusutrombopag is a substrate of P-gp and BCRP. Administration of lusutrombopag with cyclosporine (an inhibitor of P-gp and BCRP) to healthy adults increased lusutrombopag AUC by 19% and C_{max} by 18% compared with lusutrombopag alone.
DISTRIBUTION	
Volume of Distribution	The apparent volume of distribution (% CV) during the terminal phase after a single oral dose of lusutrombopag 3-mg in healthy adult subjects was 39.5 (23.5) L.
Plasma Protein Binding	Lusutrombopag was highly bound to plasma proteins (≥ 99.9%).
Blood-to-Plasma ratio	Lusutrombopag exhibited limited distribution to red blood cells. The blood-to-plasma ratio was 0.56.
ELIMINATION	
Mean Terminal Half-Life	The mean terminal half-life of lusutrombopag (geometric mean [%CV]) after a single oral dose of 3-mg in healthy adult volunteers was 26.8 (8.8) hours.
METABOLISM	
Primary Metabolic Pathways	Lusutrombopag is metabolized by ω-oxidation followed by β-oxidation of *O*-hexyl group. Lusutrombopag is the main moiety in plasma in addition to other trace metabolites that were mostly undetectable. The main

	enzymes involved in lusutrombopag metabolism are CYP4, including CYP4A11.
Transporter Substrate	*In vitro,* lusutrombopag is not a substrate of OATP1B1, OATP1B3, or OCT1.
DDI Potential	Enzyme Inhibition *In vitro,* lusutrombopag had low potential to inhibit CYP enzymes (CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5). Enzyme Induction Lusutrombopag did not cause concentration-dependent increases in marker activities of CYP1A2, 2C9, 3A4, UGT1A2, 1A6, or 2B7 *in vitro.* Transporter Inhibition Lusutrombopag also has low potential to inhibit P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1, MATE2-K, and BSEP *in vitro.*
EXCRETION	
Primary Excretion Pathway	In the mass balance study with a 2-mg dose of ^{14}C-lusutrombopag, 83% of radioactivity was recovered in feces and 1% was recovered in urine.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes, the clinical pharmacology program provides supportive evidence of effectiveness. The applicant submitted results from several clinical trials to demonstrate the safety and efficacy of lusutrombopag for the proposed indication and to support dose selection (**Table 14**).

Table 14: A Summary Description of Clinical Studies Conducted to Support Dose Selection and Approval for the proposed Indication

Study	Description	Number of Subjects	Dose (mg)
1017M0623 **(M0623)**	Multiple-dose study in Japanese thrombocytopenic patients with CLD undergoing percutaneous liver ablation for primary hepatic cancer to determine PK after once daily doses for up to 7 days	35 (5 to 12 per dose group) PK subjects	0.25, 0.5, 1, 1.5, and 2-mg
1112M0625 **(M0625)**	Multiple-dose study in Japanese thrombocytopenic patients with CLD undergoing percutaneous liver ablation for primary hepatic cancer to determine PK after once daily doses for up to 7 days	21 (6 to 8 per dose group)	2.5, 3, and 4-mg

1208M0626 **(M0626)**	Multiple-dose, placebo-controlled study in Japanese thrombocytopenic patients with CLD undergoing percutaneous liver ablation for primary hepatic cancer to determine PK after once daily doses for up to 7 days	61 (15 to 16 per dose group and 15 for placebo)	2, 3, and 4-mg and placebo
1304M0631 **(M0631)**	Multiple-dose, placebo-controlled study in Japanese thrombocytopenic subjects with CLD undergoing and invasive procedure to determine the PK after once-daily doses for up to 7 days	48 per group	3-mg and placebo
1423M0634 **(M0634)**	Multiple-dose, placebo-controlled study in thrombocytopenic subjects with CLD undergoing an elective invasive procedure to determine PK after once-daily doses for up to 7 days	107 per group	3-mg and placebo

Evidence of safety and efficacy were obtained from two randomized, double-blind, placebo-controlled trials [M0631 (L-PLUS1) and M0634 (L-PLUS2)]. The two trials included patients with chronic liver disease who were undergoing an invasive procedure and had a platelet count less than 50×10^9/L. Patients received a 3-mg daily dose of lusutrombopag or placebo for 7 days.

The primary endpoint was the proportion of patients who did not require platelet transfusion prior to the invasive procedure or rescue therapy for bleeding from randomization through 7 days after the invasive procedure. The secondary endpoint was the proportion of responders. In study M0631, the proportion of patients who met the primary endpoint was 76% in the MULPLETA® arm compared to 13% in the placebo arm. In study M0634, the proportion of patients who met the primary endpoint was 65% in the MULPLETA® arm compared to 29 % in the placebo arm. Study results reached statistical significance.

Dose Selection

To support dose selection for the registration trial, a range of doses was investigated in Japanese subjects with CLD. Study M0623 investigated 0.25 mg (n=5), 0.5 mg (n=6), 1 mg (n=5), 1.5 mg (n=7), and 2-mg (n=12) doses administered every day for 7 days. There were no responders (subjects who had a platelet count of ≥ 50,000/μL and change from baseline ≥ 20,000/μL) in patients receiving doses 0.25 mg to 1.5 mg. At 2-mg dose, the proportion of responders was 33%. The proportion of patients who received platelet transfusion was decreased with increasing doses of lusutrombopag (**Figure 1**).

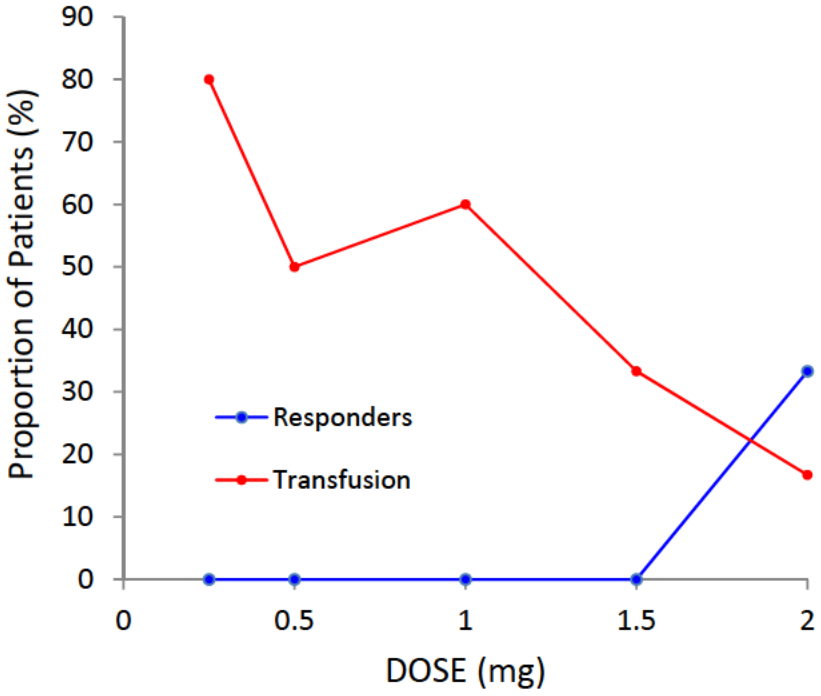


Figure 1: Proportion of responders (blue line) and proportion of patients who received transfusion (red line) in each dose cohort of lusutrombopag in study M0623

In a subsequent study (M0625), the sponsor investigated 2.5 mg (n=6), 3-mg (n=7), and 4-mg (n=8) daily dosing for 7 days. There was no clear trend in the proportion of responders or the proportion of patients who received transfusion with the administered dose level. Thus, the applicant conducted Study M0626 in larger cohorts of patients to support dose selection. Study M0626 is a multicenter, randomized, double-blind, parallel-group, placebo-controlled study of a once-daily oral dose of lusutrombopag 2-mg (n=15), 3-mg (n=16), and 4-mg (n=15) once daily for 7 days, in addition to a placebo group (n=15). The primary endpoint was the proportion of subjects who required no preprocedural transfusion platelet transfusion and the secondary endpoint was the proportion of responders.

The proportion of patients receiving no transfusion during the study was significantly higher in the lusutrombopag treatment groups relative to the placebo group. There was a dose-dependent increase in duration of platelet counts > 50,000/mL and the peak increase in platelet counts (**Figure 2**). Similarly, the duration of response was higher in the lusutrombopag treatment group and was dose-dependent; the number of days on which the proportion of responders exceeded 50% was highest on the 4-mg dose cohort (from day 8 to day 21) compared to the 3-mg cohort (day 11 to day 21) (**Figure 3**).

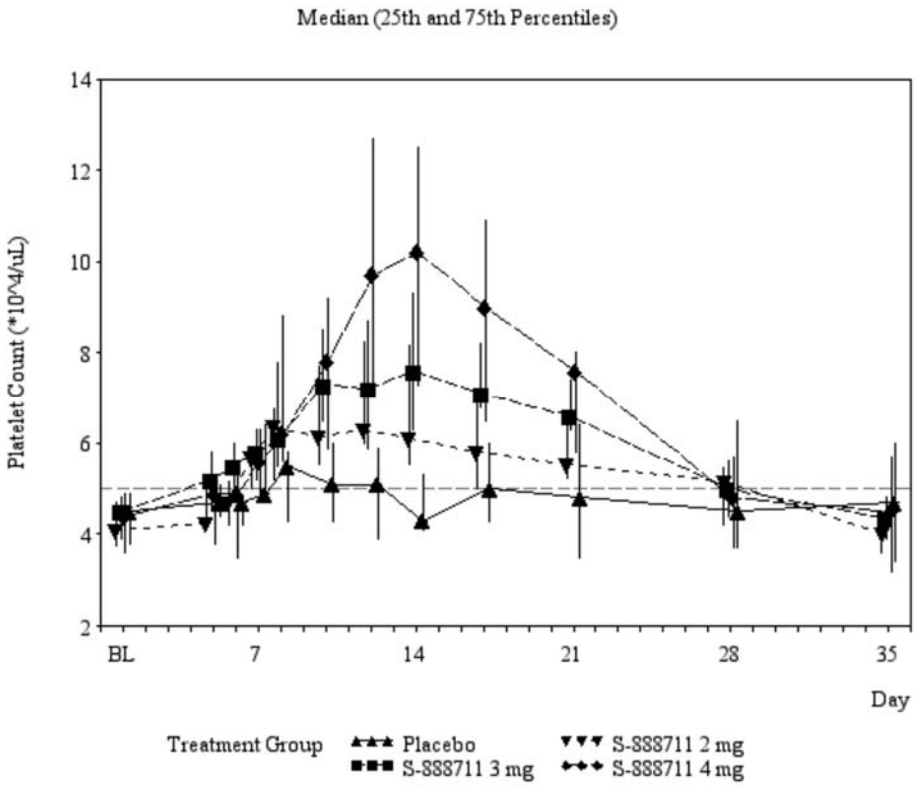


Figure 2: Time course of platelet counts after administration of placebo or 2-mg, 3-mg, or 4-mg doses of lusutrombopag. Data are presented as median platelet counts and error bars represent 25th and 75th percentiles.

A 3-mg dose was chosen for further development to minimize the probability of achieving platelet count higher than 200,000/μL. Of note, a platelet count of 200,000/μL has been associated with increased level of thrombotic events with another TPO agonist (PMID: 22913681). To further support the choice of the 3-mg dose, the applicant stated that high variability in platelet count may occur over a brief period and an increase in platelet counts beyond 200,000/μL may occur. For instance, one subject in study M0626 had a platelet count varying from 45,000/μL to 65,000 at baseline, and the platelet count increased immediately after the first dose of 3-mg to 195,000/μL.

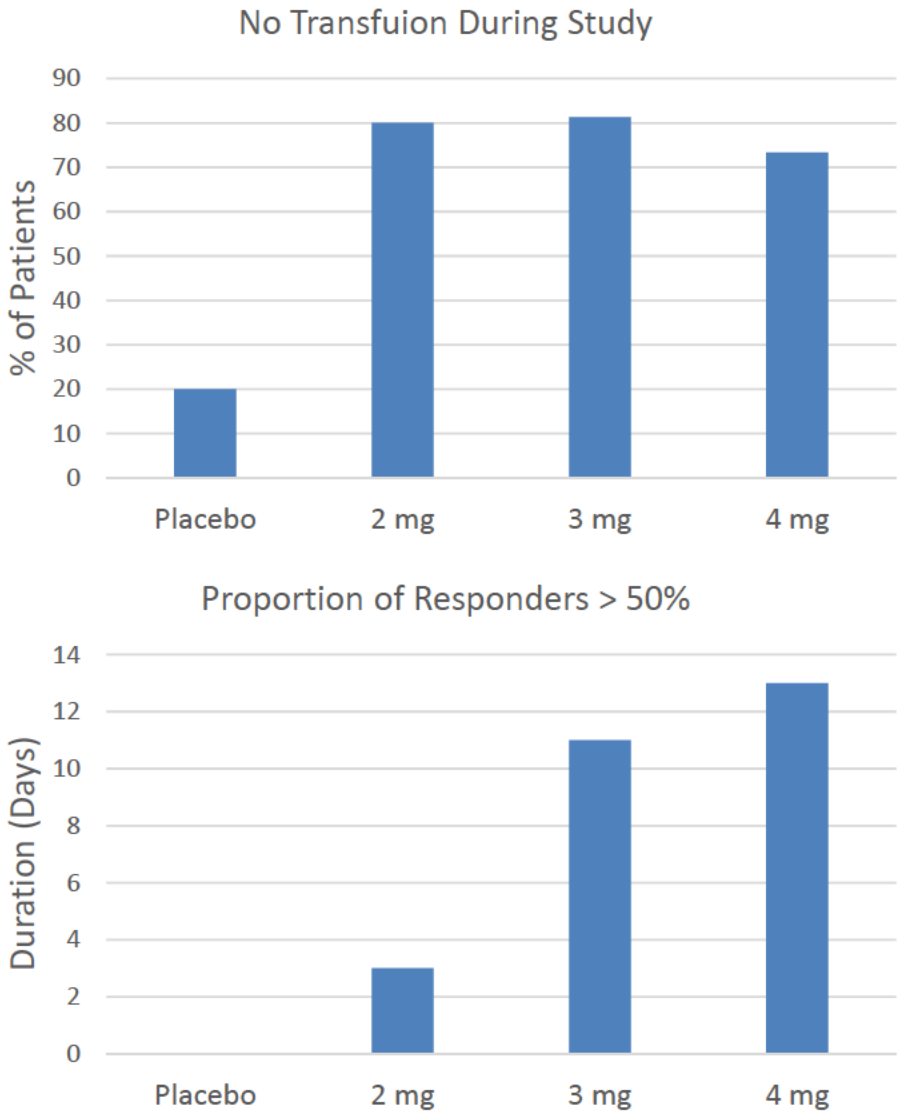


Figure 3: The proportion of patients receiving no transfusion during the study (top panel) and number of days on which the proportion of responders (defined as platelet count ≥ 50000/μL and change from baseline ≥ 20000/μL) exceeded 50% (bottom panel)

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

Yes, the proposed dosing regimen is appropriate based on evidence of effectiveness and safety from two randomized, double-blind, placebo-controlled trials (L-PLUS1 and L-PLUS2) and exposure response analyses.

Evidence of safety and effectiveness at the proposed dosing regimen were obtained from two registration trials:

- L-PLUS1(M0631) is a multicenter, randomized, double-blind, parallel-group, placebo-controlled study in Japanese patients
- L-PLUS2 (M0634) is a global multicenter, randomized, double-blind, parallel-group, placebo-controlled study.

Thrombocytopenic patients with CLD who had platelet count ≤ 50,000/μL and were scheduled to undergo an invasive procedure were randomized 1:1 to receive 3-mg of lusutrombopag once daily or placebo for 7 days prior to conducting the procedure on Day 9 to Day 14. Monitoring for platelet count and rescue transfusion were continued for 28 days' post-treatment. Patients were stratified by the planned primary invasive procedure (liver ablation/coagulation or other invasive procedures) and platelet count at screening (< 35,000/μL or ≥ 35,000/μL).
In study M0631, the primary endpoint was the proportion of patients who received no transfusion before the primary invasive procedure. The proportion of subjects who received no preprocedural platelet transfusion was significantly greater in the lusutrombopag group (79.2%, 38/48) compared to the placebo group (12.5%, 6/48) with a p-value < 0.0001.

In study M0634, the primary endpoint was the proportion of patients who received no transfusion before the primary invasive procedure and no rescue therapy for bleeding from randomization through 7 days after the primary invasive procedure. The proportion of subjects who met the primary endpoint was significantly higher in the lusutrombopag group (64.8%, 70/108) compared to the placebo group (29%, 31/107) with a p-value < 0.0001.

Exposure-Response Relationship

Population PK/PD model was developed to investigate the relationship between lusutrombopag plasma concentrations – pooled from multiple clinical studies in healthy subjects and patients – and the time course of platelet counts. Model simulations were conducted to assess the dose-response relationship. Detailed PK/PD data sources and analyses are described in Section 5.4

Population PK and/or PD Analyses.

Table 15: Summary of Simulated Platelet Indices for Dose Response

Dosage Regimen	Peak PLT Count Percentile (*10000/μL)			Pr (PLT ≥ 5) on Days 9 to 14 (%)	Pr (PLT > 20) (%)
	5th	50th	95th		
2-mg QD	4.00	6.34	10.6	75.9	0.07
3-mg QD	4.35	7.21	12.9	85.2	0.39
4-mg QD	4.68	8.05	15.0	90.4	1.05

The probability of maintaining platelet count ≥ 50,000/μL increased with increasing dose; similarly, the probability of increasing platelet count > 200,000/μL increased with increasing dose based on simulated platelet counts. At the proposed 3-mg dose, the probability of maintaining platelet counts ≥ 50,000/μL on Days 9 to 14 (i.e., days on which the invasive procedure is to be performed) was > 80%; similarly, the probability of reaching a platelet count > 200,000/μL was < 0.5% (**Table 15**).

Exposure-safety analysis was not conducted for lusutrombopag, due to the low frequency of adverse events in study M0631 and M0634. Additionally, there was no dose-dependent increase in the frequency or severity of adverse events in the dose selection study (M0626).

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

No, an alternative dosing regimen and management strategy is not required based on age, sex, race, or body weight.

Population PK analysis identified lower clearance in females (approximately 13%) compared to males and lower clearance in Japanese subjects (approximately 13%) compared to non-Japanese subjects. However, these changes were not deemed clinically significant.

Body weight had a substantial effect on the model predicted AUC and C_{max} of lusutrombopag; AUC and C_{max} decreased with increasing body weight. Patients in the with body weight >100 kg (n=9) had approximately 35% decrease in AUC compared to patients in the 60-80 kg (reference) group. Similarly, patients with body weight > 45 kg had approximately 50% increase in AUC compared to the reference group (**Figure 4**).

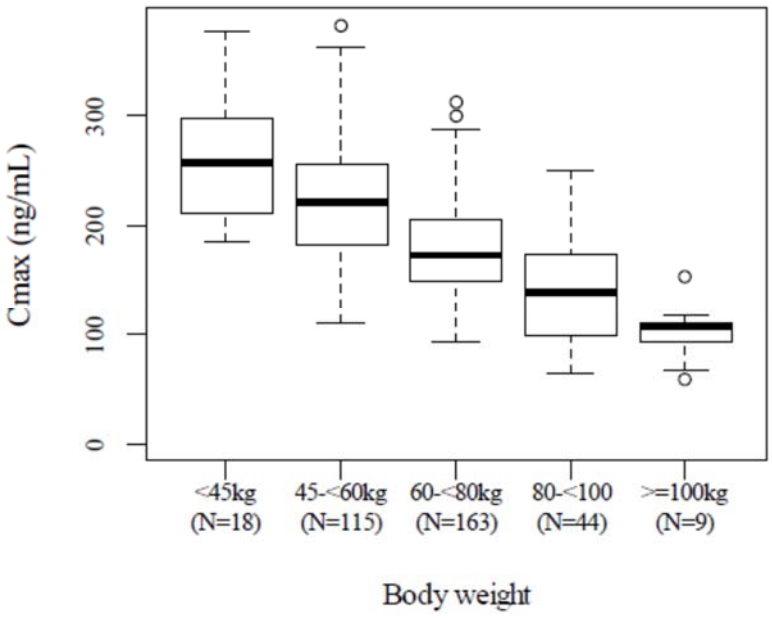
Based on model simulations, the resulting changes in platelet counts in body weight groups was less pronounced compared to the PK differences at 3-mg doses. The probability of achieving platelet counts ≥ 50,000/μL decreased by 11% in patients >100 kg and increased by 10% in patients < 45 kg when compared to the reference group. The probability of exceeding platelet

counts > 200,000 was decreased by 0.08 % in patients > 100 kg and increased by 0.25 % in patients < 45 kg.

In the lowest body weight group (< 45 kg), a dose reduction was not deemed necessary based on the favorable safety profile of lusutrombopag. There were no thrombotic events observed in these subjects in the Phase 3 studies (M0631 and M064).

In the highest body weight group (> 100 kg), a dose increase was not recommended. Obese patients are more likely to develop thrombotic events compared to normal body weight patients and invasive procedures further increase the risk of thrombotic events in the obese population (PMID: 16164883 & PMID: 22394567).

Additionally, patients with chronic liver disease are predisposed to increased thrombotic events, as well as bleeding events, due to imbalances in the coagulation and fibrinolysis processes (PMID: 29511162). In clinical practice, patients with liver disease are often given prophylaxis treatment to prevent thrombotic events (PMID: 28088580 & PMID: 21244669). The proposed dose of 3-mg is acceptable since the safety profile of a higher dose was not characterized in the highest body weight group – who have an increased predisposition to thrombotic events.



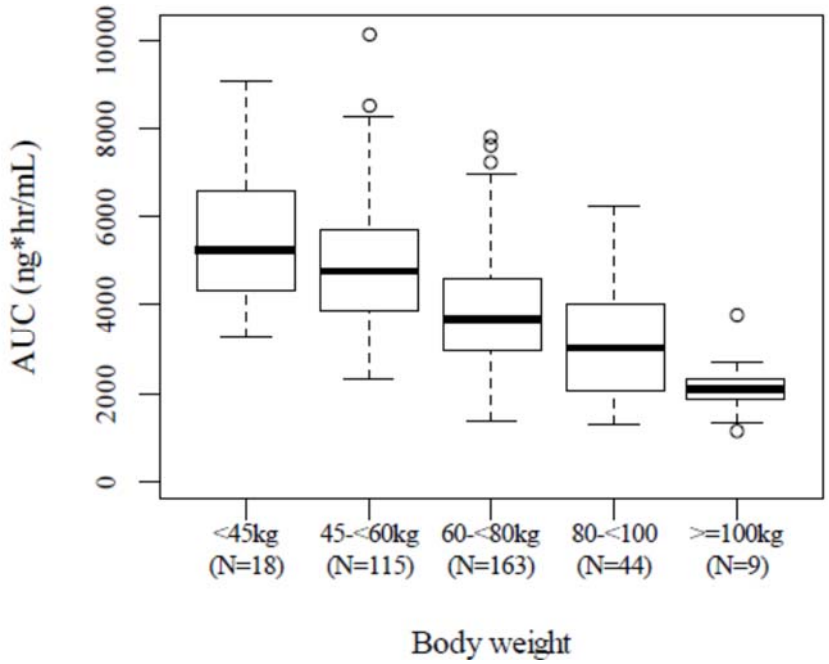


Figure 4: Effect of body weight on population PK predicted C_{max} and AUC

Hepatic Impairment

No dose adjustment is required for patients with hepatic impairment. The safety and efficacy of lusutrombopag were characterized in patients with Child-Pugh Class A and Class B. There are limited data in patients with Child-Pugh Class C liver disease.

Study M0616 was conducted in subjects with mild and moderate hepatic impairment after a single dose of lusutrombopag 0.75 mg. The AUC and C_{max} of lusutrombopag in subjects with mild hepatic impairment (Child-Pugh Class A) were increased by approximately 5% compared to subjects with normal hepatic function. In subjects with moderate hepatic impairment (Child-Pugh Class B), AUC increased by 20% and C_{max} increased by 5% compared to normal subjects (**Figure 5**).

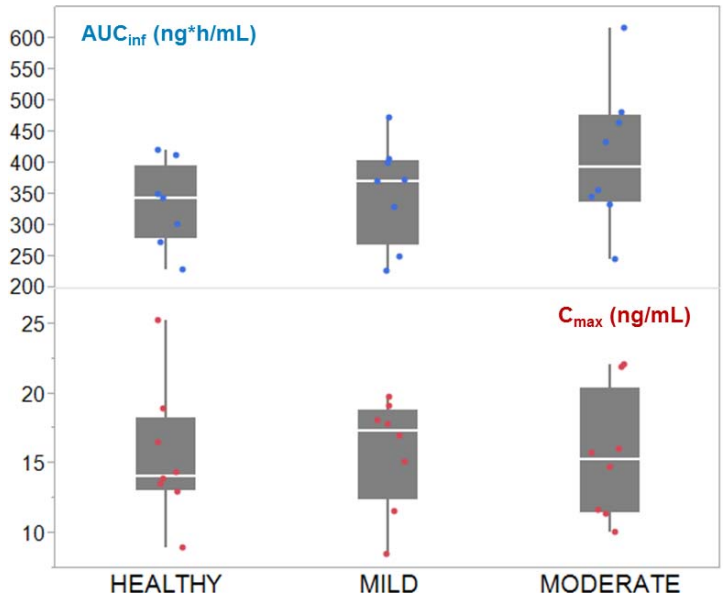


Figure 5: Effect of mild and moderate hepatic impairment on the pharmacokinetics of lusutrombopag

Study M0627 compared the PK of 3-mg lusutrombopag dose in patients with severe (Child-Pugh Class C), n=5), moderate (Child-Pugh Class B), and mild (Child-Pugh Class A) hepatic impairment. AUC and C_{max} decreased by 20-30% in patients with severe hepatic impairment compared to those with mild and moderate hepatic impairment. The decrease in exposure was attributed to decrease in absorption due to gastrointestinal changes rather than altered clearance (**Figure 6**).

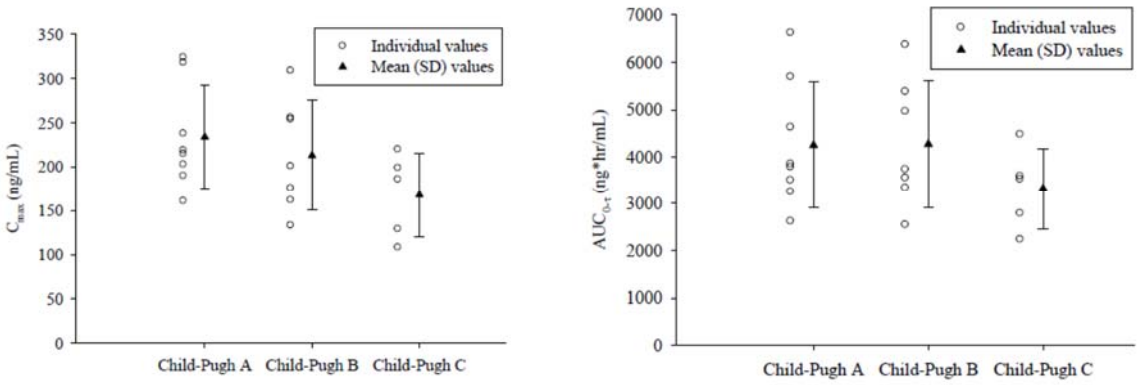


Figure 6: Lusutrombopag AUC and C_{max} among patients with Child-Pugh Class A, B, and C liver disease

Renal Impairment

No dose adjustment is required for patients with renal impairment. Renal clearance has minimal contribution to the elimination of lusutrombopag. After a 2-mg dose of [^{14}C]-lusutrombopag dose, approximately 1% of the administered radioactivity was recovered in urine.
Population PK analysis included 142 subjects with normal renal function (CLcr ≥ 90 mL/min), 139 subjects with mild renal impairment (CLcr 60 to > 90 mL/min), 67 subjects with moderate renal impairment (CLcr 30 to < 60 mL/min), and 1 subject with severe renal impairment (CLcr < 30 mL/min). Creatinine clearance was not identified as a statistically significant covariate on lusutrombopag clearance (**Figure 7**).

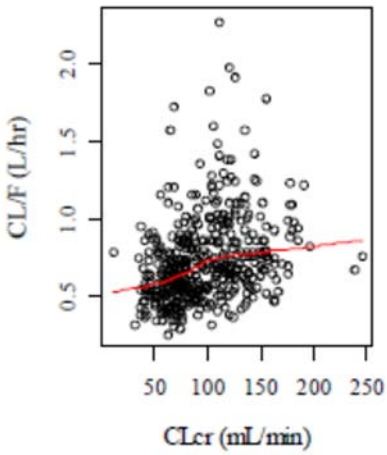


Figure 7: Relationship between creatinine clearance and clearance estimates of lusutrombopag

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

There are no clinically relevant food-drug or drug-drug interactions; hence, lusutrombopag can be administered without regard to food or concomitant medications.

Food Effect
Study M061A characterized the effect a high-fat and high-calorie meal (1050 calories: 120 calories from protein, 400 calories from carbohydrates, and 530 calories from fat) on the relative bioavailability of a 4-mg lusutrombopag dose. Compared to administration under fasting conditions, the AUC of lusutrombopag decreased by approximately 9% and C_{max} decreased by 8% after administration with high-fat, high-calorie meal (**Figure 8**). The 4-mg formulation used in study M061A is (b) (4) to the 3-mg formulation used in the registration trial.

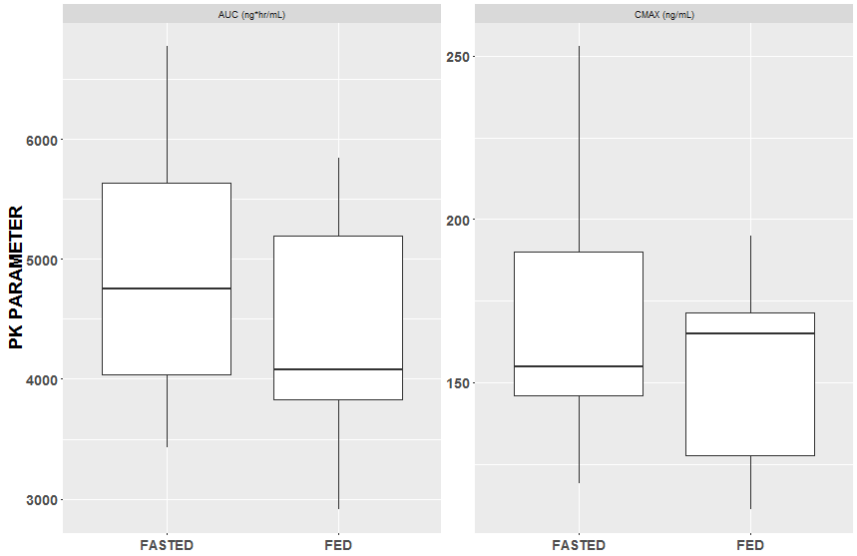


Figure 8: Effect of a high-fat, high-calorie meal on the relative bioavailability of lusutrombopag. AUC (left panel) decreased by 9% and C_{max} (right panel) decreased by 8% in the fed state relative to the fasted state

Drug-Drug Interactions

Effect of Other Drugs on Lusutrombopag

In vitro studies demonstrated that lusutrombopag is metabolized by CYP4 enzymes, including CYP4A11. There are no clinical reports suggesting drug interactions based on the induction or inhibition of CYP4 enzymes. Of note, lusutrombopag is the main moiety in plasma with other trace metabolites that are predominantly undetectable.

In vitro studies indicated lusutrombopag is a substrate of P-gp and BCRP transporters. Clinical study M061E investigated the effect of 400 mg cyclosporine (an inhibitor of P-gp and BCRP) co-administration with 3-mg dose of lusutrombopag. Cyclosporine co-administration resulted in an 18% increase in C_{max} and 19% increase in AUC relative to lusutrombopag alone (**Figure 9**). These changes were not deemed clinically significant.

Study M0618 investigated the effect of 0.75 mg lusutrombopag administered alone or in combination with antacid containing a multivalent cation (4 g sodium carbonate) compared to lusutrombopag alone. The PK of lusutrombopag was not influenced by the co-administration of sodium carbonate similar (**Figure 10**).

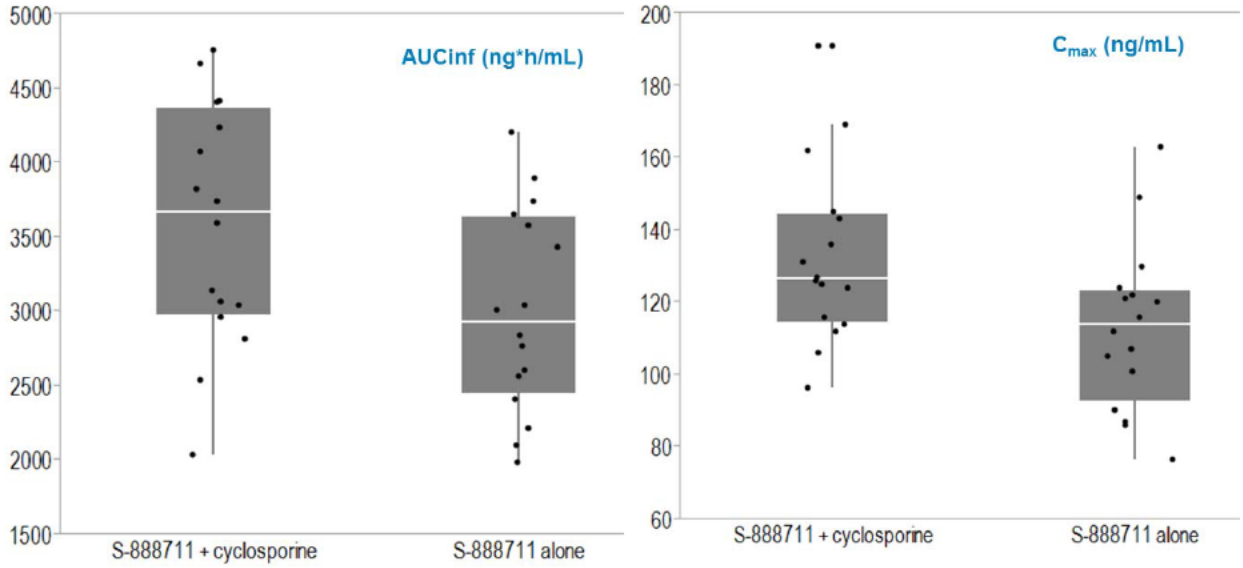


Figure 9: Effect of cyclosporine co-administration on the exposure of lusutrombopag

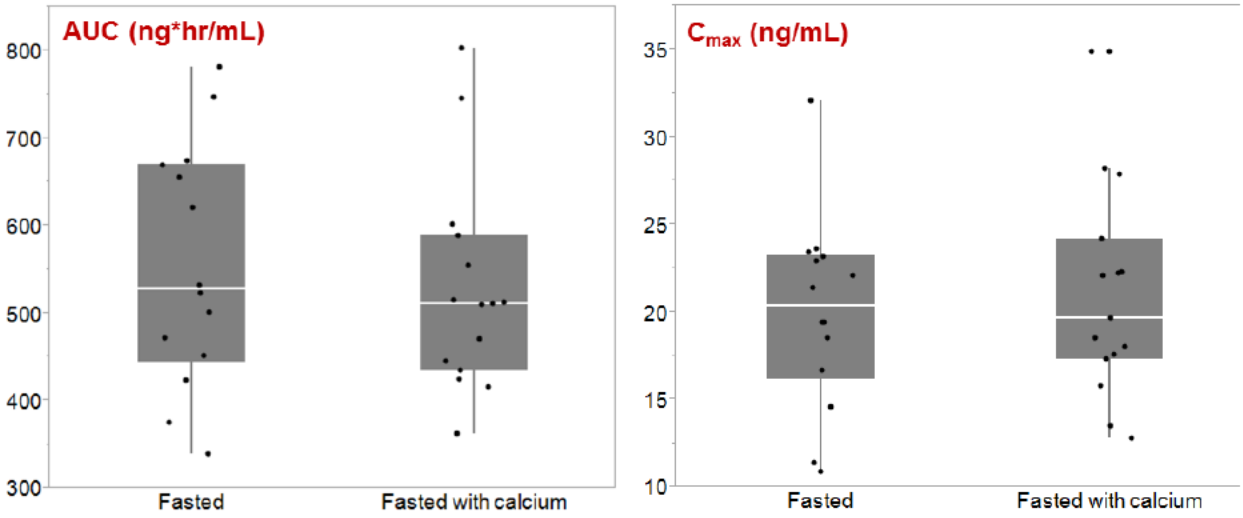


Figure 10: Effect of 4 g of sodium carbonate of on lusutrombopag exposure

Effect of Lusutrombopag on Other Drugs

In vitro studies demonstrated that lusutrombopag did not inhibit CYP enzymes at clinical concentrations. Based on *in vitro* IC_{50} values and the mechanistic static model, the R values was less than 1.01 for all CYP enzymes.

Study M0617 investigated the effect of 1.5 mg lusutrombopag on day 1 followed by a daily dose of 0.75 mg for 6 days on the PK of midazolam (a substrate of CYP3A) relative to midazolam alone. AUC increased by 4% and C_{max} increased by 1% when midazolam was administered in after lusutrombopag dosing compared to midazolam alone. This increase in exposure was deemed not clinically relevant.

In vitro studies demonstrated that lusutrombopag did not cause concentration-dependent increase in marker activities of CYP1A2, CYP2C9, CYP3A4, UGT1A2, UGT1A6, or UGT2B7 in primary human hepatocyte cultures. Lusutrombopag did not inhibit BCRP, OATP1B1, OATP1B3, P-gp, OCT1, OAT1, OAT3, OCT2, MATE, or BSEP *in vitro* at clinical concentrations.

Salaheldin S. Hamed, PhD
Zvada Simbarashe, PhD
Primary Reviewers

Pengfei Song, PhD
Chao Liu, PhD
Team Leaders

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The 3-mg/ day dosing of lusutrombopag was evaluated in 2 randomized, placebo-controlled Phase 3 studies, (M0631/L-PLUS1 and M0634/L-PLUS2). These two studies will be the primary focus of determining the efficacy of lusutrombopag in patients with thrombocytopenia with chronic liver disease undergoing an elective invasive medical procedure. Studies M0626, M0631 and M0364 will be the studies evaluated to support the safety of lusutrombopag.

Study 1304M0631 (L-PLUS1).

The study was conducted in Japan across 89 sites, of which 63 sites screened a subject and 58 sites randomized a subject.

Study 1423M0634 (L-PLUS2)
The study was conducted in 22 countries across 138 sites, of which 102 sites screened a subject and 88 sites (Argentina [2], Australia [2], Austria [3], Belgium [2], Canada [3], Czech Republic [2], France [2], Germany [3], Hungary [2], Israel [9], Italy [7], Poland [3], Republic of Korea [8], Romania [3], Russian Federation [3], Spain [5], Taiwan [3], Thailand [4], Turkey [4], Ukraine [5], United Kingdom [UK; 2], and United States of America [USA; 11]) randomized a subject.

The table below describes the studies submitted as part of the application for NDA 210923.

Table 16: Listing of Clinical Trials Relevant to NDA 210923

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
M0626	N/A	A Phase 2b study of S-888711 in thrombocytopenic patients with chronic liver disease (Dose Selection)	2,3,4-mg orally once daily	Proportion who required no platelet transfusion prior to primary invasive procedure	7 days' treatment/ 28-day follow-up	N = 16	≥ 20 years of age thrombocytopenic patients due to chronic liver disease undergoing a percutaneous liver ablation for primary hepatic cancer	63 Centers/ Japan
M0631	N/A	A Phase 3 study of S-888711 in thrombocytopenic patients with chronic liver disease (L-PLUS1)	3-mg orally daily vs placebo	Proportion who required no platelet transfusion prior to primary invasive procedure	7 days' treatment/ 28-day follow-up	N = 97	≥ 20 years of age thrombocytopenic patients due to chronic liver disease undergoing invasive procedures between 9 and 14 days after the initiation of the study treatment	63 Centers/ Japan
M0634	NCT02389621	A Phase 3 Randomized, Double-blind, Placebo-controlled Study to Assess the Safety and Efficacy of S-888711 (Lusutrombopag) for the Treatment of Thrombocytopenia in Patients with Chronic Liver Disease Undergoing Elective Invasive Procedures (L-PLUS2)	3-mg orally daily	Proportion who required no platelet transfusion prior to primary invasive procedure and no rescue therapy for bleeding from randomization through 7 days after primary invasive procedure	7 days' treatment/ 28-day follow-up	N = 215	≥ 18 years of age of thrombocytopenic patients due to chronic liver disease limited to Child-Pugh Class A/B disease undergoing an elective invasive procedure between Days 9 and 14	138 Centers/ Japan, Europe and US
		Studies to Support Safety						
M0631	N/A	A Phase 3 study of S-888711 in thrombocytopenic patients with chronic liver disease (L-PLUS1)	3-mg orally daily vs placebo	Proportion who required no platelet transfusion prior to primary invasive procedure	7 days' treatment/ 28-day follow-up	N = 49	≥ 20 years of age thrombocytopenic patients due to chronic liver disease undergoing invasive procedures between 9 and 14 days after the initiation of the study treatment	63 Centers/ Japan

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
M0634	NCT02389621	A Phase 3 Randomized, Double-blind, Placebo-controlled Study to Assess the Safety and Efficacy of S-888711 (Lusutrombopag) for the Treatment of Thrombocytopenia in Patients with Chronic Liver Disease Undergoing Elective Invasive Procedures (L-PLUS2)	3-mg orally daily	Proportion who required no platelet transfusion prior to primary invasive procedure and no rescue therapy for bleeding from randomization through 7 days after primary invasive procedure	7 days' treatment/ 28-day follow-up	N = 108	≥ 18 years of age of thrombocytopenic patients due to chronic liver disease limited to Child-Pugh Class A/B disease undergoing an elective invasive procedure between Days 9 and 14	138 Centers/ Japan, Europe and US
M0626	N/A	A Phase 2b study of S-888711 in thrombocytopenic patients with chronic liver disease (Dose Selection)	2,3,4-mg orally once daily	Proportion who required no platelet transfusion prior to primary invasive procedure	7 days' treatment/ 28-day follow-up	N = 16	≥ 20 years of age thrombocytopenic patients due to chronic liver disease undergoing a percutaneous liver ablation for primary hepatic cancer	63 Centers/ Japan
		Other Studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
M061B	N/A	Evaluation of platelet functions in thrombocytopenic patients with chronic liver disease treated with S-888711	3-mg orally daily	Evaluate the efficacy, safety, and pharmacokinetics of S-888711 in thrombocytopenic patients with chronic liver disease following multiple doses of 3-mg of S-888711	7 days' treatment/ 28-day follow-up	N = 8	≥ 20 years of age of thrombocytopenic patients due to chronic liver disease with platelet count of < 50,000/μL at screening	13 Centers/ Japan
M0625	N/A	A Phase 2 higher-dose study of S-888711 in thrombocytopenic patients with chronic liver disease	2.5, 3, 3.5, or 4-mg of S-888711 once daily	Assess the safety, pharmacokinetics, and efficacy of S-888711 after a 7-day multiple oral administration as a pretreatment for percutaneous liver ablation in thrombocytopenic patients with chronic liver disease.	7 days' treatment/ 28-day follow-up	N = 16	≥ 20 years of age thrombocytopenic patients due to chronic liver disease undergoing a percutaneous liver ablation for primary hepatic cancer	22 Centers/ Japan
M0627	N/A	A Clinical Pharmacology Study of S-888711 in Thrombocytopenic Patients with Child-Pugh Class C Liver Disease	3-mg orally daily	Evaluate the safety and pharmacokinetics of S-888711 in Child-Pugh class C	7 days' treatment/ 28-day follow-up	N = 5	≥ 20 years of age of thrombocytopenic patients due to chronic liver disease with	35 Centers/ Japan

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
				patients with thrombocytopenic due to chronic liver disease			platelet count of < 50,000/µL and with Child-Pugh Class C at screening	

7.2. Review Strategy

The Applicant submitted the application electronically. The clinical and statistical reviewers, Patricia Oneal, MD and Jingiing Ye, PhD, respectively, served as the primary reviewers and conducted a joint review of the efficacy data and safety data in this application. Reviewer comments are identified individually.

This clinical reviewer's strategy included:

- Review of regulatory histories of NDA 210923 and IND 104047;
- Examination of all clinical study reports and amendments
- Subjecting datasets to queries using JMP;
- Examination of approximately 100 CRFs, selected at random;
- Studying the Applicant's presentation to the FDA on 30 January 2018;
- Searching published literature relative to chronic liver disease and thrombocytopenia and patient experiences related to all treatment modalities used in this setting;
- Consulting the FDA Division of Scientific Investigation;
- Review of the Periodic Safety Update Reports and Annual Reports for lusutrombopag NDA;
- Review of guidelines and other published literature regarding the diagnosis, treatment, and monitoring of patients with chronic liver disease and thrombocytopenia;
- Review of FDA reviews of previous drugs approved for the treatment of thrombocytopenia;
- Review and analysis of raw data conducted throughout studies for responders on the treatment arm;
- Review of pooled safety data from the aforementioned trials to detect additional safety signals.

Analysis by Dr. Oneal was performed using JMP 13.0 (SAS Institute, Inc). Unless specifically referenced, all analyses and presentation of findings are the work of FDA reviewers.

The statistical evaluation was based on data from study 1304M0631/L-PLUS1and 1423M0634/L-PLUS2.

Data Sources

Analysis datasets, SDTM tabulations, and software codes are located on network with network path: \\CDSESUB1\evsprod\NDA210923\0002\m5\datasets\1304m0631

\\CDSESUB1\evsprod\NDA210923\0002\m5\datasets\1423m0634

Data Quality and Integrity

The efficacy endpoints such as proportion of patients with no platelet transfusion prior to invasive procedures were derived and saved in analysis datasets ‘‘ADSL” and “ADPLCUM”, demographic and disease characteristics were derived and saved in analysis datasets “ADSL” respectively. The statistical reviewer was able to reproduce the derived datasets from the NDA tabulation dataset.

-

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study 1304M0631/L-PLUS1

Trial Design

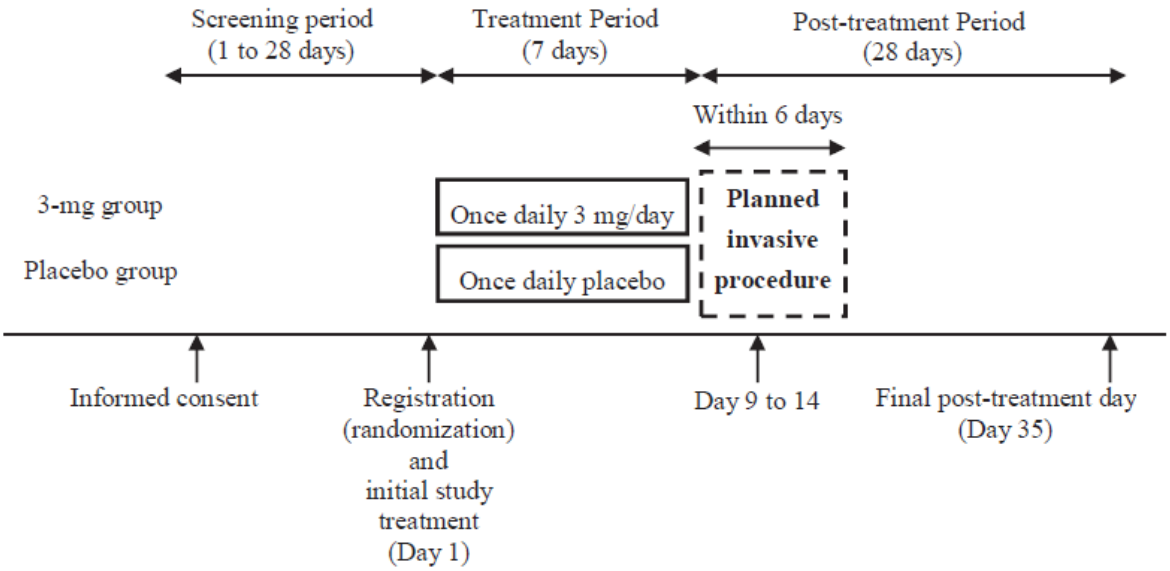
The L-PLUS1 study was a multicenter, randomized, double-blind, parallel-group, placebo-controlled study. The study consisted of 3 study periods: the Screening Period for 1 to 28 days, the Treatment Period for 7 days, and the Post-treatment Period for 28 days. Eligible patients were randomized 1:1 to either of the treatment groups (registration day): 3-mg of S-888711 (3-mg group) or placebo (placebo group). Randomization was stratified by:

- Primary invasive procedure (liver ablation/coagulation or other invasive procedures)
- Platelet counts at screening (< 35,000/μL, ≥ 35,000/μL to < 45,000/μL, or ≥ 45,000/μL)

Patients started receiving the assigned study drug once daily (Day 1) and received the study drug for 7 days (Treatment Period). After the final study treatment, patients underwent specified post-treatment study assessments (Posttreatment Period). The planned invasive procedure was performed between Days 9 and 14. Determination of need for platelet transfusion was performed based on platelet counts after Day 8 and immediately before performing the invasive procedure. Preoperative platelet transfusion was to be performed only when the platelet count is <50,000/μL.

The study schematic of L-PLUS1 is shown below in Figure 11.

Figure 11: Study Schematic of L-PLUS1 Study



[Source: 1304M0631 Statistical Methods and Interim Analysis Plan Page 8]

The primary objective of the study was:

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

The secondary objectives of the study were:

- To compare the efficacy, safety, and pharmacokinetics of S-888711 with those of placebo in thrombocytopenic patients with chronic liver disease receiving 3-mg of S-888711 as a pretreatment of invasive procedures based on the following variables:
  - Proportion of patients who required no platelet transfusion during the study
  - Proportion of patients who have a platelet count of ≥ 50,000/μL with an increase of ≥ 20,000/μL from baseline
  - Duration of increased platelet count
  - Time course of platelet count
  - Adverse events (AEs) and adverse drug reactions (ADRs)
  - Bleeding-related AEs
  - Thrombosis-related AEs
  - Assessment of portal vein thrombosis and portal blood flow
  - Laboratory test, vital sign, and electrocardiogram
  - Plasma S-888711 concentration

The sample size was planned to be 45 per treatment arm and 90 in total. The assumptions were 90% power, the % of patients in placebo arm was 20% and 70% in treatment arm and 2-sided significance level 0.05.

Study Endpoints

The primary efficacy endpoint was

- The proportion of patients who required no platelet transfusion prior to the initial invasive procedure

The primary endpoint was defined by the proportion of patients who received no platelet transfusion prior to the primary invasive procedure in respective analysis population. Any patient who discontinued the study during the Treatment Period without receiving invasive procedure was handled as being in need of platelet transfusion (a failure for the primary efficacy endpoint).

The secondary endpoints were

- The proportion of patients who required no platelet transfusion, frequency of platelet transfusion, and dose of platelet transfused during the study
- Proportion of responders
- Duration of increased platelet count
- Time course of platelet count

The proportion of patients who required no platelet transfusion during the study is defined as the proportion of patients who completed the study without receiving platelet transfusion in respective analysis population. Any patient who discontinued the study during the Treatment Period without receiving invasive procedure was handled as being in need of platelet transfusion (a failure for the endpoint).

A responder is defined as a patient who had a platelet count of ≥ 50,000/μL with an increase of ≤20,000/μL from baseline.

Two duration endpoints were used:

- The number of days during which a platelet count of ≥ 50,000/μL was maintained
- The number of days during which a platelet count of ≥70,000/μL was maintained
- The number of days during which a patient had a platelet count of ≥ 50,000/μL with an increase of ≥ 20,000/μL from baseline

For time course of platelet count, the analysis included platelet counts at the scheduled time points (Days 1 (baseline), 5, 6, 7, 8, 10, 12, 14, 17, 21, 28, and 35). If a patient received platelet transfusion, the platelet counts of this patient measured on the day of the first platelet

transfusion (i.e., the first day), the next day of the first platelet transfusion (i.e., the second day), and the day after the next day of the first platelet transfusion (i.e., the third day) was included in the analysis. A recipient of platelet transfusion may have multiple platelet counts on the same day because of an overlap between the scheduled time points from Days 5 through 35 and the 3 days following the first transfusion. In such a case, the platelet count after the first transfusion was used.

Statistical Analysis Plan

As the efficacy primary endpoint, the proportion of patients who required no platelet transfusion prior to the primary invasive procedure were calculated by each treatment group, and its 95% confidence interval (CI) were calculated using the Clopper-Pearson method. The 3-mg and placebo groups were compared using the Cochran-Mantel-Haenszel test with the stratification factors (i.e., the classification of invasive procedure and the platelet count at screening) as adjustment factors. Through this, the relative risk in the 3-mg group as compared with the placebo group and its 95% CI were calculated. The same analyses were performed in the per protocol set (PPS) for the purpose of sensitivity analysis.

For secondary endpoint of the proportion of patients who required no platelet transfusion during the study, the 3-mg and placebo groups were compared using the Cochran-Mantel-Haenszel test with the stratification factors as adjustment factors.

Platelet count data were analyzed as follows. These analyses excluded any data obtained after the first platelet transfusion.

1. The number and proportion of patients who meet the responder criteria at least once during the study were calculated. The 3-mg and placebo groups were compared using the Cochran-Mantel-Haenszel test with the stratification factors as adjustment factors. Through this, the relative risk in the 3-mg group as compared with the placebo group and its 95% CI were calculated. The number and proportion of responders by category of the stratification factors were calculated in each treatment group.
2. At each time point (Days 5, 6, 7, 8, 10, 12, 14, 17, 21, 28, and 35), the number and proportion of responders were determined in each treatment group.

The following analyses were performed including the data obtained after the first platelet transfusion. A patient who has a platelet count meeting the responder criteria at any time point after the first platelet transfusion were handled as a nonresponder at that time point.
1. The number and proportion of responders were calculated at each time point (Days 5, 6, 7, 8, 10, 12, 14, 17, 21, 28, and 35). The 3-mg and placebo groups were compared using the Cochran-Mantel-Haenszel test with the stratification factors as adjustment factors at each time point.

The duration of increased platelet count of a patient was calculated using the platelet counts measured at the following time points: baseline; Days 5, 6, 7, 8, 10, 12, 14, 17, 21, 28, and 35;

and the day of the first transfusion (i.e., the first day), the next day of the first platelet transfusion (i.e., the second day), and the day after the next day of the first platelet transfusion (i.e., the third day) if the patient had received platelet transfusion. A recipient of platelet transfusion may have multiple platelet counts on the same day because of an overlap between the scheduled time points from Days 5 through 35 and the 3 days following the first transfusion. In such a case, the platelet count after the first transfusion was used in the calculations of the duration of increased platelet count. If a patient had a baseline platelet count of ≥ 50,000/μL, the duration of increased platelet count of this patient will not be calculated and was handled as missing data.

The following comparisons were performed using an analysis of covariance (ANCOVA) where the duration of increased platelet count is the dependent variable, the group according to the combination of treatment and platelet transfusion is the explanatory variable, and the classification of invasive procedure, the baseline platelet count (continuous), and the duration of the observation of platelet counts (Day # of the last observation of the platelet counts for the calculation of the duration of increased platelet count minus 1) are covariates.

- A comparison of non-recipients of platelet transfusion in the 3-mg group vs those in placebo group
- A comparison of non-recipients' transfusion in the 3-mg group vs recipients in the placebo group

For time course of platelet count, the median platelet count (interquartile range) of each group was graphically represented.

Missing data due to dropouts or similar were not imputed. All analyses were conducted using actual observations.

Subgroup analysis was conducted:

- Classification of invasive procedure
- The platelet count at screening
- Child-Pugh class: A, B

A summary of the planned analyses is summarized in Table 17.

Table 17: Endpoints and Methods of Analysis

Endpoint		Method of Analysis	Outputs[a)]	Analysis population	
				FAS	PPS
Primary	Proportion of patients who required no platelet transfusion	Cochran-Mantel-Haenszel test	1, 2	X	X
	- Subgroup analyses		1, 2	X	
Secondary	Proportion of patients who required no platelet transfusion during the study	Cochran-Mantel-Haenszel test	1, 2	X	
	Proportion of responders	Cochran-Mantel-Haenszel test	1, 2	X	
	Duration of increased platelet count	ANCOVA (as necessary)	1, 3	X	
	Time course of platelet count		1, 4, 5	X	

a) Output 1: Summary statistics of the variable
Output 2: Relative risk and its 95% CI, p-value (excluding subgroup analyses of the primary endpoint)
Output 3: Adjusted mean, difference between groups in adjusted mean and its 95% CI, p-value
Output 4: A plot of the median (interquartile range)
Output 5: A plot of the mean (SD)

[Source: 1304M0631 Statistical Methods and Interim Analysis Plan Page 18]

Protocol Amendments

Study 1304M0631 (L-PLUS1)

The protocol amendment made in Version 2 issued on 6 September 2013 listed an additional number of invasive procedures amended based on request from regulatory authority, Pharmaceuticals and Medical Devices Agency (PMDA). These procedures included endoscopic metallic stenting of the biliary/pancreas as well as endoscopic polypectomy of the gastrointestinal tract.

The list of example procedures is listed below:

Table 18 Amendment to the Allowed Invasive Procedure Allowed on Study 1304M0631 (L-PLUS1) and Study 1423M0634 (L-PLUS2)

Region	Type of Surgery
Liver	● Radiofrequency Ablation (RFA) ● Percutaneous Microwave Coagulation Therapy (PMCT) ● Percutaneous Ethanol Injection Therapy (PEIT) ● Transcatheter Arterial Embolization (TAE)/Transhepatic Arterial Infusion (TAI)/Transcatheter Arterial Chemoembolization (TACE) ● Endoscopic Ultrasound-Guided Fine Needle Aspiration (EUS-FNA) ● Laparoscopic Radiofrequency Ablation (LRA) ● Laparoscopic Microwave Coagulation (LMC)
Biliary-pancreas	● Endoscopic Metallic Stenting (EMS) ● Endoscopic Sphincteropapillotomy (EST) ● Endoscopic Papillary Balloon Dilatation (EPBD) ● Endoscopic Ultrasound-Guided Fine Needle Aspiration (EUS FNA)
Gastrointestinal tract	● Argon Plasma Coagulation (APC) ● Endoscopic Polypectomy ● Endoscopic Submucosal Dissection (ESD) ● Endoscopic Mucosal Resection (EMR) ● Percutaneous Endoscopic Gastrostomy (PEG) ● Endoscopic Variceal Ligation (EVL) ● Endoscopic Injection Sclerotherapy (EIS) ● Endoscopic Ultrasound-Guided Fine Needle Aspiration (EUS-FNA)
Urinary system	● Transurethral Resection of The Bladder Tumor (TURBT) ● Transurethral Ureterolithotripsy (TUL)
Other regions	● Percutaneous Needle Biopsy ● Laparoscopy ● Arthroscopic Surgery ● Endoscopy with Possible Biopsy ● Various Paracenteses ● Tooth Extraction

Reviewer's Comments: Extending the list of different types of invasive procedures allowed in clinical study mimics real-world scenarios where lusutrombopag would be used. Removing the fixed 5-day treatment reduced the chance for delay in the scheduled planned invasive procedures.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant provided attestation that all clinical studies were conducted with respect for the

individual participants in accordance with the study protocol, Good Clinical Practice (GCP) guidelines, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (E6), and local regulatory requirements.

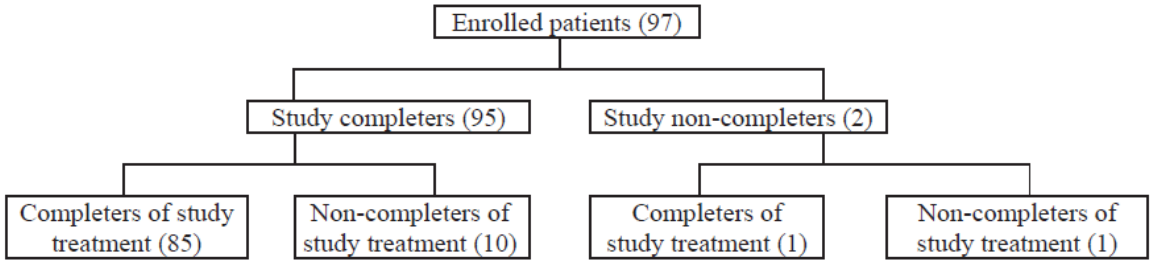
Financial Disclosure

Phase 3 Studies 1304M0631 and 1423M0634
Financial disclosure forms were collected for both Phase 3 Studies 1304M0631 (M0631) and 1423M0634 (M0634). No Principal Investigators or sub-investigators (if applicable) in these studies were or are a full-time or part-time employee of Shionogi. No principal investigators or sub investigators (if applicable) reported any disclosable financial interests or arrangements as described in 21 CFR § 54.4(a)(3). Refer to appendix 19.2 for additional details.

Patient Disposition

The patient disposition is summarized in Figure 12.

Figure 12: L-PLUS1 Subject Disposition



[Source: study report 1304M0631 Page 81 and statistical reviewer's analysis]

Analysis population

The FAS (Full Analysis Set) population was defined as who receive at least 1 study drug and have a measurement of platelet counts at baseline and at least 1 measurement of platelet counts after the initiation of study drug administration. The FAS population was used for the primary efficacy.

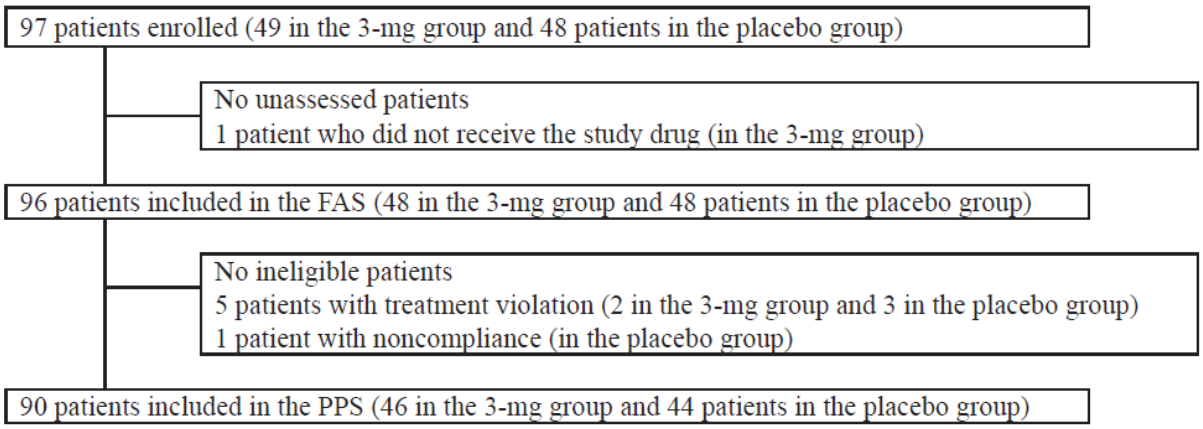
The PPS (Per-Protocol Set) population was defined as all randomized patients included in FAS and not meeting any of the following conditions:

- Ineligible patients (patients with any protocol inclusion or exclusion violations and patients who are ineligible for efficacy evaluation)
- Patients with treatment-related violations (patients with any violations of restrictions on concomitant drugs or therapy and patients who violate any evaluation procedure)
- Patients with insufficient treatment compliance

The PPS was used as sensitivity analyses of the primary endpoint.

The safety population was defined as all randomized patients who received at least 1 dose of the study drug.

Figure 13: Efficacy Evaluation Population in L-PLUS1 Study



[Source: L-PLUS1 study report Page 83]

Statistical Reviewer's Comment:
The sponsor's definition of FAS is not ITT (Intent-To-Treat). The ITT definition would be patients randomized to the treatments whether or not they received the actual treatment. FDA conducted analysis in the ITT population to assess the treatment effect.

Protocol Violations/Deviations

Protocol deviations are summarized in Table 19. The protocol deviations appear to be independent of the treatment arms.

Table 19: L-PLUS1 Protocol Deviations

Institution	Patient ID (b) (6)	Type [a]	Deviation
Saiseikai Niigata Daini Hospital		3	The patient received 1 tablet of the study drug at 12:50 on Day 1 but misguidedly received 1 tablet of the study drug at 18:50 on the same day (overdose).
Shimane Prefectural Central Hospital		3	On Day 11, PEIT, planned invasive procedure, was cancelled and RFA was performed.
Osaka City General Hospital		3	On Day 11, EVL, planned invasive procedure, was cancelled and argon plasma coagulation was performed.
Matsuyama Red Cross Hospital		4	Thoracentesis, a prohibited concomitant therapy, was performed on Day 25 to treat an SAE of pleural effusion (reported term, aggravation of pleural effusion) (emergency deviation).
Okayama University Hospital		4	Gran Syringe 75, a prohibited concomitant drug, was used on Day 19 to treat an AE of pancytopenia (emergency deviation).
Kagawa Prefectural Central Hospital		4	Kenketu Nonthron 1500 for injection, a prohibited concomitant drug, was used from Day 15 to 17 to treat an AE of portal vein thrombosis (emergency deviation).
Japan Red Cross Wakayama medical center		4	Emergency EIS, a prohibited concomitant therapy, was performed from Day 21 until 22 to treat an SAE of oesophageal varices haemorrhage (reported term, esophageal varices ruptured) (emergency deviation).
Chiba University Hospital		4	Percutaneous liver biopsy was performed with TACE.
The University of Tokyo Hospital		4	Thoracentesis was performed on Day 21 to treat an AE of pleural effusion (reported term, right pleural effusion caused by RFA).

Abbreviations: adverse event (AE), endoscopic injection sclerotherapy (EIS), endoscopic variceal ligation (EVL), percutaneous ethanol injection therapy (PEIT), radiofrequency ablation (RFA), serious adverse event (SAE), transcatheter arterial chemoembolization (TACE).

[a] Type of deviation: 1, GCP noncompliance; 2, violation of inclusion/exclusion criteria; 3, violation of study treatment; 4, violation of prohibited/restricted concomitant drug/therapy; 5, violation of withdrawal criteria.

[Note in translation: Gran Syringe and Kenketu Nonthron are brand names of filgrastim and freeze-dried concentrated human antithrombin III in Japan, respectively.]

[Source: L-PLUS1 Study Report Page 82]

Table of Demographic Characteristics

The baseline demographic characteristics are summarized in Table 20. The table was based on the ITT population. Fifty-five percent of women were randomized to the lusutrombopag arm whereas sixty-two percent of men were randomized to the placebo arm. All participants in both arms were of Asian decent.

Table 20: Baseline Demographic for L-PLUS1 Study-ITT Population

		S-888711 3-mg	Placebo	Overall
		N=49	N=48	N=97
		n (%)	n (%)	n (%)
Sex	Male	22 (44.9)	30 (62.5)	52 (53.6)

		S-888711 3-mg	Placebo	Overall
		N=49	**N=48**	**N=97**
		n (%)	**n (%)**	**n (%)**
	Female	27 (55.1)	18 (37.5)	45 (46.4)
Age (years)	n	49	48	97
	Mean	68.7	66.8	67.7
	SD	6.7	10.2	8.7
	Min	51	40	40
	Median	70	65.5	67
	Max	81	88	88
Ethnicity	Hispanic or Latino	0	0	0
	Not Hispanic or Latino	49 (100)	48 (100)	97 (100)
Race	American Indian or Alaska	0	0	0
	Native	0	0	0
	Asian	49 (100)	48 (100)	97 (100)
	Black or African American	0	0	0
	Native Hawaiian or Other	0	0	0
	Pacific Islander	0	0	0
	White	0	0	0

[Source: Statistical reviewer's analysis]

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Other baseline characteristics are summarized in Table 21 based on ITT population. Eighty-two percent of patients randomized to the lusutrombopag arm and sixty-six percent of patients in the placebo arm had chronic Hepatitis C. Nearly eighty-seven percent of patients overall did not have a history of chronic Hepatitis B. There was a slight increase of patients in the lusutrombopag arm (55%) with the Child-Pugh Grade A score compared to more patients with Child-Pugh Grade B score (54.2%) in the placebo arm. There was balance shown between both arms in their history of transfusion, baseline platelet count greater than 35,000/µL to less than 45,000/µL, performance status, gastrointestinal varices, splenomegaly and WHO bleeding scale.

Table 21: Other Baseline Characteristics L-PLUS1 Study-ITT Population

		S-888711 3-mg	**Placebo**	**Overall**
		N=49	**N=48**	**N=97**
		n (%)	**n (%)**	**n (%)**
Medical History of Chronic Hepatitis B	Yes	4 (8.2)	8 (16.7)	12 (12.4)
	No	45 (91.8)	40 (83.3)	85 (87.6)
Medical History of Chronic Hepatitis C	Yes	40 (81.6)	32 (66.7)	72 (74.2)
	No	9 (18.4)	16 (33.3)	25 (25.8)
History of Transfusion	Yes	29 (59.2)	26 (54.2)	55 (56.7)
	No	20 (40.8)	22 (45.8)	42 (43.3)
Child-Pugh Grade	A	27 (55.1)	22 (45.8)	49 (50.5)
	B	22 (44.9)	26 (54.2)	48 (49.5)
Planned Surgery	RFA/MCT	21 (42.9)	21 (43.8)	42 (43.3)
	Other	28 (57.1)	27 (56.3)	55 (56.7)
Baseline Platelet Count ($x10^4/\mu L$)	<3.5	7 (14.3)	10 (20.8)	17 (17.5)
	>=3.5 to <4.5	26 (53.1)	25 (52.1)	51 (52.6)
	>=4.5	16 (32.7)	13 (27.1)	29 (29.9)
	n	49	48	97
	Mean	4.12	3.99	4.06
	SD	0.67	0.69	0.68
	Min	2.3	2.3	2.3
	Median	4.3	4.2	4.2
	Max	5.9	5.5	5.9

		S-888711 3-mg	Placebo	Overall
		N=49	**N=48**	**N=97**
		n (%)	**n (%)**	**n (%)**
Performance Status	0	44 (89.8)	45 (93.8)	89 (91.8)
	1	5 (10.2)	3 (6.3)	8 (8.2)
Gastroesophageal Varix	Yes	42 (85.7)	41 (85.4)	83 (85.6)
	No	7 (14.3)	7 (14.6)	14 (14.4)
Splenomegaly	Yes	46 (93.9)	46 (95.8)	92 (94.8)
	No	3 (6.1)	2 (4.2)	5 (5.2)
Ascites	Yes	11 (22.5)	14 (29.2)	25 (25.8)
	No	38 (77.5)	34 (70.8)	72 (74.2)
WHO Bleeding Scale	0	43 (87.8)	42 (87.5)	85 (87.6)
	1	6 (12.2)	6 (12.5)	12 (12.4)

[Source: Statistical reviewer's analysis]

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Study 1304M0631/L-PLUS1

Patients in the lusutrombopag arm received a median of seven daily doses (range 4 to 7 doses compared to a median of seven daily doses (range 3 to 7 doses) for the patients in the control arm. The dose intensity was 3-mg/day for lusutrombopag and 0-mg/day for the control.

There was no evidence of any differences with treatment compliance between the treatment arm and the control group. One patient on the lusutrombopag arm did elect not to proceed with the invasive procedure until a pre-procedural transfusion of platelets was given. One patient in the placebo group received the study drug twice daily.

Of 96 patients who received the study drug, 86 patients received the study drug for 7 days. Ten patients who met the criteria for withdrawal (platelet count ≥ 50,000/µL with an increase of ≥ 20,000/µL from baseline) were withdrawn from the study treatment. Of 10 patients who were withdrawn from the study treatment, the study drug was administered for 6 days (4 patients), 5 days (1 patient) and 4 days (5 patients).

Thirty-nine patients (81%) on the control arm did require transfusion of platelets during the timed interval of the planned invasive procedure (Days 9-14) compared to eleven patients (22%) on the lusutrombopag arm requiring platelet transfusion during the planned invasive procedural dates.

Concomitant medications were reviewed for medications that may have impacted the evaluation of efficacy. Antithrombin agents were given to one patient in the lusutrombopag arm on Day 10 of the post treatment period. A prohibited investigational agent, Proheparum was given to four patients in the control arm and one patient in the lusutrombopag arm. This non-approved drug has been used for liver regeneration. Warfarin was used in one patient in the lusutrombopag arm on Day 10 during the post-treatment period. One patient in the placebo arm was given a granulocyte stimulating agent for treatment of pancytopenia on Day 19.

Prohibited procedures and therapies which may insinuate a safety issue were reviewed. Two patients in the placebo arm underwent a non-approved invasive technique, a thoracentesis, on Days 11 and 25, respectively during the post-treatment period. Cryotherapy was done on a patient in the lusutrombopag arm on Day 9 and 28 during the post-treatment period. Three patients (2: lusutrombopag and 1: placebo) did undergo unapproved procedures (i.e. radiofrequency ablation, argon plasma coagulation and percutaneous liver biopsy) prior to the amendment of other allowed invasive procedures available for eligible patients.

Reviewer's Comments: The patients who received prohibited agents did not have any documented complications during the treatment or post-treatment period. Patients who underwent invasive procedures outside the scheduled period did not have any complications

identified in the post-treatment period.

Efficacy Results – Primary Endpoint

The primary endpoint results are summarized below. The sponsor's analysis was done in FAS population, which excluded one patient in Lusutrombopag arm. Their results are included in Table 22. The statistical reviewer did the analysis using ITT population and the results are in Table 23. The statistical reviewer also included sensitivity analysis using Fisher's exact test. A minor numerical difference was seen between the sponsor's FAS and FDA's ITT analysis. All of the results showed that there are statistically significant differences between lusutrombopag and placebo arms.

Table 22: FAS Analysis Set Primary Endpoint

	S-888711 3 mg N=48	Placebo N=48
Proportion of patients who required no platelet transfusion	79.2% (38/48)	12.5% (6/48)
Exact 95% confidence interval	(65.0, 89.5)	(4.7, 25.2)
Comparison with placebo		
- P value from CMH test [a]	<.0001	
- Relative risk (95% confidence interval)	6.16 (2.92, 13.00)	

[a] Cochran-Mantel-Haenszel test with planned surgery and platelet count at screening as stratification factors.

[Source: L-PLUS1 Study Report Page 86]

Table 23: FDA Analysis on the Primary Endpoint using ITT Population

	Lusutrombopag N=49	**Placebo N=48**
% of patients who required no platelet transfusion	77.6%(38/49)	12.5% (6/48)
Exact 95% CI	63.4, 88.2	4.7, 25.3
Comparison with placebo		
Difference (95% CI)	65.6% (50.7, 80.5)	
Relative Risk (95% CI)	5.81 (2.73, 12.38)	
P-value from CMH	<0.0001	
P-value from Fisher	<0.0001	

Efficacy Results – Secondary and other relevant endpoints

The results on secondary endpoints are summarized in Table 24 by the Sponsor using FAS set and Table 25 by the statistical reviewer using ITT set. Sensitivity analysis using Fisher's exact test was conducted by the statistical reviewer and included in the results in Table 25. There is a minor numerical difference seen between the sponsor's FAS and FDA's ITT analysis. The results

showed that there are statistically significant differences between lusutrombopag and placebo arms.

Table 24: Secondary Endpoint of % of Responders

	S-888711 3 mg N=48	Placebo N=48
Proportion of responders	77.1% (37/48)	6.3% (3/48)
Exact 95% confidence interval	(62.7, 88.0)	(1.3, 17.2)
Comparison with placebo		
- P value from CMH test [a]	<.0001	
- Relative risk (95% confidence interval)	11.91 (4.00, 35.44)	
Stratified by planned surgery		
- RFA/MCT	65.0% (13/20)	9.5% (2/21)
- Other	85.7% (24/28)	3.7% (1/27)
Stratified by platelet count (*10^4/uL) at screening		
- < 3.5	55.6% (5/9)	0.0% (0/9)
- >= 3.5 to < 4.5	77.3% (17/22)	4.2% (1/24)
- >= 4.5	88.2% (15/17)	13.3% (2/15)

[a] Cochran-Mantel-Haenszel test with planned surgery and platelet count at screening as stratification factors.
The responder is defined as the patient whose platelet count achieved >=50,000/uL and increased >=20,000/uL from baseline.
The data of platelet counts observed after the first platelet transfusion are excluded from the analysis.

[Source: 1304M0631 Study Report Page 137]

Table 25: FDA Analysis on % of Responders

	Lusutrombopag N=49	Placebo N=48
% of patients who required no platelet transfusion	75.5 (37/49)	6.3 (3/48)
Exact 95% CI	61.1, 86.7	1.3, 17.2
Comparison with placebo		
Difference (95% CI)	71.5% (58.1%, 84.8%)	
Relative Risk (95% CI)	10.53 (3.52, 31.55)	
P-value from CMH	<0.0001	
P-value from Fisher-exact	<0.0001	

Additional secondary endpoint on the duration of maintenance of increase in platelet count is reported in Table 26. The results showed that there are statistically significant differences between lusutrombopag and placebo arms.

Table 26: Secondary Endpoint Results on the Duration of Maintenance of Platelet Count Increase in L-PLUS1 Study

		S-888711 3 mg		Placebo	
		With PT	Without PT	With PT	Without PT
Summary statistics	n	10	38	40	7
	Mean	11.2	21.7	5.1	18.1
	SD	8.0	6.5	6.2	10.8
	Min	0.0	5.7	0.0	4.2
	Median	10.3	22.1	3.3	18.5
	Max	23.0	33.5	22.3	34.8
Parameter estimates	LS mean (SE)	12.25 (1.89)	21.09 (0.99)	6.05 (0.96)	15.96 (2.31)
Treatment comparisons	vs. S-888711 3 mg without PT				
	- Difference of LS mean (SE)	---		15.04 (1.38)	5.13 (2.49)
	- 95% confidence interval	---		12.30, 17.78	0.19, 10.07
	- P value	---		<.0001	0.0420
P value for test of fixed effect	- Planned surgery	0.5131			
	- Baseline platelet count	<.0001			
	- Observation period	0.1896			
	- Group	<.0001			

PT: Platelet transfusion.

[Source: 1304M0631 Study Report Page 140 and Statistical reviewer's analysis]

Dose/Dose Response

Dose/Dose Response was not applicable in this application.

Durability of Response

In the L-PLUS 1 trial, the initial platelet count in both arms was below 50,000/µL at the time of screening and Day 1 of treatment. The mean platelet count achieved by patients on the lusutrombopag 3-mg arm was 52,300 ± 11,500/µL by Day 7, whereas patients on the placebo arm achieved a mean platelet count of 40,200 ± 8,567/µL. By Day 8 (day prior to planned invasive procedure), the mean platelet count achieved reached 58,800 ± 15,700/µL in the lusutrombopag arm. The mean platelet count achieved among the placebo patients on Day 8 was 39,700 ± 9,550/µL. By Day 14, the lusutrombopag 3-mg patients achieved the highest mean platelet count of 76,700 ± 23,000/µL compared to the placebo patients who achieved a mean platelet count of 45, 600 ± 11,600/µL. The dose of the investigational drug was terminated in nine patients in the lusutrombopag arm. Their mean platelet count was 58,800 ± 15,700 µL. Three patients in the placebo arm mean platelet count was 59,000 ± 7,000/µL.

Persistence of Effect

By Day 35 (end of the treatment period), patients in the L-PLUS1 trial in both the lusutrombopag and placebo arms returned to platelet count levels near the screening platelet count levels (L-PLUS1: Lusutrombopag: 42,400 ± 10,100/µL; Placebo: 42,100 ± 9,555/µL).

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Secondary or exploratory COA endpoints was not submitted in this application.

Additional Analyses Conducted on the Individual Trial

- The trial was conducted in Japan and enrolled 100% of Asian patients. The subgroup analysis by gender was not conducted. The statistical reviewer reported the primary endpoint results by gender in Table 27. No outlier subgroups were observed.

Table 27: Subgroup Analysis on the Primary Endpoint in L-PLUS1 Study

	#	S-888711 3mg	Placebo	Difference (95% CI)
Male	52	16/22 (72.7%)	4/30 (13.3%)	61.3% (39.1, 83.4)
Female	45	22/27 (81.5%)	2/18 (11.1%)	67.9% (46.6, 89.2)

[Source: Statistical reviewer's analysis]

8.1.3 Study 1423M0634/L-PLUS2

Trial Design

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

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

The maximum study duration for each patient was 63 days. Eligible patients were randomized in a 1:1 ratio to either S-888711 3-mg once daily for up to 7 days or matched placebo control. The randomization was stratified by primary invasive procedure (liver ablation/coagulation or other invasive procedures) and baseline platelet count ($< 35 \times 10^9$/L or $\geq 35 \times 10^9$/L).

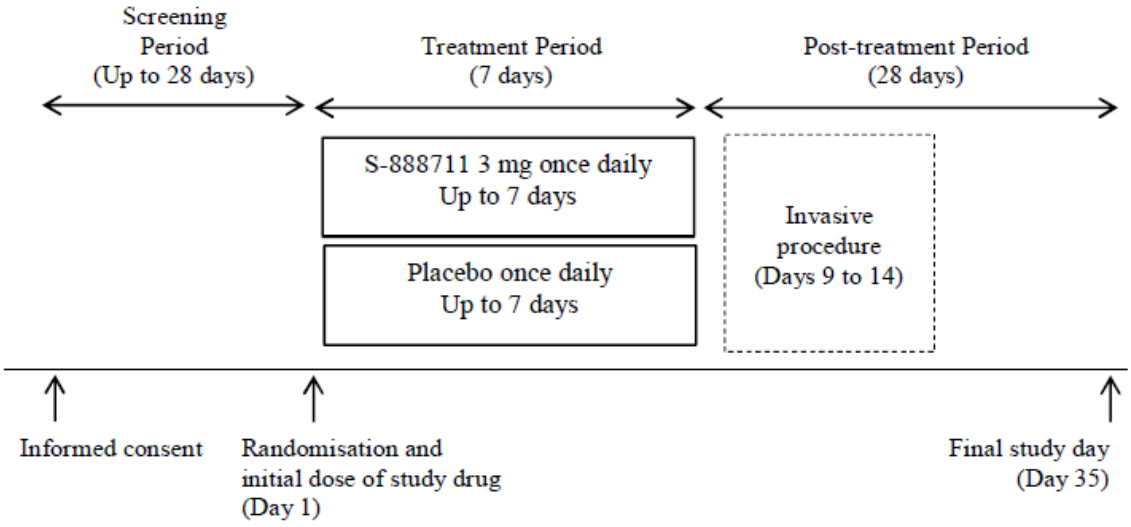
Patients received once daily treatment on day 1 after randomization and continued up to 7 days. A platelet count was performed on day 5, 6 and 7 prior to administration of the study medication. The planned invasive procedure was performed in the post-treatment period between days 9 and 14. A platelet count was performed on or after Day 8, but no more than 2 days prior to the elective invasive procedure, in order to assess the need for a platelet transfusion before the elective invasive procedure. A pre-operative platelet transfusion must be performed if the platelet count was $< 50 \times 10^9$/L.

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

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

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

Figure 14: L-PLUS2 Study Schematic



[Source: 1423M0634 Protocol and Amendment Page 19]

The primary objective of the study is:

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

The secondary objectives of the study are:

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

The sample size was planned to be total of 200. The assumptions were 20% success in placebo group and 70% in the S-888711 treatment group, 99% power to detect a difference of 50% difference at a two-sided significance level of 0.05. A total of 215 patients were enrolled.

Study Endpoints

The primary endpoint was proportion of patients who require no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomization through 7 days after the primary elective procedure.

Secondary endpoints were:

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

Statistical Analysis Plan

For the analysis of the primary endpoint, the number and proportion of patients who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomization through 7 days after the primary elective procedure were calculated by treatment group. The proportion of patients who required no platelet transfusion in the S-888711 group were compared with that in the placebo group using the Cochran-Mantel-Haenszel test adjusted by stratification factors. The primary endpoint was presented along with 95% confidence intervals (CIs), which will be calculated with the Clopper-Pearson method.

In addition, the difference in the primary endpoint and its 95% CI using Wald method was calculated.

The patients were to be determined as a success for the primary endpoint if all of the following conditions are satisfied:

- Patients received no platelet transfusion from the date of randomization through at least 7 days after the primary invasive procedure (i.e., the first invasive procedure in the study)
- Patients received no rescue therapy for bleeding (including any of the following) from the date of randomization through 7 days after the primary invasive procedure
    - Platelet preparations
    - Other blood preparations, including red blood cells and plasma
    - Volume expanders
- Patients underwent an invasive procedure

The following patients were considered as failures for the primary endpoint:

- Patients received at least one platelet transfusion prior to the primary invasive procedure

- Patients received at least one rescue therapy for bleeding from the date of randomization through 7 days after the primary invasive procedure
- Patients who withdrew from the study before receiving the primary invasive procedure
- Patients who did not receive the invasive procedure.

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

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

- Proportion of patients who require no platelet transfusion during the study: A patient was considered as success for this endpoint if he/she required no platelet transfusion and received the invasive procedure during the study. All other patients were considered as failures.
- Proportion of responders: patients who achieve a platelet count of $\geq 50 \times 10^9$/L, with an increase of $\geq 20 \times 10^9$/L from baseline at any time during the study
- Duration of the platelet count $\geq 50 \times 10^9$/L
- The comparison between S-888711 without platelet transfusion and placebo with platelet transfusion in the duration of platelet count $\geq 50 \times 10^9$/L

A responder was defined as the patient who achieved the following criterion, that is a $\geq 50 \times 10^9$/L with an increase of $\geq 20 \times 10^9$/L from baseline without platelet transfusion at least once during the study. All patients in the ITT population were classified into either responder or nonresponder for evaluating the proportion of responders during the study. A patient who had platelet transfusion was considered as a responder if he/she achieved the responder criterion before receiving the first platelet transfusion. However, a patient was considered as nonresponder if their platelet count met the responder criterion only after platelet transfusion.

In evaluating the proportion of responders at each scheduled time point (Day 5, 6, 7, 8, 10, 12, 14, 17, 21, 28, and 35), a patient was counted as a responder if all of the following conditions are satisfied:

- Patients achieved $\geq 50 \times 10^9$/L with an increase of $\geq 20 \times 10^9$/L from baseline at the evaluation point.
- Patients received no platelet transfusion through the evaluation point.

Missing platelet count at each scheduled time point will not be imputed.

The duration of the increase in platelet count will be defined as the number of days during which the platelet count was maintained as $\geq 50 \times 10^9$/L, and it will be calculated based on the

platelet count at scheduled time points (Days 1, 5, 6, 7, 8, 10, 12, 14, 17, 21, 28, and 35). If there was missing assessment of platelet count in certain visit, it was calculated from the previous visit to the next available visit.

The proportion of patients who required no platelet transfusion in the S-888711 group was compared with that in the placebo group using the Cochran-Mantel-Haenszel test adjusted by the stratification factors. The proportions were presented along with 95% CI and differences in the secondary endpoints and the 95% CI were calculated.

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

Median and quartiles for the duration of increased platelet count were calculated in each treatment group with or without platelet transfusions. The duration was compared between the S-888711 group and placebo group using Wilcoxon rank sum test. The duration in the S-888711 group was compared with that in the placebo group using van Elteren test stratified with platelet transfusion during the study.

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

Missing data were not imputed. All analyses were performed using actual observations.

If a patient received platelet transfusion on the same day as an invasive procedure but the time of either platelet transfusion or invasive procedure was missing, the patient will be considered as he/she underwent the invasive procedure after receiving platelet transfusion.

If a patient had a platelet transfusion and platelet count on the same day but the time of either platelet transfusion or collection of blood sample for platelet count was missing, the patient will be considered as he/she received the platelet transfusion after collection of the blood sample for platelet count.

No interim analysis was planned for the study.

Subgroup analysis was performed for primary endpoint in the following subgroups:

- Platelet count at baseline: $< 35 \times 10^9$/L, $\geq 35 \times 10^9$/L
- Received primary invasive procedure: Percutaneous RFA/MCT, Laparoscopic RFA/MCT, EVL, EIS, TACE, TAE, other, and not performed
- Sex: male, female
- Age: < 65 years, ≥ 65 years

- Baseline body weight: <75 kg, ≥75 kg
- Race: White, Nonwhite
- Child-Pugh class: A, B, C

Sensitivity analysis was performed:

- Per Protocol (PP) Population
- Handling withdrawal

For classification of patients into success and failure, the primary endpoint was modified as follows to explore the impact of missing data, withdrawals, or patients who did not undergo an invasive procedure.

- Patients who withdrew from the study before undergoing the primary invasive procedure but whose last observation of platelet count was ≥ 50×10^9/L with an increase of ≥ 20×10^9/L from baseline will be classified as success, if he/she did not receive platelet transfusion and rescue therapy for bleeding.
- Patients who did not undergo an invasive procedure but whose platelet count was ≥ 50×10^9/L with an increase of ≥20×10^9/L from baseline at least once within 14 days after randomization will be classified as success, if he/she did not receive platelet transfusion and rescue therapy for bleeding.

Patients Data Based Analysis

For classification of patients into success and failure, the primary endpoint was modified as follows based on platelet count at platelet transfusion assessment.

- Patients whose platelet count was ≥ 50×10^9/L at platelet transfusion assessment will be considered as success regardless of preoperative platelet transfusion, if he/she (1) underwent invasive procedure, (2) did not receive platelet transfusion within 7 days after the primary invasive procedure, and (3) did not receive rescue therapy for bleeding from the date of randomization through 7 days after the primary invasive procedure. If platelet count at platelet transfusion assessment was missing, the patients would be considered as failure.

Protocol Amendments

The protocol was amended once for the removal of the fixed 5-day treatment arm resulting in a decrease in the total number of patients from 300 to 200 patients. The number of patients selected to undergo intensive blood sampling for S-888711 plasma concentrations and PK analysis increased from 15 patients to 20 patients. The primary analysis population was changed from a modified ITT population to an ITT patient population which would include all randomized patients from feedback with the FDA (Type C Written Responses dated 07 May 2015).

These protocol amendments to this study were made after discussion at an End of Phase 2 (EOP2) meeting held on October 2014 and agreed upon by the Agency:

1. The Sponsor provided rationale for the target sample size and stratification factors to maintain power in the study.
2. The Study design allowed eligible patients to randomized in a 1:1 ratio to either S-888711 3-mg once daily for up to 7 days versus the fixed 5-day treatment arm. The randomization would be stratified by primary invasive procedure (liver ablation/coagulation or other invasive procedure) and baseline platelet count (< 35,000/µL or ≤ 35,000/µL.
3. The study population was reduced from 300 to a total of 200 adult patients with CLD and thrombocytopenia.
4. Barrier method with or without spermicide, double barrier contraception and oral contraceptive pill are insufficient methods for prevention of female eligible patients who are not postmenopausal or surgically sterile.
5. The duration of treatment was revised such that if the patient met the administration stopping criterion (i.e., platelet count ≥ 50,000/µL with an increase of ≥ 20,000/µL from baseline), no additional dose of study drug will be administered.
6. The secondary endpoint was revised to include the proportion of patients who require rescue therapy for bleeding at any time during the study.
7. S-888711 plasma concentrations and PK studies would be collected from 20 patients versus 15 patients.
8. The statistical methods were revised to satisfy the primary endpoint of 20% in the placebo group and 70% in the S-888711 treatment group, 100 patients per arm would provide 99% power to detect a difference of 50% between S-888711 and placebo groups at a two-sided significance of 0.05. The analysis of the primary endpoint would be conducted using the Cochran-Mantel-Haenszel test adjusted by stratification factors.
9. The proposed analyzed population will be the intention-to-treat (ITT) population versus the modified ITT population. The ITT population would include all randomized patients.
10. The rationale of removing the fixed, 5-day treatment arm did remove variables in the protocol that would delay the designated days for the planned invasive procedure to occur.
11. The assessment of the severity of bleeding according the WHO Bleeding Scale and measurements of a resting blood pressure and pulse rate were revised.
12. The responder rate and duration of the increase in the platelet count was revised to be based on the treatment for up to 7 days versus the fixed 5-day dosing regimen.

Reviewer's Comments: Extending the list of different types of invasive procedures allowed in clinical study mimics real-world scenarios where lusutrombopag would be used. Removing the fixed 5-day treatment reduced the chance for delay in the scheduled planned invasive procedures.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Study 1423M0634/L-PLUS2

One patient in the lusutrombopag group (Patient (b) (6) did not want to continue in the study and did not receive study drug.

In the lusutrombopag arm, 73/107 (68.2%) received the study drug for seven days. Of the remaining 34 patients, the study drug was administered for 6 days (11 patients), 5 days (8 patients) and 4 days (15 patients). Thirty of the 34 patients who received short duration of lusutrombopag was because they met the administration stopping criterion. Other reasons included withdrawal by patient, ineligibility and other.

In the placebo group, 94/107 (87.9%) received the study drug for 7 days. Of the remaining 13 patients in the placebo group, the study drug was administered for 6 days (4 patients), 5 days (4 patients) and 4 days (5 patients). Other reasons cited for early withdrawal included withdrawal by subject, adverse event and other. The remaining 3 patients in the placebo group did not receive the study drug for 7 days due to missing the first day of dosing because of diarrhea and vomiting.

The proportion of patients who received no platelet transfusion during the study was 63.0% (68/108 patients) in the lusutrombopag group and 29.0% (31/107 patients) in the placebo group.

Concomitant medications were reviewed for medications that may have impacted the evaluation of efficacy. One patient in the lusutrombopag arm took a prohibited concomitant medication. Patient (b) (6) self-medicated with a prohibited TPO agonist (Revolade® [eltrombopag]) during the screening period, but stopped 4 days prior to randomization. The subject resumed Revolade® treatment on Day 18 and continued self-medicating for the remainder of the study despite being requested to stop by the investigator. This patient was excluded from the ITT Population.

Prohibited procedures and therapies were also reviewed. Of note, gastrointestinal endoscopies were not performed within 180 days prior to randomization for 7 of the 10 patients enrolled with planned invasive procedures other than endoscopic treatment of gastroesophageal varices at the selected OSI inspected site (Site 8EC). EVL was the most commonly planned procedure (32.4% vs. 38.3%), followed by gastrointestinal endoscopy (regardless of polypectomy or biopsy, except for EVL and EIS; 25.9% vs. 20.6%) and dental extraction (13.0% vs. 15.0%). The remaining procedures were planned for < 10% of patients in either treatment group. A total of 15 patients (6 patients in the lusutrombopag group and 9 patients in the placebo group) did not undergo an invasive procedure, primarily due to withdrawal by the patient or platelet count < 50×10^9/L. All patients except 8 (1 patient in the lusutrombopag group and 7 patients in the placebo) underwent the invasive procedure within the scheduled period. Various reasons were cited for the 8 patients who underwent the invasive procedure outside the scheduled period,

but these primarily related to administrative and technical issues. An additional patient in each treatment group ((b) (6) in the lusutrombopag group and (b) (6) in the placebo group) underwent the primary invasive procedure within the scheduled period, and underwent an additional invasive procedure outside the scheduled period. No other patient had an additional procedure.

As for prohibited therapies, one patient on the lusutrombopag arm had been on cardioaspirin since (b) (6) and the subject was directed after the planned procedure to take 100 mg cardioaspirin daily. One patients in the placebo arm received an antithrombotic agent, heparin, on Days 31 and 34 when the invasive procedure was performed on Day 10.

Reviewer's Comments: Treatment compliance was similar in both arms of the L-PLUS1 and L-PLUS2 clinical trials. The patient who self-medicated with another TPO agonist reached a maximum platelet count of 219,000/µL without any serious complications. Patients who underwent invasive procedures outside the scheduled period did not have any complications as well.

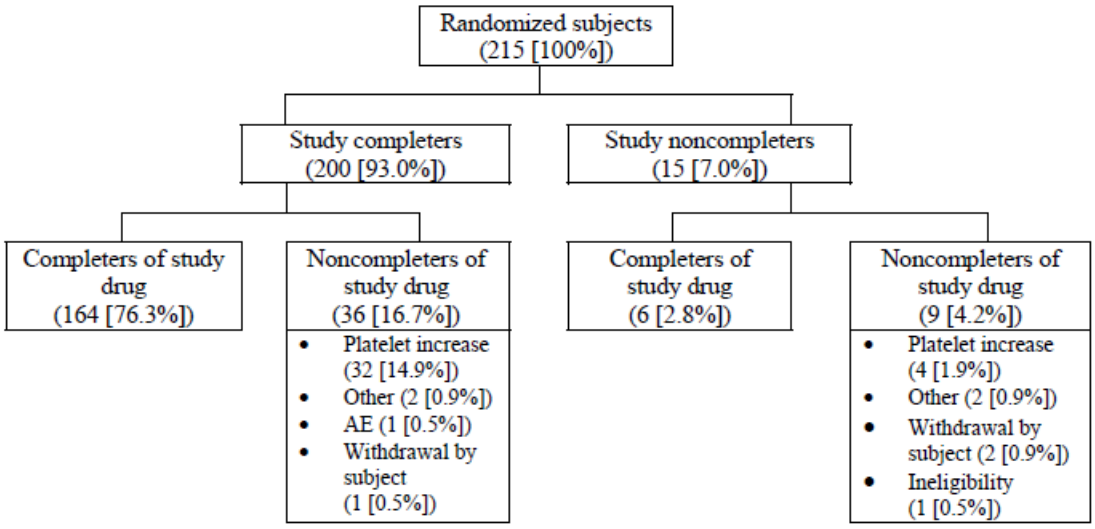
8.1.3. Study Results

Patient Disposition

The study was conducted in 22 countries across 138 sites, of which 102 sites screened a subject and 88 sites randomized a subject.

A total of 215 subjects were randomized in the study: 108 in the S-88871 arm and 107 in the placebo arm. The subject disposition is included in Figure 15 and Table 28.

Figure 15: L-PLUS2 Subject Disposition



AE = adverse event
(Source: Table 14.1.1.1 and Table 14.1.1.2)

[Source: 1423M0634 Study Report Page 63; Statistical reviewer's analysis]

Table 28: Subject Disposition (ITT)

Disposition	Lusutrombopag 3 mg N = 108	Placebo N = 107	Overall N = 215
Subjects who completed the study [a]	98 (90.7)	102 (95.3)	200 (93.0)
Subjects who discontinued in the treatment period	1 (0.9)	1 (0.9)	2 (0.9)
Withdrawal by subject	1	1	2 [b]
Subjects who discontinued in the posttreatment period	9 (8.3)	4 (3.7)	13 (6.0)
Adverse event	3	1	4 [c]
Withdrawal by subject	3	2	5 [d]
Lost to follow up	1	1	2 [e]
Other	2	0	2 [f]

[Source: 1423M0634 Study Report Page 62; Statistical reviewer's analysis]

There appears to be balanced in the subject disposition between the randomized arms.

Analysis Population

The ITT (Intent-to-Treat) population included all randomized patients. Any mis-randomized patients were analyzed according to the treatment randomized to. This population is the primary population for the analysis of efficacy.

The safety population was defined as all randomized patients who received at least 1 dose of the study drug.

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

Protocol Violations/Deviations

The protocol violation and deviations are summarized in Table 29. It appears to be similar between the treatment arms.

Table 29: L-PLUS2 Protocol Deviation

Category of Exclusion	Primary Reason for Exclusion	Number of Subjects (%)		
		Lusutrombopag 3 mg N = 108	Placebo N = 107	Overall N = 215
Efficacy criteria	Noncompliance with preprocedure platelet transfusion instructions	8 (7.4) [a]	10 (9.3) [a]	18 (8.4) [a]
	Out of window of preprocedure platelet transfusion assessment	2 (1.9)	3 (2.8)	5 (2.3)
IMP compliance	Poor study drug administration: subject received less than 5 days of study drug but did not fulfill the stopping criterion for study drug	1 (0.9)	0	1 (0.5)
	No study drug administration	1 (0.9)	0	1 (0.5)
Eligibility and entry criteria	Child-Pugh class C	3 (2.8)	0	3 (1.4)
	Received other TPO receptor agonist	1 (0.9)	0	1 (0.5)
	Platelet count $> 50 \times 10^9$/L at baseline on Day 1 prior to randomization	1 (0.9)	1 (0.9)	2 (0.9)
Concomitant medication	Use of prohibited concomitant medications and therapies	0	4 (3.7)	4 (1.9)
Total number of excluded subjects [b]		17 (15.7)	18 (16.8)	35 (16.3)

[Source: 1423M0634 Study Report Page 64]

Table of Demographic Characteristics

Patients' baseline characteristics and demographics are summarized in Table 30. The baseline characteristics appears balanced between the treatment arms on sex, age and race. Seventy-nine percent of patients overall did not have chronic Hepatitis B. However, forty-seven percent of patients overall had the diagnosis of chronic Hepatitis C versus fifty-three percent of patients not having the diagnosis of chronic Hepatitis C. More patients in the placebo arm (57.9%) had a history of transfusion. The majority of patients in both arms shared Child-Pugh classification (Class A), ECOG (Grade 0) classification, gastroesophageal varices, splenomegaly, and WHO Bleeding Scale score of Grade 0. The majority of patients did not have ascites at time of screening.

Table 30: Demographics and Baseline Characteristics (ITT)

		Lusutrombopag 3 mg N = 108	Placebo N = 107	Overall N = 215
Sex (n [%])	Male	65 (60.2)	69 (64.5)	134 (62.3)
	Female	43 (39.8)	38 (35.5)	81 (37.7)
Age (years)	n	108	107	215
	Mean (SD)	55.2 (11.6)	56.1 (11.0)	55.7 (11.3)
	Range	19 to 81	19 to 83	19 to 83
Height (cm)	n	108	106	214
	Mean (SD)	168.32 (9.80)	168.29 (10.47)	168.31 (10.11)
	Range	146.0 to 193.0	142.2 to 189.0	142.2 to 193.0
	Missing (n [%])	0	1 (0.9)	1 (0.5)
Weight (kg)	n	108	106	214
	Mean (SD)	77.86 (17.77)	78.53 (19.22)	78.19 (18.46)
	Range	39.0 to 142.0	43.2 to 156.0	39.0 to 156.0
	Missing (n [%])	0	1 (0.9)	1 (0.5)
Ethnicity (n [%])	Hispanic or Latino	14 (13.0)	12 (11.2)	26 (12.1)
	Not Hispanic or Latino	93 (86.1)	95 (88.8)	188 (87.4)
	Unknown	1 (0.9)	0	1 (0.5)
	Not provided	0	0	0
Race (n [%])	American Indian or Alaska Native	2 (1.9)	0	2 (0.9)
	Asian	15 (13.9)	17 (15.9)	32 (14.9)
	Black or African American	1 (0.9)	0	1 (0.5)
	Native Hawaiian or Other Pacific Islander	0	0	0
	White	85 (78.7)	86 (80.4)	171 (79.5)

		Lusutrombopag 3 mg N = 108	Placebo N = 107	Overall N = 215
	Other	3 (2.8)	0	3 (1.4)
	Not provided	2 (1.9)	4 (3.7)	6 (2.8)
Medical history of CLD due to hepatitis B (n [%])	Yes	24 (22.2)	21 (19.6)	45 (20.9)
	No	84 (77.8)	86 (80.4)	170 (79.1)
Medical history of CLD due to hepatitis C (n [%])	Yes	51 (47.2)	51 (47.7)	102 (47.4)
	No	57 (52.8)	56 (52.3)	113 (52.6)
Medical history of CLD due to alcoholic hepatitis (n [%])	Yes	24 (22.2)	26 (24.3)	50 (23.3)
	No	84 (77.8)	81 (75.7)	165 (76.7)
Medical history of CLD due to nonalcoholic hepatitis (n [%])	Yes	12 (11.1)	15 (14.0)	27 (12.6)
	No	96 (88.9)	92 (86.0)	188 (87.4)
Medical history of CLD due to autoimmune hepatitis (n [%])	Yes	5 (4.6)	5 (4.7)	10 (4.7)
	No	103 (95.4)	102 (95.3)	205 (95.3)
History of any transfusion (n [%])	Yes	48 (44.4)	62 (57.9)	110 (51.2)
	No	60 (55.6)	45 (42.1)	105 (48.8)
Child-Pugh class (n [%])	A	72 (66.7)	63 (58.9)	135 (62.8)
	B	33 (30.6)	43 (40.2)	76 (35.3)
	C	3 (2.8)	0	3 (1.4)
	Missing	0	1 (0.9)	1 (0.5)
Planned invasive procedure (n [%])	Liver ablation/ coagulation	7 (6.5)	5 (4.7)	12 (5.6)
	Other	101 (93.5)	102 (95.3)	203 (94.4)
Baseline platelet count ($\times 10^9$/L)	n	107	106	213
	Mean (SD)	37.7 (9.0)	37.4 (7.8)	37.6 (8.4)
	Range	13 to 54	12 to 55	12 to 55
	< 35 (n [%])	36 (33.3)	38 (35.5)	74 (34.4)
	≥ 35 (n [%])	71 (65.7)	68 (63.6)	139 (64.7)
	Missing (n [%])	1 (0.9)	1 (0.9)	2 (0.9)
ECOG PS (n [%])	Grade 0	83 (76.9)	95 (88.8)	178 (82.8)
	Grade 1	25 (23.1)	12 (11.2)	37 (17.2)
Gastro-esophageal varices (n [%])	Yes	92 (85.2)	90 (84.1)	182 (84.7)
	No	15 (13.9)	14 (13.1)	29 (13.5)
	Missing	1 (0.9)	3 (2.8)	4 (1.9)
Splenomegaly (n [%])	Yes	95 (88.0)	95 (88.8)	190 (88.4)
	No	13 (12.0)	12 (11.2)	25 (11.6)
Ascites (n [%])	Yes	22 (20.4)	25 (23.4)	47 (21.9)
	No	86 (79.6)	82 (76.6)	168 (78.1)

		Lusutrombopag 3 mg N = 108	Placebo N = 107	Overall N = 215
WHO Bleeding Scale (n [%])	Grade 0	101 (93.5)	97 (90.7)	198 (92.1)
	Grade 1	6 (5.6)	10 (9.3)	16 (7.4)
	Missing	1 (0.9)	0	1 (0.5)

CLD = chronic liver disease; ECOG = Eastern Cooperative Oncology Group; PS = performance status; SD = standard deviation; WHO = World Health Organization

[Source: 1423M0634 Study Report Pages 66-68; Statistical reviewer's analysis]

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Study 1423M0634/L-PLUS2

One patient in the lusutrombopag group (Patient (b) (6) did not want to continue in the study and did not receive study drug.

In the lusutrombopag arm, 73/107 (68.2%) received the study drug for seven days. Of the remaining 34 patients, the study drug was administered for 6 days (11 patients), 5 days (8 patients) and 4 days (15 patients). Thirty of the 34 patients who received short duration of lusutrombopag was because they met the administration stopping criterion. Other reasons included withdrawal by patient, ineligibility and other.

In the placebo group, 94/107 (87.9%) received the study drug for 7 days. Of the remaining 13 patients in the placebo group, the study drug was administered for 6 days (4 patients), 5 days (4 patients) and 4 days (5 patients). Other reasons cited for early withdrawal included withdrawal by subject, adverse event and other. The remaining 3 patients in the placebo group did not receive the study drug for 7 days due to missing the first day of dosing because of diarrhea and vomiting.

The proportion of patients who received no platelet transfusion during the study was 63.0% (68/108 patients) in the lusutrombopag group and 29.0% (31/107 patients) in the placebo group.

Concomitant medications were reviewed for medications that may have impacted the evaluation of efficacy. One patient in the lusutrombopag arm took a prohibited concomitant medication. Patient (b) (6) self-medicated with a prohibited TPO agonist (Revolade® [eltrombopag]) during the screening period, but stopped 4 days prior to randomization. The subject resumed Revolade® treatment on Day 18 and continued self-medicating for the remainder of the study despite being requested to stop by the investigator. This patient was excluded from the ITT Population.

Prohibited procedures and therapies were also reviewed. Of note, gastrointestinal endoscopies were not performed within 180 days prior to randomization for 7 of the 10 patients enrolled with planned invasive procedures other than endoscopic treatment of gastroesophageal varices at the selected OSI inspected site (Site 8EC). EVL was the most commonly planned procedure (32.4% vs. 38.3%), followed by gastrointestinal endoscopy (regardless of polypectomy or biopsy, except for EVL and EIS; 25.9% vs. 20.6%) and dental extraction (13.0% vs. 15.0%). The remaining procedures were planned for < 10% of patients in either treatment group. A total of 15 patients (6 patients in the lusutrombopag group and 9 patients in the placebo group) did not undergo an invasive procedure, primarily due to withdrawal by the patient or platelet count < 50×10^9/L. All patients except 8 (1 patient in the lusutrombopag group and 7 patients in the placebo) underwent the invasive procedure within the scheduled period. Various reasons were cited for the 8 patients who underwent the invasive procedure outside the scheduled period,

but these primarily related to administrative and technical issues. An additional patient in each treatment group ([redacted] in the lusutrombopag group and [redacted] in the placebo group) underwent the primary invasive procedure within the scheduled period, and underwent an additional invasive procedure outside the scheduled period. No other patient had an additional procedure.

As for prohibited therapies, one patient on the lusutrombopag arm had been on cardioaspirin since [redacted] and the subject was directed after the planned procedure to take 100 mg cardioaspirin daily. One patients in the placebo arm received an antithrombotic agent, heparin, on Days 31 and 34 when the invasive procedure was performed on Day 10.

Reviewer's Comments: Treatment compliance was similar in both arms of the L-PLUS1 and L-PLUS2 clinical trials. The patient who self-medicated with another TPO agonist reached a maximum platelet count of 219,000/µL without any serious complications. Patients who underwent invasive procedures outside the scheduled period did not have any complications as well.

Efficacy Results – Primary Endpoint

The primary endpoint is the proportion of subjects who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomization through 7 days after primary invasive procedure. The sponsor reported the primary endpoint results as in Table 31.

The statistical reviewer performed analysis and ran the Fisher's exact test as a sensitivity analysis. The results are reported in Table 32. The results confirmed the sponsor's analysis and showed statistically significant difference observed between lusutrombopag and placebo.

Table 31: Primary Endpoint Results

	Lusutrombopag 3 mg N = 108	Placebo N = 107
Proportion of subjects who met the primary endpoint [a]	64.8% (70/108)	29.0% (31/107)
Exact 95% CI	(55.0, 73.8)	(20.6, 38.5)
Comparison with placebo		
Difference in proportion (95% CI)	36.7 (24.9, 48.5)	
p-value from CMH test	< 0.0001	

CI = confidence interval; CMH = Cochran-Mantel-Haenszel

[a] Proportion of subjects who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomization through 7 days after the primary invasive procedure. In addition to subjects who received platelet transfusion, subjects who did not undergo an invasive procedure regardless of the reason were considered as receiving platelet transfusion.

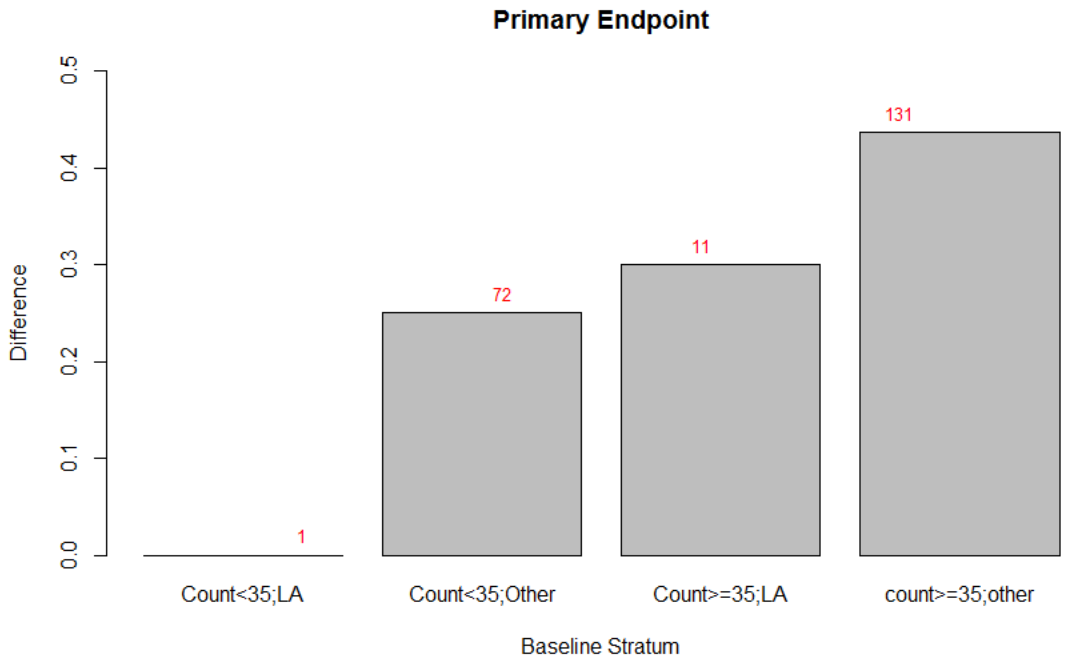
[Source: 1423M0634 Study Report Page 72]

Table 32: FDA Analysis on the Primary Endpoint for the Difference between the Treatment Groups

P-value from CHM test	<0.0001
P-value from Fisher's test	<0.0001

The statistical reviewer also did analysis for number of patients in the trial separately for each baseline strata and the differences observed with respect to the baseline strata. The results are reported in Figure 16. As can be seen from the break-down, majority of the patients were in stratum of baseline platelet count ≥ 35 x 10^9 and other invasive procedures. The difference observed between Lusutrombopag and placebo is driven primarily by the stratum.

Figure 16: FDA Analysis of Difference of Proportions in each Baseline Stratum



3.2.4.2 Sensitivity Analysis on Primary Endpoint

The primary endpoint analysis for PP population is summarized in Table 34. The statistical reviewer's analysis on the difference between the treatment and placebo with sensitivity analysis using Fisher's exact test is included in Table 35. The results confirmed the sponsor's results with minor numerical differences.

Table 34: Primary Endpoint for per Protocol Population (PP)

	S-888711 3 mg N=91	Placebo N=89
Proportion of patients who met the primary endpoint [a]	72.5% (66/91)	20.2% (18/89)
Exact 95% confidence interval	(62.2, 81.4)	(12.4, 30.1)
Comparison with placebo		
- Difference of proportion (95% confidence interval)	53.3 (42.1, 64.5)	
- P value from Cochran-Mantel-Haenszel test	<.0001	

[a] Proportion of patients who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomization through 7 days after the primary elective procedure. In addition to patients who received platelet transfusion, patients who did not receive an invasive procedure regardless of the reason were considered as receiving platelet transfusion.

[Source: 1423M0634 Study Report Page 143]

Table 35: PP Population for Primary Endpoint

FDA Analysis	
Difference in proportion (95% CI)	52.5% [40.1, 64.9]
P-value from CHM test	<0.0001
P-value from Fisher's test	<0.0001

Impact of missing data was evaluated based on the two methods specified in the statistical analysis plan. The results are summarized in Table 36 and Table 37.

Statistical reviewer's comment:

Two methods were explored to redefine the responders in the withdrawal population and who received platelet transfusion. The first sensitivity analysis relaxed the definition of responders, and define those patients as responders even if they withdrew or did not go through invasive procedure yet achieving the platelet count and change from baseline. The observed difference between treatment and placebo is about the same magnitude. The second sensitivity analysis relaxed the platelet transfusion requirement and redefined responders regardless of preoperative platelet transfusion. The treatment difference is about the same magnitude. Both results confirmed the robustness of the treatment differences between lusutrombopag and placebo.

Table 36: Primary Endpoint for Handling Withdrawal ITT Population

	S-888711 3 mg N=108	Placebo N=107
Proportion of patients who met the primary endpoint [a]	65.7% (71/108)	29.0% (31/107)
Exact 95% confidence interval	(56.0, 74.6)	(20.6, 38.5)
Comparison with placebo		
- Difference of proportion (95% confidence interval)	37.6 (25.9, 49.3)	
- P value from Cochran-Mantel-Haenszel test	<.0001	

[a] Proportion of patients who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomization through 7 days after the primary elective procedure. The following patients without rescue therapy were considered successes: (1) Patients who withdrew from the study before receiving the primary invasive procedure, but whose last observation of platelet count was >= 50*10^9/L with an increase of >= 20*10^9/L from baseline. (2) Patients who did not receive an invasive procedure, but whose platelet count was >= 50*10^9/L with an increase of >= 20*10^9/L from baseline at least once within 14 days after randomization.

[Source: 1423M0634 Study Report Page 144]

Table 37: Primary Endpoint for Handling Platelet Transfusion Assessment

	S-888711 3 mg N=108	Placebo N=107
Proportion of patients who met the primary endpoint [a]	67.6% (73/108)	19.6% (21/107)
Exact 95% confidence interval	(57.9, 76.3)	(12.6, 28.4)
Comparison with placebo		
- Difference of proportion (95% confidence interval)	48.8 (38.2, 59.4)	
- P value from Cochran-Mantel-Haenszel test	<.0001	

[a] Proportion of patients who met all criteria below: (1) Patients whose platelet count was >= 50*10^9/L at platelet transfusion assessment regardless of preoperative platelet transfusion. (2) Patients who underwent an invasive procedure. (3) Patients who received no platelet transfusion within 7 days after the primary invasive procedure. (4) Patients who received no rescue therapy for bleeding from the date of randomization until 7 days after the primary elective procedure. If platelet count at platelet transfusion assessment was missing, the patients were considered as failure.

[Source: 1423M0634 Study Report Page 145]

Efficacy Results – Secondary and Other Relevant Endpoints

The pre-specified secondary endpoint results are summarized in Table 38, Table 40 and Table 42 conducted by the sponsor. The statistical reviewer's analyses are summarized in Table 39 and Table 41 with sensitivity analysis using Fisher's exact test. Minor numerical differences were observed. The statistical reviewer also did analysis for secondary endpoints separately for baseline strata. The results are included in Figure 17 and Figure 18.

Statistical reviewer's comment:

Most of the patients were in the stratum of baseline platelet count ≥ 35 x 10^9 /L and other invasive procedures.

Table 38: Secondary Endpoint: Proportion of Subjects Who Required no Platelet Transfusion During the Study

	Lusutrombopag 3 mg N = 108	Placebo N = 107
Proportion of subjects who required no platelet transfusion [a]	63.0% (68/108)	29.0% (31/107)
Exact 95% CI	(53.1, 72.1)	(20.6, 38.5)
Comparison with placebo		
Difference in proportion (95% CI)	34.8 (22.8, 46.8)	
p-value from CMH test	< 0.0001	

CI = confidence interval; CMH = Cochran-Mantel-Haenszel

[a] Proportion of subjects who required no platelet transfusion and underwent the invasive procedure during the study.

[Source: 1423M0634 Study Report Page 74]

Table 39: FDA Analysis on Secondary Endpoint of % of Subjects Who Required no Platelet Transfusion During the Study

FDA Analysis	
Difference in proportion (95% CI)	34.2% [21.6, 46.8]
P-value from CHM test	<0.0001
P-value from Fisher's test	<0.0001

Figure 17: FDA Analysis of Difference Between Lusutrombopag and the Placebo of % of Subjects Who Required no Platelet Transfusion During the Study in Baseline Stratum

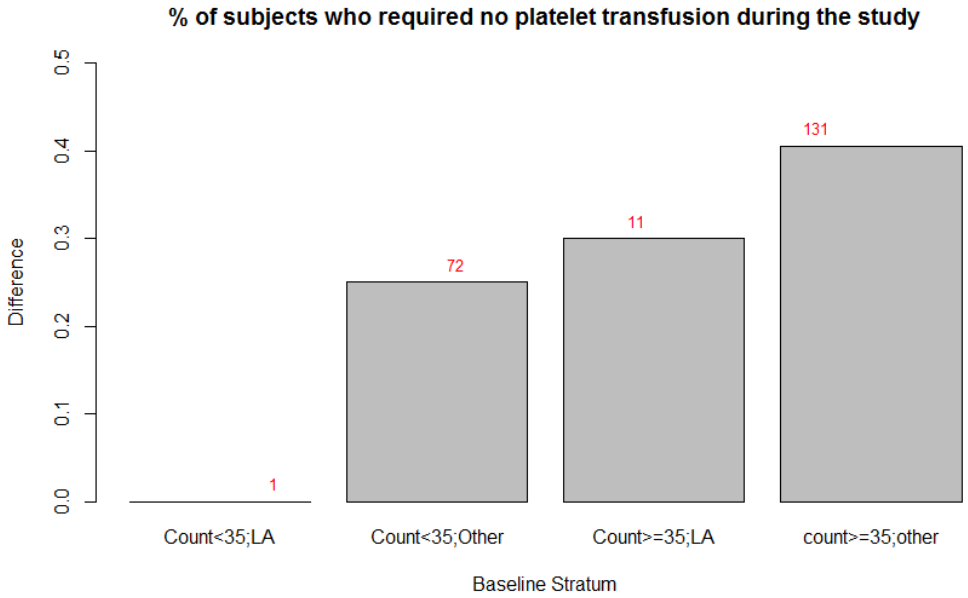


Table 40: Secondary Endpoint: Proportion of Responders

	Lusutrombopag 3 mg N = 108	Placebo N = 107
Proportion of subjects who met the responder criterion at least once during the study [a]		
Proportion of responders	64.8% (70/108)	13.1% (14/107)
Exact 95% CI	(55.0, 73.8)	(7.3, 21.0)
Comparison with placebo		
Difference in proportion (95% CI)	52.5 (42.0, 62.9)	
p-value from CMH test	< 0.0001	
Summary of proportion of responders [b] by time point		
Day 5	11.3% (12/106)	3.7% (4/107)
Day 6	16.3% (17/104)	4.8% (5/104)
Day 7	27.2% (28/103)	4.9% (5/103)
Day 8	41.0% (41/100)	3.0% (3/101)
Day 10	55.2% (53/96)	5.6% (5/90)
Day 12	61.1% (55/90)	6.2% (6/97)
Day 14	52.6% (50/95)	5.2% (5/96)
Day 17	42.2% (35/83)	8.4% (7/83)
Day 21	26.3% (26/99)	6.3% (6/95)
Day 28	14.9% (14/94)	5.2% (5/96)
Day 35	12.5% (12/96)	4.0% (4/100)

CI = confidence interval; CMH = Cochran-Mantel-Haenszel

[a] Responders were defined as subjects who achieved a platelet count of $\geq 50 \times 10^9$/L with an increase of $\geq 20 \times 10^9$/L from baseline at any time during the study. Subjects who met the responder criterion only after the platelet transfusion were considered as nonresponders.

[b] Responders were defined as subjects who achieved a platelet count of $\geq 50 \times 10^9$/L with an increase of $\geq 20 \times 10^9$/L from baseline at the time point. Subjects with platelet transfusion were considered as nonresponders at any time point after the first platelet transfusion.

[Source: 1423M0634 Study Report Page 75]

Table 41: FDA Analysis of Difference between Lusutrombopag and Placebo of % of Responders

FDA Analysis	
Difference in proportion (95% CI)	54.3% [43.2, 65.5]
P-value from CHM test	<0.0001
P-value from Fisher's test	<0.0001

Figure 18: Difference between Lusutrombopag and Placebo in % of Responders by Baseline Stratum

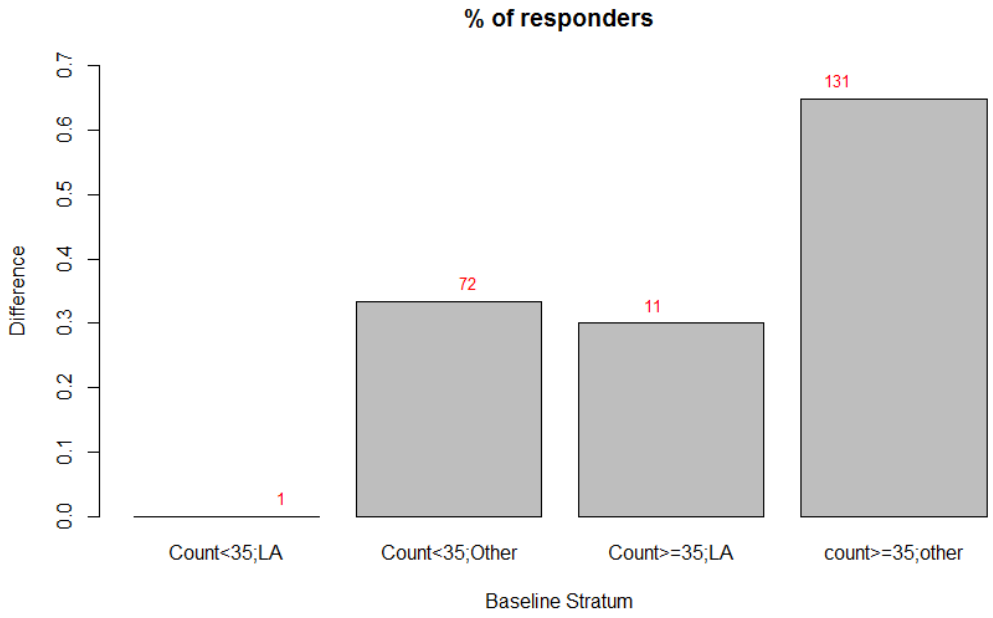


Table 42: Secondary Endpoint: Duration of Increase in Platelet Count >= 50 x 10^9/L

	Lusutrombopag 3 mg			Placebo		
	With PT N = 34	W/O PT N = 74	Total N = 108	With PT N = 73	W/O PT N = 34	Total N = 107
n	34	73	107	73	34	107
Median (25 to 75 percentile)	1.73 (0.00, 14.00)	19.21 (12.64, 28.00)	15.11 (6.59, 23.88)	0.00 (0.00, 5.04)	8.86 (0.00, 18.73)	0.98 (0.00, 9.22)
p-value	-	< 0.0001 [a]	0.0002 [b]	-	-	-

PT = platelet transfusion; W/O = without

[a] Comparison between lusutrombopag without platelet transfusion and placebo with platelet transfusion by Wilcoxon rank sum test.

[b] Comparison between lusutrombopag and placebo by van Elteren test stratified by platelet transfusion during the study.

[Source: 1423M0634 Study Report Page 76 and Statistical reviewer's analysis]

Table 43: Number of Patients with Non-Zero Duration of Platelet Count

	Non-Responders		Responders	
	W PT (%; out of total # in the group)	W/O PT (%; out of total # in the group)	W PT (%; out of total # in the group)	W/O PT (%; out of total # in the group)
Placebo (N=107)	31 (43.7%; 31/71)	13 (59.1%; 13/22)	2 (100%; 2/2)	12 (100%; 12/12)
Lusutrombopag (N=108)	17 (56.7%; 17/30)	3 (36.5%; 3/8)	4(100%; 4/4)	66 (100%; 66/66)

Statistical reviewer's comment:

The statistical reviewer did additional analysis on the number of patients with non-zero duration of platelet count and the result is shown in Table 43. The table reported the number of patients separately for non-responders and responders stratified by with or without platelet transfusion. Usually, in other hematology clinical trials, the duration of response is reported and the duration of response is only calculated for those patients who are responders. In other words, for non-responders, the duration of response would be expected to be 0.

The objective of the analysis is to show that unlike duration of response in other hematology trials, the duration of platelet count can be non-zero in non-responders. The reason is because the definition of duration of platelet count is who achieves a platelet count of ≥ 50 x 10^9/L. This is different from the definition of proportion of responders, which is defined as who achieves a platelet count of ≥ 50 x 10^9/L with an increase of ≥20 x 10^9/L from baseline at any time during the study. Both definitions were agreed upon with the agency. Therefore, the analysis is to point out that the interpretation of duration of platelet count is different from the duration of response. But nonetheless, the statistically significant improvement was shown in the duration of platelet counts in Lusutrombopag arm compared to placebo.

Dose/Dose Response

Dose/Dose Response was not applicable in this application.

Durability of Response

In the L-PLUS2 trial, the initial platelet count was below 50,000/µL at the time of Day 1 of treatment. By Day 7, the mean platelet count achieved by patients reached 60,000/µL in the lusutrombopag arm compared to 47,000/µL in the placebo arm. The day prior to the invasive procedure (Day 8) a higher platelet count of 67,000/µL compared to 48,000/µL in the lusutrombopag arm versus the placebo arm was achieved, respectively. By Day 12, the mean

platelet count in the lusutrombopag arm was 76,000/µL compared to 56, 000/µL in the placebo arm. By Day 35, the platelet counts in both arms returned close to the baseline platelet counts.

Persistence of Effect

By Day 35 (end of the treatment period), patients in the L-PLUS2 trial in both the lusutrombopag and placebo arms returned to platelet count levels near the screening platelet count levels (L-PLUS2: Lusutrombopag: 49,000 ± 21,000/µL; Placebo: 47,000/µL ± 18,000/µL), respectively.

Additional Analyses Conducted on the Individual Trial

Study 1423M0634/L-PLUS2

Subgroup analysis results for sex, age, and race is reported in Table 44. No outlier groups are observed.

Table 44: Subgroup Analysis of the Primary Endpoint

Subgroup	Lusutrombopag 3 mg N = 108	Placebo N = 107	Comparison with Placebo [a]	Test of Homogeneity [b]
Sex				
Male	56.9% (37/65)	23.2% (16/69)	< 0.0001	0.8152
Female	76.7% (33/43)	39.5% (15/38)	0.0008	
Age (years)				
< 65	65.5% (55/84)	28.4% (25/88)	< 0.0001	0.7001
≥ 65	62.5% (15/24)	31.6% (6/19)	0.0666	
Race				
White	69.4% (59/85)	29.1% (25/86)	< 0.0001	0.2185
Nonwhite	47.8% (11/23)	28.6% (6/21)	0.2279	

[Source: 1423M0634 Study Report Page 84-85]

Integrated Review of Effectiveness

8.1.4. Assessment of Efficacy Across Trials

The integrated pivotal data (L-PLUS1 and L-PLUS2) includes 312 number of patients from two similarly designed randomized, double-blind, placebo controlled, Phase 3 studies in the target patient population and proposed indication and doses.

Patients were assigned to receive treatment (i.e. lusutrombopag or placebo) once daily for 7 days and 8-14 days prior to scheduled procedure. The individual data as well as the pooled efficacy analysis of the L-PLUS1 and L-PLUS2 trials support the efficacy of lusutrombopag in the treatment of thrombocytopenia in patients with chronic liver disease. Both studies met their primary and secondary efficacy endpoints.

Lusutrombopag administration did demonstrate a statistically significant increase in the proportion of patients who did not require a platelet transfusion prior to the initial invasive procedure as well as the proportion of patients who did not require platelets prior to the procedure and no rescue therapy for bleeding up to seven days after the procedure occurred as primary endpoints in L-PLUS1 and L-PLUS2 studies, respectively.

The impact of missing data was evaluated and revealed a small difference between the treatment arms in both L-PLUS1 and L-PLUS2 trials which did not impact the overall statistical conclusion.

Primary Endpoints

The integrated pivotal data (L-PLUS1 and L-PLUS 2) includes 312 patients from two similar designed randomized, double-blind, placebo controlled phase 3 studies in the target population. The primary endpoints in both L-PLUS1 and L-PLUS2 studies were achieved and demonstrated a higher proportion of patients in the lusutrombopag treatment arm who required no platelet transfusions prior to the procedure and/or no rescue therapy for bleeding up to seven days after the procedure occurred in the placebo arms, respectively.

Additional Efficacy Considerations

During the review by the clinical pharmacology team it was noted that body weight may be a significant covariate influencing the PK and PK/PD of lusutrombopag. Based on this concern, analysis was done by identifying all patients at 100 kg or greater in M0626, M0631, and M0634 clinical studies in determining if there was a notable difference in achieving the primary efficacy endpoints between both arms in all clinical studies.

The following efficacy results are shown below in Tables 45-47:

Table 45: Efficacy Results Based on Weight (kg) in Study M0626

Efficacy Rate Dosage/Weight(kg) (n = 61)	Responders (%) (n = 42)	Non-Responders (%) (n = 19)
2-mg/ < 100 kg (n=15)	12 (26.7%)	3 (15.8%)
2-mg/ > 100 kg (n = 0)	0	0
3-mg/ <100 kg (n =16)	13 (31.0%)	3 (15.8%)
3-mg/ >100 kg (n = 0)	0	0
4-mg/ < 100 kg (n = 15)	13 (31.0%)	2 (10.5%)
4-mg/ > 100 kg (n = 0)	0	0
Placebo/< 100 kg (n = 15)	4 (9.52%)	11 (57.9%)

Responder: defined as a patient who achieved platelet count of ≥ 50,000/µL with an increase of ≥ 20,000/µL from baseline.

Table 46: Efficacy Results Based on Weight (kg) in Study M0631*

Efficacy Rate Dosage/Weight (n = 97)	Responders (%) (n = 58)	Non-Responders (%) (n = 39)
3-mg/ <100 kg (n = 49)	44 (75.9%)	5 (12.8%)
3-mg/ > 100 kg (n = 0)	0	0
Placebo / < 100 kg (n = 47)	14 (24.1%)	33 (84.6%)
Placebo/ > 100 kg (n = 1)	0	1 (2.56%)

Responder: defined as a patient who achieved platelet count of ≥ 50,000/µL with an increase of ≥ 20,000/µL from baseline.
* 400 mg not used in this trial

Table 47: Efficacy Results Based on Weight (kg) in Study M0634*

Efficacy Rate Dosage/ Weight (kg) (n = 214)	Responders (%) (n = 83)	Non-Responders (%) (n = 131)
3-mg/ < 100 kg (n =98)	64 (77.1%)	34 (26.0%)
3-mg/ > 100 kg (n = 10)	5 (6.02%)	5 (3.82%)
Placebo/ < 100 kg (n = 93)	14 (16.9%)	79 (60.3%)
Placebo/ > 100 kg (n =13)	0	13 (9.92%)

Responder: defined as a patient who achieved platelet count of ≥ 50,000/µL with an increase of ≥ 20,000/µL from baseline.
* 400 mg not used in this trial

Reviewer Comment: There were no patients greater than 100 kg in the M0626 clinical study to evaluate for dose response at the 3mg or 4mg dose. The sample size in the M0634 was too small to demonstrate if the efficacy would be impacted by the higher body weight.

8.1.5. Integrated Assessment of Effectiveness

The same study designs were used in L-PLUS1 and L-PLUS2 studies. The primary endpoint in L-PLUS1 was proportion of patients not requiring platelet transfusion prior to invasive procedure. The primary endpoint in L-PLUS2 was proportion of patients not requiring platelet transfusion prior to invasive procedure or rescue therapy for bleeding through 7 days after invasive procedure. The secondary endpoints in the pre-specified hierarchical testing procedures were the same in both studies. The L-PLUS1 study was conducted in Japan and L-PLUS2 was conducted a few years after L-PLUS1 and in the US and the rest of the world.

Lusutrombopag treatment demonstrated statistically significant increases in the proportion of patients who did not require a platelet transfusion in L-PLUS-1 study compared to the placebo treatment group. In the L-PLUS2 study, the lusutrombopag treatment arm demonstrated statistically significant increases in the proportion of patients who did not require a platelet transfusion prior to the invasive procedure or rescue therapy for bleeding through 7 days after the procedure. The median duration of the platelet count to at least 50,000/µL without transfusion was 19 (13,28) days.

The 3-mg lusutrombopag dosing regimen resulted in an increase in platelet counts that peaked 7 days after the last dose without the need of platelet transfusion in the L-PLUS1 trial and up to 3 to 7 days after the last dose without the need of platelet transfusion in the L-PLUS2 trial.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety database consists of primary data from the Phase 2b (Dose-finding study/M0626) and the two Phase 3 clinical studies (M0631 and M634) consisting of 371 patients who were randomized and received at least one dose of the study drug. Safety endpoints listed below were used to evaluate the safety and tolerability of lusutrombopag in thrombocytopenic patients with chronic liver disease. Analyses included:

- Incidence and severity of AEs, bleeding-related AEs, and thrombosis-related AEs
- Incidence of TEAEs, SAEs and adverse drug reactions (ADRs)
- Incidence of discontinuation, dose interruptions and dose delays
- Assessment of portal vein thrombosis and portal blood flow
- Laboratory tests, vital signs, and electrocardiogram results
- Plasma S-888711 concentration
- Analysis of deaths.

8.2.2. Review of the Safety Database

Overall Exposure

The 341 subjects in the Safety Population were randomized to either lusutrombopag 3-mg daily (n=171) or placebo daily (n=170), and received at least one dose of study drug. The demographics and characteristics of the M0626, M0631, and M0634 safety population are presented in Table 48. Refer to the summary of drug exposure presented in Table 49.

Table 48 Demographics of the Safety Population at Randomization

Safety Database for Lusutrombopag 3-mg[1] Individuals exposed to any treatment in this development program for the indication under review N=341			
Safety Population Demographic Parameters	**Lusutrombopag 3-mg (n=171)**	**Placebo (n= 170)**	**Total (n = 341)**
Sex			
Male	94 (55.0%)	107 (62.9%)	203 (59.5%)
Female	77 (45.0%)	63 (37.1%)	140 (41.1%)
Age			
Mean (SD)	60.3 (11.8)	60.4 (12.0)	60.4
Median	61.0	61.5	61.3
Age Group			
>18 – < 65 years	104 (60.8%)	110 (64.7%)	214 (62.8%)
≥ 65 years	67 (39.2%)	60 (35.3%)	127 (37.2%)
Race			
White	84 (49.1%)	86 (50.6%)	170 (49.9%)
Black	1 (0.59%)	0	1 (0.29%)
Asian	79 (46.2%)	80 (47.1%)	159 (46.6%)
Other/Not Provided	5 (2.92%)	4 (2.35%)	9 (2.64%)
Ethnicity			
Hispanic	15 (8.19%)	12 (7.06%)	27 (7.92%)
Not Hispanic	155 (93.0%)	158 (92.9%)	313 (91.8%)
Region			
North America	19 (11.1%)	11 (6.47%)	30 (8.80%)
Europe	73 (42.7%)	79 (46.5%)	152 (44.6%)
Asia	77 (45.0%)	80 (47.1%)	157 (46.0%)
Other	2 (1.17%)	2 (1.18%)	4 (1.17%)
Performance Status			
0	139 (81.3%)	154 (90.6%)	293 (85.9%)
1	30 (17.5%)	16 (9.41%)	46 (13.5%)
History of[2]			
Hepatitis B	31 (18.1%)	30 (17.6%)	61 (17.9%)
Hepatitis C	101 (59.1%)	95 (55.9%)	196 (57.5%)
Alcohol Hepatitis	28 (16.4%)	33 (19.4%)	61 (17.9%)
Non-Alcohol Hepatitis	15 (8.77%)	20 (11.8%)	35 (10.3%)
Autoimmune Hepatitis	5 (2.92%)	5 (2.94%)	10 (2.93%)

Safety Database for Lusutrombopag 3-mg[1] Individuals exposed to any treatment in this development program for the indication under review N=341			
Safety Population Demographic Parameters	**Lusutrombopag 3-mg (n=171)**	**Placebo (n= 170)**	**Total (n = 341)**
Other	15 (8.8%)	7 (4.1%)	22 (6.45%)
Child Pugh[3]			
A	106 (62.0%)	94 (55.3%)	200 (58.7%)
B	62 (36.2%)	75 (44.1%)	137 (40.2%)
C	3 (1.75%)	0	3 (.88%)
Splenomegaly			
Yes	152 (88.9%)	153 (90.0%)	305 (89.4%)
No	19 (11.1%)	17 (10%)	36 (10.6%)
Ascites			
Yes	36 (21.1%)	43 (25.3%)	79 (23.2%)
No	135 (78.9%)	127 (74.7%)	262 (76.8%)
Gastrointestinal Varices[3]			
Yes	145 (84.8%)	145 (85.3%)	290 (85.0%)
No	29 (17.0%)	22 (12.9%)	51 (15.0%)
BMI[3]			
Below 18.5	11 (6.43%)	5 (2.89%)	16 (4.69%)
18.5-24.9	92 (53.8%)	71 (41.8%)	163 (47.8%)
25.0-29.9	44 (25.7%)	60 (35.3%)	104 (30.5%)
30 and above	29 (17.0%)	29 (17.1%)	58 (17.0%)
Baseline Platelet Count			
Mean (SD)	3.97 (6.18)	3.80 (3.03)	3.89 (4.3)

[1] *Study drug* means the drug being considered for approval.
[2] Patients shared more than one type of chronic liver disease.
[3] Missing data

Table 49 Duration of Exposure

Exposure	Safety Population Overall	
	Lusutrombopag 3-mg N = 171[a]	**Placebo N=170**
Duration (Days)		
1	0	0
2	0	0
3	0	0
4	19 (11.1%)	7 (4.1%)
5	12 (7.0%)	4 (2.4%)
6	5 (8.8%)	4 (2.4%)
7	125 (73.1%)	155 (91.2%)
Subjects who Discontinued Study Drug		
Total	46 (26.9%)	12 (7.1%)
Platelet Increase*	41 (24%)	8 (4.7%)
Ineligibility	1 (0.6%)	0
Adverse Event	0	1 (0.6%)
Withdrawal	2 (1.2%)	1 (0.6%)
Other	2 (1.2%)	2 (1.2%)

*Protocol specified stopping rules (responder definition met: increase in platelet count ≥ 50K with an increase of ≥ 20K from baseline
[a] Two subjects in the pooled lusutrombopag arm withdrew without receiving study drug

Relevant characteristics of the safety population:

Subject demographics were balanced between arms. Most patients were male (55% vs 63%), and 63% of the patients were less than 65 years of age. Most patients were either Asian (47%) or Caucasian (50%). The locations from which most patients were enrolled were from Europe (45%) and Asian (46%). Only 9% were from North America. The performance status of zero, Child-Pugh score of A, and no ascites were balanced between both arms. The majority of patients were diagnosed with Hepatitis C (58%) with splenomegaly (89%) and gastrointestinal varices (85%). The majority of patients had a normal BMI of 48% with a mean baseline platelet count of 38,000/µL.

The majority of patients completed the recommended seven days of administration of the treatment drug (lusutrombopag 3-mg: 73% vs placebo: 91%). Among the patients who discontinued the study drug (27% vs 7%), the majority of patients were discontinued because they met the protocol study stopping rules (24% vs 5%).

Adequacy of the safety database:

The applicant submitted primary datasets containing data for each patient, including demographics, disease characteristics, drug exposure, concomitant medications, vital signs, pertinent physical findings, laboratory values, and adverse events. The demographics of the safety population are adequately consistent with those of the intended patient population and generalizable to the intended patient population.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The submission was of adequate quality to enable clinical review. Overall, it was well organized with appropriate analyses and detailed reports and summaries. There are no concerns regarding the integrity of the submission. Adequate narratives were provided for subjects who experienced severe or serious adverse events.

Categorization of Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 and reported down to the investigator's verbatim term. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTAE, version 4.0). Treatment emergent events were defined as those events that occurred or worsened on, or after the first dose of study treatment up to 35 days following the final dose of study treatment.

Routine Clinical Tests

Safety assessments included physical examinations including vital signs, laboratory test measurements, ECGs, documentation of the type and severity of CLD, confirmation of gastrointestinal varices by endoscopy and splenomegaly by ultrasound, CT, or MRI scans. The components and scheduling of safety monitoring was appropriate to capture the known AEs for that are associated with CLD and possible thrombocytosis which is associated with the development of thrombosis. Safety endpoints included incidence of AEs, SAEs and deaths, clinical laboratory tests, vital signs, ECG, ultrasound/CT or MI to assess for portal vein thrombosis or the development of any thrombosis. The schedule of monitoring for both trials are presented in Tables 50 and 51.

Table 50 Time and Events Schedule for M0631 (L-PLUS1)

Appendix 1 Time and Events Schedule

	Screening	Treatment Period								Post-treatment Period (Invasive procedure, Days 9 to 14)											At withdrawal[a]
										Inpatient (the day before the procedure to Day 14)											
Study Day	From Day −28	Day 1 Pre-dosing	Day 1 Post-dosing	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 17	Day 21	Day 28	Day 35	
Informed consent	X																				
Patient characteristics	X																				
ECOG Performance Status	X																				
Severity of liver disorder (Child-Pugh)	X																				
WHO bleeding scale	X																				
Gastroesophageal varices[b]	X																				
Splenomegaly and severity of ascites[c]	X																				
Portal vein thrombosis[d]	X									X[e]				←		X[e] →					
Portal blood flow (direction)[g]	X									X[e]				←		X[e] →					
Spleen size[h]	X													←		X[e] →					
Blood pressure, pulse rate	X	(X)[i]					X	X	X	X		X		X		X	X	X	X	X	X
Electrocardiography	X	(X)[i]								X[j]						X				X	X
Platelet count, immature platelet fraction*, reticulated platelet fraction*	X	(X)[i]					X[k]	X[k]	X[k]	X		X		X		X	X	X	X	X	X
Platelet count after platelet transfusion[l]										at the 1st (immediately) to 3rd days after platelet transfusion											
Hematology except for platelet count	X	(X)[i]								X[j]						X				X	X
Blood chemistry	X	(X)[i]								X[j]						X				X	X
Blood Coagulation/fibrinolysis assay[m]	X	(X)[i]								X[j]						X				X	X
Immunological tests/Other tests	X																				
Pregnancy test	X																				
Adverse events	←																			→	X
Enrollment		X																			
Administration of S-888711			X	X	X	X	X[n]	X[n]	X[n]												
Invasive procedure											←		X[o]	→							
Sampling for plasma drug concentration[p]							X[q]		X[q]												

Table 51 Time and Events Schedule for M0634 (L-PLUS2)

Appendix 1: Time and Events Schedule

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

8.2.4. Safety Results

Deaths

There were four deaths reported in this safety population. The information from their narratives in shown in Table 52.

Table 52 Deaths in the Safety Population

Patient/ARM/Country	Age/Sex/Race	Time (days) from date of last study drug to date of death	Summary of Death Narrative
(b) (6) /Lusutrombopag 2-mg/Japan	61/Female/Asian	27 days	The upper gastrointestinal hemorrhage was considered due to esophageal variceal rupture which was found before the initial administration of the study drug. The event occurred 28 days after the last administration of the study drug; platelet counts 2 days before death decreased to 5.2×10^4/L within the range of that before dosing. No portal vein thrombosis was found, and portal blood flow was hepatopetal. The event was considered not related to the study drug. History is significant for hepatocellular carcinoma, chronic hepatitis C and esophageal varices. Cause of death not confirmed.
(b) (6) /Lusutrombopag 3-mg/Romania	41/Male/White	27 days	Multiple organ failure leading to cardiac arrest was considered by the investigator to be probably secondary to sepsis caused by the C. difficile infection. History is significant for alcoholic liver disease with encephalopathy and Child-Pugh class C liver disease.
(b) (6) / Lusutrombopag 3-mg/Russia	54/Male/White	22 days	Lower abdominal pain was reported by patient. Ultrasound showed no evidence of portal vein thrombosis. Condition progressed to decompensated hepatic cirrhosis. Patient suffered cardiopulmonary arrest and died. History is significant for chronic hepatitis B and hepatic cirrhosis.
(b) (6) /Lusutrombopag 3-mg/United Kingdom	55/Female/White	14 days	Vessel perforation of the terminal branch of internal mammary artery during the percutaneous radiofrequency ablation (RFA). Patient later showed acute on chronic liver failure and died on Day 24. History was significant for Child-Pugh class B liver disease, autoimmune hepatitis and hepatocellular carcinoma.

Reviewer's Comments: Three subjects (2.8%), all in the lusutrombopag group of Study M0634 (L-PLUS2), had serious TEAEs with an outcome of death. In Study M0626, one subject died was not successfully resuscitated after suffering a severe upper gastrointestinal hemorrhage due to variceal bleeding. None of these deaths were the result of a thrombotic or thromboembolic event.

Serious Adverse Events

Table 53 Summary of All Serious Adverse Events (Safety Population)

SOC Preferred Term	Lusutrombopag 3-mg N = 171 n(%)	Placebo N = 170 n (%)
Subjects with at least 1 serious TEAE	14 (8.18%)	7 (4.12%)
Neoplasms benign, malignant and unspecified	2 (1.17%)	2 (1.18%)
Hepatocellular carcinoma	2 (1.17%)	2 (1.18%)
Blood and lymphatic system disorders	1 (0.58%)	1 (0.58%)
Anemia	1 (0.58%)	1 (0.58%)
Cardiac disorders	3 (1.75%)	0
Cardiac arrest	1 (0.58%)	0
Cardiac ventricular thrombosis	1 (0.58%)	0
Sick sinus syndrome	1 (0.58%)	0
Gastrointestinal disorders	1 (0.58%)	5 (2.94%)
Abdominal pain lower	1 (0.58%)	0
Nausea	0	1 (00.58%)
Vomiting	0	1 (0.58%)
Esophageal variceal hemorrhage	0	1 (0.58%)
Oropharyngeal pain	0	1 (0.58%)
Gingival bleeding	0	1 (0.58%)
General disorders and administration site conditions	4 (2.34%)	9 (50.29%)
Multiorgan failure	1 (0.58%)	0
Procedural pain	1 (0.58%)	2 (1.17%)
Procedural nausea	1 (0.58%)	0
Postoperative fever	1 (0.58%)	3 (1.76%)
Post procedural diarrhea	0	1 (0.58%)
Post procedural constipation	0	1 (0.58%)
Procedural hypertension	0	1 (0.58%)
Hiccups	0	1 (0.58%)
Hepatobiliary disorders	2 (1.17%)	0
Hepatic cirrhosis	1 (0.58%)	0

SOC Preferred Term	Lusutrombopag 3-mg N = 171 n(%)	Placebo N = 170 n (%)
Portal vein thrombosis	1 (0.58%)	0
Metabolism and nutrition disorders	3 (1.75%)	6 (3.53%)
Dehydration	0	1 (0.58%)
Fluid retention	1 (0.58%)	1 (0.58%)
Hypokalemia	0	1 (0.58%)
Alanine aminotransferase increased	1 (0.58%)	0
Aspartate aminotransferase increased	0	1 (0.58%)
C-reactive protein increased	1 (0.58%)	0
Blood creatinine increased	0	1 (0.58%)
Fibrin D dimer increased	0	1 (0.58%)
Musculoskeletal disorders	0	1 (0.58%)
Patella fracture	0	1 (0.58%)
Nervous system disorders	1 (0.58%)	4 (2.35%)
Hepatic encephalopathy	1(0.58%)	2 (1.17%)
Encephalopathy	0	1 (0.58%)
Insomnia	0	1 (0.58%)
Pulmonary disorders	0	5 (2.94%)
Influenza	0	2 (1.17%)
Asthma	0	1 (0.58%)
Hemoptysis	0	1 (0.58%)
Pleural effusion	0	1 (0.58%)
Renal and urinary disorders	1 (0.58%)	0
Acute kidney injury	1 (0.58%)	0
Skin disorders	0	1 (0.58%)
Urticaria	0	1 (0.58%)
Vascular disorders	2 (1.17%)	2 (1.17%)
Circulatory collapse	0	1 (0.58%)
Hypertensive crisis	0	1 (0.58%)
Vessel perforation	1 (0.58%)	0
Incision site hemorrhage	1 (0.58%)	0

Dropouts and/or Discontinuations Due to Adverse Effect

In Study M0634, no patients in the lusutrombopag group had a TEAE leading to discontinuation of study drug. In the placebo group, 1 patient (0.9%; (b) (6)) had TEAEs leading to discontinuation of study drug, including dehydration, hypokalemia, nausea, and vomiting, all of which were considered by the investigator to be related to study drug.

Significant Adverse Events

In Study M0626, significant TEAEs were reported in 9 of 15 patients (60.0%) in the 2-mg group, 10 of 16 patients (62.5%) in the 3-mg group, 7 of 15 patients (46.7%) in the 4-mg group, and 10 of 15 patients (66.7%) in the placebo group. No incidence of the TEAEs increased with increasing dose of lusutrombopag. The frequent TEAEs (incidence ≥ 10% in any treatment group) were procedural hypertension, AST increased, blood pressure increased, and ALT increased. The trend of a dose-related increase was found for the incidence of AST increased: 2 of 15 patients (13.3%) in the 2-mg group, 3 of 16 patients (18.8%) in the 3 mg group, 5 of 15 patients (33.3%), and 1 of 15 patients (6.7%) in the placebo group. No trend of a dose-related increase was found for the incidence of the other significant TEAEs.

In Study M0631, significant TEAEs were reported in 20 each of 48 patients (41.7%) in the 3-mg and the placebo groups, respectively. The frequent TEAEs (incidence ≥ 5% in any treatment group) were procedural hypertension (27.1% in the 3-mg group vs. 35.4% in the placebo group), AST increased (8.3% in the 3-mg group vs. 14.6% in the placebo group), and ALT increased (6.3% in the 3-mg group vs. 0% in the placebo group). Of these events, only ALT increased occurring in the 3-mg group had a higher incidence relative to placebo.

In the safety population, five of six thrombotic or thromboembolic events identified in M0631 and M0634 clinical studies were considered as serious adverse events. These thrombotic or thromboembolic events occurred after an invasive procedure was performed. Of the portal vein thromboses identified, two were found in the lusutrombopag 3-mg arm and the other two were found in the placebo arm. Of note, one patient with a history of a cardiac ventricular thrombosis was diagnosed with a reoccurrence of the thrombosis on Day 14 where the platelet count was 60,000/µL; the patient did reach a platelet count of 119,000/µL on Day 12. The portal vein thrombosis (in the placebo arm) which was identified by the investigator as not serious did occur after the patient underwent a diagnostic paracentesis of the abdomen. An ultrasound was performed as per protocol on Day 14 where the platelet count reached 167,000/µL. The patient did have a maximum platelet count of 141,000/µL on Day 12, as per protocol.

Treatment Emergent Adverse Events and Adverse Reactions

The majority of patients in both trials experienced at least one AE (76% on lusutrombopag arm and 83% on placebo arm. Headache was the most common event for lusutrombopag. Injury, poisoning and procedural complications and investigational adverse events occurred in higher frequency from both arms which were documented after the primary invasive procedure.

Table 54 Treatment Emergent Adverse Events and Adverse Reactions

Patients with any TEAEs	Lusutrombopag 3mg N = 171 n (%)	Placebo N =170 n (%)	Total N = 341 n (%)
Blood and Lymphatic System Disorders			
Anemia	4 (2.34%)	0	4 (1.17%)
Splenomegaly	2 (1.17%)	0	2 (0.59%)
Cardiac Disorders			
Atrial fibrillation	2 (1.17%)	0	0
Arrhythmia	0	1 (0.59%)	1 (0.29%)
Cardiac arrest	1 (0.58%)	0	1 (0.29%)
Cardiac ventricular thrombosis	1 (0.58%)	0	1 (0.29%)
Sick sinus thrombosis	1 (0.58%)	0	1 (0.29%)
Gastrointestinal Disorders			
Ascites	10 (5.85%)	9 (50.29%)	19 (5.57%)
Abdominal distention	2 (1.17%)	1 (0.59%)	3 (0.88%)
Constipation	11 (6.43%)	7 (4.11%)	18 (5.27%)
Diarrhea	7 (4.09%)	8 (4.71%)	15 (4.40%)
Hemorrhage erosive gastritis	1 (0.58%)	0	1 (0.29%)
Large intestinal hemorrhage	0	1 (0.59%)	1 (0.29%)
Mesenteric vein thrombosis	1 (0.58%)	2 (1.18%)	3 (.88%)
Nausea	3 (1.75%)	6 (3.53%)	9 (2.63%)
Rectal hemorrhage	1 (0.58%)	0	1 (0.29%)
Upper gastrointestinal hemorrhage	1 (0.58%)	0	1 (0.29%)
Vomiting	2 (1.17%)	4 (2.35%)	6 (1.76%)
Hepatobiliary Disorders			
Portal Vein Thrombosis	4 (2.34%)	2 (1.18%)	6 (1.76%)
Acute hepatic failure	1 (0.58%)	0	1 (0.29%)
Hepatic function abnormal	2 (1.17%)	1 (0.59%)	3 (.88%)
Portal hypertension	1 (0.58%)	0	1 (0.29%)
Retrograde portal vein flow	0	1 (0.59%)	1 (0.29%)
Infections and Infestations			
Nasopharyngitis	9 (5.26%)	7 (4.12%)	16 (4.69%)
Bronchitis	1 (0.58%)	2 (1.18%)	3 (0.88%)

Patients with any TEAEs	Lusutrombopag 3mg N = 171 n (%)	Placebo N =170 n (%)	Total N = 341 n (%)
Upper respiratory tract infection	2 (1.17%)	0	2 (0.59%)
Injury, poisoning and procedural complications			
Postoperative fever	45 (26.3%)	34 (20%)	79 (23.2%)
Procedural hypertension	44 (25.7%)	18 (10.6%)	62 (18.2%)
Procedural pain	50 (29.2%)	29 (17.1%)	79 (23.2%)
Post procedural hemorrhage	7 (4.09%)	4 (2.45%)	11 (3.23%)
Procedural hypotension	3 (1.75%)	2 (1.18%)	5 (1.47%)
Investigations			
Aspartate aminotransferase increased	41 (24.0%)	20 (11.8%)	61 (17.9%)
Alanine aminotransferase increased	28 (16.4%)	10 (5.88%)	38 (11.1%)
Fibrin D dimer increased	12 (7.01%)	10 (5.88%)	22 (6.45%)
Fibrin degradation products increased	10 (5.85%)	6 (3.53%)	16 (4.69%)
Blood bilirubin increased	13 (7.60%)	4 (2.35%)	17 (4.99%)
Oxygen saturation decreased	18 (10.5%)	11 (6.47%)	29 (8.50%)
General disorders and administration site conditions			
Fatigue	6 (3.51%)	8 (4.70%)	14 (4.11%)
Peripheral edema	1 (0.58%)	0	1 (0.29%)
Pyrexia	8 (4.68%)	6 (3.53%)	14 (4.11%)
Metabolism and nutrition disorders			
Decreased appetite	1 (0.58%)	0	1 (0.29%)
Dehydration	2 (1.17%)	0	2 (0.59%)
Musculoskeletal and connective tissue disorders			
Back pain	5 (2.92%)	4 (2.35%)	9 (2.63%)
Neoplasms benign, malignant and unspecified			
Hepatic neoplasm	2 (1.17%)	2 (1.18%)	4 (1.17%)
Focal nodular hyperplasia	1 (0.58%)	0	1 (0.29%)
Respiratory, thoracic and mediastinal disorders			
Pleural effusion	5 (2.92%)	6 (3.53%)	11 (3.23%)

Patients with any TEAEs	Lusutrombopag 3mg N = 171 n (%)	Placebo N =170 n (%)	Total N = 341 n (%)
Cough	2 (1.17%)	2 (1.18%)	4 (1.17%)
Nervous System disorders			
Headache	10 (5.85%)	6 (3.53%)	16 (4.69%)
Skin and subcutaneous tissue disorders			
Pruritis	5 (2.92%)	5 (2.94%)	10 (2.93%)
Rash	4 (2.34%)	0	1 (0.29%)
Vascular Disorders			
Orthostatic hypotension	1 (0.58%)	1 (0.59%)	2 (0.59%)
Hypertensive crisis	0	1 (0.59%)	1 (0.29%)
Vessel perforation	1 (0.58%)	0	1 (0.29%)

Treatment Emergent Adverse Events of Special Interest (AESI)

Thrombotic and thromboembolic adverse events were identified as adverse events of special interest. In the analysis, these adverse events were reported in 6 patients (1.8%) in the lusutrombopag arm and 4 patients (1.2%) in the placebo group.

In study M0626, the thrombotic event occurred in 1 patient (6.7%) in the lusutrombopag 2-mg group, 2 (13.3%) in the 4-mg group, and 1 (6.7%) in placebo group. All of the thromboses were found on CT or MRI performed after the percutaneous liver ablation as per protocol. The portal vein thrombosis and the superior mesenteric vein thrombosis were noted in the 4-mg group and were considered related to the study drug.

In study M0631, one patient (2.1%) in the lusutrombopag arm and 1 (2.1%) in the placebo arm were found to have a thrombotic event. The thromboses were found on CT or MRI performed after their planned and performed transcatheter arterial chemoembolization. A portal vein thrombosis was identified in the patient on the lusutrombopag arm which was considered related to the study drug. The mesenteric vein thrombosis found in the placebo arm patient was not considered to be related to the study drug.

In study M0634, two patients (1.9%) in the lusutrombopag arm and 2 (1.9%) in the placebo arm were identified with a thrombotic/thromboembolic event. The patient on the lusutrombopag arm was identified with a cardiac ventricular thrombosis had a previous history of a cardiac ventricular thrombosis which was identified prior to the invasive procedure. The thrombosis was identified by CT performed after the performed endoscopic variceal ligation procedure. The cardiac thrombosis was considered related to the study drug. The second patient on the lusutrombopag arm was identified with the development of a portal vein thrombosis that was identified after the dental extraction procedure was performed. This thrombosis was not considered to be related to the study drug. The two patients on the placebo arm were

identified with portal vein thromboses which were not evident at the time of screening but were identified after the liver puncture biopsy and diagnostic paracentesis procedures were performed as per protocol. The former was considered related to the study drug while the latter was not.

None of these treatment emergent serious adverse events occurred where the maximum platelet count reached at or above 200,000/µL prior to the procedure or near the onset of the event. The maximum platelet count reached among all of the patients was 127,000/µL.

Another adverse event of special interest analyzed was hepatic dysfunction. Since this population of this study involves patients with various degree of hepatic dysfunction secondary to their chronic liver disease while undergoing liver-related procedures, it was noted that there may be a causal relationship to the study drug among these patients. Reportedly, there were noted adverse drug reactions which appeared to occur 100% of the time after the percutaneous liver ablation procedure in study M0626. These adverse drug reactions included positional vertigo, abnormal hepatic function levels, increase in blood bilirubin, blood pressure, D-dimer levels, fibrin degradation products and a decrease in blood fibrinogen and white blood cell count.

In Study M0631, similar adverse drug reactions appeared to have occurred after the performed invasive procedure at a higher incidence (93.8%) in both arms. These adverse drug reactions included abnormal hepatic function levels, procedural fever, pain, hypertension, hemorrhage, nausea and vomiting along with increases in blood bilirubin, blood pressure, D-dimer levels, and fibrin degradation products.

In Study M0634, similar treatment related adverse events appeared to have occurred after the performed invasive procedure at a higher incidence (40%) in both arms. The events most frequently reported were gastrointestinal disorders, administration site conditions, nervous system disorders and investigations such as increased blood bilirubin levels. Of note, most of these adverse events occurred more frequently in the placebo arm.

Laboratory Findings

Laboratory abnormalities were classified as Grade 2 or higher (Grade 3 or higher for hyponatremia). The mean change from baseline in ALT and AST was higher in the lusutrombopag group than in the placebo group on Day 14 (ALT, 5.0 vs. 1.1 U/L; AST, 6.6 vs. 2.7 U/L); however, by Day 35, values had returned to normal in the lusutrombopag group. Most notably, three patients had changes from baseline in ALT, AST or PT-INR which could be associated to their underlying hepatic function.

Table 55: Patients Who Demonstrated Hepatic Function Abnormalities Based on Hy's Law Criteria

Criteria		Lusutrombopag 3-mg N = 107	Placebo N = 107
AST or ALT ≥ 3 × ULN and total bilirubin ≥ 2 × ULN	Baseline	2.9% (3/103)	1.9% (2/104)
	Day 8	1.0% (1/97)	2.0% (2/99)
	Day 14	2.2% (2/91)	3.2% (3/94)
	Day 35	1.1% (1/94)	3.0% (3/100)
AST or ALT ≥ 3 × ULN and PT-INR ≥ 1.5	Baseline	3.0% (3/99)	2.0% (2/100)
	Day 8	1.0% (1/96)	3.2% (3/94)
	Day 14	1.1% (1/89)	1.1% (1/89)
	Day 35	2.2% (2/91)	2.1% (2/96)
Ratio of AST/ALT ≥ 3	Baseline	1.9% (2/104)	4.8% (5/104)
	Day 8	3.1% (3/97)	5.1% (5/99)
	Day 14	1.1% (1/91)	5.3% (5/94)
	Day 35	2.1% (2/94)	5.0% (5/100)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; PT-INR = prothrombin time-international normalized ratio; ULN = upper limit of normal]

Drug induced liver injury (DILI) was of concern among this patient population for which all manifested preexisting liver disease and documented primarily among those patients in the M0634 study.

The incidence of probable drug induced liver injury was very low in both arms. Of note, among those patients on the lusutrombopag arm, alterations in hepatic function levels were higher at baseline; however, the hepatic function levels had decreased within 7 days after completion of the study drug or occurring within 2 days after the invasive procedure. However, the number of patients in the placebo arm who demonstrated evidence of hepatic injury consistent with Hy's

law were slightly higher and their hepatic function tests remained high 7 days after completion of the study drug, within 2 days after the invasive procedure and up to the treatment end study date. A higher AST/ALT ratio of ≥ 2 clinically identifies those individuals with alcoholic hepatitis. It appears that there was a higher percentage of patients in the placebo arm diagnosed with alcoholic hepatitis (19.4% vs 16.8%).

Vital Signs

The applicant obtained routine vital signs including temperature, respiratory rate, pulse, systolic and diastolic blood pressure at the scheduled times at screening, Days 5, 8, 10, 12, 14, 21, 28 and 35.

No clinically significant differences were found for mean or median changes in any vital sign parameters from baseline in the lusutrombopag group compared with those in the placebo group.

Electrocardiograms (ECGs)

Electrocardiograms were collected during the screening period and on Day 35.

Based on investigator assessment, no subject in either treatment group had a clinically significant abnormal ECG finding.

QT

Study M061D compared the effect of single doses of 6 mg (exposure is equal to multiple dose of 3-mg, a therapeutic dose) and 24-mg (supratherapeutic dose) of S-888711 on the electrocardiogram (ECG) QT interval corrected for heart rate by Fridericia's correction (QTcF) with placebo in healthy subjects.

The Interdisciplinary Review Team for QT studies was consulted under the IND for lusutrombopag. The QT-IRT team concluded that there was no significant QTc prolongation effect of S-888711 (6mg and 24mg) which is equivalent to multiple dose of 3mg/day. Using Fridericia corrected QTc (QtcF), the largest upper bound of the 2 sided 90% CI for the man difference between S-888711 (6mg) and placebo and between S-888711 (24mg) and placebo are below 10ms, the threshold for regulatory concerns described in ICH E14 guidance. Please refer to the review by the interdisciplinary review team for QT studies (final review submission on July 8, 2015).

Immunogenicity

There was no evidence of immunogenicity safety issues in the data submitted related to lusutrombopag.

8.2.5. Analysis of Submission-Specific Safety Issues

Thrombotic or Thromboembolic Events
There was no pattern to suggest a difference in the incidence of thrombotic and thromboembolic events by maximum platelet count, with incidences of 2.4%, 1.8%, and none reported for patients with maximum platelet counts of < 100,000, ≥ 100,000 to < 150,000, and ≥ 150,000/µL, respectively.

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 Subgroup

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 review.

Human Reproduction and Pregnancy

There was no documentation of pregnancy or exposure to pregnant/lactating women.

Pediatrics and Assessment of Effects on Growth

There was no pediatric data submitted with this application.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There was documentation of one patient who received one tablet of the study drug (lusutrombopag 3-mg) at 12:50 on Day 1 and received another tablet of the study drug at 18:50 of the same day. (b) (6) platelet count reached a maximum level of 73,000/µL on Day 5 which was determined by the investigator that this situation did not result in a treatment emergent adverse event.

Overall, there is no abuse potential for lusutrombopag.

Safety Concerns Identified Through Postmarket Experience

No new safety issues have been identified during this review from post-marketing data.

Expectations on Safety in the Postmarket Setting

A similar safety profile for lusutrombopag is expected in the postmarketing setting compared to that observed in the clinical trials. Studies L-PLUS1 and L-PLUS2 patient populations are generalizable to the intended patient population. Notably, low exposure in patients with high bodyweight found in pharmacology findings did not affect efficacy nor safety. However, in a real-world setting, this issue may pose concerns of extending the patient to a longer duration of treatment which potentiates risk of thromboembolic events and early mortality. The concern is that the efficacy may not be optimal for patients > 100kg and that providers may decide to use a second round of dosing before a procedure. In the label, we state that dosing to obtain a normal platelet count is not recommended or is not indicated.

8.2.8. Integrated Assessment of Safety

The 3-mg dose of lusutrombopag in the L-PLUS1 and L-PLUS2 studies study demonstrated greater tolerability and most subjects could complete the required duration of lusutrombopag, allowing analysis of primary and secondary efficacy endpoints while not revealing any unexpected safety concerns.

In general, lusutrombopag was well tolerated. Safety results were presented from pooled data from L-PLUS 1, L-PLUS 2 and Study MO626. In all three studies, patients with chronic liver disease and thrombocytopenia were treated at a dose of 3mg daily for up to 7 days prior to a scheduled procedure. The majority of patients in both trials experienced at least one TEAE (76% on lusutrombopag arm and 83% on placebo arm). Headache was the most common treatment emergent adverse event (occurring in at least 3%) for lusutrombopag treatment group. The incidence of serious adverse events was 5% in the lusutrombopag treatment group and 7% in the placebo group. Serious adverse events were primarily post-procedural general disorders and administration site events. The most common serious adverse event reported with lusutrombopag was portal vein thrombosis.

Thromboembolic events were a pre-defined adverse event of special interest(AESI) given previous experience with other TPO receptor agonists. In the thromboembolic category, treatment emergent AESIs were reported in 6 patients (1.8%) in the lusutrombopag arm and 4 patients (1.2%) in the placebo group. Portal vein thrombosis was reported in 1% (2 of 171) of lusutrombopag-treated patients and 1% (2 of 170) of placebo-treated patients in 3 randomized, double-blind trials and was identified post-procedure in protocol-specified imaging. The thromboses were not associated with a marked increase in platelet count. In addition, no hepatotoxicity was identified in lusutrombopag treated patients.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

No statistical issues were identified in the review of the application.

8.4. Conclusions and Recommendations

Lusutrombopag treatment demonstrated statistically significant increase in the proportion of patients who did not require a platelet transfusion in the study. In both the L-PLUS 1 and L-PLUS 2 trials, responders were defined as patients who had a platelet count of $\geq 50 \times 10^9$/L with an increase of $\geq 20 \times 10^9$/L from baseline. In L-PLUS 1, the proportion of patients who did not

require a platelet transfusion was 78% (95% CI: 63%,88%) in the lusutrombopag treatment group and 13% (95% CI: 4.7%, 25%) in the placebo treatment group (p<0.0001). In the L-PLUS2 study, the proportion of patients in the lusutrombopag treatment arm not requiring platelet transfusion prior to invasive procedure or rescue therapy for bleeding was 65% (95% CI: 55%, 74%) compared to 29% (95% CI: 21%,39%) in the placebo treatment group (p<0.001). The median (quartiles Q1, Q3) duration of platelet count increase to at least 50×10^9/L was 22 (17, 27) days in lusutrombopag-treated patients without platelet transfusion and 1.8 (0.0, 8.3) days in placebo-treated patients with platelet transfusion in L-PLUS 1 trial and 19 (13, 28) days in lusutrombopag-treated patients without platelet transfusion and 0.0 (0.0, 5.0) days in placebo-treated patients with platelet transfusion in L-PLUS 2 trial.

In conclusion, the L-PLUS1 and L-PLUS2 clinical trials showed superiority of primary endpoint in the lusutrombopag arm compared to the placebo arm. The clinical reviewer recommends regular approval of lusutrombopag for the treatment of thrombocytopenia in patients with chronic liver disease undergoing a procedure. This conclusion is supported by the comparable safety profile of lusutrombopag to placebo in Studies L-PLUS-1 and L-PLUS 2.

Jingjing Ye, PhD
Primary Statistical Reviewer

Lei Nie, PhD
Statistical Team Leader

Patricia Oneal, MD
Primary Clinical Reviewer

Tanya Wroblewski, MD
Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

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

10 Pediatrics

An agreed Initial Pediatric Study Plan (iPSP) Agreement Letter was issued on June 5, 2015 under IND 104047 for lusutrombopag. The iPSP requested a full waiver for the pediatric assessment requirement for lusutrombopag based on the small number of pediatric patients with chronic liver disease and thrombocytopenia making it impractical to conduct safety and efficacy trials in this pediatric population.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The following are recommended major revisions to the prescribing information based on the review and are summarized below:

Summary of Significant Labeling Changes		
Section	**Proposed Labeling**	**Approved Labeling**
Indications and Usage	(b) (4)	Indicated for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure.
Dosage and Administration		Begin MULPLETA dosing 8-14 days prior to a scheduled procedure. (2.1) Patients should undergo their procedure 2-8 days after the last dose. (2.1) Recommended Dosage: 3-mg orally once daily with or without food for 7 days. (2.1) evised to better describe that appropriate dosing.
Warnings and Precautions	(b) (4)	Thrombotic/Thromboembolic Complications: MULPLETA is a thrombopoietin (TPO) receptor agonist, and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with chronic liver disease. Monitor platelet counts and for thromboembolic events and institute treatment promptly. (5.1)
Clinical Trials Experience		The demographics of all studies overall were included.

Clinical Studies	(b) (4)	It was recommended to separate the two trials into two separate tables. (b) (4) were recommended to be removed and recommended including the details on types of procedures to be included in the PI.

The Applicant's submitted proposed Prescribing Information (PI) and Patient Labeling were reviewed for consistency with the 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 revisions of the PI. As labeling negotiations are ongoing, these recommendations should be considered preliminary and may not represent DHP's final recommendations for the MULPLETA® labeling.

12 Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not necessary for this supplement. No new safety issues were identified that would require a REMS.

13 Postmarketing Requirements and Commitment

No post-marketing requirements or commitments were identified for this application.

14 Division Director (DHOT)

John K Leighton, PhD

15 Division Director (OCP)

NAM Atiqur Rahman, PhD

16 Division Director (OB)

Rajeshwari Sridhara, Ph.D.

17 Division Director (Clinical)

Thrombocytopenia associated with liver disease can be a significant health problem as the condition may negatively impact the care of patients by potentially interfering with diagnostic and therapeutic procedures. Lusutrombopag is an orally administered small-molecule thrombopoietin (TPO) receptor agonist which has been marketed in Japan since 2015. The product is a 3-mg tablet taken orally once daily with or without food for 7 days. The Applicant submitted data from two randomized controlled trials conducted in patients with chronic liver disease and thrombocytopenia who needed to undergo an invasive procedure. The trials' results demonstrated that lusutrombopag administration resulted in fewer patients needing platelet transfusions and a greater number of patients who maintained a platelet count above a threshold value compared with results in patients in the placebo arms. Headache was the most common event for lusutrombopag. The treatment emergent adverse reactions (incidence ≥ 10% were procedural hypertension, AST increased, blood pressure increased, and ALT increased. Thrombotic events were observed in both treatment arms. Some occurred after an invasive procedure was performed. Trial safety results showed all deaths occurred in the lusutrombopag arms. Further review did not suggest a causal relationship. I concur with the recommendations of the review staff that lusutrombopag should be approved.

Ann T. Farrell, M.D.

18 Office Director (or designated signatory authority)

The risk-benefit of lusutrombopag was assessed by Drs. Farrell, Wroblewski and Oneal, and I concur with their recommendation to approve this drug.

Rick Pazdur, M.D.

19 Appendices

19.1. References

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19.2. Financial Disclosure

The Applicant requested financial disclosures from all investigators participating in the clinical trials supporting this NDA.

Covered Clinical Study (Name and/or Number): Studies 1208M0626, 1304M0631 (L-PLUS1) and 1423M0634 (L-PLUS2)

Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1053		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
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: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____		

Significant equity interest held by investigator Sponsor of covered study: _____		
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) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

19.3. Nonclinical Pharmacology/Toxicology

[Insert carci data as needed. Limit to 2 pages].

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Summary of Bioanalytical Method Validation and Performance

The plasma concentrations of lusutrombopag (S-888711) were determined by a validated LC/MS/MS method using S-8887711-racemate-d_{13} as the internal standard. Samples are analyzed by LC and a triple quadrupole mass spectrometer. As summarized in the **Table 1**, the method satisfied the criteria for method validation and application to routine analysis as outlined in the *Guidance for Industry: Bioanalytical Method Validation*.

Table 1: Lusutrombopag Method Validation Summary

Parameter	**Details**
Method	LC/MS/MS
Analyte	Lusutrombopag (S-888711 (b) (4)
Internal Standard	S-888711-racemate-d_{13}
Calibration Range	0.1, 0.2, 0.5, 2, 5, 20, 50, and 100 ng/mL
Validation Range	0.1, 0.2, 5, 80, and 100 ng/mL
Intra-Day Reproducibility	CV% less than 4.3% and RE% less than 3% for all concentrations
Inter-Day Reproducibility	CV% less than 5% and RE% less than 2.4% for all concentrations
Recovery	79.1% to 92.1%
Selectivity	No interfering peaks at the retention time of the standard or internal standard substances in chromatogram in plasma samples

Linearity	Linearity within the calibration range with $R^2 > 0.999$
LLOQ	0.1 ng/mL
Dilution Factor	Demonstrated for 100-fold
Stability	
Freeze/Thaw Cycles	Demonstrated stability after 3 cycles at -20 °C and -80 °C
Short Term Stability	Demonstrated stability for 6 hours at room temperature
Long Term Stability	Demonstrated stability up to 3 months at -20 °C and -80 °C
Post-Operative Stability	Demonstrated stability up to 50 hours at 15 °C
Standard Solution Stability	Demonstrated stability up to 3 months at 1 °C to 8 °C

19.4.2. Population PK and/or PD Analyses

Introduction

Applicant conducted population PK analysis for lusutrombopag using plasma concentration data from three Phase 1 studies in healthy adult volunteers (Studies 0713M0611, 0806M0613, 0823M0615), three Phase 2 studies (Study 1017M0623, 1112M0625, 1208M0626) in Japanese thrombocytopenic patients with chronic liver disease (CLD), three Phase 3 studies (1304M0631, 1338M0633, 1423M0634) in both Japanese and non-Japanese patients, and one Phase 1/2 study (Study 1525M0627). Platelet count data from studies 1017M0623, 1112M0625, 1208M0626, 1304M0631, 1338M0633, and 1423M0634 were used for population PK/PD analysis. This review will be focusing on evaluation of the adequacy of recommended dose and whether the labeling language is supported by the applicant's final population PK and/or PD based on intrinsic or extrinsic factors.

The objectives of the applicant's population PK/PD analysis were to:

1. To build a population PK model based on plasma lusutrombopag concentration data following oral administration of lusutrombopag in healthy subjects and thrombocytopenic subjects with CLD,
2. To build a population PK/PD model based on the data for platelet counts following oral administration of lusutrombopag in thrombocytopenic subjects with CLD,
3. To identify the factors (covariates) that potentially impact the PK of lusutrombopag and PK/PD relationship.

In addition to PK/PD analysis, the applicant conducted Monte Carlo simulations aimed at:

1. Comparing the PK and PK/PD relationships of lusutrombopag in Japanese and non-Japanese subjects,
2. Assessing the dose-response relationship following lusutrombopag administration,
3. Assessing the necessity of a stopping rule for administration of lusutrombopag based on platelet count.

Datasets

The population PK analysis conducted by the applicant included data from both healthy adult subjects and thrombocytopenic participants with CLD, while for population PK/PD analysis, only data from thrombocytopenic participants with CLD was used. These studies are briefly described below and their dosing regimen and sampling times summarized in Table 2 and

Table 3 below.

The studies used in population PK analysis were:

1. Phase 1 single ascending dose study in healthy adult subjects in Japan (Study 0713M0611),
2. Phase 1 multiple ascending dose study in healthy adult subjects in Japan (Study 0806M0613),

3. Phase 1 multiple ascending dose study in healthy adult subjects in the US (Study 0823M0615),
4. Phase 2 dose-ranging exploratory study in Japanese thrombocytopenic subjects with CLD scheduled for radiofrequency ablation (Study 1017M0623),
5. Phase 2 higher-dose study in Japanese thrombocytopenic subjects with CLD scheduled for radiofrequency ablation (Study 1112M0625),
6. Phase 2 dose finding study in Japanese thrombocytopenic subjects with CLD scheduled for radiofrequency ablation (Study 1208M0626),
7. Phase 3 pivotal study in Japanese thrombocytopenic subjects with CLD (Study 1304M0631),
8. Phase 3 open-label study in Japanese thrombocytopenic subjects with CLD (Study 1338M0633),
9. Phase 3 pivotal study in non-Japanese thrombocytopenic subjects with CLD (Study 1423M0634),
10. Phase 1/2 study in thrombocytopenic subjects with Child-Pugh class C hepatic impairment disease (Study 1525M0627).

The studies used in population PK/PD analysis were:

1. Phase 2 dose-ranging exploratory study in Japanese thrombocytopenic subjects with CLD scheduled for radiofrequency ablation (Study 1017M0623),
2. Phase 2 higher-dose study in Japanese thrombocytopenic subjects with CLD scheduled for radiofrequency ablation (Study 1112M0625),
3. Phase 2 dose finding study in Japanese thrombocytopenic subjects with CLD scheduled for radiofrequency ablation (Study 1208M0626),
4. Phase 3 pivotal study in Japanese thrombocytopenic subjects with CLD (Study 1304M0631),
5. Phase 3 open-label study in Japanese thrombocytopenic subjects with CLD (Study 1338M0633),
6. Phase 3 pivotal study in non-Japanese thrombocytopenic subjects with CLD (Study 1423M0634).

Table 2: Summary of Dosing Regimens and Sampling Times for Studies Conducted in Healthy Adult Participants (Source: Applicant's population PK/PD report, Page 31, Table 1a)

Study No.	Population	Dosage regimen	PK sampling
M0611	Healthy male subjects, N = 36	1, 2, 4, 10, 25, and 50 mg single dose; solution, fasted	1 and 2 mg: predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hours postdose. 4 to 50 mg: the above time points and 144, 216, and 312 hours postdose.
M0613	Healthy male subjects, N = 18	0.25, 0.5, and 2 mg dose QD for 14 days; 0.25 and 0.5 mg: solution, fed 2 mg: 2-mg tablet, fed	Days 1,7 and 14: predose, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 16 hours postdose. Days 2 to 6, 8, and 10: predose. Days 15 to 20: 24, 48, 72, 96, 120, and 144 hours postdose.
M0615	Healthy male and female subjects, N = 24	0.25, 0.5, 0.75, and 1 mg dose QD for 14 days; 0.25-mg tablets, fed	Days 1,7 and 14: predose, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 16 hours postdose. Days 2 to 6, 8, 10, and 12: predose. Days 15 to 20: 24, 48, 72, 96, 120, and 144 hours postdose.

QD = once daily

Table 3: Summary of Dosing Regimens and Sampling Times for Studies Conducted in Thrombocytopenic Patients with CLD (Source: Applicant's population PK/PD report, Page 32, Table 1b)

Study No.	Population	Dosage regimen	PK sampling	PD sampling
M0623	Male and female patients, N = 34	0.25, 0.5, 1, 1.5, and 2 mg dose QD for 7 days with the stopping criteria based on platelet counts; 0.25-mg tablets irrespective of meals	Predose, 2, 4, 6, 8, 24, 48, 72, 120, and 168 hours after the final dosing.*	Days 1 (predose), 3, 5, 6, 7, 8, 9 to 11, 9 to 16, 14, 17, 21, and 28, and at drug withdrawal and/or early termination of assessment.
M0625	Male and female patients, N = 21	2.5, 3, and 4 mg dose QD for 7 days with the stopping criteria based on platelet counts; 0.25-mg and 2-mg tablets irrespective of meals	Predose, 2, 4, 6, and 8 hours postdose on Day 5; predose on Day 6; 24, 48, 72, and/or 96 hours after the final dosing.*	Days 1 (predose), 3 to 8, 9 to 11, 9 to 16, 14, 17, 21, 28, and 35, and at drug withdrawal and/or early termination of assessment.
M0626	Male and female patients, N = 46	2, 3, and 4 mg dose QD for 7 days with the stopping criteria based on platelet counts; 1-mg tablets irrespective of meals	Predose and one point from 6 to 8 hours postdose on Day 5; 24, 48, 72, 120, and168 hours after the final dosing.*	Days 1 (predose), 5 to 8, 10, 12, 14, 17, 21, 28, and 35, and at drug withdrawal and/or early termination of assessment.
M0627	Male and female patients, N = 5	3 mg dose QD for 7 days with the stopping criteria based on platelet counts; 3-mg tablets irrespective of meals	Predose, 2, 4, 6, and 8 hours postdose on Day 5; 24, 48, 72, 120, and 168 hours after the dosing on Day 5.*	Days 1 (predose), 3 to 8, 10, 12, 14, 17, 21, 28, and 35, and at drug withdrawal and/or early termination of assessment.
M0631	Male and female patients, N = 48	3 mg dose QD for 7 days with the stopping criteria based on platelet counts; 3-mg tablets irrespective of meals	Predose on Day 5 and 6 to 8 hours after the final dosing.*	Days 1 (predose), 5 to 8, 10, 12, 14, 17, 21, 28, and 35, and at drug withdrawal and/or early termination of assessment.
M0633	Male and female patients, N = 94	3 mg dose QD for 7 days with the stopping criteria based on platelet counts; 3-mg tablets irrespective of meals	Intensive sampling: predose, 2, 4, 6, and 8 hours on Day 5, predose on Day 6, and at least 4 time points of 24, 48, 72, 120, and 168 hours after the final dosing.* Sparse sampling: predose at any 2 time points from Days 5 to 7.*	Days 1 (predose), 3, 5 to 8, 10, 12, 14, 17, 21, 28, and 35, and at drug withdrawal and/or early termination of assessment.
M0634	Male and female patients, N = 101	3 mg dose QD for 7 days with the stopping criteria based on platelet counts; 3-mg tablets irrespective of meals	Intensive sampling: predose, 2, 4, 6, 8, 24, and 48 hours after the dosing on Day 5. Sparse sampling: predose, 2 to 4, 24, and 48 hours after the dosing on Day 5.	Days 1 (predose), 5 to 8, 10, 12, 14, 17, 21, 28, and 35, and at drug withdrawal and/or early termination of assessment.

QD = once daily; N = number of subjects in the PPK analysis population

* The PK sampling for patients who received for 7 days was described. The sampling was changed according to the day when the the administration was discontinued.

Data handling

All participants with at least one quantifiable plasma lusutrombopag concentration were included in population PK analysis and for PK/PD participants with at least one platelet count measurement following lusutrombopag dosing in addition to meeting population PK inclusion. Furthermore, Lusutrombopag has been shown to reach steady state within 5 days after the initiation of multiple-dose therapy. Accordingly, the applicant excluded the trough plasma lusutrombopag concentration data on Day 10 from Study 0806M0613 to avoid biasing the results. For the population PK/PD analyses, the platelet count data of subjects who received placebo were excluded since the effect of placebo on the platelet response was minimal based

on the observed platelet counts in the previous phase 2 and 3 studies (Studies 1208M0626 and 1304M0631). The platelet count data after platelet transfusion were also excluded for the lusutrombopag and placebo groups. The demographic characteristics of participants in population PK and population PK/PD analysis are summarized in Table 4 and

Table *5*, respectively. The population PK analysis was performed in NONMEM (version 7.3.0, ICON Development Solutions, US) and Perl Speaks NONMEM (PsN, version 4.2.0).

Table 4: Demographics of the Population PK Analysis Population (Source: Applicant's population PK/PD report, Page 33, Table 2)

Subject (Study No.)	Background data	Mean (SD)[a]	Median (range)
All subjects N = 427	Age (years)	58.0 (17.3)	63.0 (19.0 - 84.0)
	Body weight (kg)	65.9 (14.6)	64.0 (34.9 - 142.0)
	CLcr (mL/min)	96.71 (37.21)	90.16 (10.73 - 246.64)
	Male : female	263 (61.6%) : 164 (38.4%)	
	Child-Pugh class (normal : A : B : C)	78 (18.3%) : 207 (48.5%) : 135 (31.6%) : 7 (1.6%)	
	Japanese : non-Japanese	302 (70.7%) : 125 (29.3%)	
	White : non-White	99 (23.2%) : 328 (76.8%)	
	(White : Asian : Black or African American : American Indian or Alaska Native : Other : Not Provided)	99 (23.2%) : 317 (74.2%) : 4 (0.9%) : 2 (0.5%) : 3 (0.7%) : 2 (0.5%)	
Japanese healthy subjects N = 54 (M0611/M0613)	Age (years)	25.3 (4.1)	24.0 (20.0 - 37.0)
	Body weight (kg)	63.8 (7.0)	63.2 (50.2 - 77.0)
	CLcr (mL/min)	140.01 (21.60)	138.84 (99.54 - 195.87)
	Male : female	54 (100.0%) : 0 (0.0%)	
	Child-Pugh class (normal : A : B : C)	54 (100.0%) : 0 (0.0%) : 0 (0.0%) : 0 (0.0%)	
	White : Asian : Black or African American : American Indian or Alaska Native : Other : Not Provided	0 (0.0%) : 54 (100.0%) : 0 (0.0%) : 0 (0.0%) : 0 (0.0%) : 0 (0.0%)	
Non-Japanese healthy subjects N = 24 (M0615)	Age (years)	37.5 (9.0)	36.5 (21.0 - 54.0)
	Body weight (kg)	76.0 (9.0)	77.4 (57.6 - 93.7)
	CLcr (mL/min)	108.03 (18.58)	114.73 (73.56 - 138.28)
	Male : female	17 (70.8%) : 7 (29.2%)	
	Child-Pugh class (normal : A : B : C)	24 (100.0%) : 0 (0.0%) : 0 (0.0%) : 0 (0.0%)	
	White : Asian : Black or African American : American Indian or Alaska Native : Other : Not Provided	21 (87.5%) : 0 (0.0%) : 3 (12.5%) : 0 (0.0%) : 0 (0.0%) : 0 (0.0%)	
Japanese patients N = 248 (M0623/M0625/M0626/ M0627/M0631/M0633)	Age (years)	68.1 (8.2)	69.0 (49.0 - 84.0)
	Body weight (kg)	60.7 (11.4)	60.2 (34.9 - 96.7)
	CLcr (mL/min)	80.97 (29.94)	75.00 (31.82 - 246.64)
	Male : female	134 (54.0%) : 114 (46.0%)	
	Child-Pugh class (normal : A : B : C)	0 (0.0%) : 141 (56.9%) : 103 (41.5%) : 4 (1.6%)	
	White : Asian : Black or African American : American Indian or Alaska Native : Other : Not Provided	0 (0.0%) : 248 (100.0%) : 0 (0.0%) : 0 (0.0%) : 0 (0.0%) : 0 (0.0%)	
Non-Japanese patients N = 101 (M0634)	Age (years)	55.2 (11.6)	55.0 (19.0 - 81.0)
	Body weight (kg)	77.3 (17.9)	74.0 (39.0 - 142.0)
	CLcr (mL/min)	109.52 (39.17)	110.04 (10.73 - 239.33)
	Male : female	58 (57.4%) : 43 (42.6%)	
	Child-Pugh class (normal : A : B : C)	0 (0.0%) : 66 (65.4%) : 32 (31.7%) : 3 (3.0%)	
	White : Asian : Black or African American : American Indian or Alaska Native : Other : Not Provided	78 (77.2%) : 15 (14.9%) : 1 (1.0%) : 2 (2.0%) : 3 (3.0%) : 2 (2.0%)	

CLcr = creatinine clearance; SD = standard deviation

[a] Number of subjects (percentage of the subjects) for categorical data.

Table 5: Demographics of the Population PK Analysis Population (Source: Applicant's population PK/PD report, Page 34, Table 3)

Subject	Background data	Mean (SD)[a]	Median (range)
All patients	Age (years)	64.4 (11.0)	66.0 (19.0 - 84.0)
N = 347	Body weight (kg)	65.5 (15.6)	63.8 (34.9 - 142.0)
	Observed baseline platelet count (*10^4/μL)	3.9 (0.8)	4.0 (1.2 - 6.7)
	Male : female	190 (54.8%) : 157 (45.2%)	
	Child-Pugh class (A : B : C)	206 (59.4%) : 135 (38.9%) : 6 (1.7%)	
	Japanese : non-Japanese	247 (71.2%) : 100 (28.8%)	
	White : non-White	77 (22.2%) : 270 (77.8%)	
	(White : Asian : Black or African American : American Indian or Alaska Native : Other : Not Provided)	77 (22.2%) : 262 (75.5%) : 1 (0.3%) : 2 (0.6%) : 3 (0.9%) : 2 (0.6%)	

SD = standard deviation

[a] Number of subjects (percentage of the subjects) for categorical data.

19.4.3. Population PK/PD analysis

Population PK modeling

Firstly, the population PK model was developed, then then PK/PD modeling was conducted using empirical Bayes- estimated PK parameters from the final PK model to provide individual plasma lusutrombopag concentrations. PK covariates tested (more details in Table 4 and

Table 5) included Age, body weight, sex, Child-Pugh classification, CLcr, ethnicity (Japanese or non-Japanese subjects), and subject population (healthy subjects or thrombocytopenic patients with CLD) were tested as a covariate on clearance (CL/F). PK covariates tested on volume of distribution in the central compartment (V/F) were Age, body weight, sex, ethnicity, and subject population, while effect of body weight was tested on peripheral volume of distribution (V3/F). The effect of drug formulation (solution, 0.25-mg tablet, 1-mg tablet, 2-mg tablet, and 3-mg tablet) and food condition (fasted state and fed state) as relative bioavailability were parameterized on the oral bioavailability (F1) of lusutrombopag in the model. The relative oral bioavailability was based on the results in the previous clinical studies.

Table 6 shows the summary of F1 in the population PK analysis.

Table 6: Summary of Effects of Drug Formulation and Food Condition on F1 in the Population PK analysis (Source: Applicant's population PK/PD report, Page 34, Table 3)

Drug Formulation/ Food Condition	F1	Source
Solution/fasted	Fixed to 1 as a reference	Not applicable
Solution/fed	Estimated	Not applicable
2-mg tablet/fasted	Fixed to 0.931	AUC0-inf ratio relative to the reference (Study S-888711-CB-160-C)
2-mg tablet/fed	Fixed to 0.857	0.931 × 0.920 based on AUC0-inf ratios between the 2-mg tablet in the fasted and fed states and the reference (Study S-888711-CB-160-C)
0.25-mg tablet/fed	0.820 × F1 estimated for the solution in the fed state	AUC0-inf ratio relative to the solution in the fed state (Study S-888711-CB-199-C)
1-mg tablet/fed	Estimated	Not applicable
3-mg tablet/fed	Estimated	Not applicable

Population PK/PD modeling

The model applied a 5-compartment pharmacodynamic (PD) model, which was reported in the previous population PK/PD analysis (Study S-888711-CB-263-N) to the platelet counts following the administration of lusutrombopag. The applicant optimized the number of compartments

based on the goodness-of-fit. The mass-balance equations of the base model are given by Equations 1 to 5

$$dP1/dt = KPR\cdot(1 + E) - KM\cdot P1 \quad (1)$$
$$dP2/dt = KM\cdot P1 - KM\cdot P2 \quad (2)$$
$$dP3/dt = KM\cdot P2 - KM\cdot P3 \quad (3)$$
$$dP4/dt = KM\cdot P3 - KM\cdot P4 \quad (4)$$
$$dPLT/dt = KM\cdot P4 - KL\cdot PLT \quad (5)$$

where KPR is a zero-order rate for the production of platelet precursor, KM is a first-order rate constant for the maturation of platelet, and KL is a first-order rate constant- for the elimination of platelet. P1 to P4 are hypothetical precursor counts and PLT is observational variables of platelet counts. KM, KL, and the baseline platelet count (PLT0) were estimated. The following initial conditions as a steady state of platelet and precursor counts were used by the applicant:

P1(0) to P4(0) = KPR/KM, PLT(0) = PLT0, and KPR = PLT0 × KL.

The applicant tested a linear model given in Equation 6 based on the previous analysis (Study S-888711-CB-263-N) to explain the drug effect (E in Equation 3). The applicant did not test a sigmoid
Emax model given that the linear model was adequate based on goodness-of-fit plots. The sigmoid
Emax model was tested by the FDA reviewer and no significant difference was found to the linear model.

$$E = SLOP \times C \quad (6)$$

where SLOP represents a slope relating plasma lusutrombopag concentrations, C represents plasma lusutrombopag concentrations. The PD model was linked with the population PK model. The covariates tested for applicant's PK/PD included age, sex, Child-Pugh class, and ethnicity which were tested on SLOP. Body weight, observed baseline platelet count and Child-Pugh score were also tested. The predictive performance of a final model was evaluated by dose-normalized (PK) or prediction-corrected visual predictive check (VPC) with 200 replications calculating a 95% confidence interval (CI) for median prediction and each limit of 95% prediction interval. In addition, the bootstrap with 300 replications was performed to calculate the associated median parameter and their corresponding 95% CI.

Results

The 4196 plasma concentration data from the 427 subjects (78 healthy subjects and 349 patients) and 3526 platelet count data from 347 patients were used for the population PK and PK/PD analyses. The 46 BLQ data for plasma lusutrombopag concentrations after the initial dosing were treated as missing in the analyses as planned.

Population PK results

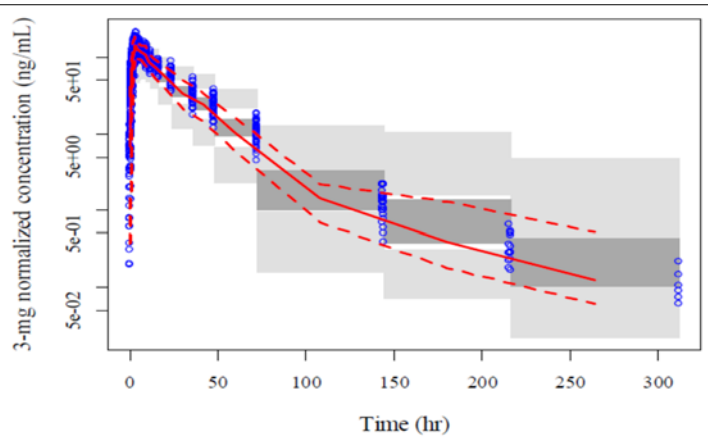
Table 7: Population Pharmacokinetic Parameter Estimates for Base and Final Models (Source: Applicant's population PK/PD report, Page 36, Table 5)

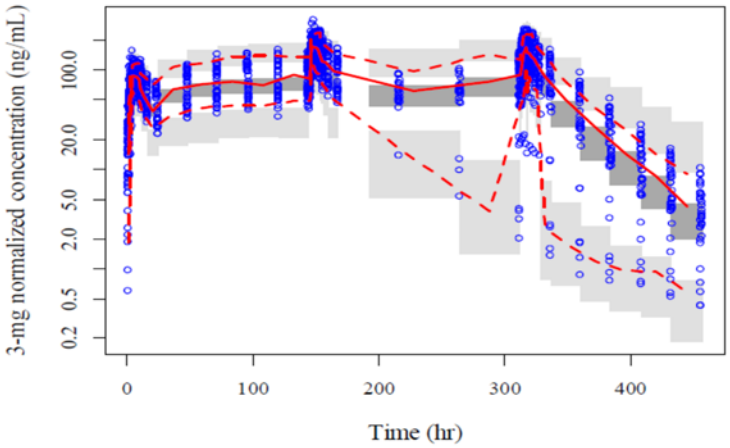
	Base model (Model No. 4)		Final model (Model No. 36)		Bootstrap estimates	
	Estimates	%RSE	Estimates	%RSE	Median	95% CI (lower - upper)
CL/F (L/hr)	0.649	3.0	0.874	3.9	0.876	0.810 - 0.935
V2/F (L)	15.3	5.2	12.2	5.9	12.3	5.75 - 13.9
Q3/F (L/hr)	0.696	14.8	0.872	8.0	0.851	0.672 - 0.993
V3/F (L)	8.51	8.0	9.04	6.6	8.95	7.71 - 12.1
Q4/F (L/hr)	0.0232	11.0	0.0265	9.7	0.0267	0.0216 - 0.0341
V4/F (L)	3.21	20.4	3.48	15.2	3.43	2.79 - 5.38
KA (hr^{-1})						
Solution in the fed	0.199	7.8	0.166	8.6	0.165	0.0925 - 0.197
Others	0.197	10.1	0.218	6.7	0.218	0.117 - 0.249
Lag time (hr)						
Solution in the fed	0.569	6.1	0.568	6.0	0.568	0.504 - 0.677
Others	0.196	3.4	0.193	3.3	0.193	0.183 - 0.208
F1 of solution in the fasted	1.00	Fixed	1.00	Fixed	-	
F1 relative to solution in the fasted						
Solution in the fed	0.884	Fixed	0.884	Fixed	-	-
2-mg tablet in the fed	0.857	Fixed	0.857	Fixed	-	-
0.25-mg tablet in the fed	0.725	Fixed	0.725	Fixed	-	-
2.5 mg (2x0.25-mg tablets and 1x2-mg tablet) in the fed	0.831	Fixed	0.831	Fixed	-	-
3.0 mg (4x0.25-mg tablets and 1x2-mg tablet) in the fed	0.813	Fixed	0.813	Fixed	-	-
1-mg tablet in the fed	1.00	5.1	0.973	5.2	0.971	0.860 - 1.08
3-mg tablet in the fed	0.783	4.0	0.843	4.2	0.837	0.766 - 0.915
Effect of WT on CL/F	N.E.	N.E.	0.750	Fixed	-	-
Effect of Sex on CL/F	N.E.	N.E.	0.874	3.5	0.874	0.816 - 0.941
Effect of Ethnicity on CL/F	N.E.	N.E.	0.868	4.1	0.866	0.809 - 0.940
Effect of Subject Population on CL/F	N.E.	N.E.	0.870	4.9	0.865	0.788 - 0.952
Effect of WT on V2/F	N.E.	N.E.	1.00	Fixed	-	-
Effect of Subject Population on V2/F	N.E.	N.E.	1.46	7.1	1.45	1.25 - 2.17
Effect of WT on V3/F	N.E.	N.E.	1.00	Fixed	-	-
Variance for inter-individual variability (CV%) [sh_ηp]						
CL/F	0.140 (37.4) [4.7]	9.0	0.0880 (29.7) [5.8]	9.6	0.0870 (29.5)	0.0714 (26.7) - 0.104 (32.3)
V2/F	0.0738 (27.2) [49.7]	53.9	0.104 (32.2) [38.1]	23.0	0.106 (32.6)	0.0493 (22.2) - 0.273 (52.2)
V3/F	0.124 (35.2) [47.6]	30.7	N.E.	N.E.	-	-
KA	0.301 (54.9) [39.9]	30.2	0.169 (41.1) [47.1]	22.7	0.169 (41.1)	0.00701 (8.4) - 0.252 (50.2)
SD for intra-individual variability (CV%) [sh_ε]						
Proportional residual error	0.176 (17.6) [8.9]	4.0	0.180 (18.0) [7.5]	3.9	0.181 (18.1)	0.167 (16.7) - 0.195 (19.5)

CI = confidence interval; CL/F = apparent total clearance; F1 = bioavailability; KA = first-order rate constant of absorption; Lag time = lag time for absorption;
N.E = not estimated; Q3/F and Q4/F = apparent inter-compartmental clearance; SD = standard deviation;
sh_ηp = shrinkage in the standard deviation of inter-individual variability parameters η;
sh_ε = shrinkage in the standard deviation of intra-individual variability parameters ε;
V2/F = apparent volume of distribution in central compartment; V3/F and V4/F = apparent volume of distribution in peripheral compartment; WT = body weight;
%RSE = relative standard error in percent;
CL/F in the final model = $0.874*(WT/64.0)^{0.750}*0.874^{Sex}*0.868^{Ethnicity}*0.870^{Subject\ population}$
V2/F in the final model = $12.2*(WT/64.0)*1.46^{Subject\ population}$
V3/F in the final model = 9.04*(WT/64.0)
(Sex = 0 for male and Sex = 1 for female; Ethnicity = 0 for non-Japanese and Ethnicity = 1 for Japanese;
Subject population = 0 for healthy subjects and Subject population = 1 for thrombocytopenic patients)

The final population PK parameter estimates along with bootstrap (N=300) parameter estimates (median and 95% CI) are shown in Table 7 while Figure 16 shows VPC results of the final model. The final model was a three-compartment model with lag time (to cater for absorption delay) and first-order elimination. The applicant identified the following significant covariates:

- Body weight which was incorporated through allomeric scaling on CL/F and Volume of distribution in the central
- Ethnicity, Japanese had 13% lower CL/F than non-Japanese
- Sex, females had 12.6% lower CL/F than males
- CLD patients had 13.5% lower CL than healthy volunteers
- Formulation effect, different bioavailabilities (F1) per formulation and lusutrombopag strength





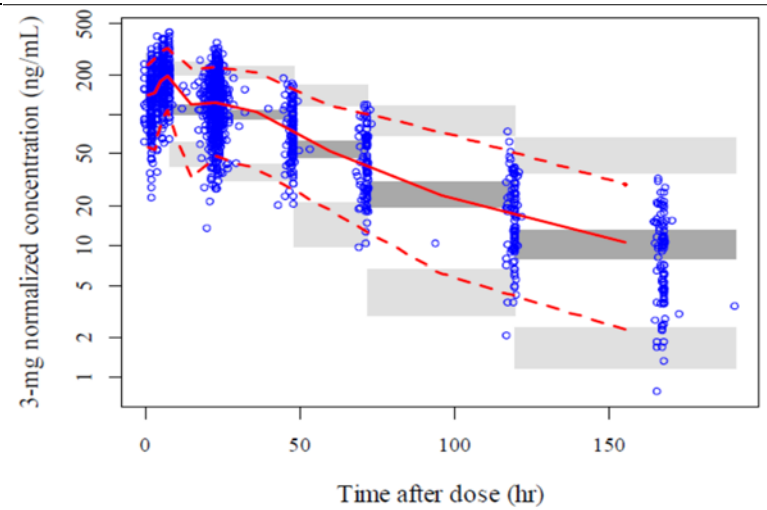


Figure 16: Dose-normalized Visual Predictive Check for the Final Pharmacokinetic Model for single-dose in healthy volunteers (top panel), multiple doses in healthy volunteers (middle panel), and multiple doses in patients (bottom panel). Open circle: observed data. Solid line: observed median. Dashed line: observed 2.5th and 97.5th percentiles. Dark grey shaded area: model predicted 95% CI of median. Grey shaded area: model predicted 95% CIs of 2.5th and 97.5th percentiles. 200 replications (Source: Applicant's population PK/PD report, Page 62-68, Figure 3)

Effect of body weight

Body weight had a negative correlation with exposure following a flat dose of 3-mg. The effect of body weight on lusutrombopag Cmax and AUC is shown in below.

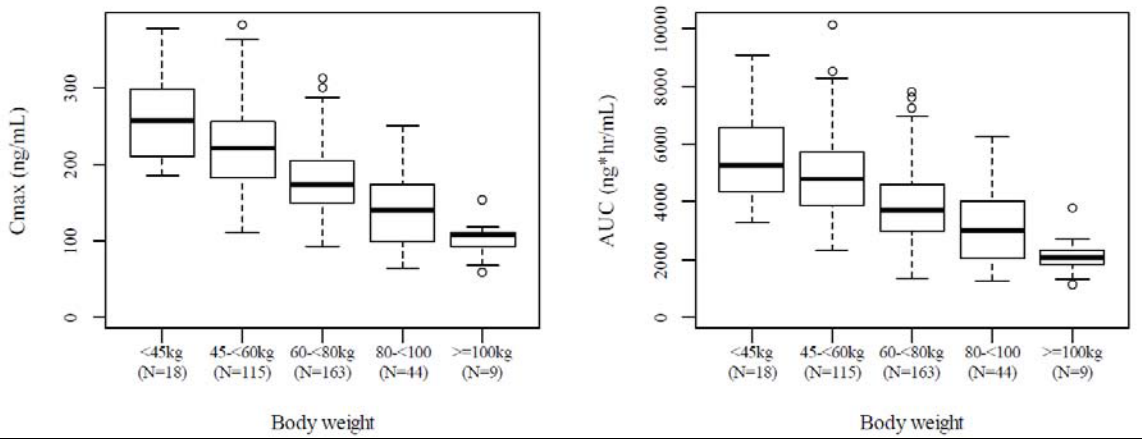


Figure 17: Boxplots of Steady-state Cmax and AUC0-τ in Patients by Body Weight Groups Estimated Using Post-hoc Pharmacokinetic Parameters following 3-mg Doses Once Daily for 7 Days (Source: Applicant's population PK/PD report, Page 66, Figure 10)

Reviewer's comment: Applicant's population PK analysis reasonably described the population of lusutrombopag as shown in the visual predictive check. The submitted final population PK model is reproducible and FDA reviewer agree with the identified covariates, which supports applicant's labelling claims. There was a negative correlation between body weight and exposure, such that individuals weighting more than 100 kg had approximately 55% lower AUC compared with 60 to <80kg reference group. FDA reviewer conducted independent analysis to assess the clinical impact by increasing the dose to 4-mg in patients weighting more than 100 kg (Section 4.4.2).

Population PK/PD results

The applicant's final model is illustrated in Figure 18, and estimates of the final population PK/PD model along with bootstrap (N=300) parameter estimates (median and 95% CI) are shown in

Table 8 and Figure 19 shows the prediction-corrected VPC of the final PK/PD model. The final model included the effect of Child-Pugh score (< 9 or ≥ 9) on SLOP. The IIV was high for KL and SLOP (CV% of 65.0% and 53.6%, respectively), and moderate for KM and PLT0 (33.0% and 26.5%, respectively).

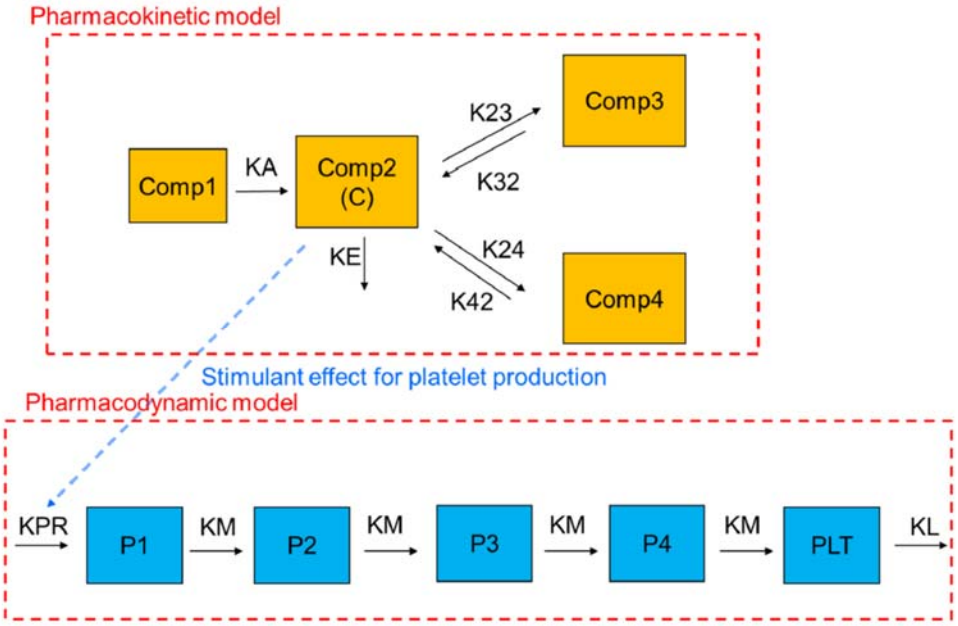


Figure 18: Scheme of Final Pharmacokinetic/Pharmacodynamic Model for Lusutrombopag. Comp1: absorption compartment. Comp2: central compartment. Comp3 and Comp4: peripheral compartment. P1, P2, P3, and P4: hypothetical platelet precursor compartment. PLT: platelet compartment. KA: first-order rate constant of absorption. K23, K32, K24, and K42: first-order transfer rate constant between compartments. KE: first-order rate constant of elimination. C: plasma lusutrombopag concentration. KPR: zero-order rate for the production of platelet precursor. KM: first-order rate constant for the maturation of platelet. KL: first-order rate constant for the elimination of platelet (Source: Applicant's population PK/PD report, Page 104, Appendix 12)

Table 8: Population Pharmacodynamic Parameter Estimates for Base and Final Pharmacokinetic/Pharmacodynamic Models (Source: Applicant's population PK/PD report, Page 40, Table 9)

	Base model (Model No. 101)		Final model (Model No. 113)		Bootstrap estimates	
	Estimates	%RSE	Estimates	%RSE	Median	95% CI (lower - upper)
KM (hr^{-1})	0.0321	5.1	0.0320	5.3	0.0318	0.0288 - 0.0353
KL (hr^{-1})	0.00859	10.1	0.00863	10.2	0.00871	0.00720 - 0.0108
SLOP (mL/μg)	9.40	4.8	9.08	4.8	9.09	8.28 - 10.0
PLT0 ($*10^4$/μL)	3.92	1.6	3.92	1.6	3.92	3.80 - 4.05
Effect of CPS >= 9 on SLOP	NE	NE	1.69	12.7	1.69	1.26 - 2.13
Variance for inter-individual variability (CV%) [sh_ηp]						
KM	0.109 (33.0) [33.0]	21.0	0.109 (33.0) [33.1]	21.3	0.107 (32.8)	0.0642 (25.3) - 0.168 (41.0)
KL	0.415 (64.4) [35.9]	18.4	0.423 (65.0) [35.6]	18.3	0.419 (64.7)	0.273 (52.3) - 0.591 (76.9)
SLOP	0.308 (55.5) [20.3]	14.5	0.287 (53.6) [20.9]	15.2	0.283 (53.2)	0.199 (44.7) - 0.393 (62.7)
PLT0	0.0699 (26.4) [4.2]	11.8	0.0703 (26.5) [4.2]	11.7	0.0707 (26.6)	0.0551 (23.5) - 0.0880 (29.7)
SD for intra-individual variability (CV%) [sh_ε]						
Proportional residual error	0.106 (10.6) [12.5]	6.2	0.106 (10.6) [12.5]	6.2	0.106 (10.6)	0.0933 (9.3) - 0.118 (11.8)
Additive residual error ($*10^4$/μL)	0.247	19.8	0.245	20.0	0.246	0.130 - 0.332

CI = confidence interval; CPS = Child-Pugh score; KL = first-order rate constant for the elimination of platelet;
KM = first-order rate constant for the maturation of platelet; PLT0 = baseline platelet count; SD = standard deviation;
sh_ηp = shrinkage in the standard deviation of inter-individual variability parameters η;
sh_ε = shrinkage in the standard deviation of intra-individual variability parameters ε;
SLOP = slope relating plasma lusutrombopag concentrations;
%RSE = relative standard error in percent;
SLOP in the final model = $9.08*1.69^{CPS2}$ (CPS2 = 0 for CPS < 9 and CPS2 = 1 for CPS >= 9)

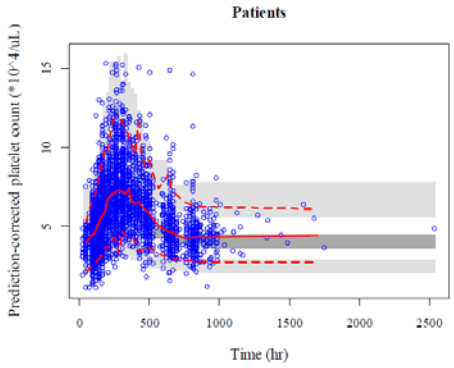


Figure 19: Prediction-corrected Visual Predictive Check for the Final Pharmacokinetic/Pharmacodynamic Model for Patients. Upper figure: Linear scale. Lower figure:

Semi-log scale. Open circle: observed data. Solid line: observed median. Dashed line: observed 2.5th and 97.5th percentiles. Dark grey shaded area: model predicted 95% CI of median. Grey shaded area: model predicted 95% CIs of 2.5th and 97.5th percentiles. 200 replications (Source: Applicant's population PK/PD report, Page 80, Figure 20)

Reviewer's comment: Applicant's population PK/PD analysis reasonably described the population PK/PD of lusutrombopag as shown in the visual predictive check and the reviewer agrees with the final model and identified covariates.

Applicant's Conclusions

Population PK Analyses:

1. The PK of lusutrombopag is was well described,
2. Body weight was an influential covariate on lusutrombopag PK,
3. Volume of distribution in the patients with CLD was higher than healthy subjects. However, the post-hoc analysis indicated that steady-state Cmax was similar between healthy subjects and the patients,
4. The effects of age, CLcr, sex, Child-Pugh class, and ethnicity (Japanese vs non-Japanese subjects) on PK were not clinically meaningful.

Population PK/PD Analyses:

1. The PK/PD of lusutrombopag is well described,
2. No difference in PD response is suggested between Japanese and non-Japanese subjects,
3. SLOP was higher in the patients with higher Child-Pugh score (≥ 9).

Reviewer's comments: The reviewer accepts the final population PK/PD models submitted by the applicant. Given that patients weighting more than 100 kg had lower lusutrombopag exposures, FDA reviewer conducted independent analysis to evaluate the benefit of increasing the dose to 4-mg in patients weighting more than 100 kg (Section 4.4.2).

19.4.4. Exposure-Response Analyses

Methods for exposure-response analysis

Platelet count estimation based on post-hoc parameters
The applicant conducted exposure-response analysis using the final population PK/PD model. Individual peak platelet counts of the patients who received 3-mg dose were calculated by empirical Bayesian estimations of PK and PD parameters of the patients from the final population PK/PD model. Individual peak platelet counts were obtained by simulation of the platelet count profiles every 24 hours from 0 to 696 hours and summarized by subpopulation. The actual date and time of dosing were used for the analyses.
Simulations for Platelet Count Profiles
The developed model was employed to assess (1) effect of ethnicity/race, (2) dose response relationship, and (3) necessity of a dose stopping rule based on simulated platelet responses. For simulation scenarios, 200-replicate simulations were performed with generating virtual subjects by resampling the influential background data used for lusutrombopag PK/PD modeling. Baseline platelet counts were simulated based on the estimated PLT0 in the modeling with a maximum value of 5×10^4/μL. As the dose stopping criteria, if predicted platelet counts represent ≥ 5×10^4/μL with an increase of 2×10^4/μL from the baseline, administration of lusutrombopag was discontinued. Platelet counts of virtual subjects following once daily dosing for 7 days with or without the stopping criteria were simulated every 24 hours from 0 to 696 hours. The simulation conditions for ethnicity/race, dosage, and dose stopping criteria after daily dose of either 2-mg, 3-mg or 4- mg for 7 days on either day 1 to 3 days of 5 to 7 days, and 7-day fixed dosing.
Then the following platelet indices were calculated from the simulated platelet counts for each simulation scenario:

- 5^{th}, 50^{th}, and 95^{th} percentiles of peak platelet count,
- Probability to exceed 20×10^4/μL of platelet count,
- Probability to attain 5×10^4/μL of platelet count from Days 9 to 14

Results

Platelet count estimation based on post-hoc parameters
The applicant summarized individual peak platelet counts predicted with the post-hoc analyses by Child-Pugh score (< 9 or ≥ 9) or body weight (< 45, 45 to < 60, 60 to < 80, 80 to < 100, and ≥ 100 kg) as shown in Table 9. The peak platelet counts were similar between these Child-Pugh groups identified by the model. However, high body weight patients had lower platelet count.

Table 9: Post-hoc Predicted Individual Peak Platelet Counts in Patients Who Received 3-mg Dose by Child-Pugh Score or Body Weight (Source: Applicant's population PK/PD report, Page 80, Figure 20)

Subpopulation	N	Peak platelet count (*10^4/μL)
Child-Pugh score < 9	249	7.62 (2.26-17.6)
Child-Pugh score >= 9	20	7.61 (2.35-18.8)
WT < 45 kg	10	10.4 (4.68-17.6)
WT 45 to < 60 kg	87	7.83 (3.21-18.8)
WT 60 to < 80 kg	120	7.52 (2.26-16.5)
WT 80 to < 100 kg	43	7.13 (2.35-11.4)
WT >= 100 kg	9	6.18 (2.48-8.95)

Mean (range). WT = body weight
The peak platelet counts were predicted for the patients who received 3-mg dose.

Simulations

The applicant's simulation results are categorized by body weight are shown in Table 10. These results showed that with the 7-day fixed dosing (no platelet monitoring), the probabilities to exceed 20 × 10^4/μL were 0.43% for non-Japanese patients. With the platelet monitoring on Day 5, 6, or 7, the probabilities to exceed 20 × 10^4/μL were 0.2% to 0.3% for non-Japanese patients. With the platelet monitoring on Days 5 to 7, the probabilities to exceed 20 × 10^4/μL were 0.13% for non-Japanese patients. The tested dose stopping did not change the probability to attain 5 × 10^4/μL. The simulation suggests (1) the absolute difference between with and without platelet monitoring in the probability of platelet overshooting (i.e. >20 × 10^4/μL) is very small and (2) one-day platelet monitoring on Day 5, 6, or 7 reduced the probability to exceed 20 × 10^4/μL by half, which were still very small as the absolute difference. Furthermore, With the 7-day fixed dosing, the differences in median peak platelet counts were up to 1.2 × 10^4/μL between each body weight and the reference group (60 to < 80 kg), and the probability to exceed 20 × 10^4/μL was 2.05% in the lowest body weight groups (35 to < 45 kg). The probability to attain 5 × 10^4/μL on Days 9 to 14 was approximately 70% in the highest body weight group (100 to 130 kg) in any platelet monitoring designs.

Table 10: Summary of Simulated Platelet Indices by Body Weight (Source: Applicant's population PK/PD report, Page 44, Table 14)

Day for platelet monitoring	Body weight	Peak PLT count percentile ($*10^4$/μL)			Pr(PLT>=5) on Days 9 to 14	Pr(PLT>20)
		5th	50th	95th	(%)	(%)
7-day fixed dosing	35 - < 45 kg	4.67	8.00	16.5	90.8	2.05
	45 - < 60 kg	4.34	7.37	14.0	84.8	0.74
	60 - < 80 kg	4.12	6.78	12.4	81.0	0.49
	80 - < 100 kg	3.97	6.39	11.4	77.8	0.31
	100 - 130 kg	3.81	5.96	9.99	69.5	0.12
Day 5	35 - < 45 kg	4.67	7.97	15.5	90.8	0.81
	45 - < 60 kg	4.34	7.35	13.5	84.8	0.49
	60 - < 80 kg	4.12	6.78	12.1	80.9	0.31
	80 - < 100 kg	3.97	6.39	11.0	77.7	0.12
	100 - 130 kg	3.81	5.96	9.95	69.5	0.12
Day 6	35 - < 45 kg	4.67	7.95	14.8	90.8	0.81
	45 - < 60 kg	4.34	7.33	12.9	84.8	0.37
	60 - < 80 kg	4.12	6.78	12.0	81.0	0.25
	80 - < 100 kg	3.97	6.38	11.0	77.8	0.06
	100 - 130 kg	3.81	5.96	9.83	69.5	0.06
Day 7	35 - < 45 kg	4.67	7.93	15.2	90.8	1.24
	45 - < 60 kg	4.34	7.33	13.3	84.8	0.55
	60 - < 80 kg	4.12	6.74	11.9	81.0	0.43
	80 - < 100 kg	3.97	6.38	10.9	77.7	0.06
	100 - 130 kg	3.81	5.96	9.85	69.4	0.06
Days 5, 6, 7	35 - < 45 kg	4.67	7.87	14.0	90.8	0.43
	45 - < 60 kg	4.34	7.30	12.5	84.8	0.25
	60 - < 80 kg	4.12	6.74	11.4	80.9	0.18
	80 - < 100 kg	3.97	6.37	10.5	77.6	0.00
	100 - 130 kg	3.81	5.96	9.68	69.4	0.06

2000 simulations. Body weight was simulated according to uniform distribution. Child-Pugh score was set to less than 9.
The simulations were performed based on male : female of 1 : 1 for non-Japanese patients.
PLT = platelet; Pr(PLT>=5) = probability to attain $5*10^4$/μL of platelet counts
Pr(PLT>20) = probability to exceed $20*10^4$/μL of platelet counts

Applicant's conclusions

1. The post-hoc analysis indicated that there was no significant difference in the peak platelet counts between the Child-Pugh score groups,
2. The PK/PD simulation supports the dose regimen of 3-mg once daily for 7 days in non-Japanese patients,
3. With the 7-day fixed dosing (no platelet monitoring), the probabilities to exceed 20 × 10^4/μL of platelet counts were 0.43% for non-Japanese patients. A difference between with and without platelet monitoring in the probability of platelet overshooting (i.e. > 20 × 10^4/μL) was very small,
4. A higher platelet count increase in patients with low body weight (< 45 kg) was suggested. In the patients with low body weight, the simulated peak platelet counts were higher by 1.2 × 10^4/μL than in the reference group (body weight of 60 to < 80 kg) and the probability to exceed 20 × 10^4/μL was 2.05% with the 7-day fixed dosing,

5. The lower platelet increase in patients with high body weight (≥ 100 kg) was suggested. The probability to attain $5 \times 10^4/\mu L$ was approximately 70% in the patients with high body weight.

Reviewer's comments: The applicant's results showed that patients weighting more than 100 kg had low peak platelet count when dosed with 3-mg daily for 7 days. This could be attributed to low baseline platelet count and body weight effect. In the Monte Carlo simulation, the applicant's definition of responder was an individual who ever achieved peak platelet count of $5 \times 10^4/\mu L$ any day from day 9 to day 14. As a conservative approach, the FDA reviewer conducted an independent analysis (Section 4.4.2) where the responder was defined as an individual who maintains minimal platelet count of $5 \times 10^4/\mu L$ between day 9 and day 14. Any individual who had platelet count less than $5 \times 10^4/\mu L$ on any day between day 9 and day 14 was defined as non-responder. The benefits of increasing the dose in subjects with high body weight and low baseline platelet count were evaluated in the reviewer's analysis.

Reviewer's independent Analysis

The objectives of analysis were to:

- Assess the adequacy of applicant's population PK and PK/PD models to describe the PK data,
- Evaluate the effect body weight and baseline platelet count on efficacy,
- Assess the benefit of increasing the dose in patients weighting more than 100 kg.

Data sets

The data sets and files used in the analyses are summarized in Table 11.

Table 11: Analysis Datasets for FDA Reviewer's Analysis

File name	Description	Link to EDR
nmdata.xpt	Dataset for population PK analysis	\\CDSESUB1\evsprod\NDA210923\0002\m5\datasets\cb-315-n\analysis\adam\datasets
Nmdata_pkpd.xpt	Dataset for population PK/PD analysis	\\CDSESUB1\evsprod\NDA210923\0002\m5\datasets\cb-315-n\analysis\adam\datasets
ppk_final_model36_ctl.txt	Final population PK model	\\CDSESUB1\evsprod\NDA210923\0002\m5\datasets\cb-315-n\analysis\adam\programs
ppkpd_final_model113_ctl.txt	Final population PK/PD model	\\CDSESUB1\evsprod\NDA210923\0002\m5\datasets\cb-315-n\analysis\adam\programs
ppk_final_model36_out.txt	Population PK output file	\\CDSESUB1\evsprod\NDA210923\0002\m5\datasets\cb-315-n\analysis\adam\programs
ppkpd_final_model113_out.txt	Population PK/PD output file	\\CDSESUB1\evsprod\NDA210923\0002\m5\datasets\cb-315-n\analysis\adam\programs

Software

NONMEM 7 and R were used for the reviewer's analysis.

Method

The FDA reviewer explored the applicant's final population PK and PK/PD models by evaluating the diagnostic plots. Using applicant's final population PK/PD model, the reviewer conducted Monte Carlo simulation to assess the effect of body weight and/or baseline platelet count on the response. CDC dataset was used to get the natural distribution of influential covariates, where patients weighting more than 100 kg constituted 16.6%. The FDA reviewer defined a responder as a patient who would achieve platelet count of at least $5 \times 10^4/\mu L$ in all days from day 9 to day 14. The target population were Caucasians with Child-Pugh score less than 9. Impact on platelet count by increasing the dose from 3-mg to 4-mg was evaluated.

Results

The applicant's final model was repeatable. According to FDA reviewer's evaluation, the diagnostic plots of the applicant's final PPK model showed that the model adequately described the PK of lusutrombopag (Figure 20). The FDA reviewer also conducted a sensitivity analysis by estimating the exponent of body weight (incorporated through allometric scaling) on clearance. The estimate of the exponent was 0.76, which was comparable to 0.75, and the estimate of clearance remained the same. In addition, the drop in objective function after estimating the exponent was 1.13. Hence, the reviewer concluded that 0.75 is a valid allometric scaling factor for lusutrombopag PK on total body weight.

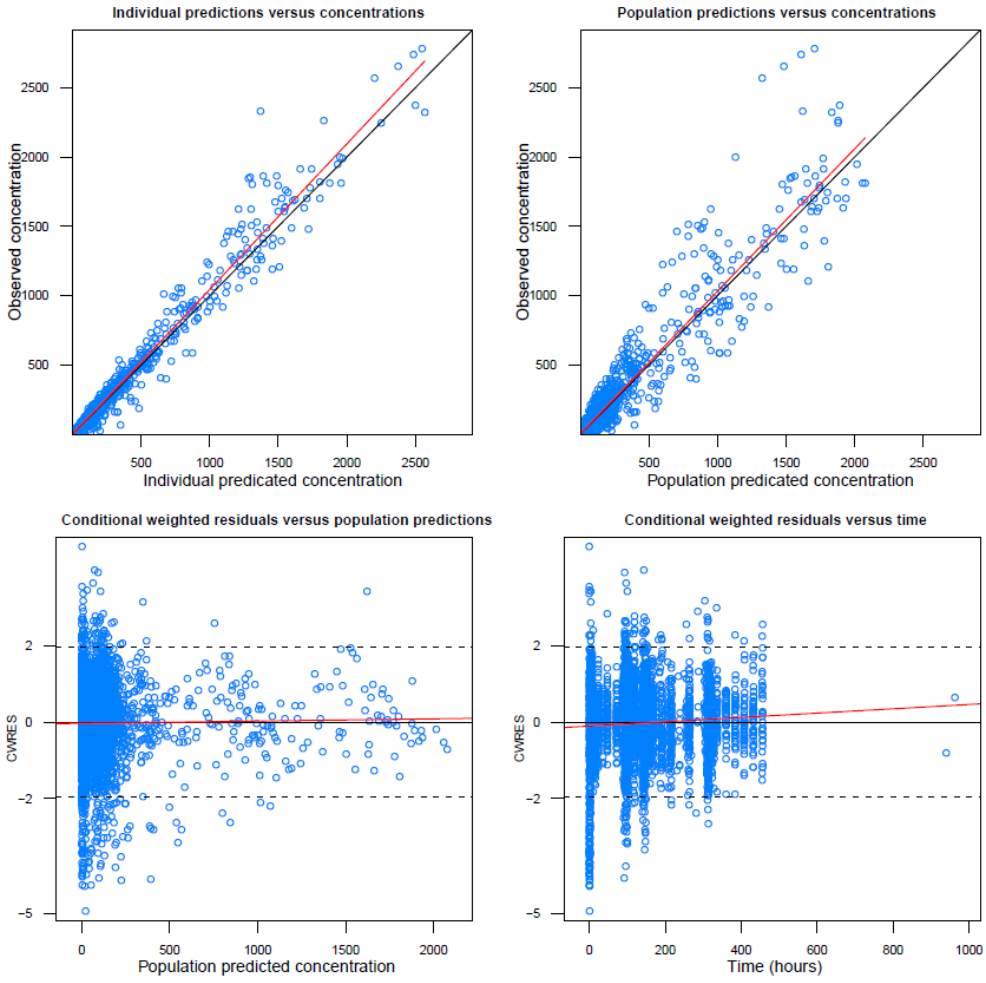


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Figure 20: Goodness-of-fit plots for lusutrombopag final population PK model using data from all phases of studies. CWRES=conditional weight residuals. The black solid line is the line of identity or the zero line, and the red solid line is the trend line. The blue circles represent observed data (FDA analysis)

The final PK/PD model developed by the applicant was also repeated and similar parameter estimates were obtained as in Appears this way on original

Table 8. The diagnostic plots are shown in Figure 21.

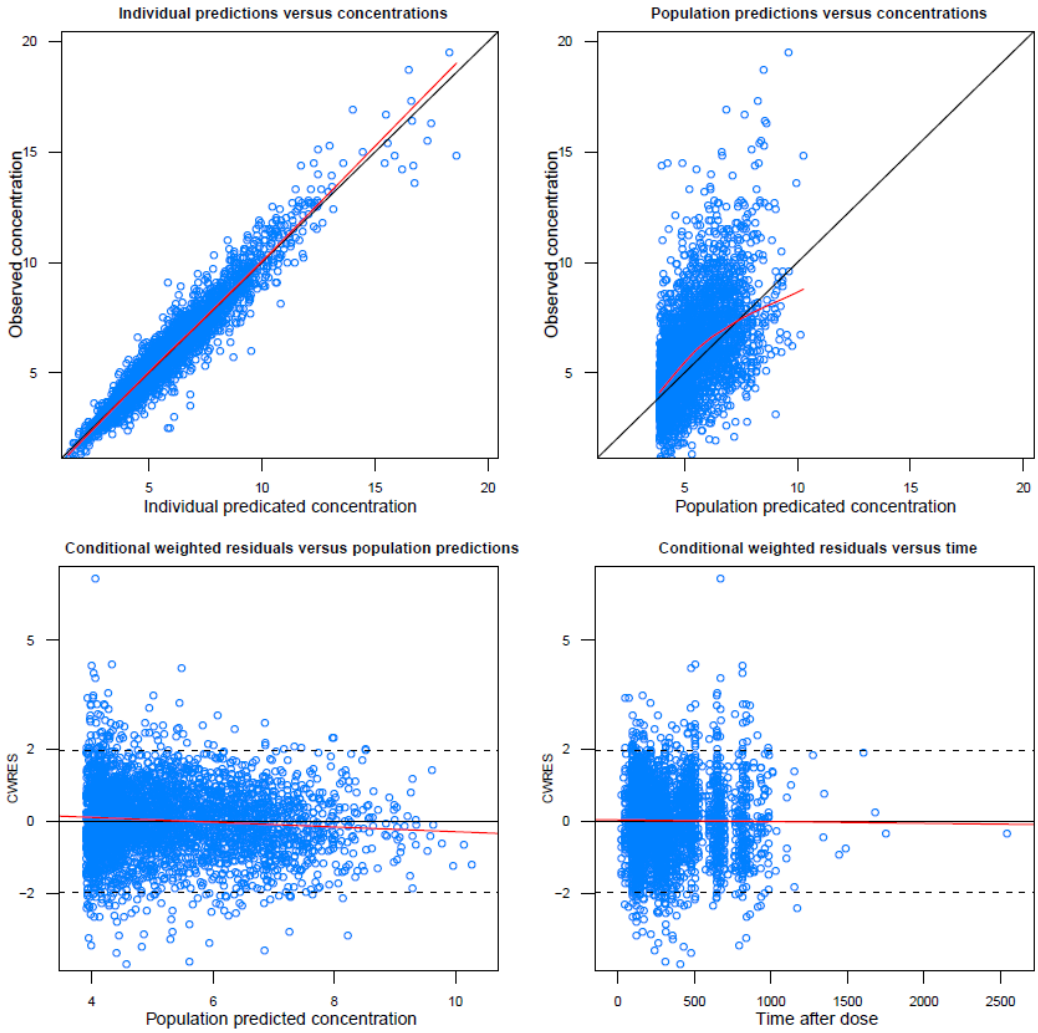

Figure 21: Goodness-of-fit plots for lusutrombopag final population PK/PD model using data from Phase2 and Phase 3 studies. CWRES=conditional weight residuals. The black solid line is the line of identity or the zero line, and the red solid line is the trend line. The blue circles represent observed data(FDA analysis)

Evaluation of body weight effect (Phase 3 data)

The effect of body weight on PK and platelet count was evaluated following 3-mg lusutrombopag dose. In addition, a virtual population of patients weighting more 100 kg and

dosed with 4-mg was created. The corresponding AUC was obtained through scaling by assuming linear PK. Using data from Phase 3 studies, the plot of lusutrombopag exposure against body weight is shown in Figure 22. The AUCs of patients who developed drug related thrombosis are shown as red-squares. Based on this observed data, it showed that the drug exposure in the over-weighted patients receiving 4-mg could be well covered by the exposure range observed in the study .

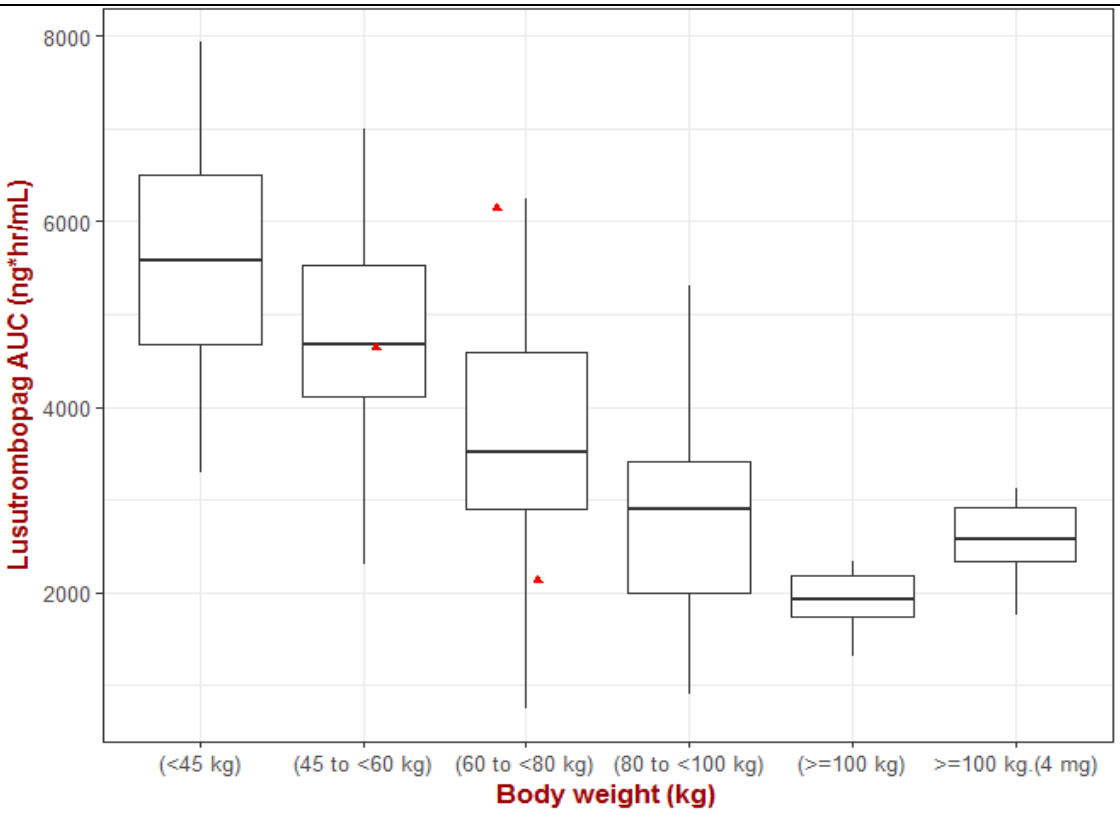

Figure 22: Box and whiskers plot for lusutrombopag AUC at day 7 against body weight using Phase 3 data. The last category ">=100 (4mg) was created to show the resulting AUC in patients weighting at least 100 kg and dosed with 4-mg lusutrombopag. The red triangles represent the AUC of patients who developed drug related thrombosis

Monte Carlo simulations

The results of simulations assuming differences in exposure is because of body weight is shown in *Figure 23*. Clearly there is benefit in increasing the dose to 4-mg in patients weighting more than 100 kg. Interestingly, switching to 4-mg dose results in approximately 10% more patients would maintain platelet count above $5 \times 10^4/\mu L$ as shown in *Figure 23*.

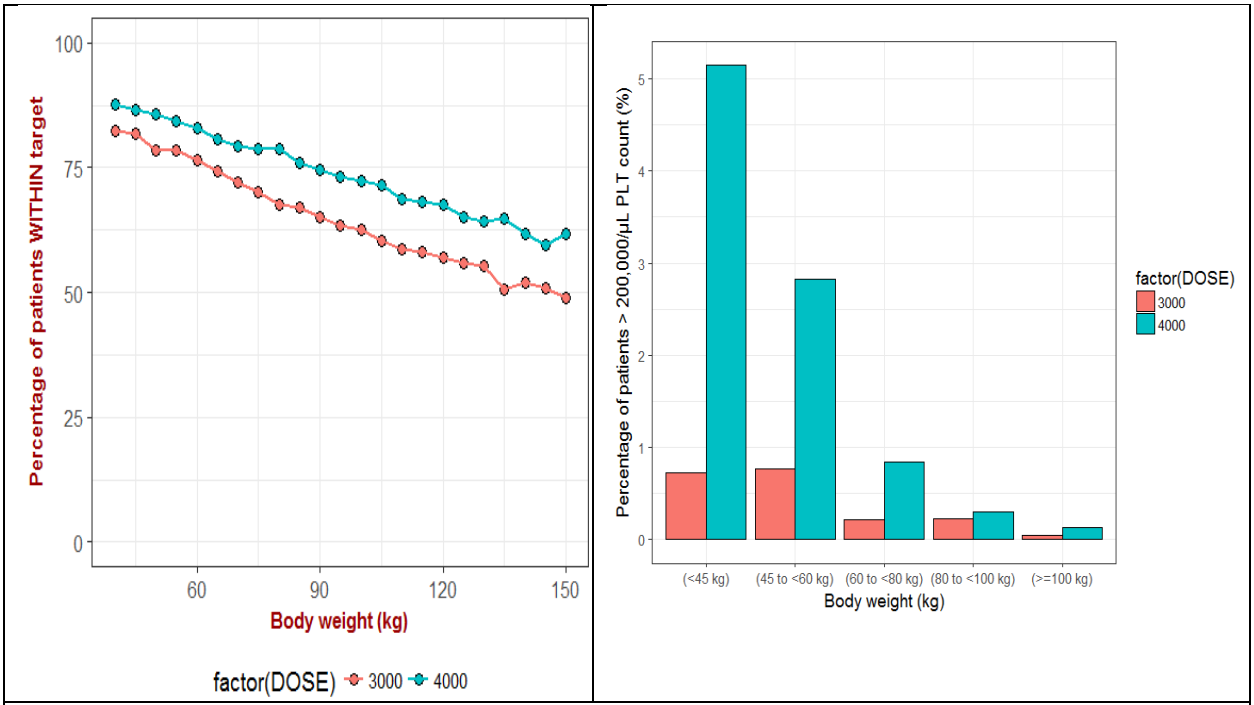

Figure 23: Plot showing the percentage of patients falling within target platelet count after 7 daily doses of 3 000 µg or 4 000 µg lusutrombopag (left panel). The right panel show the percentage of patients above the target.

In addition, as shown in *Figure 24*, there is limited efficacy benefit by dosing patients whose baseline platelet count of less than $2 \times 10^4/\mu L$. The percentage of patients whose peak platelet count above $20 \times 10^4/\mu L$ is shown in *Figure 25*.

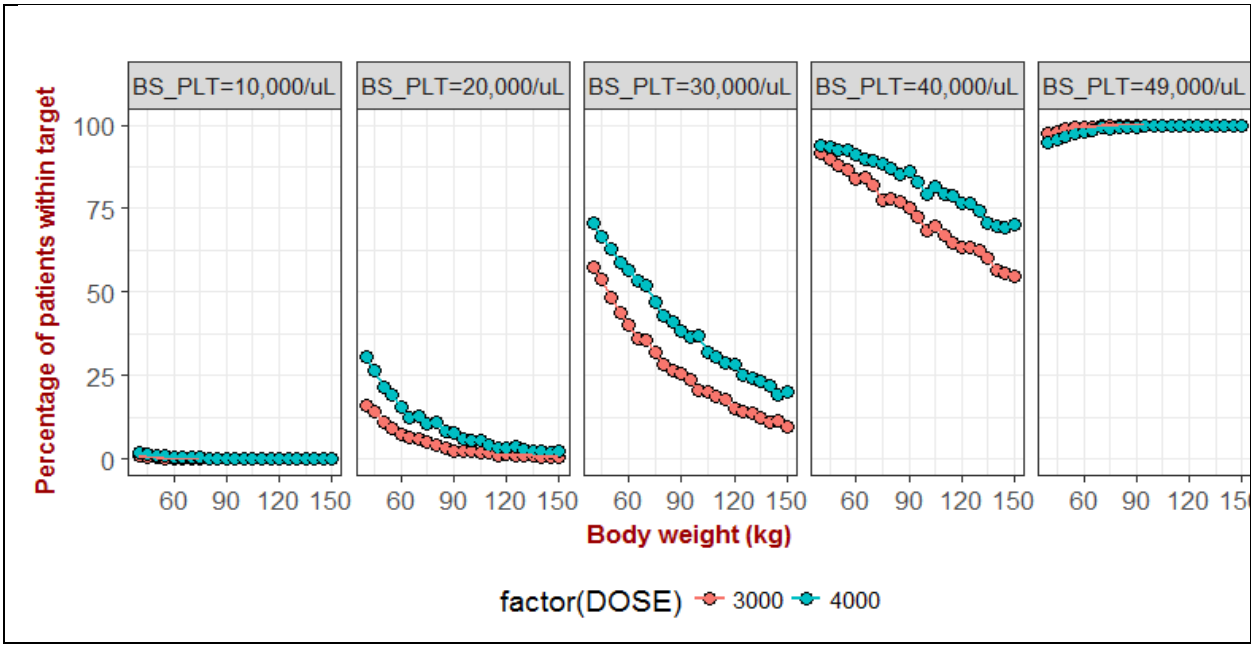

Figure 24: Plot showing the percentage of patients falling within target platelet count after 7 daily doses of 3 000 µg or 4 000 µg lusutrombopag. BS_PLT represents baseline platelet count

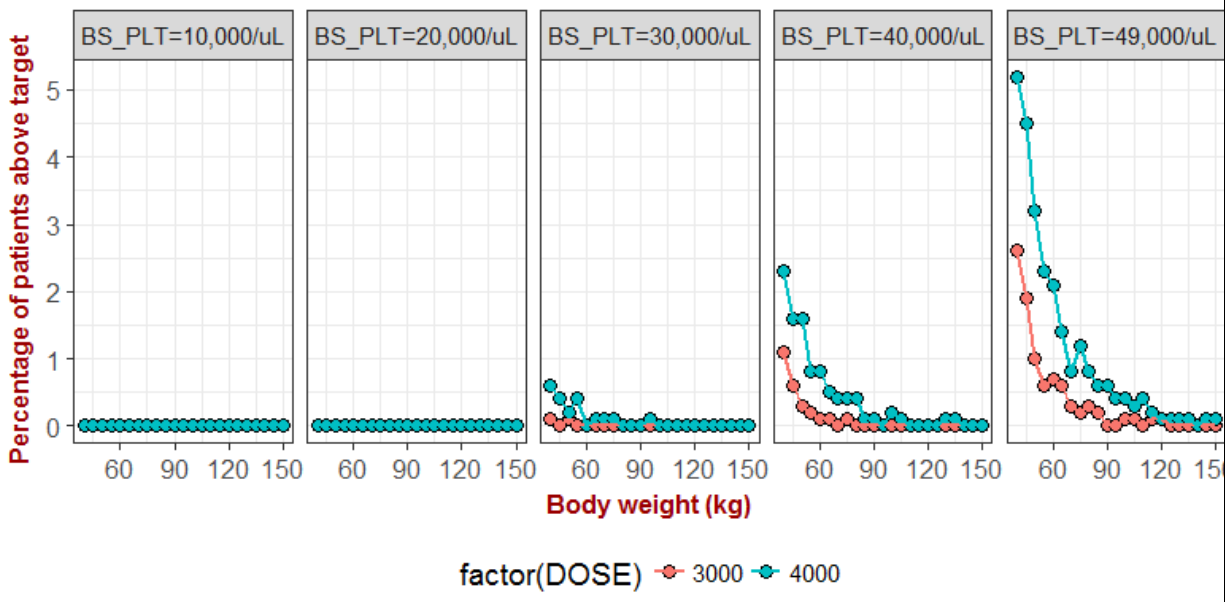

Figure 25: Plot showing the percentage of patients above target platelet count after 7 daily doses of 3 000 µg or 4 000 µg lusutrombopag. BS_PLT represents baseline platelet count

Reviewer's Conclusions:

1. *Body weight was a significant covariate influencing the PK and PK/PD of lusutrombopag*
2. *There is 10% increase in the response rate by raising the dose of lusutrombopag to 4-mg in patients weighting at least 100 kg,*
3. *When dosed with 4-mg, the risk of having peak platelet count greater than* $20 \times 10^4/\mu L$ is minimal for *patients weighting greater than 100 kg.*
4. *Few patients with baseline count less than* $2 \times 10^4/\mu L$ *are likely to benefit from lusutrombopag*

In summary, this analysis showed that raising the dose to 4-mg in subjects with high body weight (≥100 kg) may lead to about 10% increase in response rate, and the risk of having peak platelet count greater than $20 \times 10^4/\mu L$ *could be minimal. However, this simulation assumed that the risk of thrombosis was only dependent on the platelet count. The inherent higher risk of thrombosis at over-weighted patients were not considered in the simulation.*

Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
run015.mod	PK/PD simulation Model file for body weight and baseline platelet effect combined	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lusutrombopag_NDA 210923_SPZ
nm_pkpd_sim.csv	Simulation dataset with body weight and platelet count effect combined	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lusutrombopag_NDA 210923_SPZ
simtab015	Output file for run015.mod	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lusutrombopag_NDA 210923_SPZ
run019.mod	PK/PD simulation Model file for body weight effect	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lusutrombopag_NDA 210923_SPZ
cdc_pkpd_3272018	Simulation dataset (CDC)	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lusutrombopag_NDA 210923_SPZ
simtab019	Output file for run019.mod	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Lusutrombopag_NDA 210923_SPZ

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/s/

JENNIFER J LEE
07/27/2018

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07/27/2018

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I agree with the recommendation.

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Statistical Review and Evaluation

NDA/BLA: NDA210923
Drug Name: Lusutrombopag (S-888711)
Indication: for the treatment of thrombocytopenia in patients with chronic liver disease who are at increased risk for bleeding associated with elective invasive procedures
Sponsor: Shionogi
Reviewer: Jingjing Ye
Date of Receipt: Dec. 26, 2017

On Dec. 26, 2017, Shionogi submitted the results of their pivotal studies L-Plus1 and L-Plus2 in Lusutrombopag to support approval for the treatment of thrombocytopenia in patients with chronic liver disease who are at increased risk for bleeding associated with elective invasive procedures. This document briefly reviews the submitted material and conclusions made for the submission. More detailed information can be found in the unireview.

The pivotal trials L-Plus1 and L-Plus 2 were identical designs as a randomized, double-blind study to compare Lusutrombopag to placebo. Approximately 97 patients were enrolled in L-Plus 1 study and 215 patients were enrolled in L-Plus 2 study.

Analysis datasets, SDTM tabulations, and software codes are located at:
\\CDSESUB1\evsprod\NDA210923\0002\m5\datasets\1304m0631

\\CDSESUB1\evsprod\NDA210923\0002\m5\datasets\1423m0634

The primary efficacy endpoint was proportion of patients who require no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomization through 7 days after the primary invasive procedure in L-Plus 2 and percentage of patients who required no platelet transfusion prior to invasive procedures in L-Plus 1 study. The studies L-Plus1 and L-Plus2 met the primary endpoint and key secondary endpoints comparing Lusutrombopag arm to placebo arm. There was statistically significant improvement in the proportion of patients not requiring platelet transfusion prior to invasive procedures in Lusutrombopag arm to placebo in L-plus 1 study and the difference of patients was 66% with the corresponding 95% confidence interval of 51% to 83%. There was also statistically significant improvement in the proportion of patients not requiring platelet transfusion prior to invasive procedure or rescue therapy for bleeding thorough 7 days after invasive procedure in Lusutrombopag arm to placebo in L-plus 2 study and the difference was 36% with corresponding 95% confidence interval of 24% to 49%.

For secondary endpoint of proportion of responders and duration of platelet count increase to at least 50 x 10^9/L, the patients treated with Lusutrombopag showed statistically significant improvement over placebo arm in both L-Plus 1 and L-Plus 2 studies.

In conclusion, the L-Plus1 and L-Plus2 showed superiority of primary endpoint and secondary endpoints in Lusutrombopag arm compared to placebo arm.

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/s/

JINGJING YE
05/21/2018

LEI NIE
05/21/2018

THOMAS E GWISE
05/21/2018

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDIES

IND/NDA Number:	NDA 210923
Drug Name:	S-888711
Indication:	Treatment of thrombocytopenia in patients with chronic liver disease
Studies:	104 Weeks of Carcinogenicity Studies in Rats and Mice
Applicant:	Sponsor: Shionogi Inc 300 Campus Dr Florham Park, New Jersey 07932 United States Testing Facility: (b) (4)
Review Priority:	Standard
Biometrics Division:	Division of Biometrics - VI
Statistical Reviewer:	Hepei Chen
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Hematology, Oncology, Toxicology
Reviewing Pharmacologist:	Emily Place, Ph.D.
Keywords:	Carcinogenicity, Dose response

Table of Contents

1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were to assess the carcinogenic potential of S-888711 when administered orally by gavage to rats and mice for 104 weeks.

In this review the phrase "dose response relationship" refers to the linear component (trend) of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

2. Rat Study

Two separate experiments, one in male rats and one in female rats were conducted. As indicated in Table 1, in each of these two experiments there were three treated groups, one water control group, and one vehicle control group. Three hundred twenty five Crl:CD (SD) rats of each sex were assigned randomly in size of 65 rats per group. The dose levels for the three treated groups were 2, 6, and 20 mg/kg/day for male rats, and 0.5, 1, and 2 mg/kg/day for female rats, respectively. In this review these dose groups were referred to as the low (Group 3), mid (Group 4), and high (Group 5) dose groups, respectively. The rats in the water control group and the vehicle control groups were administrated with water and the vehicle [100% Polyethylene glycol 400], and handled for the same duration and in the same manner as the treated groups.

Table 1: Experimental Design in Rat Study

Group No.	No. of Animals		Test Material	Dosage Level (mg/kg/day)	
	Male	Female		Male	Female
1	65	65	Water Control	0	0
2	65	65	Vehicle Control	0	0
3	65	65	S-888711 Low	2	0.5
4	65	65	S-888711 Mid	6	1
5	65	65	S-888711 High	20	2

Animals were inspected visually at least twice daily for evidence of ill-health or reaction to treatment. Daily during the first week of treatment, twice weekly during Weeks 2 to 4 (middle and end of each week), weekly during Weeks 5 to 13, once every two weeks during Weeks 14 to 52 and once every four weeks thereafter, detailed observations were recorded. In conjunction with the weekly physical examination, palpation was performed on all animals. Debilitated animals were observed carefully and, where necessary, isolated to prevent cannibalism. All animals were subject to a detailed necropsy. After a review of the history of each animal, a full macroscopic examination of the tissues was performed. All external features and orifices were examined visually.

2.1. Sponsor's analyses

2.1.1. Survival analysis

In the sponsor’s analysis, the numbers of animal deaths during the study, up to terminal sacrifice, were analyzed by logrank tests for a trend across the groups. The numbers of animal deaths during the study were presented as life-tables and Kaplan-Meier survival curves. The following statistical tests were carried out:

1) a two-tailed test for a trend with dose levels including Groups 2, 3, 4 and 5.

2) a two-tailed pairwise comparison test of each treatment group against the vehicle control group.
3) a two-tailed pairwise comparison test of the water control group against the vehicle control group.

Where the test for trend was statistically significant, the highest dose group was excluded and the trend test repeated (using a one-tailed test), until the test was no longer statistically significant. As a check, tests for non-linearity (not presented) were carried out. In this study, the non-linearity tests were not statistically significant at the 1% level and thus the results of the trend tests are to be preferred. Significance levels were calculated using $\chi 2$ tests and adjusted with a continuity correction where there was only one degree of freedom. These p-values have been quoted in the logrank results tables.

Sponsor's findings:

The sponsor's analysis showed that the numbers of rats surviving to their terminal necropsy were 24 (37%), 29 (45%), 26 (40%), 30 (46%), and 29 (45%) in Groups 1, 2, 3, 4, and 5 for male rats, respectively, and 29 (45%), 15 (38%), 20 (31%), 17 (27%), and 18 (28%) for female rats respectively. The trend test was not statistically significant when Groups 2, 3, 4 and 5 were included in the analysis. None of the pairwise comparisons were statistically significant for both male and female rats.

2.1.2. Tumor data analysis

In the sponsor's analysis, all animals that died after terminal sacrifice commenced (Week 105) were considered terminal and the tumors observed in these animals were categorized as incidental. For incidental tumors, the following fixed time intervals were used to adjust for differential mortality between the treatment groups: 1-52, 53-78, 79-92, 93-104 weeks and terminal. Time-to-tumor log-rank analysis Log-rank methods were used to analyze the number of animals with tumors across treatment groups (Peto et al 1980). The log-rank analysis results tables show the total observed and expected number of tumors and the relative tumor rate across all time intervals. The observed and the expected frequencies were calculated for each time interval under a hypothesis of no difference between treatment groups. The observed and expected frequencies were then compared across the treatment groups. The following $\chi 2$ statistical tests were carried out:
1) a one-tailed test for a trend using dose levels including Groups 2, 3, 4 and 5
2) a one-tailed pairwise comparison test of each treatment group against the vehicle control group
3) a two-tailed pairwise comparison test of the water control group against the vehicle control group

Where the test for trend was statistically significant, the highest dose group was excluded and the trend test was repeated, using a one-tailed test until the test was no longer statistically significant. The significance levels were adjusted using a continuity correction where there was one degree of freedom. As a check, tests for non-linearity were carried out (not presented). For benign haemangioma (mesenteric lymph node) in males the non-linearity test was significant (p=0.005), therefore the pairwise tests are to be preferred to the trend test. For all other analyses the non-linearity tests were not statistically significant at the 1% level, hence the trend tests are to be preferred.

Where there were fewer than ten observed tumors, exact one-tailed p-values were calculated using permutation tests for stratified contingency tables, to test for trend and for pairwise comparisons of each treatment group against the control group (SAS Institute Inc., 2002). All p-values are quoted in the time-to-tumor tables of results.

Adjustment for multiple testing:

In the sponsor's report, the rules of summarizing the results described in Lin (Lin, 2000) were adopted. These rules require an initial designation of tumor-types into "common" or "rare".

1) Tumors with an historical frequency greater than 1%, were designated as being "common". A significance level of 0.005 was used for the trend tests, and 0.01 for each pairwise test.
2) Tumors with an historical frequency less than or equal to 1% were designated as being "rare". A significance level of 0.025 was used for the trend tests, and 0.05 for each pairwise test.

The classification of tumors was carried out based upon the overall incidence in historical control data. The following list of statistically analyzed tumors was considered to be "rare" tumors, all other tumors in this report were considered to be "common" tumors.

Males
Lungs/bronchi - Benign bronchioloalveolar adenoma
Kidneys - Benign renal lipoma
Kidneys - Benign tubular adenoma and malignant tubular carcinoma combined
Skin - Malignant haemangiosarcoma
Skin - Malignant fibrous histiocytoma
Brain - Malignant meningeal sarcoma
Haematopoietic tumor - Malignant large granular cell lymphoma

Females
Kidneys - Malignant nephroblastoma
Thyroids - Malignant C-cell carcinoma
Thyroids - Benign follicular cell adenoma
Thyroids - Benign follicular cell adenoma and malignant follicular cell carcinoma combined
Mammary areas - Benign fibroma
Mammary areas - Benign fibroma and malignant fibrosarcoma combined
Skin - Benign squamous cell papilloma
Skeletal muscle - Benign fibroma and malignant fibrosarcoma combined
Brain - Malignant astrocytoma
Haematopoietic tumor - Malignant histiocytic sarcoma

Sponsor's findings:

In the sponsor's report, there were no statistically significant tumor findings for both male and female rats.

2.2. Reviewer's analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing toxicologist, this reviewer independently performed the survival and tumor data analyses using the data provided by the sponsor electronically.

2.2.1. Survival analysis

In the reviewer's analysis, the survival distributions of rats in all five groups (Groups 1, 2, 3, 4, and 5) were estimated using the Kaplan-Meier product limit method. The dose response relationship was tested across Groups 2, 3, 4, and 5 using the likelihood ratio test, and the homogeneity of survival distributions was tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for all five groups in male and female rats, respectively. The intercurrent mortality data of all five groups and the results of the tests for dose response relationship and homogeneity of survivals for Groups 2, 3, 4, and 5 are given in Tables 1A and 1B in the appendix for male and female rats, respectively.

Reviewer's findings:

The reviewer's analysis showed that the numbers of rats surviving to their terminal necropsy were 24 (37%), 29 (45%), 26 (40%), 30 (46%), and 29 (45%) in Groups 1, 2, 3, 4, and 5 for male rats, respectively, and 29 (45%), 15 (38%), 20 (31%), 17 (27%), and 18 (28%) for female rats respectively. No statistically significant dose response relationship and pairwise comparisons in mortality was noted for both male and female rats.

Comment: There are 8 male rats in the study that died naturally but without information for their death time. These animals are #133 in vehicle control group; #196 in the low dose group, #277 in the high dose group, and #10, #16, #18, #35, and #42 in the water control group; whereas there are 2 female rats that died naturally but without information for their death time. These animals are #659 in the high dose group, and #341 in the water control group.

2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships across Groups 2, 3, 4, and 5, and pairwise comparisons of each of the three treated groups (Groups 3, 4, and 5) against the vehicle control group (Group 2), using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993).

In the ploy-k method, the adjustment for differences in mortality among treatment groups is made by modifying the number of animals at risk in the denominators in the calculations of overall tumor rates in the Cochran-Armitage test to reflect less-than-whole-animal contributions for animals that die without tumor before the end of the study (Bailer and Portier 1988). The modification is made by defining a new number of animals at risk for each treatment group. The number of animals at risk for the *i*-th treatment group R^* i is defined as $R^*_i = \sum W_{ij}$ where w_{ij} is the weight for the *j*-th animal in the *i*-th treatment group, and the sum is over all animals in the group.

Bailer and Portier (1988) proposed the weight w_{ij} as follows:

$w_{ij} = 1$ to animals dying with the tumor, and

$w_{ij} = (t_{ij} / tsacr)^3$ to animals dying without the tumor,

where t_{ij} is the time of death of the *j*-th animal in the *i*-th treatment group, and tsacr is the planned (or intended) time of terminal sacrifice. The above formulas imply that animals living up to the end of the planned terminal sacrifice date without developing any tumor will also be

assigned w*ij* =1 since t*ij* = tsacr. Also animals developed the tumor type being tested before the end of the study will be assigned as w*ij* = 1.

Certain treatment groups of a study or the entire study may be terminated earlier than the planned (or intended) time of terminal sacrifice due to excessive mortalities. However, based on the principle of the Intention-to-treat (ITT) analysis in randomized trials, the tsacr should not be affected by the unplanned early terminations. The tsacr should always be equal to the planned (or intended) time of terminal sacrifice. For those animals that were sacrificed later than tsacr, regardless their actual terminal sacrifice time, tsacr was used as their time of terminal sacrifice in the analysis.

One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data.

Multiple testing adjustment:

For the adjustment of multiple testing, this reviewer used the methodologies suggested in the FDA guidance for statistical design and analysis of carcinogenicity studies (2001). For dose response relationship tests, the guidance suggests the use of test levels of α=0.005 for common tumors and α=0.025 for rare tumors for a submission with two species where both are two-years studies, in order to keep the false-positive rate at the nominal level of approximately 10%. For multiple pairwise comparisons of treated group with control, the guidance suggests the use of test levels of α=0.01 for common tumors and α=0.05 for rare tumors, in order to keep the false-positive rate at the nominal level of approximately 10% for both submissions with two or one species.

Reviewer's findings:

The tumor rates and the p-values of the tested tumor types are listed in Tables 2A and 2B in the appendix for male and female rats, respectively. The tumor types with p-values less than or equal to 0.05 for dose response relationship and/or pairwise comparisons of treated groups and vehicle control are reported in Table 2.

Based on the criteria of adjustment for multiple testing discussed above, the reviewer's analysis showed statistically significant increases for the incidence of haemangioma in ln mesenteric in male rats when comparing the mid dose group to the vehicle control group (p-value=0.0084), and the incidence of combined endometrial adenoma and polyp in uterus in female rats when comparing the low dose group to the vehicle control group (p-value=0.0099), regardless the common or rare classification of these tumors. No corresponding statistically significant dose response relationship was noted for these tumors.

No other statistically significant findings were noted in tumor data for both male and female rats.

Table 2. Summary Table of Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship and/or Pairwise Comparisons of Treated Groups and Vehicle Control Group in Rats

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 2 mg P - VC vs. L	Mid (M) 6 mg P - VC vs. M	High (H) 20 mg P - VC vs. H	Water (WC) 0 mg P - VC vs. WC
Male						
Ln Mesenteric	Haemangioma	0/64 (48)	0/65 (43)	7/65 (52)	3/65 (48)	3/64 (41)
		0.1102	NC	0.0084 $	0.1211	0.0939
Skin	Fibroma	14/65 (50)	12/65 (45)	8/65 (51)	13/65 (49)	5/65 (44)
		0.5004	0.6457	0.9597	0.6513	0.9894
	Fibrosarcoma	1/65 (49)	3/65 (45)	1/65 (49)	1/65 (47)	0/65 (42)
		0.6977	0.2769	NC	0.7421	1.0000
	Fibroma/Fibrosarcoma	14/65 (50)	15/65 (46)	9/65 (51)	13/65 (49)	5/65 (44)
		0.6065	0.3937	0.8421	0.4754	0.0388 @
Thyroids	C-Cell Adenoma	7/65 (49)	2/65 (44)	7/65 (50)	2/65 (47)	0/65 (42)
		0.9052	0.9772	0.6287	0.9821	1.0000
	C-Cell Carcinoma	0/65 (48)	1/65 (43)	0/65 (49)	0/65 (47)	0/65 (42)
		0.7433	0.4725	NC	NC	NC
	C-Cell Adenoma/ C-Cell Carcinoma	7/65 (49)	3/65 (44)	7/65 (50)	2/65 (47)	0/65 (42)
		0.9162	0.7942	0.4029	0.9104	0.0106 @
Female						
Uterus	Endometrial Adenoma	0/65 (44)	1/65 (43)	0/65 (44)	0/65 (43)	0/65 (47)
		0.7471	0.4943	NC	NC	NC
	Endometrial Polyp	2/65 (44)	10/65 (47)	4/65 (46)	6/65 (44)	6/65 (47)
		0.3066	0.0181 @	0.3599	0.1329	0.1558
	Endometrial Adenoma/ Endometrial Polyp	2/65 (44)	11/65 (47)	4/65 (46)	6/65 (44)	6/65 (47)
		0.3501	0.0099 $	0.3599	0.1329	0.8442

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
$ = Statistically significant in common tumor at 0.01 level and rare tumor at 0.05 level for test of pairwise comparisons;
@ = Not statistically significant in common tumor at 0.01 level and rare tumor at 0.05 level for test of pairwise comparisons;
NC = Not calculable.

3. Mouse Study

Two separate experiments, one in male mice and one in female mice were conducted. As indicated in Table 3, in each of these two experiments there were three treated groups, one water control group, and one vehicle control group. Three hundred Crl:CD1(ICR) mice of each sex were assigned randomly in size of 60 mice per group. The dose levels for the three treated groups were 2, 6, and 20 mg/kg/day for both male and female mice. In this review these dose groups were referred to as the low (Group 3), mid (Group 4), and high (Group 5) dose groups, respectively. The mice in the water control group and the vehicle control group were administrated with water and the vehicle [100% Polyethylene glycol 400], and handled for the same duration and in the same manner as the treated groups.

Animals were inspected visually at least twice daily for evidence of ill-health or reaction to treatment. Daily during the first week of treatment, twice weekly during Weeks 2 to 4 (middle and end of each week), weekly during Weeks 5 to 13, once every two weeks during Weeks 14 to 52 and once every four weeks thereafter, detailed observations were recorded. In conjunction with the weekly physical examination, palpation was performed on all animals. Debilitated animals were observed carefully and, where necessary, isolated to prevent cannibalism. All

animals were subject to a detailed necropsy. After a review of the history of each animal, a full macroscopic examination of the tissues was performed. All external features and orifices were examined visually.

Table 3. Experimental Design in Mouse Study

Group No.	No. of Animals		Test Material	Dosage Level (mg/kg/day)	
	Male	Female		Male	Female
1	60	60	Water Control	0	0
2	60	60	Vehicle Control	0	0
3	60	60	S-888711 Low	2	2
4	60	60	S-888711 Mid	6	6
5	60	60	S-888711 High	20	20

3.1. Sponsor's analyses

3.1.1. Survival analysis

The sponsor used similar methodologies to analyze the mouse survival data as those used to analyze the rat survival data.

Sponsor’s findings:

The sponsor’s analysis showed that the numbers of mice surviving to their terminal necropsy were 33 (55%), 31 (52%), 34 (57%), 27 (45%), and 34 (57%) in Groups 1, 2, 3, 4, and 5 for male mice, respectively, and 22 (37%), 27 (45%), 28 (47%), 26 (43%), and 20 (33%) for female mice respectively. There were no statistically significant findings in mortality for both male or female mice.

3.1.2. Tumor data analysis

The sponsor used similar methodologies to analyze the mouse tumor data as those used to analyze the rat tumor data.

Multiple testing adjustment:

The sponsor used similar criteria to adjust the multiple testing for the mouse tumor results as those used to adjust for the rat tumor results.

Sponsor’s findings:

Sponsor’s analysis showed no statistically significant tumor findings in male and female mice.

3.2. Reviewer's analyses

Similar to the rat study, this reviewer independently performed survival and tumor data analyses of mouse data to verify sponsor’s analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

For the analysis of both the survival data and the tumor data in mice, this reviewer used similar methodologies that were used for the analyses of the rat survival and tumor data.

3.2.1. Survival analysis

The Kaplan-Meier curves for survival rates of all treatment groups are given in Figures 2A and 2B in the appendix for male and female mice, respectively. The intercurrent mortality data, and the results of the tests for dose response relationship and homogeneity of survivals for the combined vehicle control, low, mid, and high dose groups were given in Tables 3A and 3B in the appendix for male and female mice, respectively.

Reviewer's findings:

The reviewer's analysis showed that the numbers of mice surviving to their terminal necropsy were 33 (55%), 31 (52%), 34 (57%), 27 (45%), and 34 (57%) in Groups 1, 2, 3, 4, and 5 for male mice, respectively, and 22 (37%), 27 (45%), 28 (47%), 26 (43%), and 20 (33%) for female mice respectively. No statistically significant findings in mortality were noted for both male and female mice.

3.2.2. Tumor data analysis

Reviewer's findings:

The tumor rates and the p-values of the tested tumor types are listed in Tables 4A and Table 4B in the appendix for male and female mice, respectively. The tumor types with p-values less than or equal to 0.05 for dose response relationship and/or pairwise comparisons of treated groups and vehicle control are reported in Table 4.

Table 4. Summary Table of Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship and/or Pairwise Comparisons of Treated Groups and Vehicle Control Group in Mice

Organ name	Tumor name	Vehicle(VC) 0 mg P - Trend	Low (L) 2 mg P - VC vs. L	Mid (M) 6 mg P - VC vs. M	High (H) 20 mg P - VC vs. H	Water (WC) 0 mg P - VC vs. WC
Male						
Adrenals	Subcapsular Cell Adenoma	1/60 (45) 0.0075 @	5/58 (45) 0.1014	2/59 (44) 0.4915	9/59 (47) 0.0092 $	6/60 (47) 0.0623
Testes	Interstitial Cell (Leydig) Adenoma	4/60 (45) 0.0352 @	1/60 (47) 0.9752	2/60 (44) 0.8935	7/60 (47) 0.2871	1/60 (46) 0.9737
Female						
H-Poietic Tumor	Malignant Lymphoma	17/60 (50) 0.8377	26/60 (47) 0.0280 @	19/60 (47) 0.3284	16/60 (47) 0.5828	19/60 (49) 0.3879

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
$ = Statistically significant in common tumor at 0.01 level for test of pairwise comparisons;
@ = Not statistically significant in common tumor at 0.005 level for test of dose response relationship, and 0.01 level for test of pairwise comparisons;
NC = Not calculable.

Based on the criteria of adjustment for multiple testing discussed above, for male mice, the reviewer's analysis showed a statistically significant increase for the incidence of subcapsular cell adenoma in adrenals in the high dose group when compared to the vehicle control group (p-value=0.0092), regardless whether the tumor is considered to be rare or common. No corresponding statistically significant dose response relationship was noted for this tumor.

No other statistically significant findings were noted in tumor data for both male and female mice.

4. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were to assess the carcinogenic potential of S-888711 when administered orally by gavage to rats and mice for 104 weeks.

Rat Study:

Two separate experiments, one in male rats and one in female rats were conducted. In each of these two experiments there were three treated groups, one water control group, and one vehicle control group. Three hundred twenty five Crl:CD (SD) rats of each sex were assigned randomly in size of 65 rats per group. The dose levels for the three treated groups were 2, 6, and 20 mg/kg/day for male rats, and 0.5, 1, and 2 mg/kg/day for female rats, respectively.

The reviewer's analysis showed that the numbers of rats surviving to their terminal necropsy were 24 (37%), 29 (45%), 26 (40%), 30 (46%), and 29 (45%) in Groups 1, 2, 3, 4, and 5 for male rats, respectively, and 29 (45%), 15 (38%), 20 (31%), 17 (27%), and 18 (28%) for female rats respectively. No statistically significant dose response relationship and pairwise comparisons in mortality was noted for both male and female rats.

Based on the criteria of adjustment for multiple testing discussed above, the reviewer's analysis showed statistically significant increases for the incidence of haemangioma in ln mesenteric in male rats when comparing the mid dose group to the vehicle control group (p-value=0.0084), and the incidence of combined endometrial adenoma and polyp in uterus in female rats when comparing the low dose group to the vehicle control group (p-value=0.0099), regardless the common or rare classification of these tumors. No corresponding statistically significant dose response relationship was noted for these tumors. No other statistically significant findings were noted in tumor data for both male and female rats.

Mouse Study:

Two separate experiments, one in male mice and one in female mice were conducted. In each of these two experiments there were three treated groups, one water control group, and one vehicle control group. Three hundred Crl:CD1(ICR) mice of each sex were assigned randomly in size of 60 mice per group. The dose levels for the three treated groups were 2, 6, and 20 mg/kg/day for both male and female mice.

The reviewer's analysis showed that the numbers of mice surviving to their terminal necropsy were 33 (55%), 31 (52%), 34 (57%), 27 (45%), and 34 (57%) in Groups 1, 2, 3, 4, and 5 for male mice, respectively, and 22 (37%), 27 (45%), 28 (47%), 26 (43%), and 20 (33%) for female mice respectively. No statistically significant findings in mortality were noted for both male and female mice.

Based on the criteria of adjustment for multiple testing discussed above, for male mice, the reviewer's analysis showed a statistically significant increase for the incidence of subcapsular cell adenoma in adrenals in the high dose group when compared to the vehicle control group (p-value=0.0092), regardless whether the tumor is considered to be rare or common. No

corresponding statistically significant dose response relationship was noted for this tumor. No other statistically significant findings were noted in tumor data for both male and female mice.

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5. Appendix

Table 1A: Intercurrent Mortality Rate in Male Rats

	Vehicle Control		Low		Mid		High		Water Control	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	2	3.08	5	7.69	1	1.54	6	9.23	6	9.23
53 - 78	7	13.85	11	24.62	10	16.92	8	21.54	8	21.54
79 - 91	15	36.92	11	41.54	11	33.85	11	38.46	13	41.54
92 - 104	10	52.31	11	58.46	13	53.85	10	53.85	9	55.38
Accidental Death	1	1.54								
Other[a]	1	1.54	1	1.54			1	1.54	5	7.69
Terminal sacrifice	29	44.62	26	40.00	30	46.15	29	44.62	24	36.92
Total	65		65		65		65		65	

[a] Animals died naturally but missing information for death time: #133 in vehicle control group; #196 in the low dose group, #277 in the high dose group, and #10, #16, #18, #35, and #42 in the water control group.

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High
Dose-Response (Likelihood Ratio)	0.7243	0.6114	0.4958	0.8576
Homogeneity (Log-Rank)	0.7932	0.6062	0.4944	0.8568

Table 1B: Intercurrent Mortality Rate in Female Rats

	Vehicle Control		Low		Mid		High		Water Control	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	1	1.54	2	3.08	3	4.62	4	6.15	2	3.08
53 - 78	17	27.69	12	21.54	11	21.54	11	23.08	12	21.54
79 - 91	12	46.15	17	47.69	16	46.15	14	44.62	8	33.85
92 - 104	9	60.00	14	69.23	18	73.85	16	69.23	12	52.31
Accidental Death	1	1.54					1	1.54	1	1.54
Other [a]							1	1.54	1	1.54
Terminal sacrifice	25	38.46	20	30.77	17	26.15	18	27.69	29	44.62
Total	65		65		65		65		65	

[a] Animals died naturally but missing information for death time: #659 in the high dose group, and #341 in the water control group.

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High
Dose-Response (Likelihood Ratio)	0.1007	0.1687	0.0941	0.1208
Homogeneity (Log-Rank)	0.2161	0.1583	0.0853	0.1116

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 2 mg P - VC vs. L	Mid (M) 6 mg P - VC vs. M	High (H) 20 mg P - VC vs. H	Water (WC) 0 mg P - VC vs. WC
Adipose Tissue	Fibroma	1/65 (49)	0/65 (43)	0/65 (49)	0/65 (47)	0/65 (42)
		1.0000	1.0000	1.0000	1.0000	1.0000
	Haemangiosarcoma	0/65 (48)	1/65 (44)	0/65 (49)	0/65 (47)	0/65 (42)
		0.7447	0.4783	NC	NC	NC
	Mesothelioma	1/65 (49)	0/65 (43)	0/65 (49)	0/65 (47)	0/65 (42)
		1.0000	1.0000	1.0000	1.0000	1.0000
Adrenals	Cortical Adenoma	0/65 (48)	1/65 (43)	2/65 (50)	0/65 (47)	1/65 (42)
		0.6467	0.4725	0.2577	NC	0.4667
	Malignant Phaeochromocytoma	1/65 (48)	2/65 (43)	3/65 (50)	2/65 (47)	2/65 (42)
		0.3919	0.4584	0.3242	0.4920	0.4495
	Phaeochromocytoma	12/65 (50)	9/65 (45)	7/65 (50)	7/65 (47)	4/65 (42)
		0.8511	0.7625	0.9376	0.9178	0.9842
Bone	Giant Cell Tumor	0/65 (48)	0/65 (43)	0/65 (49)	1/65 (48)	0/65 (42)
		0.2553	NC	NC	0.5000	NC
	Osteoma	1/65 (49)	0/65 (43)	0/65 (49)	0/65 (47)	0/65 (42)
		1.0000	1.0000	1.0000	1.0000	1.0000
Brain	Astrocytoma	0/65 (48)	2/65 (44)	3/65 (50)	1/65 (47)	0/65 (42)
		0.4945	0.2260	0.1289	0.4947	NC
	Granular Cell Tumor	2/65 (49)	2/65 (43)	0/65 (49)	2/65 (47)	1/65 (42)
		0.4663	0.6406	1.0000	0.6756	0.8483
	Malignant Reticulosis	0/65 (48)	0/65 (43)	0/65 (49)	1/65 (47)	0/65 (42)
		0.2513	NC	NC	0.4947	NC
	Meningeal Sarcoma	0/65 (48)	1/65 (44)	0/65 (49)	1/65 (47)	0/65 (42)
		0.3102	0.4783	NC	0.4947	NC
	Oligodendroglioma	0/65 (48)	0/65 (43)	0/65 (49)	1/65 (47)	0/65 (42)
		0.2513	NC	NC	0.4947	NC
Epididymides	Mesothelioma	0/65 (48)	0/65 (43)	0/65 (49)	1/65 (47)	0/65 (42)
		0.2513	NC	NC	0.4947	NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 2 mg P - VC vs. L	Mid (M) 6 mg P - VC vs. M	High (H) 20 mg P - VC vs. H	Water (WC) 0 mg P - VC vs. WC
H-Poietic Tumor	Histiocytic Sarcoma	0/65 (48)	0/65 (43)	3/65 (50)	1/65 (47)	1/65 (42)
		0.2788	NC	0.1289	0.4947	0.4667
	Large Granular Cell Lymphoma	0/65 (48)	2/65 (44)	0/65 (49)	1/65 (47)	1/65 (42)
		0.4407	0.2260	NC	0.4947	0.4667
	Malignant Lymphoma	1/65 (48)	0/65 (43)	0/65 (49)	0/65 (47)	2/65 (43)
		1.0000	1.0000	1.0000	1.0000	0.4584
	Myeloid Cell Leukaemia	1/65 (49)	0/65 (43)	0/65 (49)	1/65 (47)	0/65 (42)
		0.4385	1.0000	1.0000	0.7421	1.0000
Head	Squamous Cell Carcinoma	1/65 (49)	1/65 (44)	0/65 (49)	0/65 (47)	0/65 (42)
		0.9338	0.7251	1.0000	1.0000	1.0000
Heart	Atriocaval Mesothelioma	0/65 (48)	1/65 (43)	0/65 (49)	0/65 (47)	0/65 (42)
		0.7433	0.4725	NC	NC	NC
Jejunum	Haemangiosarcoma	1/62 (48)	0/62 (42)	0/64 (49)	0/64 (46)	0/56 (39)
		1.0000	1.0000	1.0000	1.0000	1.0000
	Leiomyosarcoma	1/62 (47)	0/62 (42)	0/64 (49)	0/64 (46)	0/56 (39)
		1.0000	1.0000	1.0000	1.0000	1.0000
Kidneys	Renal Lipoma	2/65 (49)	1/65 (43)	0/65 (49)	1/65 (47)	1/65 (42)
		0.6740	0.8533	1.0000	0.8711	0.8483
	Tubular Adenoma	0/65 (48)	0/65 (43)	0/65 (49)	1/65 (47)	1/65 (42)
		0.2513	NC	NC	0.4947	0.4667
	Tubular Carcinoma	0/65 (48)	0/65 (43)	1/65 (50)	0/65 (47)	0/65 (42)
		0.5160	NC	0.5102	NC	NC
	Tubular Adenoma/ Tubular Carcinoma	0/65 (48)	0/65 (43)	1/65 (50)	1/65 (47)	1/65 (42)
		0.1952	NC	0.5102	0.4947	0.5333
Liver	Hepatocellular Adenoma	2/65 (48)	0/65 (43)	0/65 (49)	0/65 (47)	0/65 (42)
		1.0000	1.0000	1.0000	1.0000	1.0000
	Hepatocellular Carcinoma	0/65 (48)	1/65 (44)	0/65 (49)	0/65 (47)	0/65 (42)
		0.7447	0.4783	NC	NC	NC
	Hepatocellular Adenoma/ Hepatocellular Carcinoma	2/65 (48)	1/65 (44)	0/65 (49)	0/65 (47)	0/65 (42)
		0.9386	0.4670	0.7577	0.7474	0.2816
Ln Mesenteric	Haemangioma	0/64 (48)	0/65 (43)	7/65 (52)	3/65 (48)	3/64 (41)
		0.1102	NC	0.0084 $	0.1211	0.0939
Lungs + Bronchi	Bronchioloalveolar Adenoma	1/65 (48)	0/65 (43)	1/65 (49)	1/65 (47)	1/65 (42)
		0.4032	1.0000	0.7577	0.7474	0.7184

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 2 mg P - VC vs. L	Mid (M) 6 mg P - VC vs. M	High (H) 20 mg P - VC vs. H	Water (WC) 0 mg P - VC vs. WC
Mammary	Mammary Adenocarcinoma	1/65 (49)	0/65 (43)	1/65 (50)	0/64 (46)	1/65 (42)
		0.7619	1.0000	0.7576	1.0000	0.7128
	Mammary Adenoma	1/65 (48)	0/65 (43)	0/65 (49)	0/64 (46)	0/65 (42)
		1.0000	1.0000	1.0000	1.0000	1.0000
	Mammary Adenocarcinoma/ Mammary Adenoma	2/65 (49)	0/65 (43)	1/65 (50)	0/64 (46)	1/65 (42)
		0.8308	0.7191	0.5077	0.7366	0.5582
	Mammary Fibroadenoma	1/65 (48)	0/65 (43)	1/65 (50)	0/64 (46)	1/65 (42)
		0.7645	1.0000	0.7627	1.0000	0.7184
Mandibular S.G.	Adenocarcinoma	1/65 (49)	0/65 (43)	0/65 (49)	0/65 (47)	0/65 (42)
		1.0000	1.0000	1.0000	1.0000	1.0000
Nasal Turbinates	Squamous Cell Carcinoma	1/65 (49)	0/65 (43)	0/65 (49)	0/65 (47)	0/65 (42)
		1.0000	1.0000	1.0000	1.0000	1.0000
Pancreas	Acinar Cell Adenoma	3/65 (48)	0/65 (43)	2/65 (50)	1/65 (47)	2/64 (42)
		0.7088	1.0000	0.8315	0.9389	0.7751
	Islet Cell Adenoma	9/65 (50)	8/65 (44)	12/65 (51)	11/65 (48)	8/64 (44)
		0.2719	0.5953	0.3307	0.3620	0.5953
	Islet Cell Carcinoma	0/65 (48)	1/65 (44)	0/65 (49)	1/65 (47)	0/64 (42)
		0.3102	0.4783	NC	0.4947	NC
	Islet Cell Adenoma/ Islet Cell Carcinoma	9/65 (50)	9/65 (45)	12/65 (51)	12/65 (48)	8/64 (44)
		0.2134	0.5043	0.3307	0.2751	0.4047
Pituitary	Adenoma, Pars Distalis	19/64 (53)	15/62 (47)	30/65 (59)	25/65 (53)	26/64 (49)
		0.0880	0.7339	0.0795	0.1622	0.0605
Preputial Glands	Squamous Cell Papilloma	0/65 (48)	1/65 (43)	0/65 (49)	0/65 (47)	0/65 (42)
		0.7433	0.4725	NC	NC	NC
Prostate	Adenocarcinoma	0/65 (48)	0/65 (43)	0/65 (49)	1/65 (47)	1/65 (43)
		0.2513	NC	NC	0.4947	0.4725
Skeletal Muscle	Fibroma	1/65 (48)	0/65 (43)	1/65 (49)	0/65 (47)	0/65 (42)
		0.7645	1.0000	0.7577	1.0000	1.0000
	Haemangiosarcoma	0/65 (48)	0/65 (43)	1/65 (49)	0/65 (47)	1/65 (42)
		0.5134	NC	0.5052	NC	0.4667
	Lipoma	0/65 (48)	0/65 (43)	1/65 (49)	0/65 (47)	0/65 (42)
		0.5134	NC	0.5052	NC	NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 2 mg P - VC vs. L	Mid (M) 6 mg P - VC vs. M	High (H) 20 mg P - VC vs. H	Water (WC) 0 mg P - VC vs. WC
Skin	Basal Cell Carcinoma	0/65 (48)	1/65 (43)	0/65 (49)	0/65 (47)	1/65 (42)
		0.7433	0.4725	NC	NC	0.4667
	Basal Cell Tumor	2/65 (49)	0/65 (43)	0/65 (49)	1/65 (47)	0/65 (42)
		0.5804	1.0000	1.0000	0.8711	1.0000
	Basal Cell Carcinoma/ Basal Cell Tumor	2/65 (49)	1/65 (43)	0/65 (49)	1/65 (47)	1/65 (42)
		0.6269	0.4506	0.7526	0.4842	0.5582
	Fibroma	14/65 (50)	12/65 (45)	8/65 (51)	13/65 (49)	5/65 (44)
		0.5004	0.6457	0.9597	0.6513	0.9894
	Fibrosarcoma	1/65 (49)	3/65 (45)	1/65 (49)	1/65 (47)	0/65 (42)
		0.6977	0.2769	NC	0.7421	1.0000
	Fibroma/Fibrosarcoma	14/65 (50)	15/65 (46)	9/65 (51)	13/65 (49)	5/65 (44)
		0.6065	0.3937	0.8421	0.4754	0.0388
	Fibrous Histiocytoma	0/65 (48)	0/65 (43)	2/65 (50)	0/65 (47)	0/65 (42)
		0.5082	NC	0.2577	NC	NC
	Haemangiosarcoma	0/65 (48)	0/65 (43)	2/65 (51)	0/65 (47)	1/65 (42)
		0.5083	NC	0.2628	NC	0.4667
	Lipofibroma	0/65 (48)	0/65 (43)	1/65 (50)	0/65 (47)	0/65 (42)
		0.5160	NC	0.5102	NC	NC
	Lipoma	1/65 (48)	1/65 (43)	1/65 (49)	0/65 (47)	3/65 (43)
		0.8352	0.7245	0.7577	1.0000	0.2678
	Liposarcoma	0/65 (48)	0/65 (43)	0/65 (49)	1/65 (47)	0/65 (42)
		0.2513	NC	NC	0.4947	NC
	Lipoma/Liposarcoma	1/65 (48)	1/65 (43)	1/65 (49)	1/65 (47)	3/65 (43)
		0.4245	0.7245	0.2526	0.7474	0.7322
	Myxoma	0/65 (48)	0/65 (43)	0/65 (49)	0/65 (47)	1/65 (42)
		NC	NC	NC	NC	0.4667
	Myxosarcoma	0/65 (48)	0/65 (43)	0/65 (49)	1/65 (47)	0/65 (42)
		0.2513	NC	NC	0.4947	NC
	Myxoma/Myxosarcoma	0/65 (48)	0/65 (43)	0/65 (49)	1/65 (47)	1/65 (42)
		0.2513	NC	NC	0.4947	0.5333
	Sarcoma Nos	0/65 (48)	1/65 (44)	0/65 (49)	0/65 (47)	0/65 (42)
		0.7447	0.4783	NC	NC	NC
	Sebaceous Cell Adenoma	0/65 (48)	0/65 (43)	0/65 (49)	0/65 (47)	1/65 (42)
		NC	NC	NC	NC	0.4667
	Keratoacanthoma	1/65 (49)	1/65 (43)	2/65 (49)	0/65 (47)	1/65 (42)
		0.7950	0.7191	0.5000	1.0000	0.7128
	Squamous Cell Carcinoma	0/65 (48)	1/65 (43)	0/65 (49)	0/65 (47)	0/65 (42)
		0.7433	0.4725	NC	NC	NC
	Squamous Cell Papilloma	1/65 (49)	2/65 (44)	2/65 (50)	0/65 (47)	1/65 (43)
		0.8549	0.4593	0.5077	1.0000	0.7191
	Keratoacanthoma/ Squamous Cell Carcinoma/ Squamous Cell Papilloma	2/47 (65)	4/40 (65)	4/46 (65)	0/47 (65)	2/41 (65)
		0.9473	0.2885	0.3485	0.7421	0.3594

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 2 mg P - VC vs. L	Mid (M) 6 mg P - VC vs. M	High (H) 20 mg P - VC vs. H	Water (WC) 0 mg P - VC vs. WC
Spinal C. Cerv.	Astrocytoma	0/65 (48)	0/65 (43)	0/65 (49)	0/65 (47)	1/65 (42)
		NC	NC	NC	NC	0.4667
Spinal C. Lumb.	Haemangioma	0/65 (48)	0/65 (43)	1/65 (50)	0/65 (47)	0/65 (42)
		0.5160	NC	0.5102	NC	NC
Spleen	Haemangioma	0/65 (48)	0/65 (43)	1/65 (49)	0/65 (47)	0/65 (42)
		0.5134	NC	0.5052	NC	NC
Stomach	Fibrosarcoma	0/65 (48)	1/65 (43)	0/65 (49)	0/65 (47)	0/65 (42)
		0.7433	0.4725	NC	NC	NC
Tail	Sarcoma Nos	0/65 (48)	0/65 (43)	0/65 (49)	1/65 (47)	0/65 (42)
		0.2513	NC	NC	0.4947	NC
	Squamous Cell Papilloma	0/65 (48)	0/65 (43)	0/65 (49)	1/65 (47)	0/65 (42)
		0.2513	NC	NC	0.4947	NC
Testes	Interstitial (Leydig) Cell Adenoma	5/65 (49)	1/65 (43)	2/65 (49)	6/65 (48)	3/65 (42)
		0.1210	0.9804	0.9443	0.4853	0.8106
Thyroids	C-Cell Adenoma	7/65 (49)	2/65 (44)	7/65 (50)	2/65 (47)	0/65 (42)
		0.9052	0.9772	0.6287	0.9821	1.0000
	C-Cell Carcinoma	0/65 (48)	1/65 (43)	0/65 (49)	0/65 (47)	0/65 (42)
		0.7433	0.4725	NC	NC	NC
	C-Cell Adenoma/ C-Cell Carcinoma	7/65 (49)	3/65 (44)	7/65 (50)	2/65 (47)	0/65 (42)
		0.9162	0.7942	0.4029	0.9104	0.0106
	Follicular Cell Adenoma	1/65 (49)	1/65 (43)	0/65 (49)	0/65 (47)	4/65 (42)
		0.9331	0.7191	1.0000	1.0000	0.1362
	Follicular Cell Carcinoma	0/65 (48)	1/65 (43)	0/65 (49)	0/65 (47)	0/65 (42)
		0.7433	0.4725	NC	NC	NC
	Follicular Cell Adenoma/ Follicular Cell Carcinoma	1/65 (49)	1/65 (43)	0/65 (49)	0/65 (47)	4/65 (42)
		0.8132	0.7191	0.5000	0.4896	0.8638

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 0.5 mg P - VC vs. L	Mid (M) 1 mg P - VC vs. M	High (H) 2 mg P - VC vs. H	Positive (PC) 0 mg P - VC vs. PC
Adipose Tissue	Lipoma	1/65 (44)	0/65 (43)	0/65 (44)	0/65 (43)	0/65 (47)
		1.0000	1.0000	1.0000	1.0000	1.0000
Adrenals	Cortical Adenoma	2/65 (44)	0/63 (43)	3/65 (44)	2/65 (43)	0/65 (47)
		0.3604	1.0000	0.5000	0.6832	1.0000
	Cortical Carcinoma	0/65 (44)	0/63 (43)	0/65 (44)	0/65 (43)	1/65 (47)
		NC	NC	NC	NC	0.5165
	Cortical Adenoma/ Cortical Carcinoma	2/65 (44)	0/63 (43)	3/65 (44)	2/65 (43)	1/65 (47)
		0.3604	0.7471	0.5000	0.6832	0.4750
	Phaeochromocytoma	1/65 (44)	4/63 (43)	1/65 (44)	1/65 (43)	1/65 (47)
		0.7495	0.1730	NC	0.7471	0.7690
Brain	Astrocytoma	0/65 (44)	0/65 (43)	1/65 (44)	1/65 (43)	0/65 (47)
		0.1857	NC	0.5000	0.4943	NC
	Granular Cell Tumor	0/65 (44)	0/65 (43)	0/65 (44)	0/65 (43)	1/65 (47)
		NC	NC	NC	NC	0.5165
	Meningioma	0/65 (44)	0/65 (43)	0/65 (44)	0/65 (43)	1/65 (47)
		NC	NC	NC	NC	0.5165
	Oligodendroglioma	0/65 (44)	1/65 (43)	0/65 (44)	0/65 (43)	0/65 (47)
		0.7471	0.4943	NC	NC	NC
Caecum	Leiomyoma	0/65 (44)	0/65 (43)	0/65 (44)	0/65 (43)	1/64 (47)
		NC	NC	NC	NC	0.5165
Clitoral Glands	Adenocarcinoma	0/65 (44)	1/65 (43)	0/65 (44)	0/65 (43)	0/65 (47)
		0.7471	0.4943	NC	NC	NC
	Squamous Cell Papilloma	0/65 (44)	0/65 (43)	0/65 (44)	0/65 (43)	1/65 (47)
		NC	NC	NC	NC	0.5165
H-Poietic Tumor	Histiocytic Sarcoma	0/65 (44)	2/65 (44)	0/65 (44)	0/65 (43)	0/65 (47)
		0.8107	0.2471	NC	NC	NC
	Large Granular Cell Lymphoma	0/65 (44)	0/65 (43)	0/65 (44)	1/65 (43)	0/65 (47)
		0.2471	NC	NC	0.4943	NC
	Myeloid Cell Leukaemia	0/65 (44)	0/65 (43)	1/65 (45)	0/65 (43)	0/65 (47)
		0.5029	NC	0.5056	NC	NC
Head	Squamous Cell Carcinoma	0/65 (44)	1/65 (44)	0/65 (44)	0/65 (43)	0/65 (47)
		0.7486	0.5000	NC	NC	NC
Heart	Endocardial Schwannoma	0/65 (44)	1/65 (43)	0/65 (44)	0/65 (43)	0/65 (47)
		0.7471	0.4943	NC	NC	NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 0.5 mg P - VC vs. L	Mid (M) 1 mg P - VC vs. M	High (H) 2 mg P - VC vs. H	Positive (PC) 0 mg P - VC vs. PC
Jejunum	Leiomyosarcoma	0/65 (44)	1/65 (43)	0/65 (44)	0/64 (42)	0/64 (47)
		0.7457	0.4943	NC	NC	NC
Kidneys	Nephroblastoma	0/65 (44)	0/65 (43)	1/65 (45)	1/65 (44)	1/65 (48)
		0.1900	NC	0.5056	0.5000	0.5217
	Renal Liposarcoma	0/65 (44)	0/65 (43)	0/65 (44)	0/65 (43)	1/65 (47)
		NC	NC	NC	NC	0.5165
	Tubular Adenoma	1/65 (44)	0/65 (43)	0/65 (44)	1/65 (43)	0/65 (47)
		0.4971	1.0000	1.0000	0.7471	1.0000
Liver	Hepatocellular Adenoma	1/65 (44)	0/65 (43)	0/65 (44)	0/65 (43)	1/65 (47)
		1.0000	1.0000	1.0000	1.0000	0.7690
Mammary	Mammary Adenoacanthoma	0/65 (44)	0/65 (43)	0/65 (44)	1/65 (43)	0/65 (47)
		0.2471	NC	NC	0.4943	NC
	Mammary Adenocarcinoma	21/65 (51)	13/65 (47)	12/65 (47)	24/65 (49)	12/65 (50)
		0.1388	0.9475	0.9685	0.2800	0.9804
	Mammary Adenoacanthoma/ Mammary Adenocarcinoma	21/65 (51)	13/65 (47)	12/65 (47)	24/65 (49)	12/65 (50)
		0.1388	0.8835	0.9231	0.2800	0.0514
	Mammary Adenoma	0/65 (44)	1/65 (44)	0/65 (44)	0/65 (43)	0/65 (47)
		0.7486	0.5000	NC	NC	NC
	Mammary Sarcoma Nos	1/65 (44)	0/65 (43)	0/65 (44)	0/65 (43)	0/65 (47)
		1.0000	1.0000	1.0000	1.0000	1.0000
	Mammary Fibroadenoma	34/65 (52)	30/65 (52)	29/65 (51)	29/65 (53)	32/65 (53)
		0.8541	0.8432	0.8620	0.9059	0.7680
	Mammary Fibroma	0/65 (44)	1/65 (43)	0/65 (44)	2/65 (43)	1/65 (47)
		0.1053	0.4943	NC	0.2414	0.5165
	Mammary Fibrosarcoma	1/65 (44)	0/65 (43)	0/65 (44)	1/65 (43)	1/65 (47)
		0.4971	1.0000	1.0000	0.7471	0.7690
	Mammary Fibroadenoma/ Mammary Fibroma/ Mammary Fibrosarcoma	34/18 (65)	31/21 (65)	29/22 (65)	31/22 (65)	32/21 (65)
		0.7301	0.6572	0.7532	0.7005	0.3713
Mandibular S.G.	Adenocarcinoma	0/65 (44)	0/65 (43)	0/65 (44)	1/65 (43)	0/65 (47)
		0.2471	NC	NC	0.4943	NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 0.5 mg P - VC vs. L	Mid (M) 1 mg P - VC vs. M	High (H) 2 mg P - VC vs. H	Positive (PC) 0 mg P - VC vs. PC
Ovaries	Granulosa Cell Tumor	0/65 (44)	0/65 (43)	0/65 (44)	0/65 (43)	1/65 (47)
		NC	NC	NC	NC	0.5165
	Leiomyosarcoma	1/65 (44)	0/65 (43)	0/65 (44)	0/65 (43)	0/65 (47)
		1.0000	1.0000	1.0000	1.0000	1.0000
	Tubulostomal Adenoma	0/65 (44)	0/65 (43)	1/65 (44)	0/65 (43)	0/65 (47)
		0.5000	NC	0.5000	NC	NC
Pancreas	Acinar Cell Adenocarcinoma	0/65 (44)	0/65 (43)	0/65 (44)	1/65 (43)	0/65 (47)
		0.2471	NC	NC	0.4943	NC
	Islet Cell Adenoma	1/65 (44)	1/65 (44)	2/65 (44)	2/65 (44)	2/65 (47)
		0.2847	NC	0.5000	0.5000	0.5250
	Mixed Cell Adenoma	0/65 (44)	0/65 (43)	0/65 (44)	1/65 (43)	0/65 (47)
		0.2471	NC	NC	0.4943	NC
Parotid S.G.	Adenoma	0/65 (44)	1/65 (44)	0/65 (44)	0/65 (43)	0/65 (47)
		0.7486	0.5000	NC	NC	NC
Pituitary	Adenoma, Pars Distalis	41/65 (58)	48/63 (58)	46/65 (58)	47/65 (57)	44/65 (59)
		0.1202	0.0934	0.1957	0.1021	0.3959
	Carcinoma, Pars Distalis	0/65 (44)	1/63 (42)	0/65 (44)	1/65 (43)	2/65 (48)
		0.3092	0.4884	NC	0.4943	0.2695
	Adenoma, Pars Distalis/ Carcinoma, Pars Distalis	41/65 (58)	49/63 (58)	46/65 (58)	48/65 (58)	46/65 (59)
		0.1254	0.0590	0.1957	0.0934	0.7546
Skeletal Muscle	Fibroma	0/65 (44)	0/65 (43)	0/65 (44)	1/65 (43)	0/65 (47)
		0.2471	NC	NC	0.4943	NC
	Fibrosarcoma	0/65 (44)	0/65 (43)	0/65 (44)	1/65 (43)	0/65 (47)
		0.2471	NC	NC	0.4943	NC
	Fibroma/ Fibrosarcoma	0/65 (44)	0/65 (43)	0/65 (44)	2/65 (43)	0/65 (47)
		0.0600	NC	NC	0.2414	NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 0.5 mg P - VC vs. L	Mid (M) 1 mg P - VC vs. M	High (H) 2 mg P - VC vs. H	Positive (PC) 0 mg P - VC vs. PC
Skin	Basal Cell Carcinoma	1/65 (44)	0/65 (43)	1/65 (44)	0/65 (43)	0/65 (47)
		0.8114	1.0000	NC	1.0000	1.0000
	Fibroma	0/65 (44)	0/65 (43)	2/65 (45)	1/65 (43)	0/65 (47)
		0.1983	NC	0.2528	0.4943	NC
	Fibrosarcoma	0/65 (44)	0/65 (43)	0/65 (44)	0/65 (43)	2/65 (48)
		NC	NC	NC	NC	0.2695
	Fibroma/ Fibrosarcoma	0/65 (44)	0/65 (43)	2/65 (45)	1/65 (43)	2/65 (48)
		0.1983	NC	0.2528	0.4943	0.7305
	Keratoacanthoma	0/65 (44)	0/65 (43)	1/65 (44)	0/65 (43)	0/65 (47)
		0.5000	NC	0.5000	NC	NC
	Squamous Cell Papilloma	0/65 (44)	1/65 (43)	0/65 (44)	1/65 (43)	1/65 (47)
		0.3086	0.4943	NC	0.4943	0.5165
	Keratoacanthoma/ Squamous Cell Papilloma	0/65 (44)	1/65 (43)	1/65 (44)	1/65 (43)	1/65 (47)
		0.2928	0.4943	0.5000	0.4943	0.4835
	Lipoma	0/65 (44)	0/65 (43)	1/65 (44)	0/65 (43)	1/65 (47)
		0.5000	NC	0.5000	NC	0.5165
	Liposarcoma	0/65 (44)	1/65 (44)	0/65 (44)	0/65 (43)	0/65 (47)
		0.7486	0.5000	NC	NC	NC
	Lipoma/ Liposarcoma	0/65 (44)	1/65 (44)	1/65 (44)	0/65 (43)	1/65 (47)
		0.4943	0.5000	0.5000	NC	0.4835
	Sebaceous Cell Adenoma	1/65 (44)	0/65 (43)	0/65 (44)	0/65 (43)	0/65 (47)
		1.0000	1.0000	1.0000	1.0000	1.0000
Spinal C. Cerv.	Astrocytoma	0/65 (44)	0/65 (43)	1/65 (45)	0/65 (43)	0/65 (47)
		0.5029	NC	0.5056	NC	NC
Spinal C. Thor.	Astrocytoma	0/65 (44)	0/65 (43)	1/65 (45)	0/65 (43)	0/65 (47)
		0.5029	NC	0.5056	NC	NC
Stomach	Squamous Cell Papilloma	0/65 (44)	1/65 (43)	0/65 (44)	0/65 (43)	0/65 (47)
		0.7471	0.4943	NC	NC	NC
Thorax	Mesothelioma	1/65 (44)	0/65 (43)	0/65 (44)	0/65 (43)	0/65 (47)
		1.0000	1.0000	1.0000	1.0000	1.0000
Thymus	Thymic Adenocarcinoma	0/65 (44)	1/65 (43)	0/65 (44)	0/65 (43)	0/65 (47)
		0.7471	0.4943	NC	NC	NC
	Thymoma (Lymphoid)	0/65 (44)	0/65 (43)	1/65 (45)	0/65 (43)	0/65 (47)
		0.5029	NC	0.5056	NC	NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 0.5 mg P - VC vs. L	Mid (M) 1 mg P - VC vs. M	High (H) 2 mg P - VC vs. H	Positive (PC) 0 mg P - VC vs. PC
Thyroids	C-Cell Adenoma	7/65 (46)	3/65 (44)	4/64 (45)	2/65 (43)	4/65 (48)
		0.9481	0.9477	0.8946	0.9806	0.9136
	C-Cell Carcinoma	1/65 (44)	1/65 (43)	0/64 (44)	2/65 (43)	0/65 (47)
		0.2953	0.7471	1.0000	0.4913	1.0000
	C-Cell Adenoma/ C-Cell Carcinoma	8/65 (46)	4/65 (44)	4/64 (45)	4/65 (43)	4/65 (48)
		0.8261	0.8010	0.8124	0.7890	0.1573
	Follicular Cell Adenoma	0/65 (44)	0/65 (43)	1/64 (44)	2/65 (43)	2/65 (48)
		0.0603	NC	0.5000	0.2414	0.2695
	Follicular Cell Carcinoma	0/65 (44)	0/65 (43)	1/64 (44)	0/65 (43)	0/65 (47)
		0.5000	NC	0.5000	NC	NC
	Follicular Cell Adenoma/ Follicular Cell Carcinoma	0/65 (44)	0/65 (43)	2/64 (44)	2/65 (43)	2/65 (48)
		0.0703	NC	0.2471	0.2414	0.7305
Tongue	Squamous Cell Papilloma	0/65 (44)	1/65 (43)	0/65 (44)	0/65 (43)	0/65 (47)
		0.7471	0.4943	NC	NC	NC
Uterine Cervix	Endometrial Polyp	0/65 (44)	0/65 (43)	0/65 (44)	1/65 (44)	2/65 (48)
		0.2514	NC	NC	0.5000	0.2695
	Haemangioma	0/65 (44)	0/65 (43)	0/65 (44)	1/65 (43)	0/65 (47)
		0.2471	NC	NC	0.4943	NC
	Schwannoma	0/65 (44)	0/65 (43)	0/65 (44)	1/65 (43)	0/65 (47)
		0.2471	NC	NC	0.4943	NC
	Stromal Sarcoma	0/65 (44)	0/65 (43)	0/65 (44)	1/65 (43)	0/65 (47)
		0.2471	NC	NC	0.4943	NC
Uterus	Endometrial Adenoma	0/65 (44)	1/65 (43)	0/65 (44)	0/65 (43)	0/65 (47)
		0.7471	0.4943	NC	NC	NC
	Endometrial Polyp	2/65 (44)	10/65 (47)	4/65 (46)	6/65 (44)	6/65 (47)
		0.3066	0.0181	0.3599	0.1329	0.1558
	Endometrial Adenoma/ Endometrial Polyp	2/65 (44)	11/65 (47)	4/65 (46)	6/65 (44)	6/65 (47)
		0.3501	0.0099#	0.3599	0.1329	0.8442
	Squamous Cell Carcinoma	0/65 (44)	1/65 (43)	0/65 (44)	0/65 (43)	0/65 (47)
		0.7471	0.4943	NC	NC	NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 3A: Intercurrent Mortality Rate in Male Mice

	Vehicle Control		Low		Mid		High		Water Control	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	6	10.00	3	5.00	2	5.00	3	5.00	2	5.00
53 - 78	4	16.67	9	20.00	12	25.00	6	15.00	10	21.67
79 - 91	9	31.67	6	30.00	8	38.33	9	30.00	10	38.33
92 - 104	10	48.33	8	43.33	10	55.00	8	43.33	4	45.00
>105					1	1.67			1	1.67
Terminal sacrifice	31	51.67	34	56.67	27	45.00	34	56.67	33	55.00
Total	60		60		60		60		60	

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High
Dose-Response (Likelihood Ratio)	0.7465	0.6962	0.3354	0.6600
Homogeneity (Log-Rank)	0.5670	0.6959	0.3267	0.6601

Table 3B: Intercurrent Mortality Rate in Female Mice

	Vehicle Control		Low		Mid		High		Water Control	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	2	3.33	6	10.00	6	10.00	2	3.33	2	3.33
53 - 78	11	21.67	9	25.00	11	28.33	12	23.33	8	16.67
79 - 91	5	30.00	7	36.67	8	41.67	10	40.00	14	40.00
92 - 104	15	55.00	10	53.33	9	56.67	16	66.67	14	63.33
Terminal sacrifice	27	45.00	28	46.67	26	43.33	20	33.33	22	36.67
Total	60		60		60		60		60	

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High
Dose-Response (Likelihood Ratio)	0.2440	0.7907	0.8798	0.2672
Homogeneity (Log-Rank)	0.6627	0.7895	0.8785	0.2555

Table 4A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice

Organ name	Tumor name	Vehicle(VC) 0 mg P - Trend	Low (L) 2 mg P - VC vs. L	Mid (M) 6 mg P - VC vs. M	High (H) 20 mg P - VC vs. H	Water (WC) 0 mg P - VC vs. WC
Adrenals	Malignant Phaeochromocytoma	0/60 (45)	1/58 (45)	0/59 (43)	0/59 (46)	0/60 (46)
		0.7486	0.5000	NC	NC	NC
	Phaeochromocytoma	0/60 (45)	0/58 (45)	0/59 (43)	1/59 (46)	0/60 (46)
		0.2570	NC	NC	0.5055	NC
	MalignantPhaeochromocytoma/	0/60 (45)	1/58 (45)	0/59 (43)	1/59 (46)	0/60 (46)
	Phaeochromocytoma	0.3191	0.5000	NC	0.5055	NC
	Subcapsular Cell Adenoma	1/60 (45)	5/58 (45)	2/59 (44)	9/59 (47)	6/60 (47)
		0.0075	0.1014	0.4915	0.0092#	0.0623
Bone	Osteofibroma	0/2 (2)	0/2 (2)	0/2 (2)	1/6 (4)	0/2 (2)
		0.4000	NC	NC	0.6667	NC
Brain	Malignant Meningioma	0/60 (45)	0/60 (47)	0/60 (44)	1/60 (48)	0/60 (46)
		0.2609	NC	NC	0.5161	NC
Caecum	Adenocarcinoma	0/60 (45)	0/60 (47)	0/60 (44)	1/60 (47)	0/60 (46)
		0.2568	NC	NC	0.5109	NC
Colon	Adenocarcinoma	0/60 (45)	0/60 (47)	0/60 (44)	2/60 (48)	1/60 (46)
		0.0670	NC	NC	0.2637	0.5055
Epididymides	Malignant Schwannoma	0/60 (45)	0/60 (47)	0/60 (44)	0/60 (47)	1/60 (46)
		NC	NC	NC	NC	0.5055
Femur Inc. Joint	Haemangioma	0/60 (45)	0/60 (47)	0/60 (44)	1/60 (47)	0/60 (46)
		0.2568	NC	NC	0.5109	NC
Gall Bladder	Papilloma	0/59 (45)	0/59 (46)	0/59 (43)	0/59 (47)	1/60 (46)
		NC	NC	NC	NC	0.5055
H-Poietic Tumor	Histiocytic Sarcoma	1/60 (46)	2/60 (48)	1/60 (44)	3/60 (47)	2/60 (46)
		0.1772	0.5161	0.7416	0.3166	0.5000
	Malignant Lymphoma	6/60 (46)	8/60 (47)	5/60 (45)	6/60 (48)	12/60 (49)
		0.6289	0.4034	0.7260	0.6508	0.1226
Harderian Glands	Adenocarcinoma	0/60 (45)	0/60 (47)	2/60 (44)	1/60 (47)	0/60 (46)
		0.2067	NC	0.2416	0.5109	NC
	Adenoma	5/60 (45)	9/60 (47)	2/60 (44)	9/60 (47)	1/60 (46)
		0.1938	0.2176	0.9414	0.2176	0.9878
	Adenocarcinoma/Adenoma	5/60 (45)	9/60 (47)	4/60 (44)	10/60 (47)	1/60 (46)
		0.1372	0.2176	0.4855	0.1499	0.0965
Heart	Haemangioma	1/60 (45)	1/60 (47)	0/60 (44)	0/60 (47)	0/60 (46)
		0.9406	0.7635	1.0000	1.0000	1.0000

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 4A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 2 mg P - VC vs. L	Mid (M) 6 mg P - VC vs. M	High (H) 20 mg P - VC vs. H	Water (WC) 0 mg P - VC vs. WC
Jejunum	Adenoma	1/60 (46) 0.4467	0/60 (47) 1.0000	0/60 (44) 1.0000	1/60 (47) 0.7581	0/60 (46) 1.0000
Kidneys	Tubular Adenoma	2/60 (45) 0.9283	1/60 (47) 0.8870	1/60 (44) 0.8750	0/60 (47) 1.0000	1/60 (46) 0.8832
	Tubular Carcinoma	1/60 (45) 1.0000	0/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (47) 1.0000	0/60 (46) 1.0000
	Tubular Adenoma/ Tubular Carcinoma	3/60 (45) 0.9484	1/60 (47) 0.7080	1/60 (44) 0.6833	0/60 (47) 0.8870	1/60 (46) 0.3000
Liver	Haemangioma	1/60 (45) 0.6581	2/60 (47) 0.5165	4/60 (45) 0.1804	1/60 (47) 0.7635	2/60 (46) 0.5083
	Haemangiosarcoma	0/60 (45) 0.2067	0/60 (47) NC	2/60 (44) 0.2416	1/60 (47) 0.5109	0/60 (46) NC
	Haemangioma/ Haemangiosarcoma	1/60 (45) 0.4692	2/60 (47) 0.5165	6/60 (45) 0.0551	2/60 (47) 0.5165	2/60 (46) 0.4917
	Hepatocellular Adenoma	6/60 (45) 0.2916	5/60 (47) 0.7636	3/60 (45) 0.9214	7/60 (47) 0.5342	7/60 (46) 0.5173
	Hepatocellular Carcinoma	1/60 (45) 0.7284	0/60 (47) 1.0000	3/60 (44) 0.2997	0/60 (47) 1.0000	0/60 (46) 1.0000
	Hepatocellular Adenoma/ Hepatocellular Carcinoma	7/60 (45) 0.4076	5/60 (47) 0.6517	6/60 (45) 0.5000	7/60 (47) 0.4209	7/60 (46) 0.5964
Lungs + Bronchi	Bronchioloalveolar Adenocarcinoma	13/60 (48) 0.2531	10/60 (50) 0.8567	8/60 (45) 0.9072	14/60 (49) 0.5252	12/60 (48) 0.6788
	Bronchioloalveolar Adenoma	19/60 (49) 0.9354	20/60 (49) 0.5000	18/60 (47) 0.6015	13/60 (48) 0.9254	15/60 (47) 0.8201
	Bronchioloalveolar Adenocarcinoma/ Bronchioloalveolar Adenoma	30/60 (52) 0.7927	27/60 (52) 0.6531	25/60 (48) 0.6413	24/60 (50) 0.7828	27/60 (49) 0.4754
	Leiomyosarcoma	1/60 (46) 1.0000	0/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (47) 1.0000	0/60 (46) 1.0000
Pancreas	Islet Cell Adenoma	0/60 (45) 0.7541	1/60 (47) 0.5109	0/60 (44) NC	0/60 (47) NC	0/60 (46) NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 4A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 2 mg P - VC vs. L	Mid (M) 6 mg P - VC vs. M	High (H) 20 mg P - VC vs. H	Water (WC) 0 mg P - VC vs. WC
Pituitary	Adenoma, Pars Distalis	0/58 (45) 0.1850	0/59 (47) NC	1/59 (43) 0.4886	1/58 (46) 0.5055	0/56 (44) NC
	Carcinoma, Pars Distalis	0/58 (45) 0.4945	0/59 (47) NC	1/59 (44) 0.4944	0/58 (46) NC	1/56 (45) 0.5000
	Adenoma, Pars Distalis/ Carcinoma, Pars Distalis	0/58 (45) 0.2018	0/59 (47) NC	2/59 (44) 0.2416	1/58 (46) 0.5055	1/56 (45) 0.5000
Seminal Vesicles	Adenoma	0/60 (45) NC	0/60 (47) NC	0/60 (44) NC	0/60 (47) NC	1/60 (46) 0.5055
Skeletal Muscle	Fibrosarcoma	0/60 (45) NC	0/60 (47) NC	0/60 (44) NC	0/60 (47) NC	1/60 (46) 0.5055
	Haemangiosarcoma	0/60 (45) 0.7541	1/60 (47) 0.5109	0/60 (44) NC	0/60 (47) NC	0/60 (46) NC
	Rhabdomyosarcoma	0/60 (45) 0.6297	1/60 (47) 0.5109	1/60 (44) 0.4944	0/60 (47) NC	0/60 (46) NC
	Sarcoma, Nos	1/60 (46) 1.0000	0/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (47) 1.0000	0/60 (46) 1.0000
Skin	Fibrosarcoma	2/60 (46) 0.3600	0/60 (47) 1.0000	4/60 (46) 0.3384	2/60 (47) 0.6998	0/60 (46) 1.0000
	Malignant Schwannoma	1/60 (45) 1.0000	0/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (47) 1.0000	0/60 (46) 1.0000
	Squamous Cell Papilloma	0/60 (45) 0.3217	1/60 (47) 0.5109	0/60 (44) NC	1/60 (47) 0.5109	0/60 (46) NC
Tail	Haemangiosarcoma	0/5 (5) 0.0909	0/2 (1) NC	0/5 (4) NC	1/2 (1) 0.1667	0/2 (2) NC
Testes	Interstitial Cell (Leydig) Adenoma	4/60 (45) 0.0352	1/60 (47) 0.9752	2/60 (44) 0.8935	7/60 (47) 0.2871	1/60 (46) 0.9737
Thyroids	Follicular Cell Adenoma	0/59 (45) 0.6312	1/59 (46) 0.5055	1/60 (44) 0.4944	0/60 (47) NC	0/60 (46) NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 4B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 2 mg P - VC vs. L	Mid (M) 6 mg P - VC vs. M	High (H) 20 mg P - VC vs. H	Positive (PC) 0 mg P - VC vs. PC
Adipose Tissue	Leiomyoma	0/3 (2) 0.4545	0/6 (4) NC	1/3 (2) 0.5000	0/7 (3) NC	0/9 (7) NC
	Liposarcoma	0/3 (2) NC	0/6 (4) NC	0/3 (2) NC	0/7 (3) NC	1/9 (7) 0.7778
Adrenals	Cortical Adenoma	0/58 (44) 0.7381	1/60 (43) 0.4943	0/58 (40) NC	0/60 (41) NC	0/60 (43) NC
	Malignant Phaeochromocytoma	1/58 (44) 1.0000	0/60 (42) 1.0000	0/58 (40) 1.0000	0/60 (41) 1.0000	0/60 (43) 1.0000
	Phaeochromocytoma	0/58 (44) 0.4850	0/60 (42) NC	1/58 (40) 0.4762	0/60 (41) NC	0/60 (43) NC
	Subcapsular Cell Adenoma	1/58 (44) 0.4893	1/60 (42) 0.7412	2/58 (40) 0.4639	1/60 (42) 0.7412	1/60 (43) 0.7471
	Subcapsular Cell Carcinoma	1/58 (44) 1.0000	0/60 (42) 1.0000	0/58 (40) 1.0000	0/60 (41) 1.0000	0/60 (43) 1.0000
	Subcapsular Cell Adenoma/ Subcapsular Cell Carcinoma	2/58 (44) 0.5904	1/60 (42) 0.4824	2/58 (40) 0.6551	1/60 (42) 0.4824	1/60 (43) 0.5087
Brain	Meningeal Sarcoma	0/59 (45) 0.2471	0/60 (42) NC	0/60 (41) NC	1/60 (42) 0.4828	0/60 (43) NC
Caecum	Leiomyoma	1/60 (46) 0.4320	0/60 (42) 1.0000	0/60 (41) 1.0000	1/60 (42) 0.7296	0/60 (43) 1.0000
Clitoral Glands	Adenocarcinoma	0/60 (46) 0.7310	1/60 (43) 0.4831	0/60 (41) NC	0/60 (41) NC	0/60 (43) NC
Femur Inc. Joint	Haemangioma	1/60 (46) 1.0000	0/60 (42) 1.0000	0/60 (41) 1.0000	0/60 (41) 1.0000	0/60 (43) 1.0000
H-Poietic Tumor	Histiocytic Sarcoma	3/60 (46) 0.2766	2/60 (42) 0.7901	5/60 (42) 0.3065	4/60 (43) 0.4619	4/60 (44) 0.4748
	Malignant Lymphoma	17/60 (50) 0.8377	26/60 (47) 0.0280	19/60 (47) 0.3284	16/60 (47) 0.5828	19/60 (49) 0.3879
	Myeloid Cell Leukaemia	0/60 (46) NC	0/60 (42) NC	0/60 (41) NC	0/60 (41) NC	1/60 (44) 0.4889
Harderian Glands	Adenoma	6/60 (46) 0.6335	4/60 (43) 0.8136	2/60 (41) 0.9580	4/60 (43) 0.8136	2/60 (44) 0.9663

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 4B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 2 mg P - VC vs. L	Mid (M) 6 mg P - VC vs. M	High (H) 20 mg P - VC vs. H	Positive (PC) 0 mg P - VC vs. PC
Liver	Haemangioma	1/60 (46) 0.9279	1/60 (42) 0.7296	0/60 (41) 1.0000	0/60 (41) 1.0000	1/60 (44) 0.7416
	Haemangiosarcoma	0/60 (46) NC	0/60 (42) NC	0/60 (41) NC	0/60 (41) NC	1/60 (43) 0.4831
	Hepatocellular Adenoma	0/60 (46) 0.1777	0/60 (42) NC	1/60 (41) 0.4713	1/60 (42) 0.4773	0/60 (43) NC
Ln Mesenteric	Haemangioma	0/58 (45) NC	0/59 (41) NC	0/59 (40) NC	0/59 (41) NC	1/60 (44) 0.4944
Lungs + Bronchi	Bronchioloalveolar Adenocarcinoma	4/60 (46) 0.3297	4/60 (43) 0.6044	6/60 (41) 0.2977	5/60 (42) 0.4415	8/60 (45) 0.1662
	Bronchioloalveolar Adenoma	12/60 (47) 0.5047	9/60 (43) 0.7773	4/60 (42) 0.9890	10/60 (44) 0.7106	10/60 (44) 0.7106
	Bronchioloalveolar Adenocarcinoma/ Bronchioloalveolar Adenoma	15/60 (47) 0.4731	13/60 (44) 0.5066	10/60 (42) 0.7294	14/60 (45) 0.4436	16/60 (45) 0.5592
Mammary	Adenoacanthoma	2/60 (46) 0.8800	0/60 (42) 1.0000	1/60 (42) 0.8617	0/60 (41) 1.0000	2/60 (44) 0.6747
	Mammary Adenocarcinoma	2/60 (46) 0.8984	6/60 (44) 0.1193	2/60 (42) 0.6566	1/60 (42) 0.8617	5/60 (45) 0.2081
	Adenoacanthoma/ Mammary Adenocarcinoma	4/60 (47) 0.9461	6/60 (44) 0.3280	3/60 (42) 0.4366	1/60 (42) 0.7826	7/60 (45) 0.7636
	Mammary Fibroadenoma	1/60 (46) 0.9288	1/60 (43) 0.7357	0/60 (41) 1.0000	0/60 (41) 1.0000	1/60 (43) 0.7357

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 4B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 2 mg P - VC vs. L	Mid (M) 6 mg P - VC vs. M	High (H) 20 mg P - VC vs. H	Positive (PC) 0 mg P - VC vs. PC
Ovaries	Choriocarcinoma	0/60 (46)	0/60 (42)	1/60 (42)	0/60 (41)	0/60 (43)
		0.4854	NC	0.4773	NC	NC
	Cystadenoma	2/60 (46)	0/60 (42)	1/60 (42)	1/60 (42)	0/60 (43)
		0.5602	1.0000	0.8617	0.8617	1.0000
	Granulosa Cell Tumor	1/60 (46)	0/60 (42)	1/60 (41)	1/60 (42)	0/60 (43)
		0.3768	1.0000	0.7233	0.7296	1.0000
	Malignant Granulosa Cell Tumor	0/60 (46)	1/60 (42)	0/60 (41)	0/60 (41)	0/60 (43)
		0.7294	0.4773	NC	NC	NC
	Granulosa Cell Tumor/ Malignant Granulosa Cell Tumor	1/60 (46)	1/60 (42)	1/60 (41)	1/60 (42)	0/60 (43)
		0.4940	0.7296	0.7233	0.7296	0.5169
	Haemangioma	2/60 (46)	0/60 (42)	0/60 (41)	1/60 (41)	0/60 (43)
		0.5655	1.0000	1.0000	0.8568	1.0000
	Luteoma	3/60 (46)	1/60 (43)	2/60 (41)	2/60 (42)	2/60 (43)
		0.5119	0.9332	0.7818	0.7901	0.7979
	Tubular Adenoma	3/60 (46)	2/60 (42)	1/60 (41)	3/60 (41)	1/60 (43)
		0.3540	0.7901	0.9267	0.6052	0.9332
Oviducts	Cystadenoma	0/56 (42)	0/60 (42)	0/59 (40)	0/60 (41)	1/59 (43)
		NC	NC	NC	NC	0.5059
Pancreas	Islet Cell Adenoma	1/60 (46)	1/60 (42)	1/60 (42)	1/60 (42)	0/59 (43)
		0.4946	0.7296	0.7296	0.7296	1.0000
Pituitary	Adenoma, Pars Distalis	3/60 (46)	5/58 (41)	4/59 (41)	3/59 (41)	1/57 (41)
		0.6056	0.2937	0.4351	0.6052	0.9267
	Carcinoma, Pars Distalis	0/60 (46)	0/58 (41)	1/59 (41)	0/59 (41)	0/57 (41)
		0.4852	NC	0.4713	NC	NC
	Adenoma, Pars Distalis/ Carcinoma, Pars Distalis	3/60 (46)	5/58 (41)	5/59 (41)	3/59 (41)	1/57 (41)
		0.5888	0.2937	0.2937	0.6052	0.3529
Skeletal Muscle	Fibrosarcoma	0/60 (46)	1/60 (42)	0/60 (41)	0/60 (41)	0/60 (43)
		0.7294	0.4773	NC	NC	NC
	Liposarcoma	1/60 (46)	0/60 (42)	0/60 (41)	0/60 (41)	0/60 (43)
		1.0000	1.0000	1.0000	1.0000	1.0000
	Rhabdomyosarcoma	1/60 (46)	0/60 (42)	0/60 (41)	0/60 (41)	1/60 (44)
		1.0000	1.0000	1.0000	1.0000	0.7416
	Sarcoma, Nos	0/60 (46)	0/60 (42)	0/60 (41)	1/60 (42)	1/60 (43)
		0.2456	NC	NC	0.4773	0.4831

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 4B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 2 mg P - VC vs. L	Mid (M) 6 mg P - VC vs. M	High (H) 20 mg P - VC vs. H	Positive (PC) 0 mg P - VC vs. PC
Skin	Fibroma	0/60 (46) 0.7294	1/60 (42) 0.4773	0/60 (41) NC	0/60 (41) NC	0/60 (43) NC
	Fibrosarcoma	0/60 (46) 0.4854	0/60 (42) NC	1/60 (42) 0.4773	0/60 (41) NC	0/60 (43) NC
	Fibroma/Fibrosarcoma	0/60 (46) 0.4824	1/60 (42) 0.4773	1/60 (42) 0.4773	0/60 (41) NC	0/60 (43) NC
	Keratoacanthoma	1/60 (46) 0.8108	1/60 (42) 0.7296	1/60 (41) 0.7233	0/60 (41) 1.0000	0/60 (43) 1.0000
	Squamous Cell Carcinoma	0/60 (46) 0.2412	0/60 (42) NC	0/60 (41) NC	1/60 (41) 0.4713	0/60 (43) NC
	Keratoacanthoma/ Squamous Cell Carcinoma	1/60 (46) 0.4864	1/60 (42) 0.7296	1/60 (41) 0.7233	1/60 (41) 0.7233	0/60 (43) 0.5169
	Sarcoma, Nos	0/60 (46) 0.6037	1/60 (42) 0.4773	1/60 (42) 0.4773	0/60 (41) NC	1/60 (43) 0.4831
	Trichoepithelioma	0/60 (46) 0.2456	0/60 (42) NC	0/60 (41) NC	1/60 (42) 0.4773	0/60 (43) NC
Spleen	Haemangioma	1/60 (46) 0.8129	1/60 (42) 0.7296	1/60 (42) 0.7296	0/60 (41) 1.0000	0/60 (43) 1.0000
Stomach	Adenoma	1/60 (46) 0.4320	0/60 (42) 1.0000	0/60 (41) 1.0000	1/60 (42) 0.7296	0/60 (43) 1.0000
	Osteosarcoma	0/60 (46) 0.7310	1/60 (43) 0.4831	0/60 (41) NC	0/60 (41) NC	0/60 (43) NC
	Squamous Cell Papilloma	1/60 (46) 0.5083	1/60 (42) 0.7296	3/60 (42) 0.2745	1/60 (42) 0.7296	0/60 (43) 1.0000
Thymus	Malignant Thymoma	1/60 (46) 1.0000	0/59 (42) 1.0000	0/55 (38) 1.0000	0/56 (38) 1.0000	0/60 (43) 1.0000
Thyroids	Follicular Cell Carcinoma	0/59 (45) 0.7337	1/60 (42) 0.4828	0/60 (41) NC	0/59 (41) NC	0/58 (42) NC
Tongue	Squamous Cell Carcinoma	0/60 (46) 0.7310	1/60 (43) 0.4831	0/60 (41) NC	0/60 (41) NC	0/59 (43) NC
Uterine Cervix	Leiomyoma	0/60 (46) 0.7294	1/60 (43) 0.4831	0/59 (40) NC	0/60 (41) NC	0/59 (43) NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 4B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 2 mg P - VC vs. L	Mid (M) 6 mg P - VC vs. M	High (H) 20 mg P - VC vs. H	Positive (PC) 0 mg P - VC vs. PC
Uterus	Deciduoma	0/60 (46)	1/60 (43)	0/60 (41)	0/60 (41)	0/60 (43)
		0.7310	0.4831	NC	NC	NC
	Endometrial Adenocarcinoma	0/60 (46)	0/60 (42)	0/60 (41)	0/60 (41)	1/60 (44)
		NC	NC	NC	NC	0.4889
	Endometrial Adenoma	0/60 (46)	0/60 (42)	0/60 (41)	0/60 (41)	1/60 (44)
		NC	NC	NC	NC	0.4889
	Endometrial Adenocarcinoma/	0/60 (46)	0/60 (42)	0/60 (41)	0/60 (41)	2/60 (44)
	Endometrial Adenoma	NC	NC	NC	NC	0.7638
	Endometrial Stromal Cell	0/60 (46)	0/60 (42)	0/60 (41)	2/60 (42)	2/60 (44)
	Sarcoma	0.0592	NC	NC	0.2249	0.2362
	Endometrial/Glandular Polyp	15/60 (48)	17/60 (44)	16/60 (44)	13/60 (45)	13/60 (44)
		0.7432	0.3001	0.3828	0.6818	0.6564
	Haemangioma	4/60 (46)	0/60 (42)	2/60 (41)	0/60 (41)	2/60 (44)
		0.9540	1.0000	0.8702	1.0000	0.8881
	Haemangiosarcoma	0/60 (46)	0/60 (42)	1/60 (41)	0/60 (41)	0/60 (43)
		0.4824	NC	0.4713	NC	NC
	Haemangioma/	4/60 (46)	0/60 (42)	3/60 (41)	0/60 (41)	2/60 (44)
	Haemangiosarcoma	0.9199	0.9300	0.4351	0.9267	0.3599
	Leiomyoma	1/60 (46)	1/60 (42)	3/60 (42)	4/60 (42)	6/60 (45)
		0.0565	0.7296	0.2745	0.1531	0.0519
	Leiomyosarcoma	3/60 (46)	2/60 (42)	1/60 (41)	0/60 (41)	0/60 (43)
		0.9728	0.7901	0.9267	1.0000	1.0000
	Leiomyoma/	4/60 (47)	3/60 (42)	4/60 (42)	4/60 (42)	6/60 (45)
	Leiomyosarcoma	0.3917	0.4366	0.5779	0.5779	0.6579
Vagina	Basosquamous Cell Carcinoma	0/59 (45)	0/60 (42)	1/57 (40)	0/59 (40)	0/58 (43)
		0.4790	NC	0.4706	NC	NC
	Haemangioma	0/59 (45)	0/60 (42)	0/57 (40)	1/59 (40)	0/58 (43)
		0.2395	NC	NC	0.4706	NC
	Leiomyosarcoma	0/59 (45)	0/60 (42)	0/57 (40)	0/59 (40)	1/58 (43)
		NC	NC	NC	NC	0.4886
	Squamous Cell Papilloma	0/59 (45)	0/60 (42)	1/57 (40)	0/59 (40)	0/58 (43)
		0.4790	NC	0.4706	NC	NC

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Figure 1A: Kaplan-Meier Survival Functions for Male Rats

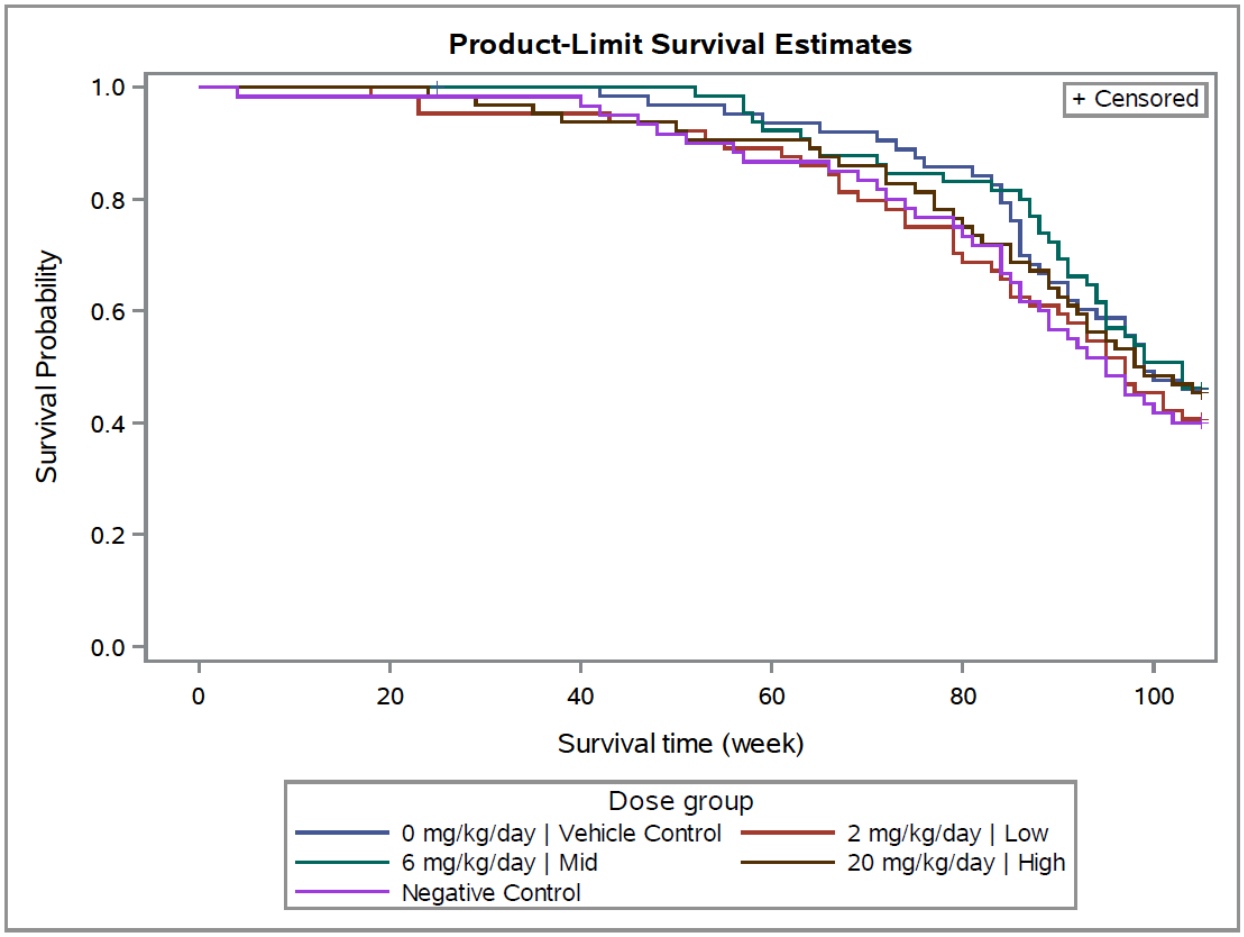


Figure 1B: Kaplan-Meier Survival Functions for Female Rats

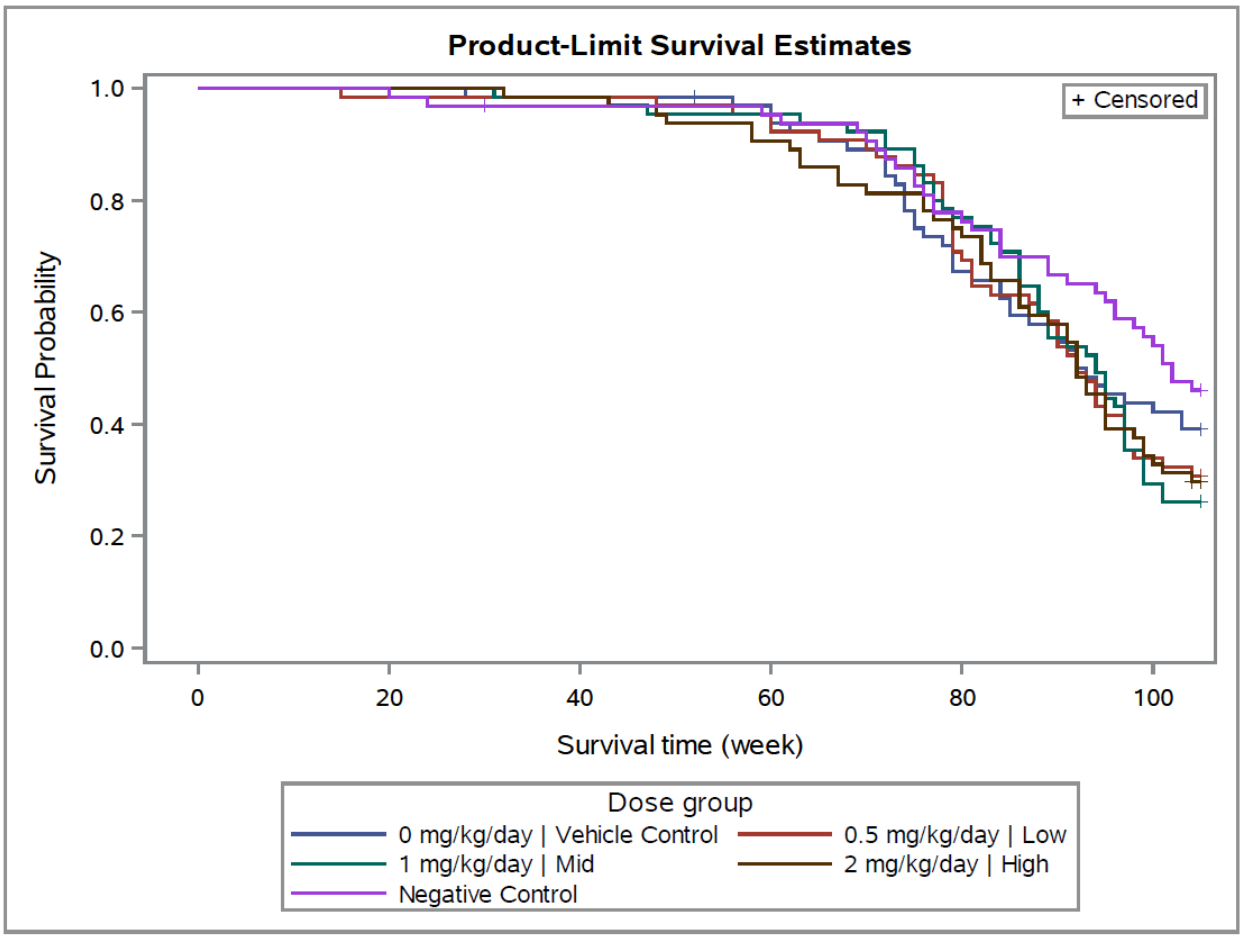


Figure 2A: Kaplan-Meier Survival Functions for Male Mice

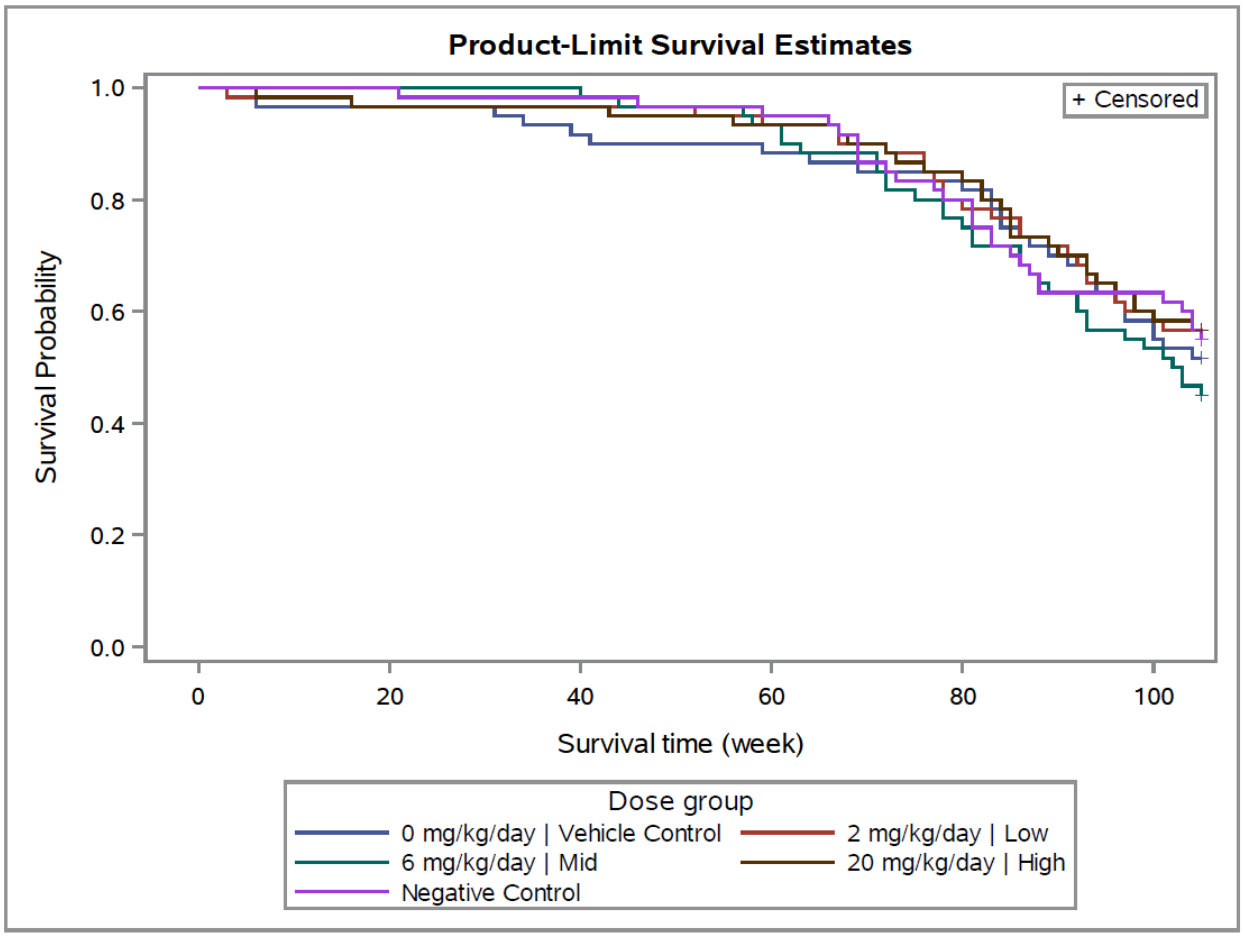
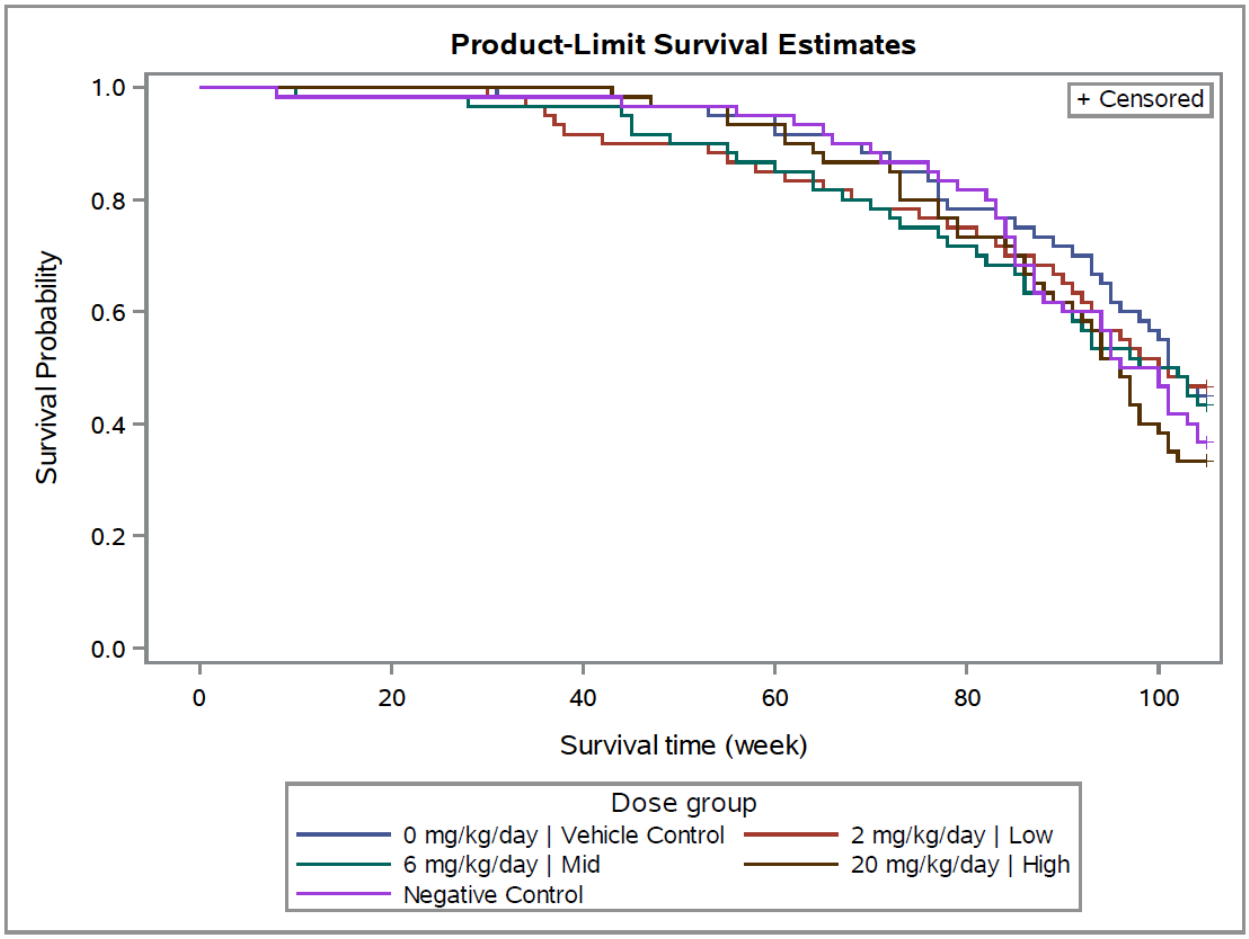


Figure 2B: Kaplan-Meier Survival Functions for Female Mice



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/s/

HEPEI CHEN
05/08/2018

KARL K LIN
05/08/2018
Concur with review