Report on the Deliberation Results

September 4, 2015

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Mulpleta Tablets 3 mg
[Non-proprietary name]	Lusutrombopag (JAN*)
[Applicant]	Shionogi & Co., Ltd.
[Date of application]	December 17, 2014

[Results of deliberation]
In the meeting held on August 28, 2015, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 8 years. Neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug. The product is not classified as a biological product or a specified biological product.

[Conditions for approval]
The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

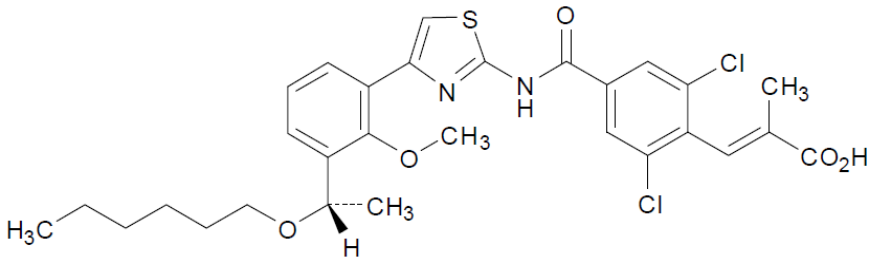
August 17, 2015

Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Mulpleta Tablets 3 mg
[Non-proprietary name]	Lusutrombopag
[Applicant]	Shionogi & Co., Ltd.
[Date of application]	December 17, 2014
[Dosage form/Strength]	Each film-coated tablet contains 3 mg of lusutrombopag.
[Application classification]	Prescription drug (1) Drug with a new active ingredient

[Chemical structure]



Molecular formula: $C_{29}H_{32}Cl_2N_2O_5S$
Molecular weight: 591.55
Chemical name:
(*2E*)-3-{2,6-Dichloro-4-[(4-{3-[(*1S*)-1-(hexyloxy)ethyl]-2-methoxyphenyl}-1,3-thiazol-2-yl)carbamoyl]phenyl}-2-methylprop-2-enoic acid

[Items warranting special mention] None

[Reviewing office] Office of New Drug II

Review Results

August 17, 2015

[Brand name]	Mulpleta Tablets 3 mg
[Non-proprietary name]	Lusutrombopag
[Applicant]	Shionogi & Co., Ltd.
[Date of application]	December 17, 2014

[Results of review]
Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in the improvement of thrombocytopenia associated with chronic liver disease in patients undergoing an elective invasive procedure has been demonstrated and its safety is acceptable in view of its observed benefits. Information on the incidence of thromboembolism as well as the safety and efficacy following re-administration of the product in clinical practice needs to be collected via post-marketing surveillance.

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration as shown below, with the following condition.

[Indication]
Improvement of thrombocytopenia associated with chronic liver disease in patients prior to elective invasive procedures

[Dosage and administration]
The usual adult dosage is 3 mg of Lusutrombopag orally administered once daily for 7 days.

[Conditions for approval]
The applicant is required to develop and appropriately implement a risk management plan.

Review Report (1)

June 23, 2015

I. Product Submitted for Registration

[Brand name]	Mulpleta Tablets 3 mg
[Non-proprietary name]	Lusutrombopag
[Applicant]	Shionogi & Co., Ltd.
[Date of application]	December 17, 2014
[Dosage form/Strength]	Each film-coated tablet contains 3 mg of lusutrombopag.
[Proposed indication]	Thrombopoiesis stimulation prior to invasive procedures in patients with chronic liver disease
[Proposed dosage and administration]	The usual adult dosage is 3 mg of Lusutrombopag orally administered once daily for 7 days.

II. Summary of the Submitted Data and Outline of Review by Pharmaceuticals and Medical Devices Agency

The submitted data and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below.

1. Origin or history of discovery, use in foreign countries, and other information

Lusutrombopag, developed by Shionogi & Co., Ltd., is a small molecule thrombopoietin (TPO) receptor agonist administered orally. Lusutrombopag induces proliferation and differentiation of hematopoietic stem cells and megakaryocytic progenitor cells into megakaryocytes by activating a part of endogenous TPO signaling pathway through TPO receptors, consequently facilitating thrombopoiesis. In patients with chronic liver disease, thrombocytopenia is frequently observed due to various causes such as suppressed production of endogenous TPO, decreased bone marrow functions, splenomegaly, etc. Patients with chronic liver disease complicated by thrombocytopenia may need platelet transfusion to prevent bleeding prior to every invasive procedure. Lusutrombopag increases platelet counts in a planned manner prior an invasive procedure in patients with chronic liver disease complicated by thrombocytopenia. Lusutrombopag was developed as a drug alternative to platelet preparations.

In Japan, clinical development of lusutrombopag was initiated by Shionogi & Co., Ltd. in 20[redacted]. Based on the results from Japanese clinical studies as the pivotal data, a marketing application for lusutrombopag has been filed.

Lusutrombopag has not been approved in any country or region as of May 2015.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

The drug substance occurs as a white to pale yellowish white crystalline powder. The determined properties include description, solubility, hygroscopicity, thermal analysis, melting point, partition coefficient, specific optical rotation, isomerism, and crystalline polymorphism. The drug substance contains its R-enantiomers and its Z geometric isomers. [redacted].

The chemical structure of the drug substance has been elucidated by elemental analysis, ultraviolet-visible spectrophotometry (UV-Vis), infrared spectrophotometry (IR), nuclear magnetic resonance spectrometry (^{1}H-NMR, ^{13}C-NMR), mass spectrometry, and X ray crystallography.

2.A.(1).2) Manufacturing process

[redacted].

In addition, the following were performed using the quality-by-design (QbD) approach.

- Determination of critical quality attributes (CQAs)
- Identification of critical process parameters (CPPs)

2.A.(1).3) Control of drug substance

[redacted].

2.A.(1).4) Stability of drug substance

Primary stability studies for the drug substance are shown in Table 1. The photostability testing showed that the drug substance was photolabile.

Table 1. Stability studies for drug substance

Study	Reference batches	Temperature	Humidity	Storage form	Storage period
Long-term	Commercial scale 3 batches	30°C	65% RH	Low density polyethylene bags (double-layered)[a]	18 months
Accelerated		40°C	75% RH		6 months

[a] The drug substance was protected from light.

A retest period of [redacted] months has been proposed for the drug substance when stored in a double-layered low density polyethylene bag protected from light at room temperature, in accordance with the "Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003) (ICH Q1E guideline). The long-term testing will be continued for [redacted] months.

2.A.(2) Drug product

2.A.(2).1) Description and composition of the drug product and formulation development

The drug product is a film-coated tablet containing 3 mg of the drug substance. The drug product contains excipients: D-mannitol, microcrystalline cellulose, magnesium oxide, sodium lauryl sulfate, hydroxypropylcellulose, carmellose calcium, magnesium stearate, hypromellose, triethyl citrate, titanium oxide, red ferric oxide, and talc.

2.A.(2).2) Manufacturing process

[redacted].

2.A.(2).3) Control of drug product

[redacted].

2.A.(2).4) Stability of drug product

Primary stability studies for the drug product are shown in Table 2. The photostability study showed that the drug product was photostable.

Table 2. Stability studies for drug product

Study	Reference batches	Temperature	Humidity	Storage form	Storage period
Long-term	Pilot scale 3 batches	25°C	60% RH	PTP package[a]	18 months
Accelerated		40°C	75% RH		6 months

PTP: Press Through Package. [a] [redacted]

[redacted]. The long-term testing will be continued for [redacted] months.

2.B Outline of the review by PMDA

Based on the submitted data, PMDA has concluded that the quality of the drug substance and the drug product is adequately controlled.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) *In vitro* studies

(a) Proliferation effect on cells expressing human thrombopoietin receptors (Attached document 4.2.1.1-01, 4.2.1.1-11)

Ba/F3 cells, mouse interleukin-3 (IL-3) dependent ProB cell line, were genetically engineered to express human thrombopoietin (TPO) receptors (Ba/F3-hMpl cells) and were incubated in medium containing lusutrombopag at 4.88 to 5000 nM or recombinant human TPO (rhTPO) at 0.00488 to 5 nM at 37°C for 3 days. In addition, Ba/F3 cells not expressing human TPO receptors were incubated under the same medium conditions. The cell proliferation activity of lusutrombopag was thus investigated (n = 6). EC_{50} was defined as the concentration at which relative proliferation activity reached 50% of the mean maximum proliferation activity in the rhTPO-added group (100%). EC_{50} was 84.0 nM for lusutrombopag and 0.08 nM for rhTPO. Neither lusutrombopag nor rhTPO induced proliferation of Ba/F3 cells not expressing human TPO receptors. In the same way, Ba/F3-hMpl cells were incubated in medium containing a plasma metabolite of lusutrombopag (lusutrombopag-de-hexyl form at 244 to 250,000 nM or lusutrombopag-5-keto form at 61 to 62,500 nM) or rhTPO at 0.00488 to 5 nM, to investigate cell proliferation activity. EC_{50} was 34,861.0 nM for lusutrombopag-de-hexyl form, 555.7 nM for lusutrombopag-5-keto form, and 0.14 nM for rhTPO (n = 6).

(b) Proliferation effect on various cytokine-dependent cell lines (Attached document 4.2.1.1-02)

The following cells were cultured in medium containing lusutrombopag at 0.0003 to 3 μM at 37°C for 3 to 4 days to investigate the cell proliferation activity of lusutrombopag (n = 6): Ba/F3 cells expressing human erythropoietin (EPO) receptors (Ba/F3-hEPOR cells); NOMO-1 cells, a human granulocyte colony-stimulating factor (G-CSF)-dependent cell line; and TF-1 cells, a human granulocyte-macrophage colony-stimulating factor (GM-CSF)-dependent and human IL-3-dependent cell line. Lusutrombopag did not induce proliferation of any type of cell.

(c) Analysis of signaling pathway by Western blotting (Attached document 4.2.1.1-03)

Ba/F3-hMpl cells were cultured in medium containing lusutrombopag at 3 μM or rhTPO at 1 nM at 37°C for 15 minutes and subjected to Western blotting to measure phosphorylation of Janus kinase

(JAK) 2, signal transducer and activator of transcription (STAT) 3, STAT5, and p44/42 mitogen-activated protein kinase (MAPK). Lusutrombopag enhanced phosphorylation of JAK2, STAT3, STAT5, and p44/42MAPK as with rhTPO.

(d) Effect on human hematopoietic cells (Attached document 4.2.1.1-04 to 4.2.1.1-05)
Human bone marrow-derived CD34 positive cells were cultured in medium containing lusutrombopag or (+)-lusutrombopag, optical isomer, at 0.0923 to 9.23 μM, or rhTPO at 1.846 nM at 37°C for 12 days, to investigate the megakaryocyte colony-forming activity (n = 6). EC_{50} was defined as the concentration at which relative megakaryocyte colony forming cell count reached 50% of the mean megakaryocyte colony forming cell count in the rhTPO-added group (100%). EC_{50} of lusutrombopag and (+)-lusutrombopag was 0.31 and 0.19 μM, respectively. The drug substance, however, contains only a trace amount of (+)-lusutrombopag, and chiral inversion from lusutrombopag to (+)-lusutrombopag does not occur *in vivo*. The megakaryocyte colony-forming activity of eltrombopag on human bone marrow-derived CD34 positive cells was determined by the same method. EC_{50} of eltrombopag was 0.86 μM.

3.(i).A.(1).2) *In vivo* studies
The applicant evaluated the thrombopoietic activity of lusutrombopag and accompanying changes including enhanced megakaryocytopoiesis in knock-in mice expressing chimera TPO receptors, namely mouse TPO receptors with human-type transmembrane region (TPOR-Ki/Shi mice).

(a) Thrombopoiesis (Attached document 4.2.1.1-06 to 4.2.1.1-08)
Lusutrombopag at 0.3, 1, 3, or 10 mg/kg/day, eltrombopag at 2, 10, or 50 mg/kg/day, or vehicle (0.5% methylcellulose [MC] solution) was orally administered once daily for 21 days to female TPOR-Ki/Shi mice (12 weeks of age), and blood was drawn from the orbital venous sinus to measure the platelet count (n = 8/group). The lusutrombopag ≥0.3 mg/kg/day groups and eltrombopag ≥10 mg/kg/day groups showed a dose- and time-dependent significant increase in the platelet count from Day 8 through to Day 22, compared with the vehicle group. Following repeated oral administration of lusutrombopag at 0.3, 1, or 3 mg/kg/day or vehicle (0.5% MC solution) to TPOR-Ki/Shi mice (10 weeks of age) for 6 weeks, the platelet count remained almost unchanged in the 0.3 mg/kg/day group from Day 8 onward and in the 1 and 3 mg/kg/day groups from Day 29 onward (n = 10).

(b) Enhanced megakaryocytopoiesis and other changes (Attached document 4.2.1.1-09)
Lusutrombopag at 0.3 or 10 mg/kg/day, eltrombopag at 10 or 50 mg/kg/day, or vehicle (0.5% MC solution) was orally administered once daily for 21 days to female TPOR-Ki/Shi mice (10-11 weeks of age). The following day of the final dose (Day 22), blood was drawn from the abdominal vena cava (n = 12/group). The lusutrombopag 10 mg/kg/day group and eltrombopag 50 mg/kg/day group showed a significant increase in the platelet count and significant decreases in the red blood cell count (RBC), hemoglobin (Hb), and hematocrit (Ht) compared with the vehicle group (Table 3). These groups showed a significant increase in megakaryocyte count in the bone marrow (megakaryocyte count measurement, n = 9-10/group). In the histopathological examination (n = 9-10/group), the lusutrombopag group showed increases in the megakaryocyte count in the lung and liver, and the eltrombopag group showed an increase in the megakaryocyte count in the lung. The blood chemistry examination (n = 3-4/group) revealed a mildly increasing trend of lactate dehydrogenase (LDH) activity. In the blood coagulation examination (n = 4/group), no noteworthy changes were observed in any dose group compared with the vehicle group.

Table 3. Thrombopoiesis and changes in erythroid parameters

Dose group	Platelet count ($\times10^4$/μL)	RBC ($\times10^6$/μL)	Hb (g/dL)	Ht (%)
Vehicle	167.7 ± 8.5	9.51 ± 0.52	14.8 ± 0.9	44.0 ± 2.6
Lusutrombopag 0.3 mg/kg/day	186.4 ± 4.1	9.02 ± 0.08	14.0 ± 0.2	41.9 ± 1.0
Lusutrombopag 10 mg/kg/day	458.3 ± 31.5**	8.64 ± 0.28*	13.4 ± 0.5*	39.9 ± 1.6*
Eltrombopag 10 mg/kg/day	213.7 ± 16.9	9.13 ± 0.22	14.2 ± 0.3	42.5 ± 0.6
Eltrombopag 50 mg/kg/day	496.9 ± 63.9**	8.75 ± 0.26*	13.9 ± 0.3	40.9 ± 0.6*

Mean ± standard deviation (SD) (n = 4)
** $P < 0.01$ (compared with the vehicle group by Dunnett's test); * $P < 0.05$ (compared with the vehicle group by Dunnett's test)

3.(i).A.(1).3) Pharmacokinetic/pharmacodynamic analysis in TPOR-Ki/Shi mice (Attached document 4.2.1.1-10)

Using data on platelet counts following repeated oral administration of lusutrombopag at 0.3, 1, 3, or 10 mg/kg/day for 21 days to TPOR-Ki/Shi mice and data on plasma lusutrombopag concentrations following single oral administration of lusutrombopag at 0.3, 3, or 10 mg/kg to TPOR-Ki/Shi mice, the relationship between the platelet increase rate (platelet count on Day 8, 15, or 22 / platelet count on Day 0) and plasma lusutrombopag concentration was investigated in the maximum pharmacological activity (E_{max}) model. The platelet increase rate was correlated with the area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0\text{-}inf}$) and maximum plasma drug concentration (C_{max}). When the platelet increase rate was 1.5, $AUC_{0\text{-}inf}$ was 0.664 μg·hr/mL (Day 8), 0.639 μg·hr/mL (Day 15), and 0.529 μg·hr/mL (Day 22), and C_{max} was 0.0662 μg/mL (Day 8), 0.0642 μg/mL (Day 15), and 0.0555 μg/mL (Day 22).

3.(i).A.(2) Secondary pharmacodynamics

3.(i).A.(2).1) Effects on hematopoietic colony-forming activities (Attached document 4.2.1.2-01)

Human bone marrow-derived CD34 positive cells were incubated with lusutrombopag (0.25, 1 μM) and recombinant human EPO (rhEPO) (0.05, 3 U/mL) or recombinant human G-CSF (rhG-CSF) (1, 10 ng/mL) at 37°C for 14 days. The resulting colony count was measured to evaluate the effects of lusutrombopag on the hematopoietic colony forming activities of human EPO and human G-CSF (n = 6). Lusutrombopag did not induce formation of erythroid or granulocyte-macrophage colonies at any concentration. The number of erythroid or granulocyte-macrophage colonies formed following treatment with rhEPO or rhG-CSF in combination with lusutrombopag was similar to those formed following treatment with rhEPO or rhG-CSF alone, showing no effects of lusutrombopag.

3.(i).A.(3) Safety pharmacology

3.(i).A.(3).1) Effects on the central nervous system (Attached document 4.2.1.3-01)

A single oral dose of lusutrombopag at 40, 200, or 1000 mg/kg or vehicle (polyethylene glycol 400 containing Tween 80 at 5% [PEG 400/Tween 80]) was administered to male Sprague-Dawley (SD) rats (6 weeks of age) to investigate effects on the behavior and clinical signs using the functional observational battery (n = 8/group). In the 40 and 1000 mg/kg groups, the locomotor activity was significantly increased at 1 or 2 hours post-dose compared with the vehicle group, but the extent of the increase was smaller than the locomotor activity at baseline and thus was mild and transient. In the 200 mg/kg group, no significant change was observed. On any observation parameter for the clinical signs and behavior, changes possibly attributable to lusutrombopag were not observed.

3.(i).A.(3).2) Effects on the cardiovascular system

(a) *In vitro* studies

i) Effects on ionic current in hERG channel-expressing cells (Attached document 4.2.1.3-04)

Lusutrombopag at 0.1, 1, or 10 μM (0.06, 0.59, 5.92 μg/mL, respectively) was added to HEK293 cells expressing human ether-a-go-go-related gene (hERG) channel to measure delayed rectifier K^+ current (n = 5/group). Lusutrombopag at 0.1, 1, and 10 μM significantly inhibited the peak tail current by 17.0%, 29.0%, and 38.3%, respectively, and the estimated 50% inhibitory concentration (IC_{50}) was 70.04 μM (41.4 μg/mL).

ii) Effects on myocardial action potential in guinea pig papillary muscle preparations (Attached document 4.2.1.3-03)

Right ventricular papillary muscle preparations isolated from male Hartley guinea pigs (4-5 weeks of age) were treated with lusutrombopag at 0.1, 1, or 10 μM (0.06, 0.59, 5.92 μg/mL, respectively) to observe action potential waveforms at 0.5 Hz electrical stimulation. The measured waveforms were analyzed to determine action potential amplitude, resting membrane potential, maximum rate of rise of action potential induced by depolarization, and action potential durations at 30% and 90% repolarization (APD_{30}, APD_{90}) (n = 5/group). Lusutrombopag did not affect APD_{30}, APD_{90}, or $APD_{30\text{-}90}$ (i.e., the difference between APD_{90} and APD_{30}) at any concentration.

(b) *In vivo* studies

i) Effects on blood pressure, heart rate, and electrocardiogram (Attached document 4.2.1.3-02)

Lusutrombopag at 100, 300, or 500 mg/kg or vehicle (0.5% MC solution) was orally administered every 7 days in a dose-escalation manner to male beagle dogs (body weight 7.7-9.2 kg) to measure blood pressure, heart rate, and electrocardiograms (ECG) by telemetry and Holter monitoring in conscious animals at pre-dose and at 1, 2, 4, 8, and 24 hours post-dose (n = 4). Lusutrombopag did not affect blood pressure, heart rate, or ECG parameters at any dose.

3.(i).A.(3).3) Effects on the respiratory system (Attached document 4.2.1.3-05)

A single oral dose of lusutrombopag at 40, 200, or 1000 mg/kg or vehicle (PEG 400/Tween 80) was administered to male SD rats (6 weeks of age) to measure respiratory rate, tidal volume, and minute ventilation in unrestrained animals by whole-body plethysmography at baseline and 1, 2, 4, and 8 hours post-dose (n = 6). Lusutrombopag did not affect any of the parameters at any dose.

3.(i).A.(3).4) Follow-up study: Effect of PEG 400/Tween 80 on ECG in dogs (Attached document 4.2.1.3-07, non-GLP)

In the 1-month repeated oral dose toxicity study in dogs [see "3.(iii).A.(2) Repeat-dose toxicity"], ECG showed second degree atrioventricular block in the lusutrombopag 3 and 10 mg/kg/day groups. In response to this finding, 0.5% MC solution at 1.5 mL/kg/day (control) or PEG 400/Tween 80 at 1.5 or 5 mL/kg/day was orally administered for 3 days to female beagle dogs (6 months of age), to investigate the effects of PEG 400/Tween 80 (vehicle) on Holter ECG from 3 hours pre-dose to 6 hours post-dose (n = 3-4/group). In the control group, the ECG was not affected on any of the 3 dosing days. In the PEG 400/Tween 80 groups, second degree atrioventricular block was observed in all animals on Day 1 (37 events in the 1.5 mL/kg/day group and 88 events in the 5 mL/kg/day group). Even on Days 2 and 3, second degree atrioventricular block was observed in all animals (42 events on Day 2 and 43 events on Day 3 in the 1.5 mL/kg/day group; 92 events on Day 2 and 129 events on Day 3 in the 5 mL/kg/day group). Analysis of the ECG parameters (PR interval, QRS duration, QT interval, QTc) indicated that these events were Wenckebach type second degree atrioventricular block. The other ECG parameters were not affected by PEG 400/Tween 80.

3.(i).A.(3).5) Follow-up study: Effects of 28-day repeated oral dose of lusutrombopag sodium on ECG in dogs (Attached document 4.2.1.3-06)

The effects of lusutrombopag on ECG were evaluated in dogs receiving lusutrombopag sodium (instead of lusutrombopag) or water for injection as vehicle (instead of PEG 400/Tween 80). Vehicle or lusutrombopag sodium 200 mg/kg/day was orally administered for 28 days to male beagle dogs (7-8 months of age). Holter ECG was measured at 7 days before and at 1, 7, 14, and 28 days after the initiation of administration (n = 3 in the vehicle group, n = 6 in the lusutrombopag sodium group). One dog receiving lusutrombopag sodium was considered to have congenital atrioventricular block. Of the remaining 5 dogs given in the lusutrombopag sodium group, 2 dogs showed second degree atrioventricular block (one event in each dog) at 7 days after the initiation of administration. The 5 dogs showed no second degree atrioventricular block at the other time points (1, 14, and 28 days after the initiation of administration); the incidence of second degree atrioventricular block in the lusutrombopag sodium group was thus lower than that in the vehicle group before administration or 14 days after the initiation of administration. No significant difference was observed in PR interval, QRS duration, QT interval, or QTc on ECG between the vehicle and lusutrombopag sodium groups on any of the dosing days. C_{max} (17.26 μg/mL) of lusutrombopag on Day 28 of this study was comparable to C_{max} (16.05 μg/mL) in the 10 mg/kg/day group on Day 29 in the 1-month repeated oral dose toxicity study in dogs.

3.(i).A.(4) Pharmacodynamic drug interactions

No data were submitted.

3.(i).B Outline of the review by PMDA

3.(i).B.(1) Appropriateness of use of TPOR-Ki/Shi mice in evaluation of pharmacological effect of lusutrombopag

The applicant's explanation for the evaluation method of pharmacological effect of lusutrombopag:

The applicant established knock-in mice expressing chimera TPO receptors, namely mouse TPO receptors with human-type transmembrane region (TPOR-Ki/Shi mice), to evaluate the thrombopoiesis

of lusutrombopag *in vivo*, for the following reasons: (1) Lusutrombopag acts on human TPO receptors but not on mouse TPO receptors *in vitro*. (2) Histidine at position 499 (H499) of the amino acid sequence in the human TPO receptor transmembrane domain is essential for the action of eltrombopag, a drug in the same class, (Erickson-Miller CL et al. *Blood.* 2004;104:2909a). (3) Butyzamide, which has a similar structure to that of lusutrombopag, also has similar specificity of action that requires H499 (Nogami W et al. *Hematologica.* 2008;93:1495-1504). Actually, TPOR-Ki/Shi mice receiving repeated oral doses of lusutrombopag at ≥0.3 mg/kg/day showed a dose-dependent and significant increase in the platelet count from Day 7 onward, compared with the vehicle group. The pharmacokinetic/pharmacodynamic analyses showed that the platelet increase rate correlated to $AUC_{0\text{-}inf}$ and C_{max}. This evaluation system is therefore considered to reflect the therapeutic effect of lusutrombopag in humans.

In the Japanese multiple dose study (Study M0613), C_{max} at which the platelet count increased by 50% in healthy adult subjects (the 0.5 mg group) was 0.0389 μg/mL, and $AUC_{0\text{-}inf}$ was 0.703 μg·hr/mL [see "4.(ii).A.(2).2) Multiple oral dose study in Japanese subjects"]. In TPOR-Ki/Shi mice, C_{max} at which the platelet count increased by 50% was 0.0642 μg/mL, and $AUC_{0\text{-}inf}$ was 0.639 μg·hr/mL. The C_{max} and $AUC_{0\text{-}inf}$ in humans thus approximate those in TPOR-Ki/Shi mice, suggesting that the TPOR-Ki/Shi mouse model is useful for prediction of clinical results.

PMDA's view:
The applicant evaluated the highly species-specific effect of lusutrombopag on the TPO receptors in TPOR-Ki/Shi mice; this decision was appropriate. In addition, lusutrombopag increased the platelet count dose-dependently in these model mice, and an *in vitro* study suggested that lusutrombopag binds to human TPO receptors specifically, stimulating signaling cascades. These findings indicate that lusutrombopag has a potential to increase platelet count in humans through a mechanism assumed by the applicant.

3.(i).B.(2) Cardiovascular risk of lusutrombopag

Second degree atrioventricular block occurred in the lusutrombopag 3 and 10 mg/kg/day groups in the 1-month repeated oral dose toxicity study in dogs [see "3.(iii).A.(2).3) One-month oral dose toxicity study in dogs and extension study"]. In response to this finding, the applicant explained the cardiovascular risk of lusutrombopag in clinical use.

The applicant's explanation:
A single oral dose of lusutrombopag up to 500 mg/kg did not affect blood pressure, heart rate, or ECG in dogs. Even 28-day repeated oral doses of lusutrombopag sodium at 200 mg/kg/day did not affect ECG parameters. Lusutrombopag did not affect the myocardial action potential of guinea pig papillary muscle at a concentration of ≤10 μM (5.92 μg/mL). Lusutrombopag at 10 μM concentration inhibited the peak tail current in hERG expressing cells by up to 38.3%. In a toxicity study, repeated oral doses of PEG 400/Tween 80 (vehicle) at 1.5 or 5 mL/kg/day was administered to dogs for 3 days. All dogs given the vehicle showed second degree atrioventricular block on Days 1, 2, and 3. The concerned finding (second degree atrioventricular block in dogs receiving lusutrombopag 3 or 10 mg/kg/day) is therefore considered attributable to PEG 400/Tween 80. Furthermore, in patients with thrombocytopenia due to chronic liver disease who received multiple doses of lusutrombopag at 3 mg, C_{max} of lusutrombopag on Day 5 was 250 ng/mL [see "4.(ii).A.(3).2) Japanese phase II study in Japanese patients with chronic liver disease"]. Thus, serious cardiovascular effects are considered unlikely to occur in clinical use of lusutrombopag.

PMDA concluded that the applicant's explanation was appropriate.

3.(i).B.(3) Appropriateness of the animal species used in safety pharmacology studies

PMDA asked the applicant to explain the appropriateness of the animal species used in safety pharmacology studies, because the concerned animal species do not respond to lusutrombopag pharmacologically.

The applicant's response:
Lusutrombopag is supposed to have no TPO-receptor-mediated pharmacological effects in conventional experimental animal species except for chimpanzees, as with eltrombopag, a drug in the same class. However, a safety pharmacology study in chimpanzees was not conducted because its historical data

and investigation methods are limited. The applicant considered it important and appropriate to evaluate the off-target effects of lusutrombopag by safety pharmacology core battery studies in SD rats or beagle dogs, animal species widely used in non-clinical studies. In a study evaluating bone marrow fibrillization potential [see "3.(iii).A.(6).3) Study of bone marrow fibrillization potential in gene-knock-in mice"], lusutrombopag 10 mg/kg/day was administered to TPOR-Ki/Shi mice for 8 weeks; neither deaths nor changes in clinical signs or body weight occurred in the mice. C_{max} on Day 56 in the mice was 2.79 μg/mL, which was higher than C_{max} (250 ng/mL) on Day 5 of lusutrombopag therapy in patients with thrombocytopenia due to chronic liver disease who received multiple doses of lusutrombopag 3 mg. In light of these findings and from a viewpoint of safety pharmacology, lusutrombopag is considered unlikely to affect the life-supporting functions seriously. Lusutrombopag and eltrombopag bind to different sites of the TPO receptors, but both drugs activate JAK-STAT and MAPK pathways after binding to the receptors, enhancing proliferation and differentiation of megakaryocytic cells, and thereby increasing platelet count.

PMDA's view:
Based on the applicant's explanation about the feasibility of safety pharmacology studies, the choice of animal species in the concerned studies is appropriate. In clinical practice, close attention should be paid to adverse drug reactions attributable to the on-target effect of lusutrombopag, because the submitted safety pharmacology data do not allow thorough evaluation of the safety pharmacology related to on-target effect.

3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the submitted data

Plasma concentrations of lusutrombopag and (+)-lusutrombopag, optical isomer, were determined by liquid chromatography-tandem mass spectrometry (LC/MS/MS). The lower limit of quantitation of lusutrombopag and (+)-lusutrombopag was 0.5 ng/mL. The pharmacokinetic parameters are expressed as mean or mean ± standard deviation (SD) unless otherwise specified.

3.(ii).A.(1) Absorption

3.(ii).A.(1).1) Single-dose administration (Attached document 4.2.2.2-02, 4.2.2.2-04 to 4.2.2.2-05)

Table 4 shows the pharmacokinetic parameters of lusutrombopag and (+)-lusutrombopag in fed male rats given a single intravenous dose of lusutrombopag at 1 or 2 mg/kg (vehicle, dimethylacetamide/polyethylene glycol 400 [PEG 400]/physiological saline [1:8:1, v:v:v]). Total body clearance (CL_t) of lusutrombopag was 1.02 ± 0.29 and 1.03 ± 0.14 mL/min/kg at 1 and 2 mg/kg, respectively, and distribution volume at a steady state (V_{ss}) was 0.543 ± 0.035 and 0.486 ± 0.017 L/kg, respectively.

Table 4 shows the pharmacokinetic parameters of lusutrombopag in fed male rats given a single oral dose of lusutrombopag at 1, 3, or 10 mg/kg (vehicle, PEG 400). The absolute bioavailability (BA) of lusutrombopag (calculated based on $AUC_{0\text{-}inf}$ following a single intravenous dose of lusutrombopag 1 mg/kg) was 51.8% ± 15.0%, 48.5% ± 8.6%, and 44.5% ± 9.8% at 1, 3, and 10 mg/kg, respectively. Time to reach the maximum plasma concentration (t_{max}), C_{max}, and $AUC_{0\text{-}inf}$ of lusutrombopag did not differ between fasted and fed animals given a single oral dose. In fed animals given a single oral dose of lusutrombopag reconstituted with 0.5% MC or PEG 400 as a vehicle, the absolute BA of lusutrombopag in 0.5% MC was approximately half that of lusutrombopag in PEG 400.

Table 4 shows the pharmacokinetic parameters of lusutrombopag and (+)-lusutrombopag in fed male dogs given a single intravenous dose of ^{14}C-labeled lusutrombopag at 1 mg/kg (vehicle, dimethylacetamide/PEG 400/physiological saline [1:8:1, v:v:v]). CL_t of lusutrombopag was 1.02 ± 0.28 mL/min/kg and V_{ss} was 0.311 ± 0.035 L/kg. Table 4 shows the pharmacokinetic parameters of lusutrombopag and (+)-lusutrombopag in fed male dogs given a single oral dose of ^{14}C-labeled lusutrombopag at 3 mg/kg. The absolute BA of lusutrombopag (calculated based on $AUC_{0\text{-}inf}$ following a single intravenous dose of ^{14}C-labeled lusutrombopag 1 mg/kg) was 74.9% ± 1.2%.

Table 4 shows the pharmacokinetic parameters of lusutrombopag in fed male dogs given a single oral dose of lusutrombopag at 1, 3, or 10 mg/kg (vehicle, PEG 400). C_{max} and $AUC_{0\text{-}inf}$ of lusutrombopag in

fed animals given a single dose were approximately 1.7 times those in fasted animals given a single dose.

Table 4. Pharmacokinetic parameters of lusutrombopag and (+)-lusutrombopag following a single dose of lusutrombopag (modified excerpt from the submitted data)

Animal species	Route of administration	Dose of lusutrombopag (mg/kg)	Sex (n)	C_{max} (μg/mL)	t_{max}[a)] (hr)	$AUC_{0\text{-inf}}$ (μg·hr/mL)	$t_{1/2}$ (hr)
Pharmacokinetic parameters of lusutrombopag							
Rat	i.v.	1	Male (4)	13.5 ± 4.4	-	17.4 ± 4.9	8.5 ± 2.0
		2	Male (4)	29.0 ± 2.8	-	32.9 ± 4.6	7.3 ± 1.1
	p.o.	1	Male (4)	0.479 ± 0.074	4.0	9.02 ± 2.61	8.4 ± 1.9
		3	Male (4)	1.47 ± 0.32	6.0	25.3 ± 4.5	8.5 ± 0.6
		10	Male (4)	4.98 ± 0.71	4.0	77.3 ± 17.1	8.5 ± 2.2
Dog	i.v.	1	Male (3)	12.9 ± 2.7	-	17.2 ± 4.1	4.6 ± 0.5
	p.o.	3	Male (3)	3.74 ± 1.12	2.0	38.6 ± 9.0	13 ± 5
		1	Male (4)	0.727 ± 0.286	4.0	9.89 ± 1.99	4.9 ± 0.4
		3	Male (4)	3.87 ± 0.65	2.0	45.5 ± 7.0	5.3 ± 0.7
		10	Male (4)	10.2 ± 0.9	4.0	137 ± 25	5.9 ± 0.8
Pharmacokinetic parameters of (+)-lusutrombopag							
Rat	i.v.	1	Male (4)	0.228 ± 0.048	-	0.405 ± 0.150	6.7 ± 2.4
		2	Male (4)	0.493 ± 0.045	-	0.713 ± 0.054	6.6 ± 1.0
	p.o.	1	Male (4)	0.00795 ± 0.00121	4.0	0.139 ± 0.036	8.2 ± 1.2
		3	Male (4)	0.0209 ± 0.0080	5.0	0.326 ± 0.100	8.4 ± 1.0
		10	Male (4)	0.101 ± 0.004	4.0	1.43 ± 0.26	8.6 ± 1.6
Dog	i.v.	1	Male (3)	0.0349 ± 0.0086	-	0.0394 ± 0.0098	5.1 ± 1.0
	p.o.	3	Male (3)	0.00618 ± 0.00155	2.0	0.0754 ± 0.0214	N.C.

i.v., Intravenous administration; p.o., Oral administration; $t_{1/2}$, Elimination half-life
-, Not calculated; N.C., Not calculable; [a)] Median

3.(ii).A.(1).2) Repeat-dose administration (Attached document 4.2.2.2-03)

Table 5 shows the pharmacokinetic parameters of lusutrombopag in male rats given repeated oral doses of ^{14}C-labeled lusutrombopag at 3 mg/kg for 14 days.

Table 5. Pharmacokinetic parameters of lusutrombopag in rats following repeated oral doses of lusutrombopag at 3 mg/kg (modified excerpt from the submitted data)

Measurement time point	n	C_{max} (μg/mL)	t_{max}[a)] (hr)	$AUC_{0\text{-inf}}$ (μg·hr/mL)	$t_{1/2}$ (hr)
Day 1	4	1.13 ± 0.21	4.0	17.4 ± 1.9	7.0 ± 1.4
Day 7	4	0.993 ± 0.101	4.0	19.4 ± 4.1	12 ± 4
Day 14	4	1.10 ± 0.35	8.0	20.0 ± 2.3	9.4 ± 0.1

[a)] Median

3.(ii).A.(2) Distribution

3.(ii).A.(2).1) Tissue distribution following a single-dose administration (Attached documents 4.2.2.3-01, 4.2.2.3-03, 4.2.2.3-05 [Reference data])

Following a single oral dose of ^{14}C-labeled lusutrombopag at 3 mg/kg to male and female albino rats, radioactivity concentrations at 2, 4, 8, 12, 24, and 72 hours post-dose were measured by quantitative whole-body autoradiography (n = 1/sex/time point). Radioactivity concentrations peaked at 8 to 24 hours post-dose in most tissues and blood. The maximum radioactivity concentrations in blood was 1.45 μg/g in males and 1.99 μg/g in females (calculated as lusutrombopag concentrations). The maximum radioactivity concentrations in the following tissues were higher than those in blood: the liver (8.52 μg/g in males, 12.1 μg/g in females; the same applies hereafter); adrenal cortex (3.48 μg/g, 4.73 μg/g); renal cortex (2.78 μg/g, 3.22 μg/g); adrenal medulla (2.72 μg/g, 3.85 μg/g); pancreas (2.38 μg/g, 3.05 μg/g); myocardium (2.37 μg/g, 2.68 μg/g); pineal gland (2.18 μg/g, 2.59 μg/g); brown fat (2.10 μg/g, 2.28 μg/g); Harderian gland (1.88 μg/g, 4.13 μg/g); clitoris (2.29 μg/g in females only); ovary (2.55 μg/g in females only). The maximum radioactivity concentrations in the spinal cord (0.124 μg/g, 0.293 μg/g) and brain (0.086 μg/g, 0.156 μg/g) were lower than that in blood. At 72 hours post-dose, radioactivity

concentrations in the brain and spinal cord were below the lower limit of quantitation, while a relatively high amount of radioactivity was detected in the adrenal cortex, preputial gland, adrenal medulla, and ovary.

Following a single oral dose of ^{14}C-labeled lusutrombopag at 3 mg/kg to male pigmented rats, radioactivity concentrations at 8 and 24 hours as well as 7, 14, and 35 days post-dose were measured by quantitative whole-body autoradiography (n = 1/time point). Radioactivity concentrations peaked at 8 to 24 hours post-dose in most tissues and blood. The maximum radioactivity concentrations in the following tissues were higher than those in blood (1.68 μg/g): the liver (8.24 μg/g); pancreas (2.40 μg/g); myocardium (2.28 μg/g); renal cortex (2.23 μg/g); adrenal cortex (2.20 μg/g); Harderian gland (1.80 μg/g). The maximum radioactivity concentrations in the spinal cord (0.108 μg/g) and brain (0.133 μg/g) were lower than that in blood. At 14 days post-dose, radioactivity concentrations in most tissues such as blood, brain, and the spinal cord were below the lower limit of quantitation. In the adrenal cortex, radioactivity was detected even at 35 days post-dose.

Following a single oral dose of ^{14}C-labeled lusutrombopag at 3 mg/kg to pregnant albino rats, radioactivity concentrations in maternal animals and fetuses at 2, 4, 8, and 24 hours post-dose were measured by quantitative whole-body autoradiography (n = 1/time point). In most tissues in maternal animals, radioactivity concentrations peaked at 4 to 8 hours post-dose. The maximum radioactivity concentrations in the liver (11.9 μg/g) and adrenal cortex (5.26 μg/g) were higher than that in plasma (4.10 μg/g). The maximum concentrations in the cerebellum (0.111 μg/g) and cerebrum (0.097 μg/g) were lower than that in plasma. In most of the fetal tissues, radioactivity concentrations peaked at 24 hours post-dose, and the maximum radioactivity concentration was highest in the adrenal gland (2.29 μg/g), followed by brown fat (1.13 μg/g) and liver (0.962 μg/g).

Following a single oral dose of ^{14}C-labeled lusutrombopag at 10 mg/kg to male albino rats, the ratio of radioactivity concentration in the adrenal gland to plasma radioactivity concentration was 2.9 at 24 house post-dose and 23.7 at 72 hours post-dose. This indicates that radioactivity in the adrenal gland is eliminated more slowly than radioactivity in plasma (n = 15/time point). Covalent binding rate in the adrenal gland was 0.6% at 24 hours post-dose and 0.4% at 72 hours post-dose.

3.(ii).A.(2).2) Tissue distribution following repeat-dose administrations (Attached document 4.2.2.3-02)

Male albino rats received repeated oral doses of ^{14}C-labeled lusutrombopag 3 mg/kg once-daily for 14 days. Radioactivity concentrations at 24 hours after the seventh and 13th dose and those at 4, 12, 24, 72, 168, and 336 hours after the 14th dose were measured by quantitative whole-body autoradiography (n = 1/time point). Radioactivity concentrations in most tissues and blood peaked at 4 to 24 hours after the 14th dose. The maximum radioactivity concentrations (calculated as lusutrombopag concentrations) in the liver (12.0 μg/g), adrenal cortex (8.13 μg/g), preputial gland (4.34 μg/g), adrenal medulla (4.27 μg/g), and Harderian gland (3.23 μg/g) were higher than that in plasma (2.16 μg/g). In most tissues, radioactivity elimination following repeated administration was delayed compared with that following a single-dose administration. Even at 336 hours after the 14th dose, radioactivity was detected in the tissues including adrenal cortex (4.24 μg/g), adrenal medulla (1.89 μg/g), and the liver (0.21 μg/g).

3.(ii).A.(2).3) Plasma protein binding and distribution in blood cells (Attached document 5.3.2.1-01, 5.3.2.1-02, 4.2.2.2-01, 4.2.2.2-04)

Lusutrombopag at 5 to 50 μg/mL (final concentration) was added to plasma samples from male mice, female mice, male rats, female rabbits, and male dogs. The plasma protein binding was 99.953% to 99.999%.

^{14}C-labeled lusutrombopag at 0.5 to 50 μg/mL (final concentration) was added to blood samples from male mice, female mice, male rats, female rabbits, and male dogs. Lusutrombopag distribution in blood cells was 0% in male mice, 0% in female mice, 1.53% to 1.80% in male rats, 0% in female rabbits, and 1.72% to 2.86% in male dogs.

A single oral dose of ^{14}C-labeled lusutrombopag at 3 mg/kg was administered to male rats or male dogs. Radioactivity distribution in blood cells was 1.4% to 6.1% at 2 to 48 hours post-dose in male rats and 0% to 4.4% at 15 minutes to 96 hours post-dose in male dogs (rats, n = 4; dogs, n = 3).

3.(ii).A.(3) Metabolism (Attached document 4.2.2.4-01 to 4.2.2.4-03, 4.2.2.4-05, 4.2.2.4-06)

A single oral dose of ^{14}C-labeled lusutrombopag was administered at 3 mg/kg to male rats to investigate plasma metabolites at 4, 8, and 24 hours (n = 1/time point). Lusutrombopag accounted for 73.9% to 78.2% of the total plasma radioactivity. M4 (beta-oxidation carboxylate of lusutrombopag) accounted for less than the detection limit to 1.1% of the total plasma radioactivity. M3 (5-keto form of lusutrombopag) accounted for 1.8% to 5.0% of the total plasma radioactivity. A single oral dose of ^{14}C-labeled lusutrombopag 3 mg/kg was administered to male rats, to evaluate urinary and fecal metabolites at 48 hours post-dose In addition, a single oral dose of ^{14}C-labeled lusutrombopag 3 mg/kg was administered to a bile duct-cannulated male rat, to evaluate biliary metabolites at 48 hours post-dose (n = 1 each for urine, feces, and bile). In feces, lusutrombopag, M4, and M3 were mainly detected by 48 hours post-dose, accounting for 22.8%, 22.7%, and 2.4%, respectively, of the administered radioactivity. In bile, lusutrombopag, M4, and M2 (taurine conjugate of M4) were mainly detected by 48 hours post-dose, accounting for 0.1%, 1.5%, and 9.4%, respectively, of the administered radioactivity. Lusutrombopag, M4, M3, or M2 were not detected in urine by 48 hours post-dose.

A single oral dose of ^{14}C-labeled lusutrombopag was administered at 3 mg/kg to male dogs to investigate plasma metabolites at 2, 6, and 24 hours (n = 1/time point). Lusutrombopag, M4, and M3 accounted for 50.0% to 83.9%, 0.4% to 1.6%, and 3.7% to 5.8%, respectively, of the total plasma radioactivity. A single oral dose of ^{14}C-labeled lusutrombopag 3 mg/kg was administered to male dogs, to evaluate urinary and fecal metabolites at 48 hours post-dose. In addition, a single oral dose of ^{14}C-labeled lusutrombopag 3 mg/kg was administered to a bile duct-cannulated male dog, to evaluate biliary metabolites at 48 hours post-dose (n = 1 each for urine, feces, and bile). In feces, lusutrombopag, M4, and M3 were mainly detected by 48 hours post-dose, accounting for 40.5%, 4.1%, and 4.6%, respectively, of the administered radioactivity. In bile, lusutrombopag, M4, M3, and M5 (de-hexyl form of lusutrombopag) were mainly detected by 48 hours post-dose, accounting for 0.8%, 1.5%, 0.4%, and 4.6%, respectively of the administered radioactivity. In urine, lusutrombopag was mainly detected by 48 hours post-dose, accounting for <0.05% of the administered radioactivity.

A single oral dose of ^{14}C-labeled lusutrombopag was administered at 10 mg/kg to male mice to investigate plasma metabolites at 2 and 6 hours (n = 15/time point). Lusutrombopag, M5, M3, and M1 (acyl-glucuronide of lusutrombopag) accounted for 67.0% to 79.1%, 1.8% to 2.0%, 1.7% to 1.8%, and 7.7% to 15.9%, respectively, of the total plasma radioactivity.

A single oral dose of ^{14}C-labeled lusutrombopag was administered at 3 mg/kg to female TPOR-Ki/Shi mice to investigate plasma metabolites at 2, 6, and 24 hours (n = 5-15/time point). Lusutrombopag and M3 accounted for 36.9% to 79.5% and 1.5% to 3.8%, respectively, of the total plasma radioactivity.

A single oral dose of ^{14}C-labeled lusutrombopag was administered at 10 mg/kg to a female rabbit to investigate plasma metabolites at 2 and 6 hours (n = 1). Lusutrombopag, M5, M4, and M3 accounted for 88.5% to 90.4%, 0.4% to 0.6%, 0.2% to 0.3%, and 1.8% to 3.5%, respectively, of the total plasma radioactivity.

3.(ii).A.(4) Excretion

3.(ii).A.(4).1) Excretion in urine and feces (Attached document 4.2.2.5-01, 4.2.2.5-03, 4.2.2.2-04)

Following a single oral dose of ^{14}C-labeled lusutrombopag at 3 mg/kg to male rats, 0.5% and 98.0% of the administered radioactivity were excreted in urine and feces, respectively, by 96 hours post-dose (n = 4).

Following 14-day repeated oral doses of ^{14}C-labeled lusutrombopag at 3 mg/kg to male rats, 0.4% and 98.2% of the administered radioactivity were excreted in urine and feces, respectively, by 168 hours after the final dose (n = 4).

Following a single oral dose of ^{14}C-labeled lusutrombopag at 3 mg/kg to male dogs, 0.4% and 97.6% of the administered radioactivity were excreted in urine and feces, respectively, by 168 hours post-dose (n = 3).

3.(ii).A.(4).2) Excretion in bile and enterohepatic circulation (Attached document 4.2.2.5-01, 4.2.2.5-02, 4.2.2.2-04)

Following a single oral dose of ^{14}C-labeled lusutrombopag at 3 mg/kg to bile duct-cannulated male rats, 23.7%, 0.2%, and 70.6% of the administered radioactivity were excreted in bile, urine, and feces, respectively, by 48 hours post-dose (n = 4).

A single oral dose of ^{14}C-labeled lusutrombopag 3 mg/kg was administered to bile duct-cannulated male rats. Bile collected from these rats were intraduodenally administered to recipient rats. In the recipient rats, 4.4%, 0.1%, and 13.2% of the administered radioactivity were excreted in bile, urine, and feces, respectively by 48 hours post-dose (n = 3).

Following a single oral dose of ^{14}C-labeled lusutrombopag at 3 mg/kg to bile duct-cannulated male dogs, 20.6%, 0.3%, and 75.5% of the administered radioactivity were excreted in bile, urine, and feces, respectively, by 96 hours post-dose (n = 3).

3.(ii).A.(4).3) Excretion in milk (Attached document 4.2.2.5-04)

A single oral dose of ^{14}C-labeled lusutrombopag 3 mg/kg was administered to postpartum lactating rats. Radioactivity concentrations in maternal animals peaked at 4 hours in plasma and 12 hours in milk. The milk-to-plasma ratio of radioactivity concentration was 0.558 at 2 hours, 1.13 at 4 hours, 2.00 at 8 hours, 2.73 at 12 hours, 4.24 at 24 hours, and 6.74 at 48 hours (n = 5).

3.(ii).A.(5) Pharmacokinetic interactions

3.(ii).A.(5).1) Enzyme induction (Attached document 4.2.2.6-01, 4.2.2.6-02)

Liver microsome was prepared from male and female rats given repeated oral doses of lusutrombopag at 0 (vehicle) to 1000 mg/kg once daily for 1 month, to evaluate whether lusutrombopag induces cytochrome P450: CYP1A, CYP2B1, CYP2C11, and CYP3A. In male and female rats, the testosterone 16-β hydroxylation (CYP2B1) activity and ethoxyresorufin O-deethylation (CYP1A) activity were higher in the lusutrombopag 200 mg/kg group than in the vehicle group. In female rats, the testosterone 6-β hydroxylation (CYP3A) activity was higher in the lusutrombopag 200 mg/kg group than in the vehicle group.

Liver microsome was prepared from male and female dogs given repeated oral doses of lusutrombopag at 0 (vehicle) to 300 mg/kg once daily for 1 month, to evaluate whether lusutrombopag induces CYP1A, CYP2B11, CYP2C21, and CYP3A12. In male dogs, the testosterone 16-α hydroxylation (CYP2B11 and CYP2C21) activity was higher in the lusutrombopag 300 mg/kg group than in the vehicle group. In female dogs, the testosterone 6-β hydroxylation (CYP3A12) activity was lower in the lusutrombopag 300 mg/kg group than in the vehicle group.

3.(ii).A.(5).2) Studies on transporters

(a) Effects on P-glycoprotein and breast cancer resistance protein (Attached document 5.3.2.2-05, 5.3.2.2-06)

Caco-2 cells were incubated in medium containing ^{14}C-labeled lusutrombopag at 10 μM (final concentration), to investigate the transport of lusutrombopag to the basolateral (B) side or apical (A) side of the cells. The ratio of the apparent permeability coefficient (P_{app}) of lusutrombopag from B side to A side to that from A side to B side (P_{app} ratio) was 2.6. The P_{app} ratios in the presence of verapamil and cyclosporine, inhibitors of P-glycoprotein (P-gp), were 3.0 and 1.6, respectively.

LLC-PK1 cells expressing breast cancer resistance protein (BCRP) and LLC-PK1 cells not expressing BCRP were incubated in medium containing ^{14}C-labeled lusutrombopag at 2 μM (final concentration). The corrected P_{app} ratio (P_{app} ratio in LLC-PK1 cells expressing BCRP/P_{app} ratio in LLC-PK1 cells not expressing BCRP) was 5.3. The corrected P_{app} ratio in the presence of Ko143, an inhibitor of BCRP, was 0.8.

(b) Effects on organic anion transport polypeptide 1B1 and 1B3 and organic cation transporter 1 (Attached document 5.3.2.2-06)

HEK293 cells expressing organic anion transport polypeptide 1B1 (OATP1B1), OATP1B3, or organic cation transporter 1 (OCT1) and HEK293 cells not expressing OATP1B1, OATP1B3, or OCT1 were incubated in media containing ^{14}C-labeled lusutrombopag at 2 μM (final concentration). The uptake clearance of lusutrombopag into HEK293 cells expressing OATP1B1, 1B3, or OCT1 was comparable to that in HEK293 cells not expressing the proteins and was not inhibited by rifampicin (an inhibitor of OATP1B1 and OATP1B3) or quinidine (an inhibitor of OCT1).

(c) Inhibitory effects against P-gp and BCRP (Attached document 5.3.2.2-05)

Caco-2 cells were incubated in medium containing ^{3}H-labeled digoxin 1.0 μM (a P-gp substrate) and lusutrombopag (0-100 μM), to investigate the P-gp inhibitory effects of lusutrombopag. The P_{app} ratio of digoxin in the presence of lusutrombopag at 0, 50, and 100 μM was 6.3, 4.7, and 2.8, respectively, showing a lusutrombopag concentration-dependent decrease.

LLC-PK1 cells expressing BCRP and LLC-PK1 cells not expressing BCRP were incubated in medium containing lusutrombopag (0-30 μM) and ^{3}H-labeled prazosin 0.01 μM (a BCRP substrate), to investigate the BCRP inhibitory effects of lusutrombopag. IC_{50} against BCRP was 4.04 μM.

(d) Inhibitory effects against OATP1B1 and OATP1B3 (Attached document 5.3.2.2-07)

HEK293 cells expressing OATP1B1 or OATP1B3 and HEK293 cells not expressing OATP1B1 or OATP1B3 were incubated in medium containing lusutrombopag (1-100 μM) and a substrate of OATP1B1 and OATP1B3 (^{3}H-estradiol-17β-D-glucuronide 0.05 μM), to investigate the inhibitory effects of lusutrombopag against OATP1B1 and OATP1B3. IC_{50} against OATP1B1 was 2.63 μM. IC_{50} against OATP1B3 was 9.58 μM.

3.(ii).B Outline of the review by PMDA

A repeat-dose study in rats to evaluate tissue distribution of lusutrombopag showed high radioactivity concentrations in the liver, adrenal cortex, and adrenal medulla, with delayed elimination of lusutrombopag from these tissues. PMDA asked the applicant to explain whether the distribution of lusutrombopag or its metabolites in the liver, adrenal cortex, and adrenal medulla and the delayed elimination from these tissues potentially raises safety issues.

The applicant's response:

The 1-month repeat-dose toxicity study in rats revealed increased activities of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in the ≥200 mg/kg/day groups and increased liver weight in females in the 200 mg/kg/day group, without any histopathological changes in the liver. In the 6-month repeat-dose toxicity study in rats, neither blood chemistry nor histopathology showed effects on the liver in the highest dose group at 100 mg/kg/day. The 1- and 3-month repeat-dose toxicity studies in dogs showed increased AST and ALT activities, without any histopathological changes in the liver. The 9-month repeat-dose toxicity study in dogs showed slightly increased ALT activity in the highest dose group at 100 mg/kg/day, without any histopathological effects on the liver.

In repeat-dose toxicity studies in rats (6 months) and dogs (9 months), lusutrombopag exposure (AUC_{0-24}) at the 100 mg/kg/day dose (which was determined not to affect the liver) was 483μg·hr/mL in rats and 97.3 μg·hr/mL in dogs. These values, 483 and 97.3μg·hr/mL, were approximately 100 and 20 times, respectively, the exposure ($AUC_{0-\tau}$, 4.799 μg·hr/mL) in patients with thrombocytopenia due to chronic liver disease who received the clinical dose of 3 mg. The metabolites of lusutrombopag observed in a mass balance study (Study M619) were also observed in rats and dogs, indicating that the safety of lusutrombopag and its metabolites has been evaluated in the repeat-dose toxicity studies.

In clinical studies, the incidence of adverse events classified as hepatobiliary disorders did not tend to increase with increasing doses from 0.25 to 4 mg, showing no large difference from the placebo group.

Based on the above, the applicant determined that lusutrombopag or its metabolites were unlikely to cause liver disorder, because (1) increased AST and ALT activities in the repeat-dose toxicity studies

were not associated with histopathological changes in the liver; (2) the lusutrombopag exposure in rats and dogs ensures an adequate safety margin because they were significantly higher than the exposure in humans at the clinical dose; and (3) in clinical studies, neither hepatobiliary laboratory values nor the incidence of hepatobiliary adverse events were correlated to doses or differed significantly between the lusutrombopag and placebo groups.

The following findings were observed in the cortex of the adrenal gland: hypertrophy of the zona fasciculata of the adrenal cortex and single cell necrosis in the ≥40 mg/kg/day groups in the 1-month repeat-dose toxicity study in rats; atrophy of the zona glomerulosa and decreased cellular lipid droplets in the zona fasciculata of the adrenal cortex in the ≥20 mg/kg/day groups in the 6-month repeat-dose toxicity study in rats; mild cellular atrophy of the zona fasciculata of the adrenal cortex in the ≥10 mg/kg/day groups in the 1-month repeat-dose toxicity study in dogs; mildly to moderately decreased lipid droplets at ≥80 mg/kg/day doses in the 3-month repeat-dose toxicity study in dogs; and very mildly decreased lipid droplets in the 100 mg/kg/day group in the 9-month repeat-dose toxicity study in dogs. Any of these histopathological changes in the adrenal cortex was, however, mild and readily reversible. Changes observed in the repeat-dose toxicity studies in rats (6 months) and dogs (9 months) were very mild, not suggestive of cytotoxicity, and not aggravated with the extension of the dosing period. The decreased lipid droplets in the adrenal cortex suggests enhanced glucocorticoid synthesis and thus have little safety concerns. In addition, no histopathological changes suggesting toxicity attributable to lusutrombopag were observed in the adrenal medulla in the 1-month or 6-month repeat-dose toxicity studies in rats.

The doses that did not affect the adrenal gland were 2 mg/kg/day ($AUC_{0\text{-}24}$, 35.7 μg·hr/mL) in 6-month repeat-dose toxicity studies in rats and 10 mg/kg/day ($AUC_{0\text{-}24}$, 14.2 μg·hr/mL) in 9-month repeat-dose toxicity studies in dogs. The exposures at these doses (2 and 10 mg/kg/day) were 7.4 and 3 times, respectively, the exposures (4.799 μg·hr/mL) in patients with thrombocytopenia due to chronic liver disease who received the clinical dose of 3 mg. In a single dose study to evaluate tissue distribution in rats, the radioactivity distributed in the adrenal gland was eliminated much more slowly than that in blood and other tissues, and the elimination following repeat-dose administration was remarkably delayed compared with that following a single-dose administration. The covalent binding rate of the radioactivity was ≤1%, indicating that the residual radioactive substances were not covalently bound to the tissues.

In a Japanese multiple dose study (Study M0613), an endocrine examination (parameters measured: plasma adrenocorticotropic hormone [ACTH], plasma aldosterone, plasma cortisol, urinary cortisol, urinary 17-hydroxycorticosteroid, 17-ketosteroid) was performed on 1, 8, 15, 21, and 28 days after the initiation of administration. The mean values over time of most of the parameters did not differ largely among the doses (0.25-2 mg). In 1 subject in the 0.5 mg group, an adverse drug reaction of plasma ACTH increased was observed on 28 days after the initiation of administration, but the only other endocrine abnormality was plasma cortisol mildly increased. No changes were observed for the other endocrine parameters.

Based on the above, the applicant determined that lusutrombopag or its metabolites were unlikely to affect the adrenal gland in humans, because a non-clinical study showed that (1) lusutrombopag was not covalently bound to tissues and thus did not remain in tissues, that (2) the changes in the adrenal gland were reversible and mild only suggesting changes in adrenocortical hormones, and that (3) in the Japanese multiple dose study (Study M0613), no changes related to lusutrombopag were revealed by the endocrine examination.

Based on the applicant's explanation, PMDA concluded that lusutrombopag or its metabolites remaining in the liver, adrenal cortex, and adrenal medulla following multiple doses of lusutrombopag are unlikely to cause safety issues.

3.(iii) Summary of toxicology studies

3.(iii).A Summary of the submitted data

The applicant submitted the results from the single dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, and other toxicity studies. Lusutrombopag does not exert a pharmacological effect (TPO receptor activation) in any animal species except for

chimpanzees. Nevertheless, the toxicity was evaluated in mice, rats, rabbits, and dogs because chimpanzees cannot be used for toxicity evaluation in practice.

3.(iii).A.(1) Single dose toxicity (Attached document 4.2.3.1-01, 4.2.3.1-02)

Oral dose toxicity studies were conducted in rats and dogs to investigate the single dose toxicity. No deaths due to lusutrombopag occurred. The applicant determined that the approximate lethal dose was >2000 mg/kg for both rats and dogs. Following administration of lusutrombopag, loose stool, watery stool, and vomiting were observed in dogs while none was observed in rats.

3.(iii).A.(2) Repeat-dose toxicity

Oral dose toxicity studies were conducted in rats (up to 6 months) and dogs (up to 9 months) to investigate the repeat-dose toxicity. Major toxicological findings were as follows: effects on the adrenal gland, such as hypertrophy of the zona fasciculata of the adrenal cortex and decreased cellular lipid droplets in the adrenal cortex (in rats and dogs); prolongation of prothrombin time (PT) and activated partial thromboplastin time (APTT) (in rats); and effects on the gallbladder, such as oedema in the lamina propria of the gallbladder and vacuolization of the mucosal epithelium (in dogs). The no observed adverse effect level (NOAEL) was 2 mg/kg/day in rats (the 6-month oral dose toxicity study) and 3 mg/kg/day in male dogs and 10 mg/kg/day in female dogs (the 9-month oral dose toxicity study). Lusutrombopag exposure (AUC) at the NOAELs in rats, male dogs, and female dogs were 7.4, 0.9, and 3.0 times, respectively, the estimated clinical exposure (AUC) at 3 mg dose.

3.(iii).A.(2).1) One-month oral dose toxicity study in rats (Attached document 4.2.3.2-01)

Lusutrombopag was orally administered at 0 (vehicle control, PEG 400/Tween80), 8, 40, 200, or 1000 mg/kg/day to male and female SD rats for 1 month (n = 12/sex/group). Deaths occurred in 1 female in the 40 mg/kg/day group and 1 male in the 200 mg/kg/day group and were determined to be caused by administration error. The following findings were observed; prolongation of PT or APTT in males in the ≥40 mg/kg/day groups; swelling of the adrenal gland, hypertrophy of the zona fasciculata of the adrenal cortex, hyperkeratosis of the skin, thickening of the epidermis, hyperkeratosis of the forestomach, and decreased cortical lymphocytes in the thymus in females in the ≥40 mg/kg/day groups; increases in AST, ALT, alkaline phosphatase (ALP) activities, decreased blood total protein, and extramedullary hematopoiesis in the spleen in males and females in the ≥200 mg/kg/day groups; swelling of the adrenal gland, hypertrophy of the zona fasciculate of the adrenal cortex, hyperkeratosis of the skin, thickening of the epidermis, hyperkeratosis of the forestomach, and decreased cortical lymphocytes in the thymus in males in the ≥200 mg/kg/day groups; and changes of clinical signs (e.g., desquamation, rough fur, piloerection, and abdominal distention), prolongation of PT or APTT, decreases in red blood cell count, hematocrit, and hemoglobin concentration, increases in weight of the liver, kidney, and adrenal gland, decreased thymus weight, renal tubular necrosis, hyaline cast, tubular distension and regeneration, vacuolization of the glomerulus and Bowman's capsule epithelium, and single cell necrosis in the zona fasciculata of the adrenal cortex in females in the ≥200 mg/kg/day groups. Necropsy showed abdominal distention, hydrothorax, and ascites in 1 female in the 200 mg/kg/day group. Histopathological findings in this animal included moderate inflammatory cell infiltration and edema in the cecal mucosa and chorion, splenic congestion, hypermegakaryocytopoiesis in the femoral bone marrow, focal necrosis and mineralization in the liver, vacuolization of the jejunal mucosal epithelium, interstitial oedema in the pancreas and salivary gland, cerebellar white matter vacuolization, and hypertrophy of principal cells in the parathyroid gland. These findings were considered attributable to cecal inflammatory lesion observed only in this animal, and not toxicological changes directly caused by lusutrombopag. The findings showing reversibility after a 1-month recovery period were desquamation, rough fur, prolonged PT, hyperkeratosis of the skin, thickening of the epidermis, hypertrophy of the zona fasciculata of the adrenal cortex. Although lusutrombopag exposure increased with increasing doses up to 200 mg/kg/day, the exposure in the 1000 mg/kg/day group was lower than that in the 200 mg/kg/day group. Based on the above, the applicant determined the NOAEL was 8 mg/kg/day.

3.(iii).A.(2).2) Six-month oral dose toxicity study in rats (Attached document 4.2.3.2-02)

Lusutrombopag was orally administered at 0 (vehicle control, PEG 400/Tween80), 2, 20, or 100 mg/kg/day to male and female SD rats for 6 month (n = 12/sex/group). Death occurred in 1 male in the 2 mg/kg/day group and was determined to be caused by administration error. The following findings

were observed: increased frequency of urine protein positive, atrophy of the zona glomerulosa of the adrenal cortex, decreased cellular lipid droplets in the zona fasciculata of the adrenal cortex, vacuolization and mineralization in the renal glomeruli in males and females in the ≥20 mg/kg/day groups; prolongation of PT or APTT and increases in blood Na and Cl in males in the ≥20 mg/kg/day groups; and increased liver weight and brown discoloration of the ovary in females in the ≥20 mg/kg/day groups; brown discoloration of the adrenal gland in males and females in the 100 mg/kg/day group, swelling in the liver in males in the 100 mg/kg/day group; and increased blood Na, increased kidney weight, decreased ovary weight, decreased corpora lutea in the ovary, cystic follicle, and mucous degeneration of the vaginal mucosal epithelium in females in the 100 mg/kg/day group. All the findings were reversible after a 1-month recovery period. Although lusutrombopag exposure increased with increasing doses up to 20 mg/kg/day, the 20 and 100 mg/kg/day groups showed a less than dose-proportional increase in exposure. Based on the above, the applicant determined the NOAEL was 2 mg/kg/day.

3.(iii).A.(2).3) One-month oral dose toxicity study in dogs and extension study (Attached document 4.2.3.2-03, 4.2.3.2-04, 4.2.3.2-09)

Lusutrombopag was orally administered at 0 (vehicle control, PEG 400/Tween80), 3, 10, 30, or 300 mg/kg/day to male and female beagle dogs for 1 month (n = 3/sex/group). The following findings were observed: muddy stool and watery stool, oedema-like degeneration of the gallbladder wall, lymphocyte infiltration and oedema of the lamina propria in the gallbladder, decreased adrenal gland weight, cellular atrophy of the zona fasciculata of the adrenal cortex in males and females in the ≥10 mg/kg/day groups; increases in AST and ALT in males and females in the ≥30 mg/kg/day groups; and increased liver weight in females in the 300 mg/kg/day group. All the findings were reversible after a 1-month recovery period. Although second degree atrioventricular block and prolonged PR occurred in 1 male each in the 3 mg/kg/day group, these changes were not dose-dependent and were also observed in the control group. They were therefore considered attributable to vehicle. Although lusutrombopag exposure increased with increasing doses up to 30 mg/kg/day, no difference was observed in exposure between the 30 and 300 mg/kg/day groups. Based on the above, the applicant determined the NOAEL was 3 mg/kg/day.

3.(iii).A.(2).4) Three-month oral dose toxicity study in dogs (Attached document 4.2.3.2-05)

Lusutrombopag was orally administered at 0 (vehicle control, 0.5% MC), 10, 80, or 600 mg/kg/day to male and female beagle dogs for 3 months (n = 4/sex/group). The following findings were observed: decreased lipid droplets in the adrenal cortex, fat-like vacuole in the lamina propria of the duodenum and jejunum in males in the ≥80 mg/kg/day groups; increased platelet count, shortened APTT, increases in AST, ALT, and creatine kinase, increased total cholesterol, increased liver weight, and brown discoloration of the adrenal gland in males and females in the 600 mg/kg/day group; and decreased lipid droplets in the adrenal cortex and fat-like vacuole in the lamina propria of the duodenum and jejunum in females in the 600 mg/kg/day group. All the findings were reversible after a 1-month recovery period. Based on the above, the applicant determined the NOAEL was 10 mg/kg/day in males and 80 mg/kg/day in females.

3.(iii).A.(2).5) Nine-month oral dose toxicity study in dogs (Attached document 4.2.3.2-06, 4.2.3.2-07)

Lusutrombopag was orally administered at 0 (vehicle control, 0.5% MC), 3, 10, or 100 mg/kg/day to male and female beagle dogs for 9 months (n = 4/sex/group). The following findings were observed: vacuolization in the gallbladder mucosal epithelium in males in the ≥10 mg/kg/day groups; increased ALT in females in the ≥10 mg/kg/day groups; decreased lipid droplets in the adrenal cortex in males and females in the 100 mg/kg/day group; and vacuolization in the gallbladder mucosal epithelium in females in the 100 mg/kg/day group. All the findings were reversible after a 1-month recovery period. Additional investigation suggested that vacuolization in the gallbladder mucosal epithelium was caused by fat accumulation. Based on the above, the applicant determined the NOAEL was 3 mg/kg/day in males and 10 mg/kg/day in females.

3.(iii).A.(3) Genotoxicity study (Attached document 4.2.3.3-01 to 4.2.3.3-03)
Genotoxicity studies consisted of bacterial reverse mutation assay, chromosomal aberration assay in mammalian cultured cells (Chinese hamster-derived cell line [CHL/IU]), and *in vivo* micronucleus assay in mouse bone marrow cells. None of the tests indicated genotoxicity.

3.(iii).A.(4) Carcinogenicity
Carcinogenicity studies were performed in mice and rats. Neither proliferative nor neoplastic changes relevant to carcinogenicity were observed.

3.(iii).A.(4).1) Carcinogenicity study in mice (Attached document 4.2.3.4-01)
Lusutrombopag was orally administered at 0 (water), 0 (vehicle control, PEG 400), 2, 6, or 20 mg/kg/day to male and female CD-1 mice for 104 weeks (n = 60/sex/group). No neoplastic lesions related to lusutrombopag were observed.

3.(iii).A.(4).2) Carcinogenicity study in rats (Attached document 4.2.3.4-02)
Lusutrombopag was orally administered for 104 weeks to male SD rats at 0 (water), 0 (vehicle control, PEG 400), 2, 6, or 20 mg/kg/day, and to female SD rats at 0 (water), 0 (vehicle control, PEG 400), 0.5, 1, or 2 mg/kg/day (n = 65/sex/group). No neoplastic lesions related to lusutrombopag were observed. Non-neoplastic lesions (dark discoloration of the adrenal gland and granulosa cellular hyperplasia in the ovary) were observed.

3.(iii).A.(5) Reproductive and developmental toxicity
Reproductive and developmental toxicity studies consisted of a study of fertility and early embryonic development in rats, studies of embryo-fetal development in rats and rabbits, and a study of pre- and postnatal development, including maternal function in rats. Major findings related to lusutrombopag treatment in rats included extended gestation period in maternal animals, suppressed development, thoracolumbar or cervical small and short extra ribs, decreased sternebra ossification count in fetuses, and decreased survival, suppressed development (decreased body weight, decreased fertility index) in neonates. The exposure at the NOAEL in rats was 82 times the human exposure at the clinical dose. It has been suggested that lusutrombopag crosses the placenta and is excreted in milk [see "3.(ii).A.(2) Distribution" and "3.(ii).A.(4) Excretion"].

3.(iii).A.(5).1) Study of fertility and early embryonic development to implantation in rats (Attached document 4.2.3.5-01)
Lusutrombopag was orally administered at 0 (vehicle control, PEG 400/Tween 80), 4, 20, or 100 mg/kg/day to male SD rats from 28 days before mating until the end of mating and to female SD rats from 14 days before mating until Gestation Day 7 (n = 20/sex/group). Desquamation of limbs was observed in females in the ≥20 mg/kg/day groups and in males in the 100 mg/kg/day group, but with no effects on the mating, fertility, or implantation. Based on the above, the applicant determined the NOAEL was 20 mg/kg/day for general toxicity in male parent animals, 4 mg/kg/day for general toxicity in female parent animals, and 100 mg/kg/day for reproductive toxicity and embryonic development.

3.(iii).A.(5).2) Study of embryo-fetal development in rats (Attached document 4.2.3.5-02)
Lusutrombopag was orally administered at 0 (vehicle control, PEG 400/Tween80), 4, 12.5, 40, or 80 mg/kg/day to pregnant SD rats from Gestation Day 7 to Gestation Day 17 (n = 19-20/group). Desquamation of limbs and decreases in body weight, body weight gain, and food consumption were observed in maternal animals in the ≥40 mg/kg/day groups. Thoracolumbar small and short extra rib were observed in fetuses in the ≥12.5 mg/kg/day groups, cervical small and short extra ribs in fetuses in the ≥40 mg/kg/day groups, and decreased fetal body weight and decreased sternebra ossification count in fetuses in the ≥80 mg/kg/day groups. Based on the above, the applicant determined the NOAEL was 12.5 mg/kg/day for maternal general toxicity and 4 mg/kg/day for embryo-fetal development toxicity. In the dose finding study (Attached document 4.2.3.5-05), cleft palate was observed in the 1000 mg/kg/day group; this may be a secondary effect due to aggravated clinical signs caused by administration of a large amount of vehicle. In this study of embryo-fetal development, however, cleft palate was not observed in any rats including those receiving the highest dose of 80 mg/kg/day, a dose expected to result in similar absorption and exposure as 1000 mg/kg/day. The applicant thus determined that the cleft palate in the dose finding study was not directly related to lusutrombopag.

3.(iii).A.(5).3) Embryo-fetal development in rabbits (Attached document 4.2.3.5-03)

Lusutrombopag was orally administered at 0 (vehicle control, 0.5% MC/Tween80), 100, 300, or 1000 mg/kg/day to pregnant Japanese white rabbits from Gestation Day 6 to Gestation Day 18 (n = 17-19/group). No effects on maternal animals or fetuses were observed. Although lusutrombopag exposure increased with increasing doses up to 300 mg/kg/day, the exposure at 300 mg/kg/day was comparable to that at 1000 mg/kg/day. Based on the above, the applicant determined the NOAEL was 1000 mg/kg/day for both maternal general toxicity and embryo-fetal development toxicity.

3.(iii).A.(5).4) Study of effects on pre- and postnatal development, including maternal function in rats (Attached document 4.2.3.5-04)

Lusutrombopag was orally administered at 0 (vehicle control, PEG 400/Tween80), 1, 4, 12.5, or 40 mg/kg/day to pregnant SD rats from Gestation Day 7 to 20 days postpartum (n = 22-23/group). One animal in the 40 mg/kg/day group died from dystocia. Maternal animals in the 40 mg/kg/day group showed desquamation of limbs, rough fur, decreased body weight, reduced body weight gain, decreased food consumption, and extended gestation period. Offspring in the ≥12.5 mg/kg/day groups showed thoracolumbar small and short extra ribs. Male and female offspring in the 40 mg/kg/day group showed decreased viability index on postnatal Day 4, decreased preweanling body weight, decreased negative geotaxis score, decreased rate of eyelid opening completion, postweaning deaths, and zonal stenosis change in the tail. Female offspring in the 40 mg/kg/day group showed decreased fertility index. The post-weaning death was considered attributable to retarded development. Thoracolumbar small and short extra ribs were observed during early lactation period, but not in F1 matured animals, and thus this change was considered to disappear with growth. Effects on F2 embryos included decreased corpus luteum count, decreased number of implantations, and increased preimplantation lethality in the 40 mg/kg/day group. Based on the above, the applicant determined the NOAEL was 12.5 mg/kg/day for maternal general toxicity and 4 mg/kg/day for offspring development toxicity.

3.(iii).A.(6) Other toxicity studies

3.(iii).A.(6).1) Skin phototoxicity study (Attached document 4.2.3.7-01)

Female HR-1 hairless mice received a single oral dose of lusutrombopag at 0 (vehicle control, PEG 400/Tween 80), 50, or 500 mg/kg. At 4 hours post-dose, the mice were subjected to ultraviolet irradiation for 1 hour at 10 J/cm^2 (n = 5 or 10/group). During the 2-day observation period, no effects of lusutrombopag were observed. The applicant thus considered that lusutrombopag had no skin phototoxicity.

3.(iii).A.(6).2) Effects of vitamin K on prolongation of PT and APTT (Attached document 4.2.3.7-02)

Male SD rats received oral administration of lusutrombopag plus vitamin K (vitamin K_1 [K_1] or vitamin K_3 [K_3]) at 0/0 mg/kg/day (vehicle control, PEG 400/Tween 80), 200/0 mg/kg/day (lusutrombopag alone), 200/0.1 mg/kg/day (lusutrombopag/K_1), 200/0.3 mg/kg/day (lusutrombopag/K_1), 200/0.1 mg/kg/day (lusutrombopag/K_3), or 200/0.3 mg/kg/day (lusutrombopag/K_3) for 1 month (n = 6/group). The 200/0 group showed prolonged PT and APTT and decreased activities of Factors II, VII, IX, and X, which are vitamin K-dependent coagulation factors. The lusutrombopag plus vitamin K groups, however, did not show prolonged PT or APTT or abnormal blood coagulation factor activities. Based on the above, the applicant explained that concomitant use of vitamin K would prevent the prolongation of PT and APTT.

3.(iii).A.(6).3) Study of bone marrow fibrillization potential in gene-knock-in mice (Attached document 4.2.3.7-03 [Reference data])

Lusutrombopag at 0 (vehicle control, 0.5% MC), 0.3, or 10 mg/kg/day or eltrombopag at 10 or 40 mg/kg/day was orally administered to female TPOR-Ki/Shi mice for 8 weeks (n = 5/group). The lusutrombopag ≥10 mg/kg/day groups showed pale discoloration of the bone marrow, increased weight and swelling of the spleen, reticulum fiber deposition in the bone marrow and spleen, bone marrow necrosis, fatty marrow, deposition of fibrillar collagen, increased fibroblasts, activated osteoblasts, increased trabeculae, and increased megakaryocytopoiesis. The eltrombopag 40 mg/kg/day group showed similar findings. All findings were reversible after a 1-month recovery period.

3.(iii).B Outline of the review by PMDA

3.(iii).B.(1) Toxicity evaluation of lusutrombopag

The on-target effect of lusutrombopag cannot be evaluated appropriately in any animal species except for chimpanzees. PMDA asked the applicant whether any toxicological findings considered attributable to TPO receptor activation caused by lusutrombopag have been found and whether any adverse events related to such findings have been reported in clinical studies.

The applicant's response:

TPOR-Ki/Shi mice receiving repeated doses of lusutrombopag or eltrombopag showed increased platelet count and reticulum fibers in the bone marrow and spleen (Attached document 4.2.3.7-03). In non-clinical safety studies of a TPO receptor agonist romiplostim (genetical recombination) in rats and monkeys, the animals showed changes in erythroid parameters, splenic extramedullary hematopoiesis, increased megakaryocytes in the bone marrow, hyperostosis and myelofibrosis of the femur and sternum, and other changes, according to the interview form for Romiplate for s.c. Injection (version 2, revised in September 2014). In addition, the package inserts for Revolade Tablets and Romiplate for s.c. Injection, other drugs in the same class, state that the following events may occur: formation of reticulin fibers and progression of fibrosis in the bone marrow, progression of existing haematologic malignancy such as myelodysplastic syndrome, and post-dose transient thrombocytopenia and associated bleeding. Toxicity findings considered associated with these TPO receptor agonists were not observed in clinical studies of lusutrombopag in patients with thrombocytopenia due to chronic liver disease. In addition, TPO receptors are expected to be expressed in the brain, liver, breast, lung, and ovary (Columbyova L et al. *Cancer Res.* 1995;55:3509-3512, Erickson-Miller C et al. *BMC Cancer.* 2012;12:405). In clinical studies, the following adverse events in these tissues occurred more frequently in the lusutrombopag group: procedural pain, procedural hypertension, procedural vomiting, AST increased, ALT increased, and blood bilirubin increased. For any event, however, the incidence hardly correlated to the dose; no large difference was observed in summary statistics of the laboratory value between the lusutrombopag group and the placebo group at any time point; and most of the events occurred after invasive procedures. The applicant therefore considered that events for which the relationship with TPO receptor activation caused by lusutrombopag could not be ruled out did not occur in any tissue potentially expressing TPO receptors.

PMDA's view:

It is understandable that toxicity attributable to the on-target effect of lusutrombopag has not been thoroughly evaluated, because chimpanzees, which respond to the on-target effect, cannot be used in toxicity studies. The package insert, therefore, should state that toxicity attributable to the on-target effect has not been investigated in the toxicity studies. In addition, the applicant should continue to evaluate the safety of lusutrombopag and take safety measures by collecting post-marketing information and updating knowledge about functions of the TPO receptor, etc.

3.(iii).B.(2) Prolongation of PT and APTT

In the 1-month and 6-month repeated oral dose toxicity studies in rats, prolongation of PT and APTT was observed. In another study (Attached document 4.2.3.7-02, Effects of vitamin K on prolongation of PT and APTT), decreased activities of vitamin K-dependent coagulation factors were caused by prolongation of PT and APTT. PMDA asked the applicant to explain the mechanism of the effect of lusutrombopag on vitamin K-dependent coagulation factor activities and safety in humans.

The applicant's response:

Although the mechanism of the effect of lusutrombopag on vitamin K-dependent coagulation factor activities remains unclear, it is suggested that lusutrombopag induces CYP2B1 and CYP1A in rats [see "3.(ii).A.(5) Pharmacokinetic interactions"]. Enhanced metabolism and excretion of vitamin K mediated by the CYP2B1 induction may have resulted in decreased activities of vitamin K-dependent coagulation factors. In addition, it is suggested that metabolism of vitamin K involves CYP2B (Bouwman CA et al. *Toxicology.* 1992;75:109-120). Moreover, the blood coagulation time in rats was prolonged by a CYP2B inducer but reversed by concomitant use of vitamin K (Mochizuki et al. *J Toxicol Sci.* 2008;33:307-314). Lusutrombopag was considered unlikely to cause prolongation of the blood coagulation time or consequent bleeding trend in humans, because (1) lusutrombopag exposure in rats showing decreased activities of vitamin K-dependent coagulation factors was 80 times the human exposure at the clinical

dose, ensuring sufficient safety margin; (2) lusutrombopag-induced decrease in vitamin K-dependent blood coagulation factor activities is reversible by concomitant use of K_1 or K_3; and (3) unlike rats, humans hardly experience vitamin K deficiency.

PMDA concluded that the applicant's reply was appropriate.

3.(iii).B.(3) Effects on the gallbladder

Vacuolization in the gallbladder mucosal epithelium was observed in the repeated oral dose toxicity study in dogs. (In this 9-month study, the exposure at the NOAEL was 0.9 to 3 times the estimated clinical exposure in humans.) PMDA asked the applicant to explain whether this finding affects the safety in humans.

The applicant's response:

The tissue with vacuolization in the mucosal epithelium in the gallbladder from the 9-month repeated oral dose toxicity study in dogs was specially stained and subjected to detailed histopathological examination. As a result, the vacuoles were found to be accumulated fats. Electron microscopy did not reveal any findings suggestive of phospholipidosis. Although lusutrombopag may have enhanced fat uptake in the gallbladder, this finding (vacuolization) has little toxicological significance for the following reasons: (1) the vacuolization (accumulated fats) did not tend to be aggravated with repeated doses; (2) the vacuolization (accumulated fats) was not accompanied by increased plasma bilirubin concentration or ALP activity suggestive of effects on the biliary tract; (3) histopathologically cytotoxic changes such as inflammatory cell infiltration and necrosis were not observed; (4) sporadic lipid droplets were considered to be physiological changes as they were also frequently observed in the control group; and (5) changes suggestive of phospholipidosis were not observed. In addition, lusutrombopag has no effects on bilirubin concentrations or biliary tract enzyme activities in clinical studies. Lusutrombopag is thus unlikely to have toxicological effects on the gallbladder.

PMDA concluded that the findings in the gallbladder observed in non-clinical studies do not affect the safety in humans, because (1) these findings were not accompanied by abnormal biliary tract enzyme activities; (2) clinical studies have not suggested the effects of lusutrombopag on the gallbladder; and (3) the proposed treatment period of lusutrombopag is short, although clinical data discussion in terms of the biliary tract enzyme activities does not completely show that lusutrombopag is unlikely to affect safety in humans.

4. Clinical data

4.(i) Summary of biopharmaceutic studies and associated analytical methods

4.(i).A Summary of the submitted data

A 3-mg tablet formulation (same as the proposed drug product) was used in the Japanese phase III study (Study M0631). A 1-mg tablet formulation (not same as the proposed drug product) was used in the Japanese phase II study (Study M0626). A 4-mg tablet formulation with the same ingredient ratio as the proposed drug product was used in the food effect study (Study M061A). The 4-mg tablets used in the food effect study were shown to be bioequivalent (BE) to the proposed drug product by dissolution test (Attached document 3.2.P.2.2), which was performed in accordance with the "Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms" (PMSB/ELD Notification No. 64 dated February 14, 2000, partially revised by PFSB/ELD Notification No. 0229-10 dated February 29, 2012).

Plasma and urinary concentrations of lusutrombopag and (+)-lusutrombopag an optical isomer, were determined by high performance liquid chromatography-tandem mass spectrometry (LC/MS/MS). The lower limit of quantitation ranged from 0.1 to 1 ng/mL. The pharmacokinetic parameters are expressed as mean ± SD unless otherwise specified.

4.(i).A.(1) Bioequivalence and food effect of 1-mg and 4-mg tablets (Study M061A, Attached document 5.3.1.2-01)

A three-treatment, three-period crossover study of lusutrombopag was conducted in 15 Japanese healthy adult men. In each period, the subjects received a single dose of (1) four 1 mg-tablets under fasted

conditions, (2) one 4 mg-tablet after a high fat meal, or (3) one 4-mg tablet under fasted conditions (with a 12-day washout period between treatments).

Maximum plasma lusutrombopag concentrations (C_{max}) and area under the plasma concentration-time curve from time 0 up to the last measurable time ($AUC_{0\text{-last}}$) were measured. The geometric mean ratios [90% confidence interval (CI)] of C_{max} and $AUC_{0\text{-last}}$ (4-mg tablet/1-mg tablet) were 0.920 [0.845-1.002] and 0.914 [0.861-0.971], respectively.

The geometric mean ratios [90% CI] of C_{max} and $AUC_{0\text{-inf}}$ (fed/fasted) were 0.917 [0.842-0.999] and 0.908 [0.855-0.964], respectively.

4.(i).A.(2) Food and calcium effects (Study M0618, Attached document 5.3.1.1-02)

A three-treatment, three-period crossover study of lusutrombopag was conducted in 15 non-Japanese healthy adult subjects. In each period, the subjects received a single dose of (1) three 0.25-mg tablets under fasted conditions, (2) three 0.25-mg tablets after a high fat meal, or (3) three 0.25-mg tablets in combination with calcium carbonate 4 g under fasted conditions (with an 11-day washout period between treatments).

C_{max} and area under the plasma concentration-time curve from time 0 up to infinity ($AUC_{0\text{-inf}}$) were measured. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0\text{-inf}}$ (fed/fasted) were 0.9715 [0.8640-1.0924] and 1.0230 [0.9447-1.1077], respectively.

The geometric mean ratios [90% CI] of C_{max} and $AUC_{0\text{-inf}}$ (lusutrombopag + calcium carbonate/lusutrombopag administered under fasted conditions) were 1.0785 [0.9591-1.2126] and 0.9885 [0.9129-1.0704], respectively.

4.(i).B Outline of the review by PMDA

PMDA' s view on the food effect on the administration of the proposed drug product:

The food effect study should have been conducted using the 3-mg tablet, the proposed drug product, because the 4 mg tablet, which was actually used in the study, had a different strength from that of the proposed product. However, the food effect on the proposed product is predictable from the data of the food effect study using the 4-mg tablet, because C_{max} and AUC of lusutrombopag have been shown to increase with increasing doses between 1 to 50 mg, and because the proposed product is bioequivalent to the 4-mg tablet. In addition, no food effect was shown in the pharmacokinetic profile of lusutrombopag following administration of the 4-mg tablet. Thus the pharmacokinetic profile of lusutrombopag in the proposed product is unlikely to be affected by food.

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

The pharmacokinetic parameters are expressed as mean or mean (coefficient of variation [CV] %) unless otherwise specified.

4.(ii).A.(1) *In vitro* studies using human biomaterials

4.(ii).A.(1).1) Plasma protein binding and distribution in blood cells (Attached document 5.3.2.1-01 to 5.3.2.1-03)

When lusutrombopag at 5, 20, or 50 μg/mL (final concentration) was added to human plasma samples, the plasma protein binding was 99.996% to 99.998%.

When ^{14}C-labeled lusutrombopag at 5 μg/mL and diazepam, warfarin, or digitoxin (0-169 μM) were added to human serum albumin (0.1%) samples, the protein binding of lusutrombopag was 99.8324% in the absence of warfarin, diazepam, or digitoxin and 99.7055% to 99.8233% in the presence of warfarin, diazepam, or digitoxin.

^{14}C-labeled lusutrombopag at 1 or 5 μg/mL and diazepam or warfarin (0-10 μM) were added to human serum albumin (4%) samples. The protein binding of lusutrombopag was not affected by diazepam or warfarin.

When ^{14}C-labeled lusutrombopag at 0.5 to 50 μg/mL was added to human blood samples, the distribution of lusutrombopag in blood cells was 0.0697% to 0.353%.

4.(ii).A.(1).2) *In vitro* metabolism

(a) Metabolism of lusutrombopag (Attached document 5.3.2.2-01)

Human hepatocytes were incubated in medium containing ^{14}C-labeled lusutrombopag at 10 or 50 μM (n = 2/dose). Lusutrombopag and M1 (acyl-glucuronide of lusutrombopag) were mainly detected after incubation. Following incubation with lusutrombopag 10 μM, lusutrombopag accounted for 83.3% (n=1) and 77.4% (n=1) of the total radioactivity; and M1 accounted for 6.7% (n=1) and 15.3% (n=1) of the total radioactivity. Following incubation with lusutrombopag 50 μM, lusutrombopag accounted for 88.0% (n=1) and 90.0% (n=1) of the total radioactivity; and M1 accounted for 6.0% (n=1) and 6.8% (n=1) of the total radioactivity. The other metabolites detected were M4 (beta-oxidation carboxylate of lusutrombopag), M3 (5-keto form of lusutrombopag), M5 (de-hexyl form of lusutrombopag), and lusutrombopag with the hexyl-side chain hydroxylated.

(b) Enzyme inhibition (Attached document 5.3.2.2-03)

Inhibitory effects of lusutrombopag at 1 to 75 μM against metabolic reactions catalyzed by cytochrome P450 (CYP) isoforms were investigated using substrates of human liver microsome and CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A, or CYP4A11). Lusutrombopag inhibited phenacetin O-deethylation activity by CYP1A2 (the 50% inhibitory concentration [IC_{50}] of 34 μM), coumarin 7-hydroxylation activity by CYP2A6 (IC_{50}, 9.8 μM), bupropion hydroxylation activity by CYP2B6 (IC_{50}, 13 μM), paclitaxel 6α-hydroxylation activity by CYP2C8 (IC_{50}, 5.0 μM), diclofenac 4'-hydroxylation activity by CYP2C9 (IC_{50}, 7.2 μM), S-mephenytoin 4'-hydroxylation activity by CYP2C19 (IC_{50}, 27 μM), dextromethorphan O-demethylation activity by CYP2D6 (IC_{50}, 26 μM), testosterone 6β-hydroxylation activity by CYP3A (IC_{50}, 30 μM), midazolam 1'-hydroxylation activity by CYP3A (IC_{50}, 8.8 μM), nifedipine oxidation activity by CYP3A (IC_{50}, 14 μM), atorvastatin o-hydroxylation activity by CYP3A (IC_{50}, 11 μM), and laurate 12-hydroxylation activity by CYP4A11 (IC_{50}, 22 μM). Lusutrombopag did not inhibit chlorzoxazone 6-hydroxylation activity by CYP2E1 (IC_{50}, >75 μM). In addition, following preincubation of human liver microsome with lusutrombopag (1-75 μM) for 30 minutes, lusutrombopag inhibited phenacetin O-deethylation activity by CYP1A2 (IC_{50}, 12 μM), coumarin 7-hydroxylation activity by CYP2A6 (IC_{50}, 2.3 μM), bupropion hydroxylation activity by CYP2B6 (IC_{50}, 6.7 μM), paclitaxel 6α-hydroxylation activity by CYP2C8 (IC_{50}, 4.8 μM), diclofenac 4'-hydroxylation activity by CYP2C9 (IC_{50}, 8.6 μM), S-mephenytoin 4'-hydroxylation activity by CYP2C19 (IC_{50}, 12 μM), dextromethorphan O-demethylation activity by CYP2D6 (IC_{50}, 12 μM), testosterone 6β-hydroxylation activity by CYP3A (IC_{50}, 14 μM), midazolam 1'-hydroxylation activity by CYP3A (IC_{50}, 5.0 μM), nifedipine oxidation activity by CYP3A (IC_{50}, 11 μM) atorvastatin o-hydroxylation activity by CYP3A (IC_{50}, 8.9 μM), and laurate 12-hydroxylation activity by CYP4A11 (IC_{50}, 23 μM), but did not inhibit chlorzoxazone 6-hydroxylation activity by CYP2E1 (IC_{50}, >75 μM).

Inhibitory effects of lusutrombopag against metabolic reactions catalyzed by CYP isoforms were investigated using substrates of human liver microsome and CYP isoforms (lusutrombopag 1.3-50 μM for CYP2C8, lusutrombopag 1.8-72 μM for CYP2C9, lusutrombopag 2.2-75 μM for CYP3A). Lusutrombopag inhibited paclitaxel 6α-hydroxylation activity by CYP2C8 (inhibitory constant, 3.5 μM), diclofenac 4'-hydroxylation activity by CYP2C9 (inhibitory constant, 5.3 μM), and midazolam 1'-hydroxylation activity by CYP3A (inhibitory constant, 4.5 μM)

.

(c) Enzyme induction (Attached document 5.3.2.2-04)

Human hepatocytes were incubated in medium containing lusutrombopag at 1 to 10 μM (final concentration) to investigate induction of CYP isoforms (CYP1A2, CYP2C9, CYP3A) and uridine-diphosphate glucuronosyltransferase (UGT) isoforms (UGT1A2, UGT1A6, UGT2B7). Lusutrombopag did not induce any of the CYP or UGT isoforms.

4.(ii).A.(2) Studies in healthy adult subjects

4.(ii).A.(2).1) Single oral dose study in Japanese subjects (Study M0611, Attached document 5.3.3.1-01)

Table 6 shows pharmacokinetic parameters of lusutrombopag and (+)-lusutrombopag in 36 Japanese healthy adult male subjects who orally received a single dose of lusutrombopag at 1, 2, 4, 10, 25, or 50 mg. In all the dose groups, urinary concentrations of lusutrombopag and (+)-lusutrombopag were below the lower limit of quantitation.

Table 6. Pharmacokinetic parameters of lusutrombopag and (+)-lusutrombopag following a single dose of lusutrombopag (modified excerpt from the submitted data)

Dose (mg)	n	t_{max}[a)] (hr)	C_{max} (μg/mL)	$AUC_{0\text{-last}}$ (μg·hr/mL)	$AUC_{0\text{-inf}}$ (μg·hr/mL)	$t_{1/2}$ (hr)	CL/F (L/hr)
Lusutrombopag							
1	6	4.0	0.0449 (29.1)	1.18 (21.1)	1.34 (21.5)	23.2 (17.8)	0.748 (21.4)
2	6	3.8	0.0897 (15.8)	2.04 (15.4)	2.21 (16.0)	20.4 (7.9)	0.905 (15.9)
4	6	3.8	0.213 (5.7)	4.84 (7.9)	5.29 (8.1)	20.5 (9.0)	0.757 (8.1)
10	6	3.5	0.593 (16.0)	13.8 (16.2)	15.2 (17.1)	21.2 (9.1)	0.657 (17.1)
25	6	4.0	1.23 (22.5)	26.4 (22.9)	28.3 (24.1)	19.3 (7.9)	0.883 (24.1)
50	6	4.0	2.14 (16.3)	48.7 (17.8)	53.5 (19.5)	21.1 (19.4)	0.934 (19.4)
(+)-lusutrombopag							
1	6	N.D.	N.D.	N.D.	N.D.	N.D.	-
2	6	N.D.	N.D.	N.D.	N.D.	N.D.	-
4	6	N.D.	N.D.	N.D.	N.D.	N.D.	-
10	6	3.3	0.00320 (11.8)	0.0186 (15.3)	0.0317 (16.7)	7.04 (36.1)	-
25	6	2.5	0.00691 (31.1)	0.0500 (29.2)	0.0599 (26.6)	5.17 (9.2)	-
50	6	3.8	0.0123 (10.9)	0.111 (12.2)	0.134 (14.5)	9.69 (27.5)	-

Geometric mean (% CV)
[a)] Median; N.D., Below the lower limit of quantitation; -, Not calculated; CL/F, Apparent total body clearance

4.(ii).A.(2).2) Multiple oral dose study in Japanese subjects (Study M0613, Attached document 5.3.3.1-02)

Table 7 shows pharmacokinetic parameters of lusutrombopag in 18 Japanese healthy adult male subjects who orally received lusutrombopag once daily at 0.25, 0.5, or 2 mg for 14 days. In all the dose groups, plasma concentrations of (+)-lusutrombopag as well as urinary concentrations of lusutrombopag and (+)-lusutrombopag were below the lower limit of quantitation.

Table 7. Pharmacokinetic parameters of lusutrombopag following multiple doses of lusutrombopag (modified excerpt from the submitted data)

Dose (mg)	Measurement time point	n	t_{max}[a)] (hr)	C_{max} (μg/mL)	$AUC_{0\text{-}\tau}$ (μg·hr/mL)	$t_{1/2}$ (hr)	R_{Cmax}[b)]	R_{AUC}[b)]
0.25	Day 1	6	8.0	0.00848 (6.8)	0.135 (8.1)	-	-	-
	Day 7	6	8.0	0.0197 (5.3)	0.333 (11.9)	-	2.32 (6.3)	2.47 (7.0)
	Day 14	6	6.5	0.0180 (11.7)	0.317 (13.0)	27.8 (6.5)	2.12 (10.4)	2.34 (8.7)
0.5	Day 1	5	8.0	0.0192 (9.6)	0.327 (7.1)	-	-	-
	Day 7	5	8.0	0.0349 (13.6)	0.657 (12.8)	-	1.81 (10.1)	2.01 (7.3)
	Day 14	5	6.0	0.0389 (13.7)	0.703 (10.4)	32.0 (10.2)	2.03 (13.5)	2.15 (7.2)
2	Day 1	6	4.0	0.0783 (16.7)	1.28 (12.3)	-	-	-
	Day 7	6	4.0	0.159 (16.6)	2.67 (12.6)	-	2.03 (7.1)	2.09 (5.7)
	Day 14	5	4.0	0.156 (5.7)	2.63 (8.1)	30.1 (11.7)	2.11 (7.5)	2.13 (11.0)

Geometric mean (% CV)
[a)] Median; [b)] Ratio to values on Day 1; -, Not calculated

4.(ii).A.(2).3) Single oral dose study in Caucasian subjects (Study M0614, Attached document 5.3.3.1-03)

Table 8 shows pharmacokinetic parameters of lusutrombopag in 8 Caucasian healthy adult male subjects who orally received a single dose of lusutrombopag at 2 mg. Plasma concentrations of (+)-lusutrombopag were below the lower limit of quantitation. Table 8 also shows pharmacokinetic parameters of lusutrombopag in 10 Caucasian healthy adult male subjects who orally received a single dose of lusutrombopag at 0.1 or 0.25 mg. Plasma concentrations of (+)-lusutrombopag following

administrations at 0.1 and 0.25 mg were not measured.

Table 8. Pharmacokinetic parameters of lusutrombopag following a single dose of lusutrombopag (modified excerpt from the submitted data)

Dose (mg)	n	t_{max}[a)] (hr)	C_{max} (μg/mL)	$AUC_{0\text{-last}}$ (μg·hr/mL)	$AUC_{0\text{-inf}}$ (μg·hr/mL)	$t_{1/2}$ (hr)	CL/F (L/hr)	MRT (hr)
0.1	10	5.0	0.00219 (19.3)	0.0594 (21.6)	0.0646 (20.7)	24.8 (15.4)	1.55 (20.6)	34.6 (14.5)
0.25	10	5.5	0.00660 (12.5)	0.194 (17.6)	0.201 (17.7)	29.5 (25.2)	1.24 (17.6)	36.6 (12.8)
2	8	5.0	0.0850 (12.9)	2.20 (13.2)	2.26 (13.7)	29.1 (20.0)	0.886 (13.9)	33.2 (14.5)

Geometric mean (% CV)
[a)] Median; MRT, Mean residence time

4.(ii).A.(2).4) Multiple oral dose study in non-Japanese subjects (Study M0615, Attached document 5.3.3.1-04 [Reference data])

Table 9 shows pharmacokinetic parameters of lusutrombopag in 24 non-Japanese healthy adult male subjects who orally received lusutrombopag once daily at 0.25, 0.5, 0.75, or 1 mg for 14 days. Urinary concentrations of lusutrombopag were below the lower limit of quantitation in all the dose groups.

Table 9. Pharmacokinetic parameters of lusutrombopag following multiple doses of lusutrombopag (modified excerpt from the submitted data)

Dose (mg)	Measurement time point	n	t_{max}[a)] (hr)	C_{max} (ng/mL)	$AUC_{0\text{-}\tau}$ (ng·hr/mL)	$t_{1/2}$ (hr)	R_{Cmax}[b]	R_{AUC}[b]
0.25	Day 1	6	5.00	6.73 (20.0)	94.8 (19.8)	-	-	-
	Day 7	6	4.50	12.2 (27.7)	194 (29.9)	-	1.81 (11.0)	2.05 (12.8)
	Day 14	6	5.00	11.5 (20.9)	190 (20.3)	29.4 (5.9)	1.71 (13.8)	2.00 (7.0)
0.5	Day 1	6	5.00	12.5 (14.7)	182 (14.2)	-		-
	Day 7	6	5.00	22.4 (14.6)	370 (14.6)	-	1.79 (4.6)	2.04 (11.6)
	Day 14	5	5.00	21.8 (16.6)	347 (17.6)	28.3 (10.3)	1.81 (5.4)	1.96 (6.1)
0.75	Day 1	6	5.00	22.8 (14.6)	287 (16.5)	-		-
	Day 7	6	5.00	37.0 (23.1)	564 (22.6)	-	1.62 (10.3)	1.93 (11.2)
	Day 14	4	4.50	35.5 (18.6)	528 (24.3)	27.0 (12.2)	1.58 (9.6)	1.82 (6.6)
1	Day 1	6	5.00	29.0 (15.0)	423 (20.6)	-	-	-
	Day 7	6	4.50	52.8 (20.1)	833 (19.8)	-	1.82 (9.5)	1.97 (11.8)
	Day 14	2	4.00	50.9 (9.2)	769 (2.7)	27.6 (15.8)	1.82 (8.5)	1.94 (23.7)

Geometric mean (% CV)
[a)] Median; [b], Ratio to values on Day 1; -, Not calculated

4.(ii).A.(2).5) Mass balance study (Study M0619, Attached document 5.3.3.1-05)

A single oral dose of ^{14}C-labeled lusutrombopag 2 mg was administered to 7 non-Japanese healthy adult subjects. The median t_{max} of radioactivity concentrations was 5.00 hours in both plasma and blood. C_{max} was 82.8 ng Eq/g (coefficient of variation [CV], 22.6%) in plasma and 44.1 ng Eq/g (CV, 23.3%) in blood. $AUC_{0\text{-inf}}$ was 3370 ng Eq·hr/g (CV, 24.7%) in plasma and 1950 ng Eq·hr/g (CV, 23.9%) in blood. $t_{1/2}$ was 70.7 hours (CV, 20.2%) in plasma and 111 hours (CV, 14.9%) in blood. Pharmacokinetic parameters of plasma lusutrombopag were as follows: the median t_{max}, 5.00 hours; C_{max}, 66.2 ng/mL (CV, 25.6%); $AUC_{0\text{-inf}}$, 1880 ng·hr/mL (CV, 30.1%); and $t_{1/2}$, 25.7 hours (CV, 6.9%).

Within 336 hours post-dose, 83.13% and 1.06% of the administered radioactivity were excreted in feces and urine, respectively. The percentages of lusutrombopag and its metabolites found in feces were as follows: lusutrombopag, 16.22% (percentage of the administered radioactivity); M5 (*O*-propanol metabolite) plus M6 (*O*-acetate metabolite) combined, 17.93% (M5 estimated to be approximately 2%, M6 estimated to be approximately 16%); M7 (*O*-ethane-1,2-diol metabolite), 16.86%; M4, 1.53%; M2 (taurine conjugate of M4), 0.66%. In urine, the radioactivity collected was too low to quantitate lusutrombopag and its metabolites.

4.(ii).A.(3) Studies in patients

4.(ii).A.(3).1) Japanese phase II study in Japanese patients with chronic liver disease (Study M0623, Attached document 5.3.5.1-01)

Lusutrombopag was orally administered once daily at 0.25, 0.5, 1.0, 1.5, or 2.0 mg for 7 days to 34 Japanese patients with chronic liver disease. Pharmacokinetic parameters of lusutrombopag following 7-day treatment are shown in Table 10.

Table 10. Pharmacokinetic parameters of lusutrombopag following multiple doses of lusutrombopag (modified excerpt from the submitted data)

Dose (mg)	n	t_{max}[a)] (hr)	C_{max} (ng/mL)	$AUC_{0-\tau}$ (ng·hr/mL)	λz (1/hr)	$t_{1/2}$ (hr)	CL/F (L/hr)
0.25	5	8.0	14.3 (32.6)	266.6 (33.7)	0.0158 (22.1)	43.9 (22.1)	0.938 (33.7)
0.5	6	8.0	27.2 (20.6)	548.0 (23.6)	0.0217 (11.8)	31.9 (11.8)	0.912 (23.6)
1	5	8.0	72.6 (39.5)	1352 (36.6)	0.0193 (25.9)	36.0 (25.9)	0.740 (36.6)
1.5	6	7.0	99.6 (40.7)	1843 (30.2)	0.0180 (22.8)	38.5 (22.8)	0.814 (30.2)
2	9	6.0	115 (53.2)	2146 (52.1)	0.0175 (23.5)	39.5 (23.5)	0.932 (52.1)

Geometric mean (% CV)
[a)] Median; λz, Terminal phase elimination rate constant

4.(ii).A.(3).2) Japanese phase II study in Japanese patients with chronic liver disease (Study M0625, Attached document 5.3.5.1-02)

Lusutrombopag was orally administered once daily at 2.5, 3, or 4 mg for 7 days to 21 Japanese patients with chronic liver disease. Pharmacokinetic parameters of lusutrombopag after 5 days of treatment are shown in Table 11.

Table 11. Pharmacokinetic parameters of lusutrombopag following multiple doses of lusutrombopag (modified excerpt from the submitted data)

Dose (mg)	n	t_{max}[a)] (hr)	C_{max} (ng/mL)	$AUC_{0-\tau}$ (ng·hr/mL)	CL/F (L/hr)
2.5	6	7.0	182 (25.0)	3540 (24.5)	0.706 (24.5)
3	7	6.0	250 (32.0)	4799 (32.9)	0.625 (32.9)
4	6	6.0	342 (27.1)	6264 (34.7)	0.639 (34.7)

Geometric mean (% CV)
[a)] Median

4.(ii).A.(3).3) Japanese phase II study in Japanese patients with chronic liver disease (Study M0626, Attached document 5.3.5.1-03)

Lusutrombopag at 2, 3, or 4 mg or placebo was orally administered once daily for 7 days to 46 Japanese patients with chronic liver disease. Plasma concentrations of lusutrombopag increased with increasing doses on Day 5 immediately before dosing and at 6 to 8 hours post-dose, as well as at 24, 48, 72, 120, and 168 hours after the final dose. $t_{1/2}$ of lusutrombopag was 35.5 hours (CV, 17.6%) in the 2 mg group, 38.3 hours (CV, 18.7%) in the 3 mg group, and 36.5 hours (CV, 20.8%) in the 4mg group.

4.(ii).A.(3).4) Platelet function study (Study M061B, Attached document 5.3.4.2-01)

Eight Japanese patients with chronic liver disease received oral lusutrombopag 3 mg once daily for 7 days. The following platelet functions were investigated 9 to 14 days after the first dose: platelet aggregation (maximum aggregation rate in the presence of adenosine diphosphate [ADP] at 1 or 10 μM and collagen at 2 or 5 μg/mL, and the presence or absence of secondary aggregation); platelet release (expression rate of P-selectin in the presence or absence of ADP); platelet morphological abnormalities (peripheral blood smear preparations). Following administration of lusutrombopag, platelet aggregation remained unchanged without abnormalities even in the presence of any of the inducer, and the maximum aggregation rate was not largely different from baseline. In terms of the platelet release, the expression of P-selectin was enhanced by an inducer (ADP) after administration of lusutrombopag, and the expression rate of P-selectin was similar for pre- and postdose. There was no trend of increasing morphological abnormality following administration of lusutrombopag. The platelet count increased during the period of 5 days to 14 days after the first dose, and peaked at 14 days after the first dose.

4.(ii).A.(3).5) Population pharmacokinetic analysis (Attached document 5.3.3.5-01)

Population pharmacokinetic (PPK) analysis was performed based on data for plasma lusutrombopag concentrations in 101 patients with chronic liver disease in Japanese phase II studies (Studies M0623, M0625, and M0626; 796 data) and in 95 subjects in the Japanese clinical pharmacology studies (Studies M0611, M0612, M0613, and M061A; 3217 data).

A PPK model was constructed by a two-stage approach. At the first stage, the PPK model was constructed from data in the Japanese clinical pharmacology studies (Studies M0611, M0612, M0613, M061A) according to the difference in lusutrombopag formulation and food effect. At the second stage, the data set used in the first stage were combined with the data in the Japanese phase II studies in patients with chronic liver disease (Studies M0623, M0625, M0626). Using the combined data, covariates in the PPK model at the first stage were examined again to construct the final PPK model.

The pharmacokinetics of lusutrombopag was described as a three-compartment model with first order absorption. At the second stage, the following patient characteristics were selected as covariates potentially affecting pharmacokinetic parameters: age (51.5 [20.0-84.0] years, median [minimum to maximum]), body weight (62.5 [37.0-96.7] kg), creatinine clearance (109.93 [31.82-195.87] mL/min), sex (155 male subjects, 41 female subjects), and Child Pugh class (normal, 95 subjects; Class A, 55 subjects; and Class B, 46 subjects). Body weight, sex, and Child Pugh class were selected as covariates significantly affecting CL/F. Age and body weight were selected as covariates significantly affecting apparent volume of distribution of the central compartment (V2/F).

The population mean of each parameter in the final PPK model was 0.725 L/hr for CL/F and 17.6 L for V2/F. The inter-individual variability was 21.8% for CL/F, 11.8% for V2/F, and 34.4% for first-order absorption rate constant (KA).

4.(ii).A.(3).6) Population pharmacokinetic analysis/pharmacodynamic analysis (Attached document 5.3.4.2-02)

PPK/pharmacodynamic (PD) analysis was performed based on 1096 data for platelet counts in 101 patients with chronic liver disease in 3 Japanese phase II studies (Studies M0623, M0625, M0626), to investigate the relationship between plasma lusutrombopag concentrations and platelet counts. In the PPK/PD model, the pharmacokinetic parameters were estimated from the final PPK model and data on plasma lusutrombopag concentrations in the 3 Japanese phase II studies by empirical Bayes method. Data on platelet counts in the 3 Japanese phase II studies were described according to the 5-compartment model with the platelet maturation process taken into account.

Age, body weight, sex, and Child Pugh class were investigated as potential covariates for therapeutic effect parameter indicating the slope of the response-concentration relationship (SLOP), but none of them were statistically significant covariates. The slope (%, relative standard error) of the relationship between plasma lusutrombopag concentrations and platelet counts in the PPK/PD model was 9.33 mL/μg (13.8%).

Patients who received lusutrombopag 3 mg once daily for 7 days were divided into subgroups according to body weight (<50 kg, ≥50 kg and <70 kg, ≥70 kg). The probability of a platelet count >200,000/μL during the treatment period was 0.60% in the <50 kg subgroup, 0.20% in the ≥50 kg and <70 kg subgroup, and 0.00% in the ≥70 kg subgroup. The probability of a platelet count >50,000/μL between 9 and 14 days after the first dose was 88.4% in the <50 kg subgroups, 83.4% in the ≥50 kg and <70 kg subgroup, and 79.2% in the ≥70 kg subgroup.

4.(ii).A.(4) Intrinsic factors

4.(ii).A.(4).1) Study in subjects with hepatic impairment (Study M0616, Attached document 5.3.3.3-01)

A single oral dose of lusutrombopag 0.75 mg was administered to non-Japanese subjects (8 with normal hepatic function, 8 with mild hepatic impairment [Child Pugh class A], and 8 with moderate hepatic impairment [Child Pugh class B]). The geometric mean ratios [90% CI] of C_{max} of lusutrombopag were 1.03 [0.80-1.33] (mild hepatic impairment/normal hepatic function) and 1.00 [0.77-1.29] (moderate hepatic impairment/normal hepatic function). The geometric mean ratios [90% CI] of $AUC_{0\text{-inf}}$ of

lusutrombopag were 1.05 [0.85-1.30] (mild hepatic impairment/normal hepatic function) and 1.20 [0.97-1.49] (moderate hepatic impairment/normal hepatic function).

4.(ii).A.(5) Drug interactions

4.(ii).A.(5).1) Midazolam (Study M0617, Attached document 5.3.3.4-01)

The effects of lusutrombopag on pharmacokinetics of midazolam were evaluated in 15 non-Japanese healthy adult male and female subjects who received a single oral dose of midazolam 5 mg alone on Day 1, a single oral dose of lusutrombopag 1.5 mg on Day 2, oral lusutrombopag 0.75 mg once daily for 6 days from Day 3 to Day 7, and a single dose of lusutrombopag 0.75 mg plus midazolam 5 mg on Day 8. The geometric mean ratio [90% CI] of C_{max} was 1.01 [0.908-1.13] (lusutrombopag plus midazolam/midazolam alone). The geometric mean ratio [90% CI] of $AUC_{0\text{-inf}}$ was 1.04 [0.967-1.11] (lusutrombopag plus midazolam/midazolam alone).

4.(ii).A.(6) Thorough QT study (Study M061D, Attached document 5.3.4.1-01)

A four-period crossover study was conducted in 60 Japanese healthy adult male and female subjects, to investigate the effects of lusutrombopag on QT interval. In each period, the subjects received a single dose of (1) lusutrombopag at 6 mg, (2) lusutrombopag at 24 mg, (3) moxifloxacin at 400 mg, or (4) placebo (with a 28-day washout period between treatments).

The median t_{max} of lusutrombopag was 4.0 hours for both 6 and 24 mg. C_{max} of lusutrombopag was 232 ng/mL (CV, 16.5%) for 6 mg and 1030 ng/mL (CV, 18.0%) for 24 mg. $AUC_{0\text{-last}}$ of lusutrombopag was 3504 ng·hr/mL (CV, 14.7%) for 6 mg and 15,170 ng·hr/mL (CV, 17.0%) for 24 mg.

The Fridericia corrected QTc interval (QTcF) was adjusted for baseline and corrected for placebo to determine ΔΔQTcF. The upper limit of the two-sided 90% CI of the least squares mean of ΔΔQTcF was up to 3.85 ms (lusutrombopag 6 mg) and up to 4.36 ms (lusutrombopag 24 mg). The estimated least squares mean of ΔΔQTcF following administration of moxifloxacin ranged from 7.68 to 15.06 ms. These data show that lusutrombopag has no clinically significant effects on the QT interval.

4.(ii).B. Outline of the review by PMDA

4.(ii).B.(1) Interactions with CYP3A inhibitors or inducers

The applicant concluded that CYP3A inhibitors and inducers had limited effects on the pharmacokinetics of lusutrombopag based on data from non-clinical studies and mass balance studies. PMDA asked the applicant to explain the reasons for the conclusion, because lusutrombopag was shown to be metabolized by CYP3A in *in vitro* study.

The applicant's response:

In the human mass balance study, approximately 83% and approximately 1% of the administered radioactivity were excreted in feces and urine, respectively. The metabolites found in feces, the main excretion route, were lusutrombopag (approximately 16% of the administered radioactivity), M5 (approximately 2% of the administered radioactivity), M3 (approximately 2% of the administered radioactivity), M1 (approximately 2% of the administered radioactivity), and 4 types of potentially β-oxidation-related metabolites (M6, M7, M4, M2) (approximately 35% of the administered radioactivity). (M6, M7, M4, and M2 are produced by 6-hydroxylation or β oxidation of O-hexyl-side chain [ω oxidation] of lusutrombopag). All the metabolites except for M1 were considered to be produced by oxidation and/or further metabolisms (oxidation, conjugation, etc.). In a study where human hepatocytes were incubated with ketoconazole to inhibit CYP3A, the inhibitory rate against oxidative metabolism including 6-hydroxylated metabolites was approximately 20%. When lusutrombopag and M1 found in feces (approximately 16% and 2%, respectively) were subtracted from the total radioactivity collected in feces (approximately 83%), the resulting 65% was of oxidative metabolites. Accordingly, CYP3A is assumed to contribute to elimination of up to approximately 13% of lusutrombopag. According to a report on the metabolism contribution rate and AUC variations (Brian W et al. *Drug-Drug Interactions Second Edition.* 2008;231-358), when CYP3A contributes to metabolism of approximately 13% of lusutrombopag, CYP3A inhibition is estimated to increase AUC by up to 1.1-fold.

Of 149 patients in Japanese phase II and III studies (Studies M0623, M0625, M0626, M0631), 33 patients received concomitant CYP3A inhibitors and 42 patients received concomitant CYP3A inducers. Plasma lusutrombopag concentrations in patients who received concomitant CYP3A inhibitors or

inducers were not largely different from those in patients who did not, and fell within the distribution range of concentrations in patients not receiving the inhibitors or inducers, although only a limited number of patients received potent or moderate CYP3A inhibitors or inducers. These results were almost consistent with the above estimates.

Based on the above, the effects of CYP3A inhibitors and inducers on pharmacokinetics of lusutrombopag were determined to be small.

PMDA has accepted the applicant's explanation that contribution of CYP3A to metabolism of lusutrombopag is small and the effects of CYP3A inhibitors and inducers on pharmacokinetics of lusutrombopag are small.

4.(ii).B.(2) Use of lusutrombopag in patients with hepatic impairment

PMDA was concerned about pharmacokinetics of lusutrombopag in patients with moderate hepatic impairment (Child Pugh class B), because a foreign clinical pharmacology study (Study M0616) showed that $AUC_{0\text{-inf}}$ was 20% greater in subjects with moderate hepatic impairment than in healthy adult subjects, and because PPK analysis showed that CL/F was 12.8% lower in patients with moderate hepatic impairment than in healthy adult subjects or patients with mild hepatic impairment (Child Pugh class A). PMDA therefore asked the applicant to explain the reasons for the applicant's conclusion that moderate hepatic impairment had only a small effect on pharmacokinetics of lusutrombopag.

The applicant's response:

Moderate hepatic impairment is considered to have only a small effect on the pharmacokinetics of lusutrombopag for the following reasons: (1) In Study M0616, the geometric mean ratio of $AUC_{0\text{-inf}}$ was 1.20 (subjects with moderate hepatic impairment/healthy adult subjects), but the 90% CI crossed 1. (2) In the PPK analysis, the ratio of CL/F estimate [95% CI] was 0.872 [0.798-0.946] (subjects with moderate hepatic impairment/ the other subjects); the upper limit of the 95% CI was below 1 but close to 1, with the lower limit being approximately 0.8. Using the PPK/PD model and data on the characteristics of 101 patients in Studies M0623, M0625, and M0626 (body weight, age, sex, Child Pugh class), platelet counts in patients with chronic liver disease following multiple doses of lusutrombopag at 3 mg were simulated. The simulated count overtime did not differ largely between patients with mild hepatic impairment and patients with moderate hepatic impairment. The following parameters were also estimated to be similar in patients with mild and moderate hepatic impairment: (1) the maximum platelet count, (2) the probability of a platelet count >200,000/μL during the treatment period (until 30 days after the first dose), and (3) the probability of a platelet count >50,000/μL between Day 9 and Day 14.

The above-presented simulation using the PPK/PD model and patient characteristics data from Studies M0623, M0625, and M0626 suggest that moderate hepatic impairment had only small effect on pharmacokinetics of lusutrombopag, without clinical significance, thus requiring no dose adjustment.

PMDA's view:

The applicant explained that moderate hepatic impairment had only a small effect on the pharmacokinetics of lusutrombopag or platelet count, because changes in platelet count were estimated to be similar in patients with moderate hepatic impairment (with 1.2 times higher $AUC_{0\text{-inf}}$ than healthy adult subjects) and patients slight hepatic impairment (with slightly higher lusutrombopag exposure than healthy adult subjects). PMDA understands this explanation. However, clinical effects of the increase in $AUC_{0\text{-inf}}$ remain unclear. Therefore the necessity of issuing alert concerning moderate hepatic impairment should be determined based on the safety data in clinical studies [see "4.(iii).B.(5).3).(a) Safety according to Child Pugh class (A or B)"].

The effects of severe hepatic impairment (Child Pugh class C) on pharmacokinetics of lusutrombopag and platelet count remain unknown, because lusutrombopag has never been administered to patients with severe hepatic impairment in clinical studies. $AUC_{0\text{-inf}}$ in subjects with moderate hepatic impairment was 1.2 times that in healthy adult subjects in Study M0616; this suggests that $AUC_{0\text{-inf}}$ in patients with severe hepatic impairment may become higher than that in those with moderate hepatic impairment. Appropriateness of lusutrombopag therapy and the necessity of cautionary statement for patients with severe hepatic impairment should be carefully determined based on the clinical usefulness in these patients, etc. Use of lusutrombopag in patients with severe hepatic impairment is discussed also

in “4.(iii).B.(5).3).(b) Use of lusutrombopag in patients with severe hepatic impairment (Child Pugh class C).”

4.(iii) Summary of clinical efficacy and safety

4.(iii).A Summary of the submitted data

The applicant submitted evaluation data: the results from 5 phase I studies, 3 phase II studies, 1 phase III study in Japan, and 4 phase I studies conducted overseas [for BE as well as pharmacokinetics and PD, see “4.(i) Summary of biopharmaceutic studies and associated analytical methods” and “4.(ii) Summary of clinical pharmacology studies”]. The main study results are shown below.

4.(iii).A.(1) Phase I studies

4.(iii).A.(1).1) Japanese single dose study (Study Protocol M0611, Attached document 5.3.3.1-01 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, double-blind study was conducted to evaluate the safety, tolerability, and pharmacokinetics of lusutrombopag following a single-dose administration at a single study center in Japan.[1)] A single dose of lusutrombopag at 1, 2, 4, 10, 25, 50 mg, or placebo (all in liquid preparation) was orally administered to 47 healthy adult male subjects (6 subjects each in the lusutrombopag groups, 11 subjects in the placebo group) under fasted conditions.

Adverse events occurred in 1 subject in the 1 mg group (white blood cell count increased), 1 subject in the 2 mg group (eosinophil percentage increased), 4 subjects in the 10 mg group (platelet count increased, platelet count increased/blood creatine phosphokinase increased, C-reactive protein increased, C-reactive protein increased/blood creatine phosphokinase increased [1 subject each]), 1 subject in the 25 mg group (platelet count increased), 3 subjects in the 50 mg group (platelet count increased [2 subjects], platelet count increased and eosinophil percentage increased [1 subject]), and 1 subject in the placebo group (C-reactive protein increased). Neither serious adverse events nor deaths occurred. Clinically relevant changes were not observed in vital signs or ECG.

4.(iii).A.(1).2) Japanese multiple dose study (Study Protocol M0613, Attached document 5.3.3.1-02 [[redacted] to [redacted] 20[redacted]])

A randomized, double-blind study was conducted to evaluate the safety, tolerability, and pharmacokinetics of lusutrombopag following multiple-dose administration at a single study center in Japan. Lusutrombopag at 0.25 mg (liquid preparation), 0.5 mg (liquid preparation), or 2 mg (tablet), or placebo (liquid preparation or tablet) was orally administered to 24 healthy adult male subjects (6 subjects per group) once daily after breakfast for 14 days.

In the study, the dose of lusutrombopag was designed to be increased in the order of 2, 4, 6 mg, but 5 subjects receiving 2 mg lusutrombopag showed a platelet count exceeding 500,000/μL, meeting the dose-increase discontinuation criteria. As previously planned, the dose was reduced, and thus the doses of 2, 0.5, 0.25 mg were administered in this order.

Adverse events occurred in 6 subjects in the 2 mg group (platelet count increased [6 subjects]), 3 subjects in the 0.5 mg group (gastroenteritis, platelet count increased, blood corticotrophin increased [1 subject each]), 1 subject in the 0.25 mg group (alanine aminotransferase [ALT] increased), and 2 subjects in the placebo group (arthropod sting, ALT increased and aspartate aminotransferase [AST] increased [1 subject each]). Neither serious adverse events nor deaths occurred. Clinically relevant changes were not observed in vital signs or ECG.

4.(iii).A.(2) Phase II studies

4.(iii).A.(2).1) Japanese phase II dose-finding study (Study Protocol M0623, Attached document 5.3.5.1-01 [[redacted] to [redacted] 20[redacted]])

A randomized, open-label, parallel-group study was conducted at 27 study sites in Japan to evaluate the efficacy and safety of lusutrombopag in patients receiving multiple oral doses of lusutrombopag prior to percutaneous hepatic cancer ablation, and to find the optimal dose. Lusutrombopag was orally

1) Designed to start at the lowest dose and increase the dose by confirming the safety. When this study was planned, further high doses of 75 and 100 mg were scheduled, but transfer to ≥75 mg doses was cancelled to ensure the safety in the subjects.

administered to patients with thrombocytopenia due to chronic liver disease once daily for 7 days prior to percutaneous hepatic cancer ablation (target sample size, 12 subjects per dose group).

In the study, the starting dose was 0.25, 0.5, or 1 mg (the 0.25, 0.5, and 1 mg groups). An interim analysis was to be performed when data from approximately 6 subjects of each dose group become available. If the interim analysis has revealed insufficient efficacy or safety issues at a starting dose, the dose was to be reviewed and a new dose group was to be added where necessary. As a result of the interim analysis, data collection at the starting doses was discontinued, and the 1.5 and 2 mg groups were added. Subsequently, data collection at 1.5 mg dose was also discontinued, as a result of the interim analysis in the 1.5 and 2 mg groups. On each day between Day 5 and Day 7, platelet count was measured before administration of the study drug, and treatment was discontinued when platelet count reached ≥50,000/μL as a result of a ≥20,000/μL increase from baseline.

The following are major inclusion criteria: Patients with current or past chronic liver disease due to type B or C hepatitis virus; patients scheduled to undergo percutaneous hepatic cancer ablation for primary hepatic cancer; patients with a platelet count <50,000/μL at screening; and patients able to be hospitalized from Days 5 to 14 after the first dose. Exclusion criteria include the following: Patients who had undergone splenectomy; patients with hepatic impairment of Child-Pugh class C; patients with current or past thrombosis; and patients in whom portal blood flow is not hepatopetal. Patients were randomized by the minimization method according to the severity of hepatic impairment (Child-Pugh class A or B).

Of 35 randomized subjects (5 in the 0.25 mg group, 6 in the 0.5 mg group, 5 in the 1.0 mg group, 7 in the 1.5 mg group, 12 in the 2.0 mg group), 34 subjects (5 in the 0.25 mg group, 6 in the 0.5 mg group, 5 in the 1.0 mg group, 6 in the 1.5 mg group, 12 in the 2.0 mg group) were included in the safety analysis and the Full Analysis Set (FAS). One subject who met the exclusion criteria was excluded and thus did not receive the study drug. The FAS was the primary efficacy analysis population. One subject in the 0.5 mg group discontinued the study because of serious adverse events during the follow-up period. One subject in the 1.5 mg group who met the exclusion criteria also discontinued the study.

The primary efficacy endpoint was the percentage of patients with a platelet count ≥50,000/μL on Day 8 as a result of a ≥20,000/μL increase from baseline (responders). The percentage of responders in the FAS on Day 8 after the first dose was 0% (0 of 5 subjects) in the 0.25 mg group, 0% (0 of 6 subjects) in the 0.5 mg group, 0% (0 of 5 subjects) in the 1 mg group, 0% (0 of 6 subjects) in the 1.5 mg group, and 33.3% (4 of 12 subjects) in the 2 mg group.

The percentage of patients who received platelet transfusion[2)] during the study period (a secondary efficacy endpoint) was 80% (4 of 5 subjects) in the 0.25 mg group, 50% (3 of 6 subjects) in the 0.5 mg group, 60% (3 of 5 subjects) in the 1 mg group, 33.3% (2 of 6 subjects) in the 1.5 mg group, and 16.7% (2 of 12 subjects) in the 2 mg group. As a result of the platelet count evaluation, 3 subjects in the 2 mg group met the study treatment discontinuation criteria (a platelet count ≥50,000/μL as a result of a ≥20,000/μL increase from baseline). Of these, 2 subjects met the criteria on Day 5 and 1 subject on Day 6. On Day 8, the 2 subjects (who met the criteria on Day 5) still met the responder criteria.

The incidence of adverse events was 100% (5 of 5 subjects) in the 0.25 mg group, 100% (6 of 6 subjects) in the 0.5 mg group, 100% (5 of 5 subjects) in the 1 mg group, 100% (6 of 6 subjects) in the 1.5 mg group, and 91.7% (11 of 12 subjects) in the 2 mg group. Adverse events reported by ≥3 subjects in any group included pyrexia (2 subjects in the 0.25 mg group, 2 subjects in the 0.5 mg group, 2 subjects in the 1 mg group, 4 subjects in the 1.5 mg group, 4 subjects in the 2 mg group; the same applies hereafter), puncture site pain (1 subject, 1 subject, 0 subjects, 4 subjects, 5 subjects), AST increased (3 subjects, 2 subjects, 3 subjects, 1 subject, 5 subjects), fibrin D dimer increased (2 subjects, 1 subject, 1 subject, 3 subjects, 5 subjects), ALT increased (2 subjects, 2 subjects, 1 subject, 1 subject, 5 subjects), blood

2) Criteria of the platelet transfusion was determined according to the platelet count on Day 8 or later. Platelet preparation was allowed for (a) patients with a platelet count <30,000/μL who were scheduled for percutaneous hepatic cancer ablation or (b) patients with a platelet count ≥30,000/μL and <50,000/μL who were scheduled for percutaneous hepatic cancer ablation. (c) Platelet preparation was prohibited in patients with a platelet count ≥50,000/μL. (d) Platelet preparation was allowed at any time when bleeding-related events have occurred irrespective of the platelet count.

pressure increased (1 subject, 2 subjects, 1 subject, 2 subjects, 3 subjects), oxygen saturation decreased (1 subject, 2 subjects, 0 subjects, 2 subjects, 3 subjects), blood lactate dehydrogenase increased (1 subject, 1 subject, 0 subjects, 0 subjects, 3 subjects), and pleural effusion (0 subjects, 0 subjects, 0 subjects, 0 subjects, 3 subjects).

Death occurred in 1 subject in the 0.5 mg group (procedural complication and pleural haemorrhage), but was considered unrelated to the study drug.

Serious adverse events occurred in 1 subject in the 0.5 mg group (procedural complication and pleural haemorrhage) and 1 subject in the 2 mg group (hepatic infarction and postoperative fever), but were considered unrelated to the study drug.

There were no adverse events leading to study drug discontinuation.

4.(iii).A.(2).2) Japanese phase II high-dose-finding study (Study Protocol M0625, Attached document 5.3.5.1-02 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label study was conducted at 22 study centers in Japan to evaluate the efficacy and safety of multiple oral doses of lusutrombopag once daily for 7 days prior to percutaneous hepatic cancer ablation in patients with thrombocytopenia due to chronic liver disease (target sample size, 6 subjects per dose group).

The study started with the 2.5 mg group, and after confirmation of the safety and efficacy of the 2.5 mg dose, proceeded to the 3 mg group. Then the safety and efficacy in the 2.5 and 3 mg groups were evaluated to select either 3.5 or 4 mg cohort for the next dose group. Based on the obtained results, the study proceeded to the 4 mg cohort. On each day between Day 3 and Day 7, platelet count was measured before administration of the study drug, and treatment was discontinued when the platelet count reached ≥50,000/μL as a result of a ≥20,000/μL increase from baseline.

The following are major inclusion criteria: Patients with current or past chronic liver disease due to type B or C hepatitis virus; patients scheduled to undergo percutaneous hepatic cancer ablation for primary hepatic cancer; patients with a platelet count <50,000/μL at screening; and patients able to be hospitalized from Day 5 to Day 14. Exclusion criteria include the following: Patients who had undergone splenectomy; patients with hepatic impairment of Child-Pugh class C; patients with current or past thrombosis; and patients in whom portal blood flow was not hepatopetal.

All of the 21 subjects enrolled in the study (6 in the 2.5 mg group, 7 in the 3 mg group, and 8 in the 4 mg group; the same applies hereafter) received the study drug and were included in the safety analysis and the FAS. The FAS was the efficacy analysis population. No subjects discontinued the study.

In the FAS, the percentage of patients with a platelet count ≥50,000/μL on Day 8 as a result of a ≥20,000/μL increase from baseline (responders), a efficacy endpoint, was 66.7% (4 of 6 subjects) in the 2.5 mg group, 42.9% (3 of 7 subjects) in the 3 mg group, and 50.0% (4 of 8 subjects) in the 4 mg group. The percentage of patients who received platelet transfusion[2)] during the study period was 16.7% (1 of 6 subjects) in the 2.5 mg group, 14.3% (1 of 7 subjects) in the 3 mg group, and 12.5% (1 of 8 subjects) in the 4 mg group. As a result of the platelet count evaluation, 3 subjects in the 2.5 mg group and 2 subjects in the 4 mg group met the study treatment discontinuation criteria (a platelet count ≥50,000/μL as a result of a ≥20,000/μL increase from baseline). Of the 2 subjects in the 4 mg group, one met the criteria on Day 2 and the other on Day 4. Of the 3 subjects in the 2.5 mg group, 1 subject met the criteria on Day 5 and the remaining 2 subjects on Day 6. All of the 5 subjects still met the responder criteria on Day 8.

The incidence of adverse events was 100% (6 of 6 subjects) in the 2.5 mg group, 100% (7 of 7 subjects) in the 3 mg group, and 100% (8 of 8 subjects) in the 4 mg group. Adverse events reported by ≥3 subjects in any group included nausea (5 subjects, 0 subjects, 2 subjects), pyrexia (2 subjects, 4 subjects, 6 subjects), puncture site pain (3 subjects, 2 subjects, 4 subjects), procedural hypertension (3 subjects, 3 subjects, 3 subjects), AST increased (4 subjects, 2 subjects, 6 subjects), fibrin D dimer increased (2 subjects, 3 subjects, 7 subjects), ALT increased (3 subjects, 2 subjects, 5 subjects), oxygen saturation

decreased (2 subjects, 5 subjects, 2 subjects), blood lactate dehydrogenase increased (1 subject, 1 subject, 3 subjects), blood bilirubin increased (3 subjects, 0 subjects, 1 subject), blood pressure increased (0 subjects, 3 subjects, 1 subject), and prothrombin level decreased (0 subjects, 3 subjects, 0 subjects).

Serious adverse events were reported by 1 subject (aspiration) in the 2.5 mg group and 1 subject (pyrexia) in the 4 mg group, but were considered unrelated to the study drug.

No patients died or experienced adverse events leading to study drug discontinuation.

4.(iii).A.(2).3) Japanese phase II dose-finding study (Study Protocol M0626, Attached document 5.3.5.1-03 [[redacted] to [redacted]])

A randomized, double-blind, parallel-group study was conducted at 63 study centers in Japan to find the optimal dose of lusutrombopag based on the percentage of patients requiring no platelet transfusion prior to percutaneous hepatic cancer ablation. Lusutrombopag at 2, 3, or 4 mg or placebo was orally administered to patients with thrombocytopenia due to chronic liver disease once daily for 7 days (target sample size: 60 subjects in total, 15 subjects per group).

The study treatment period was 7 days. On each day between Day 5 and Day 7, platelet count was measured before administration of the study drug, and the study drug was discontinued when the platelet count reached ≥50,000/μL as a result of a ≥20,000/μL increase from baseline. Percutaneous hepatic cancer ablation was performed between Day 9 and Day 14. The necessity for platelet transfusion was judged at the end of observation on Day 8 and immediately before percutaneous hepatic cancer ablation (between 2 days before percutaneous hepatic cancer ablation and the day of the procedure). Patients with a platelet count <50,000/μL on the day of judgment received platelet transfusion.

The following are major inclusion criteria: Patients with thrombocytopenia due to chronic liver disease; patients scheduled to undergo percutaneous hepatic cancer ablation for primary hepatic cancer; patients with a platelet count <50,000/μL at screening; and patients able to be hospitalized from Day 5 to Day 14. Exclusion criteria include the following: Patients who had undergone splenectomy; patients with hepatic impairment of Child-Pugh class C; patients with current or past thrombosis; and patients in whom portal blood flow was not hepatopetal. Patients were randomized by the minimization method according to platelet count at screening (<35,000/μL, ≥35,000/μL and <45,000/μL, or ≥45,000/μL) and severity of hepatic impairment (Child-Pugh class A or B).

All of the 61 randomized subjects (15 in the 2 mg group, 16 in the 3 mg group, 15 in the 4 mg group, and 15 in the placebo group) received the study drug and were included in the safety analysis and the FAS. The FAS was the primary efficacy analysis population. One subject in the 2 mg group discontinued the study (death due to adverse events during the follow-up period).

Mean ± SD (minimum to maximum) of baseline platelet count ($\times 10^4$/μL) in the FAS was 4.02 ± 0.64 (2.5-4.9) in the 2 mg group, 4.18 ± 1.32 (1.7-6.7) in the 3 mg group, 4.00 ± 0.78 (2.4-4.9) in the 4 mg group, and 4.18 ± 0.61 (3.4-4.9) in the placebo group. The percentages of subjects with Child Pugh class A and B were 60.0% (9 of 15 subjects) and 40.0% (6 of 15 subjects), respectively, in the 2 mg group; 56.3% (9 of 16 subjects) and 43.8% (7 of 16 subjects), respectively, in the 3 mg group; 60.0% (9 of 15 subjects) and 40.0% (6 of 15 subjects), respectively, in the 4 mg group; and 60.0% (9 of 16 subjects) and 40.0% (6 of 15 subjects), respectively, in the placebo group.

The primary efficacy endpoint was the percentage of patients who require no platelet transfusion prior to the first percutaneous hepatic cancer ablation. The percentage of patients requiring no platelet transfusion prior to percutaneous hepatic cancer ablation in the FAS was 80.0% (12 of 15 subjects) in the 2 mg group, 81.3% (13 of 16 subjects) in the 3 mg group, 93.3% (14 of 15 subjects) in the 4 mg group, and 20.0% (3 of 15 subjects) in the placebo group. There was a significant difference between any dose of lusutrombopag and placebo ($P = 0.0006$ for the 2 mg group, $P = 0.0014$ for the 3 mg group, $P = 0.0002$ for the 4 mg group; Cochran-Mantel-Haenszel test, including the allocation factors, not adjusted for multiplicity).

The percentage of patients requiring no platelet transfusion during the study period (a secondary efficacy endpoint) was 80.0% (12 of 15 subjects) in the 2 mg group, 81.3% (13 of 16 subjects) in the 3 mg group, 73.3% (11 of 15 subjects) in the 4 mg group, and 20.0% (3 of 15 subjects) in the placebo group. The percentage of the patients achieving a platelet count ≥50,000/μL as a result of a ≥20,000/μL increase from baseline (responders) during the study period, was 66.7% (10 of 15 subjects) in the 2 mg group, 68.8% (11 of 16 subjects) in the 3 mg group, 80.0% (12 of 15 subjects) in the 4 mg group, and 6.7% (1 of 15 subjects) in the placebo group. As a result of evaluation of the platelet count over time, 3 subjects in the 2 mg group, 3 subjects in the 3 mg group, and 5 subjects in the 4 mg group met the study treatment discontinuation criteria (a platelet count ≥50,000/μL as a result of a ≥20,000/μL increase from baseline). Of the 3 subjects in the 2 mg group, 1 subject met the criteria on Day 5 and 2 subjects on Day 6. Of the 3 subjects in the 3 mg group, 1 subject met the criteria on Day 4 and 2 subjects on Day 5. Of the 5 subjects in the 4 mg group, 1 subject met the criteria on Day 4 and 4 subjects on Day 6. All of these subjects still met the responder criteria on Day 8, except for 1 subject in the 3 mg group who met the criteria on Day 5

The incidence of adverse events was 100% (15 of 15 subjects) in the 2 mg group, 100% (16 of 16 subjects) in the 3 mg group, 93.3% (14 of 15 subjects) in the 4 mg group, and 100.0% (15 of 15 subjects) in the placebo group. Adverse events reported by ≥3 subjects in any group included constipation (3 subjects in the 2 mg group, 2 subjects in the 3 mg group, 1 subject in the 4 mg group, 3 subjects in the placebo group; the same applies hereafter), diarrhoea (1 subject, 1 subject, 1 subject, 4 subjects), postoperative fever (10 subjects, 9 subjects, 7 subjects, 6 subjects), procedural hypertension (10 subjects, 8 subjects, 6 subjects, 8 subjects), procedural pain (8 subjects, 8 subjects, 9 subjects, 7 subjects), post procedural haemorrhage (2 subjects, 0 subjects, 3 subjects, 1 subject), procedural nausea (1 subject, 0 subjects, 3 subjects, 2 subjects), AST increased (10 subjects, 10 subjects, 9 subjects, 3 subjects), ALT increased (8 subjects, 6 subjects, 5 subjects, 0 subjects), oxygen saturation decreased (4 subjects, 6 subjects, 5 subjects, 4 subjects), fibrin D dimer increased (3 subjects, 5 subjects, 3 subjects, 5 subjects), fibrin degradation products increased (2 subjects, 5 subjects, 1 subject, 4 subjects), blood bilirubin increased (4 subjects, 4 subjects, 0 subjects, 0 subjects), blood lactate dehydrogenase increased (2 subjects, 1 subject, 3 subjects, and 2 subjects), blood pressure increased (2 subjects, 1 subject, 2 subjects, 3 subjects), C-reactive protein increased (1 subject, 3 subjects, 1 subject, 1 subject), insomnia (2 subjects, 2 subjects, 3 subjects, 3 subjects), pleural effusion (2 subjects, 0 subjects, 1 subject, 3 subjects), and epistaxis (1 subject, 1 subject, 0 subjects, 3 subjects). Thrombotic averse events occurred in 1 subject (hepatic infarction and portal vein thrombosis) in the 2 mg group, 0 subjects in the 3 mg group, 2 subjects (portal vein thrombosis, mesenteric vein thrombosis [1 subject each]) in the 4 mg group, and 1 subject (mesenteric vein thrombosis) in the placebo group, but all of them were non-serious. A causal relationship to the study drug could not be ruled out for only portal vein thrombosis and mesenteric vein thrombosis in the 4 mg group.

Death occurred in 1 subject (upper gastrointestinal haemorrhage) in the 2 mg group, but was considered unrelated to the study drug.

Serious adverse events were reported by 3 subjects (upper gastrointestinal haemorrhage and hepatic neoplasm malignant, hepatic neoplasm malignant, haemorrhagic erosive gastritis [1 subject each]) in the 2 mg group, 1 subject (sick sinus syndrome and incision site haemorrhage) in the 3 mg group, and 1 subject (patella fracture) in the placebo group. All of these events were considered unrelated to the study drug.

There were no adverse events leading to study drug discontinuation.

4.(iii).A.(3) Japanese phase III study (Study Protocol M0631, Attached document 5.3.5.1-04 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, double-blind, parallel-group study was conducted at 81 study centers in Japan to verify the superiority of lusutrombopag to placebo in the percentage of patients requiring no platelet transfusion prior to an invasive procedure. Lusutrombopag at 3 mg was orally administered to patients with thrombocytopenia due to chronic liver disease once daily for 7 days prior to an invasive procedure (target sample size; 45 subjects per group, 90 subjects in total).

The study treatment period was 7 days. On each day between Day 5 and Day 7, platelet count was measured before administration of the study drug, and the study drug was discontinued when the platelet count reached ≥50,000/μL as a result of a ≥20,000/μL increase from baseline. An invasive procedure was performed between Day 9 and Day 14. The necessity for platelet transfusion was judged at the end of observation on Day 8 and immediately before an invasive procedure (between 2 days before an invasive procedure and the day of the procedure). Patients with a platelet count <50,000/μL on the day of judgment received platelet transfusion. Use of platelet preparations was prohibited from the study enrollment to the end of the follow-up period, except for platelet transfusion prior to an invasive procedure (when judged necessary) and use for rescue treatment.

The following are major inclusion criteria: (1) Patients with thrombocytopenia due to chronic liver disease; (2) patients with a platelet count <50,000/μL at screening; (3) patients scheduled to undergo an invasive procedure, which must be performed (a) between Day 9 and Day 14 and must not be (b) either "surgery involving laparotomy, thoracotomy, craniotomy, or cardiotomy" or "surgery involving organ resection or partial resection (except for procedures equivalent to tissue resection)"; and (4) patients able to be hospitalized from the day before an invasive procedure to Day 14. Exclusion criteria include the following: Patients who had undergone splenectomy; patients with hepatic impairment of Child-Pugh class C; patients with current or past thrombosis; and patients in whom portal blood flow was not hepatopetal. Patients were randomized by the minimization method according to the type of invasive procedure ("hepatic cancer ablation or hepatic cancer coagulation therapy" or "the other invasive procedure") and the platelet count at screening (<35,000/μL, ≥35,000/μL and <45,000/μL, or ≥45,000/μL).

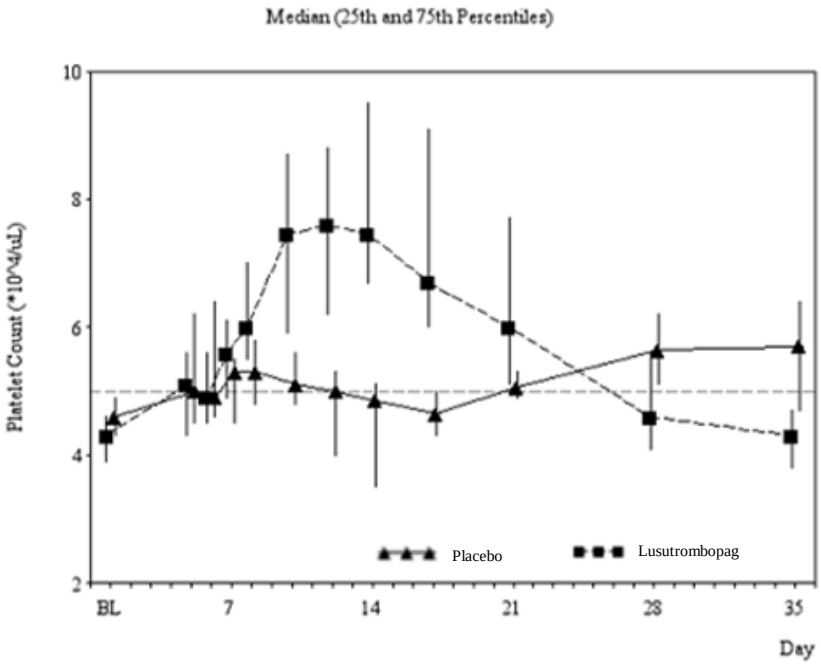
Of 97 randomized subjects (49 in the lusutrombopag group, 48 in the placebo group), 96 subjects (48 per group) treated with the study drug were included in the safety analysis and the FAS. The FAS was the primary efficacy analysis population. Study discontinuation occurred in 1 subject (high platelet count at baseline) in the lusutrombopag group and 1 subject (request from the subject) in the placebo group.

Mean ± SD (minimum to maximum) of baseline platelet count was 4.09 ± 0.63 (2.3-4.9) × 10^4/μL in the lusutrombopag group and 3.99 ± 0.69 (2.3-5.5) × 10^4/μL in the placebo group. At the time of enrollment, hepatic cancer ablation or hepatic cancer coagulation therapy had been planned in 41.7% (20 of 48) of subjects in the lusutrombopag group and 43.8% (21 of 48) of subjects in the placebo group, while the other procedures had been planned in 58.3% (28 of 48) of subjects in the lusutrombopag group and 56.3% (27 of 48) of subjects in the placebo group.

The primary efficacy endpoint was the percentage of patients requiring no platelet transfusion prior to their first invasive procedure. The percentage of patients requiring no platelet transfusion prior to the first invasive procedure in the FAS was 79.2% (38 of 48 subjects) in the lusutrombopag group and 12.5% (6 of 48 subjects) in the placebo group, showing a significant difference between these groups (P < 0.0001, Cochran-Mantel-Haenszel test using the allocation factors as the adjustment factors).

The percentage of patients requiring no platelet transfusion during the study period (a secondary efficacy endpoint) was 79.2% (38 of 48 subjects) in the lusutrombopag group and 12.5% (6 of 48 subjects) in the placebo group. The percentage of patients receiving platelet transfusion was 20.8% (10 of 48 subjects) in the lusutrombopag group and 85.4% (41 of 48 subjects) in the placebo group. Of patients receiving platelet transfusion, 9 in the lusutrombopag group and 37 in the placebo group underwent transfusion once, and 1 in the lusutrombopag group and 4 in the placebo group underwent transfusion twice. The transfusion dose was 12.0 ± 6.3 units (mean ± SD) in the lusutrombopag group and 13.7 ± 6.4 in the placebo group. The percentage of subjects who became a responder at least once at any time point during the study period (excluding the platelet count after platelet transfusion) was 77.1% (37 of 48 subjects) in the lusutrombopag group and 6.3% (3 of 48 subjects) in the placebo group.

Changes in platelet counts in patients receiving no platelet transfusion during the study period are shown in Figure 1.



No. of subjects at each time point	BL	Day 5	Day 6	Day 7	Day 8	Day 10	Day 12	Day 14	Day 17	Day 21	Day 28	Day 35
Lusutrombopag	38	38	38	38	38	38	37	38	38	38	38	38
Placebo	7	7	7	7	7	7	7	6	6	6	6	6

Figure 1. Changes in platelet counts during the study period in the FAS (subjects receiving no platelet transfusion)

The incidence of adverse events was 93.8% (45 of 48 subjects) in the lusutrombopag group and 100% (48 of 48 subjects) in the placebo group. Adverse events reported by ≥5% of subjects in either group are shown in Table 12.

Table 12. Adverse events reported by ≥5% of subjects in either group in the safety analysis set (modified excerpt from the submitted data)

MedDRA (version 17.0) System organ class Preferred term	Lusutrombopag (N = 48)	Placebo (N = 48)
Gastrointestinal disorders		
Ascites	4 (8.3)	4 (8.3)
Constipation	4 (8.3)	3 (6.3)
General disorders and administration site conditions		
Pyrexia	2 (4.2)	4 (8.3)
Infections and infestations		
Nasopharyngitis	4 (8.3)	5 (10.4)
Influenza	0 (0.0)	3 (6.3)
Injury, poisoning and procedural complications		
Postoperative fever	19 (39.6)	27 (56.3)
Procedural pain	22 (45.8)	20 (41.7)
Procedural hypertension	20 (41.7)	18 (37.5)
Procedural nausea	6 (12.5)	8 (16.7)
Procedural vomiting	7 (14.6)	6 (12.5)
Procedural discomfort	4 (8.3)	7 (14.6)
Procedural haemorrhage	3 (6.3)	1 (2.1)
Investigations		
AST increased	11 (22.9)	15 (31.3)
ALT increased	8 (16.7)	10 (20.8)
Oxygen saturation decreased	2 (4.2)	7 (14.6)
Fibrin degradation products increased	2 (4.2)	6 (12.5)
Blood bilirubin increased	4 (8.3)	3 (6.3)
Fibrin D dimer increased	1 (2.1)	5 (10.4)
C-reactive protein increased	1 (2.1)	3 (6.3)
White blood cell count decreased	0 (0.0)	4 (8.3)
Blood calcium decreased	3 (6.3)	0 (0.0)
Blood pressure increased	3 (6.3)	0 (0.0)
Nervous system disorders		
Headache	1 (2.1)	3 (6.3)
Psychiatric disorders		
Insomnia	3 (6.3)	2 (4.2)
Respiratory, thoracic and mediastinal disorders		
Pleural effusion	2 (4.2)	3 (6.3)
Epistaxis	0 (0.0)	4 (8.3)

n (%)

Thrombotic averse events occurred in 1 subject (portal vein thrombosis) in the lusutrombopag group and 1 subject (mesenteric vein thrombosis) in the placebo group.

Serious adverse events were reported by 1 subject (portal vein thrombosis) in the lusutrombopag group and 4 subjects (urticarial, asthma, oesophageal varices haemorrhage, postoperative fever and pleural effusion [1 subject each]) in the placebo group. A causal relationship of portal vein thrombosis to the study drug could not be ruled out.

No patients died or experienced adverse events leading to study drug discontinuation.

4.(iii).B Outline of the review by PMDA

4.(iii).B.(1) Clinical positioning of lusutrombopag

PMDA asked the applicant to explain the clinical positioning of lusutrombopag in comparison with the conventional therapies such as platelet transfusion, splenectomy, and partial splenic embolization (PSE).

The applicant's response:
In patients with advanced chronic liver disease, decreased platelet count is observed in peripheral blood as a consequence of imbalance between platelet production and platelet lifetime due to various causes such as suppressed production of endogenous thrombopoietin (TPO), decreased bone marrow functions,

splenomegaly, etc. Patients with chronic liver disease frequently undergo invasive examinations, procedures, or surgery that may cause haemorrhage for the diagnosis of liver disease or treatment of complications or hepatic cancer. Patients considered to be at a high haemorrhage risk due to a decreased platelet count <50,000/μL have to receive measures against thrombocytopenia prior to laparotomy or local therapy. The conventional therapies for thrombocytopenia due to chronic liver disease include platelet transfusion, PSE, and splenectomy, and of these, platelet transfusion is the standard treatment of thrombocytopenia in patients prior to an invasive procedure. Platelet transfusion, however, potentially causes adverse drug reactions (e.g., infection, graft versus host disease, shock, anaphylaxis, respiratory disorder, transfusion-related acute lung injury, and post transfusion purpura) and poses a potential risk attributable to human errors such as transfusion errors. Platelet preparations have a higher potential risk of bacterial infections than other blood preparations, because they have to be always stored at 20°C to 24°C. In addition, platelet preparations cause immediate non-hemolytic adverse drug reactions (urticaria, anaphylaxis, pyrexia, dyspnoea, blood pressure decreased, etc.) more frequently than other blood preparations (Vamvakas EC et al. *Blood*. 2009;113:3406-3417, Survey on adverse events in blood transfusion 2010 ["Research into the surveillance system for transfusion-related adverse drug reactions in medical institutions," Research project supported by Health and Labour Sciences Research Grants], Non-hemolytic Adverse Transfusion Reactions reported to JRC Blood Centers [2012], [Transfusion Information, 1310-137, Japanese Red Cross Society]). Platelet transfusion resistance is an adverse drug reaction characteristic of the platelet preparations, and patients resistant to platelet transfusion (in whom the platelet count does not increase even following platelet transfusion) have an increased haemorrhage risk, potentially resulting in critical haemorrhage. Furthermore, due to the short shelf-life and difficulty in storage control, the platelet preparations require enormous amounts of medical resources to ensure safety measures and proper use at medical institutions. Patients with chronic liver disease frequently undergo invasive procedures, and may receive platelet transfusion to prevent haemorrhage prior to every procedure; this exposes the patients to risks associated with platelet transfusion every time they undergo a procedure. Due to these circumstances, a therapeutic drug for thrombocytopenia that can be readily used with little risk of adverse drug reactions should be approved for patients with chronic liver disease who undergo invasive procedures.

In patients receiving lusutrombopag at 3 mg for 7 days, the platelet count increased by approximately 40,000/μL and remained at ≥50,000/μL for approximately 20 days. In addition, clinical studies of lusutrombopag have shown that lusutrombopag is superior to platelet transfusion as a perioperative platelet replacement therapy, because in patients receiving platelet transfusion (mean transfusion unit per session, 12.2 units), the platelet count increased by approximately 10,000/μL and then began decreasing on the next day of transfusion. Use of lusutrombopag as an alternative to platelet preparation ensures an invasive procedure without adverse drug reactions associated with platelet transfusion or risk of potential transfusion errors caused by human error during the transfusion. Furthermore, use of lusutrombopag not only reduces the burden of ensuring safety measures and the proper use of blood preparations at medical institutions, but also contributes to a stable supply of platelet preparations and reduction of health care costs, because (1) platelet preparations can be preferentially provided to patients in need emergently; (2) the platelet preparations of rare blood types (e.g., AB Rh(-)) derived from an extremely limited donors become more available; and (3) patients who refuse transfusion for religious reasons can receive lusutrombopag. In patients undergoing PSE or splenectomy, platelet count peaks at 2 weeks to 1 month post-operative and remains higher than the pre-operative level for a long period; patients undergoing PSE or splenectomy maintain an increased platelet count for a longer time than patients receiving lusutrombopag. However, it is difficult to control the extent of increase in platelet count following PSE or splenectomy, suggesting that these procedures have a high risk of thrombogenesis caused by excessively increased platelet count. Lusutrombopag also has an advantage of increasing the platelet count in outpatients readily without a risk of postoperative complications (pyrexia, portal vein thrombosis, splenic abscess) associated with PSE or splenectomy. PSE and splenectomy, however, are mainly performed before hepatectomy or liver transplantation because of their invasive nature; they are rarely performed before invasive procedures for which lusutrombopag is indicated (i.e., procedures not involving laparotomy, thoracotomy, cardiotomy, craniotomy, or organ resection).

Thus, lusutrombopag is an alternative drug to platelet preparations used prior to an invasive procedure in patients with chronic liver disease complicated by thrombocytopenia and allows for an invasive procedure without a haemorrhage risk while avoiding platelet transfusion.

PMDA's view:
Patients with chronic liver disease frequently experience thrombocytopenia due to decreased production of endogenous TPO in association with disease progression. In addition, the coagulation system is often adversely affected due to decreased production of coagulation factors. In particular, patients with advanced chronic liver disease often require the following invasive procedures: Local puncture therapy and transcatheter intra-arterial treatment for hepatocellular carcinoma; and endoscopic variceal ligation (EVL) and endoscopic injection sclerotherapy (EIS) for the complication of gastroesophageal varices. Treatment to maintain an adequate platelet count in patients with chronic liver disease complicated by thrombocytopenia is therefore considered highly useful in clinical settings, because it allows the conduct of necessary invasive procedures and decreases the critical haemorrhage risk. Until now, patients with chronic liver disease complicated by thrombocytopenia have mainly received platelet transfusion prior to an invasive procedure to ensure the platelet count potentially required, but platelet preparations have supply issues and infection risks. A treatment alternative to platelet transfusion is therefore considered to be useful. Japanese clinical studies in patients with chronic liver disease complicated by thrombocytopenia have demonstrated that lusutrombopag increases the platelet count, thereby reducing the risk of clinically significant haemorrhage associated with an elective invasive procedure [see "4.(iii).B.(3) Efficacy of lusutrombopag"], and the safety is acceptable [see "4.(iii).B.(5) Safety of lusutrombopag"]. Lusutrombopag thus increases the platelet count in patients with chronic liver disease complicated by thrombocytopenia prior to an elective invasive procedure and has a clinical significance as a treatment alternative to platelet transfusion.

4.(iii).B.(2) Dosage and administration of lusutrombopag

4.(iii).B.(2).1) Dosage and administration

The applicant's explanation on the rationale for the proposed dosage and administration:
The Japanese multiple dose study in healthy adult male subjects (Study M0613) evaluated the pharmacokinetics of lusutrombopag administered once daily for 14 days. The accumulation ratios of C_{max} and AUC (Days ≥5/Day 1) reached 2 at steady state on and after Day 5. Since lusutrombopag exposure did not tend to accumulate further after reaching steady state and the thrombopoietic effect was observed (maximum effect shown between Day 13 and Day 18), appropriate dosage regimen for lusutrombopag is oral dose once daily. In all the clinical studies in patients with thrombocytopenia due to chronic liver disease, lusutrombopag was also orally administered once daily. In addition, the treatment period in clinical studies was defined as 7 days, because the applicant considered that there would be probably ≥1 week between the decision to perform an elective invasive procedure and the conduct of the procedure, and that the fixed treatment period would help scheduling the invasive procedure. In Japanese clinical studies (Study M0623, Study M0626, Study M0631), the platelet count was measured before administration of lusutrombopag on Day 5 and thereafter to avoid a risk of thrombogenesis due to the excessively increased platelet count, and lusutrombopag was discontinued "when the platelet count reached ≥50,000/μL as a result of a ≥20,000/μL increase from baseline." In clinical studies in patients with thrombocytopenia due to chronic liver disease (Study M0625, Study M0626, Study M0631, Study M061B), 79 patients received lusutrombopag at 3 mg. Of these patients, 4 patients (5.1%) met the above discontinuation criteria on Day 4, 4 patients (5.1%) on Day 5, and 5 patients (6.3%) on Day 6. Most of the patients (66 of 79 patients, 83.5%) received lusutrombopag for 7 days. The treatment period of lusutrombopag was therefore defined as 7 days.

The applicant's explanation on the rationale for the proposed dose:
The following studies showed that AUC of lusutrombopag was proportional to the dose, and the thrombopoietic effect of lusutrombopag increased with increasing exposure: the Japanese single dose study (Study M0611) and Japanese multiple dose study (Study M0613), both in healthy adult subjects; and Japanese phase II dose-finding study (Study M0623), Japanese phase II high-dose-finding study (Study M0625), and Japanese phase II dose-ranging study (Study M0626), all in patients with thrombocytopenia due to chronic liver disease. The following studies showed that the thrombopoietic effect of lusutrombopag increased with increasing doses between 1.5 and 4 mg in patients with chronic liver disease complicated by thrombocytopenia: Japanese phase II dose-finding study (Study M0623), Japanese phase II high-dose-finding study (Study M0625), and Japanese phase II dose-ranging study (Study M0626). In the Japanese phase II dose-ranging study (Study M0626) where lusutrombopag 2, 3, or 4 mg was administered once daily for 7 days, the primary endpoint (the percentage of patients

requiring no platelet transfusion before an invasive procedure) tended to slightly increase with increasing doses, but no large differences were observed among the dose groups, and all lusutrombopag groups showed a higher percentage of patients requiring no platelet transfusion than the placebo group. The increased platelet count tended to be maintained for a longer period in patients receiving a higher dose (between 2 to 4 mg). In each dose group, the time point at which >50% of patients showed a ≥50,000/μL platelet count as a result of a ≥20,000/μL increase from baseline was evaluated. The time point (at which >50% of patients showed a ≥50,000/μL platelet count as a result of a ≥20,000/μL increase from baseline) was earlier and the increased platelet count tended to be maintained for a longer period in higher dose groups. These efficacy data showed that any dose of 2, 3, or 4 mg is effective enough to be able to avoid preoperative platelet transfusion but a higher dose was desirable to ensure more powerful and longer effects. A risk of portal vein thrombosis was observed in the Japanese phase II dose-ranging study (Study M0626) and Japanese phase III study (Study M0631), but the risk of thrombosis did not tend to increase with increasing doses in the Japanese phase II dose-ranging study (Study M0626). The maximum platelet count and the maximum increase in count from baseline tended to increase with increasing doses between 2 and 4 mg (median of the maximum platelet count in patients without platelet transfusion; 73,000/μL in the 2 mg group, 84,000/μL in the 3 mg group, 105,000/μL in the 4 mg group, 64,000/μL in the placebo group) (median of the maximum increase in count from baseline; 28,500/μL in the 2 mg group, 40,000/μL in the 3 mg group, 62,000/μL in the 4 mg group, 15,000/μL in the placebo group). Patients with a platelet count <50,000/μL and chronic liver disease progressing to hepatic cirrhosis tend to experience portal vein thrombosis. The currently available clinical data on a drug in the same class indicate that excessively increased platelet count to >200,000/μL potentially induces thrombi (Afdhal NH et al. *N Engl J Med.* 2012;367:716-724). In clinical studies, no patients showed a platelet count >200,000/μL after lusutrombopag therapy, but 1 patient receiving 3 mg in the Japanese phase II dose-ranging study (Study M0626) showed a platelet count of 195,000/μL. This patient showed largely varying platelet counts (i.e., 45,000/μL at the screening and 65,000/μL immediately before the start of administration); the platelet count at baseline was probably higher than the acceptable level for lusutrombopag therapy (<50,000/μL). Accordingly, in clinical settings, lusutrombopag may be administered to patients with largely fluctuating platelet counts or a slightly high platelet count at baseline; therefore the 3 mg dose is more desirable than the 4 mg dose. The percentage of patients requiring no platelet transfusion before an invasive procedure was significantly higher in the lusutrombopag 3 mg group than in the placebo group in both the Japanese phase II dose-ranging study (Study M0626) (81.3% [3mg] vs. 20.0% [placebo]) and the Japanese phase III study (Study M0631) (79.2% [3 mg] vs. 12.5% [placebo]). In addition, the maximum platelet count did not exceed 200,000/μL in any patients receiving lusutrombopag at 3 mg; thus 3 mg lusutrombopag does not pose a high risk of thrombogenesis due to excessively increased platelet count. Furthermore, lusutrombopag 3 mg was shown to have favorable safety profile. Thus the optimal dose of lusutrombopag was considered 3 mg for enhancing thrombopoiesis prior to an invasive procedure in patients with chronic liver disease complicated by thrombocytopenia.

PMDA's view on the dosage and administration:
Lusutrombopag is a drug used to ensure a sufficient platelet count transiently prior to an elective invasive procedure in patients with chronic liver disease complicated by thrombocytopenia. The "Guidelines for the Use of Blood Products" (Blood and Blood Products Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated September 2005 [revised in 2012]) (Guidelines for Blood Product Use) states that "For patients who undergo an elective surgery or an invasive procedure such as lumbar puncture, epidural anaesthesia, transbronchial biopsy, and liver biopsy, platelet transfusion is not usually necessary if the platelet count is ≥50,000/μL before surgery or invasive procedure." In light of the above statement, it is desirable to set the dose of lusutrombopag so that the bare minimum platelet count is ensured prior to an invasive procedure. The applicant selected the 3 mg dose for the Japanese phase III study (Study M0631), because the Japanese phase II dose-ranging study (Study M0626) showed that 2, 3, or 4 mg lusutrombopag once daily was all effective enough to be able to avoid platelet transfusion prior to an elective invasive procedure, and because any excessive increase in platelet count should be avoided, although a higher dose was more desirable to ensure earlier and longer effects. PMDA understands the applicant's view and decision. The dosing regimen was selected accordingly for the Japanese phase III study (Study M0631); Study M0631 demonstrated significant efficacy in the lusutrombopag group in comparison with the placebo group [see "4.(iii).B.(3) Efficacy of lusutrombopag"] and clinically acceptable safety [see "4.(iii).B.(5) Safety of lusutrombopag"]. Thus

the dosage and administration of lusutrombopag should be 3 mg once daily. It is acceptable to define treatment period of lusutrombopag as 7 days in principle, because most patients (83.5%) in clinical studies received lusutrombopag for 7 days, and because the fixed treatment period of 7 days would help scheduling an invasive procedure, according to the applicant's explanation. In clinical studies, however, some patients discontinued lusutrombopag between Day 4 and Day 6 because the platelet count reached the target of ≥50,000/μL. In consideration of this finding and a risk of thromboembolism, lusutrombopag should be discontinued once the platelet count reaches a target whenever possible. Taking the duration of the effect into account, the applicant should define the basic treatment period as 7 days and then specify the criteria for early discontinuation before Day 7 depending on the platelet count and patient's condition on Day 4 to Day 6 [see "4.(iii).B.(5).2) Measures to prevent excessive increases in platelet count"].

Based on the above review, PMDA has concluded that the proposed dosage and administration are appropriate and the dosage and administration should be defined as shown below.

[Dosage and administration]
The usual adult dosage is 3 mg of lusutrombopag orally administered once daily for 7 days.

4.(iii).B.(2).2) Timing of invasive procedure (timing of the first dose of lusutrombopag and invasive procedure)

The applicant explained the reason an invasive procedure was scheduled between Day 9 and Day 14 in the Japanese phase II dose-ranging study (Study M0626) and Japanese phase III study (Study M0631): In the Japanese phase II dose-finding studies (Studies M0623 and M0625), the percentage of responders in the 2 to 4 mg groups exceeded 50% was between Day 9 to Day 14. Therefore, in these upcoming studies (Studies M0626 and M0631), the platelet count in the 2 to 4 mg groups was likely to exceed 50,000/μL between Day 9 to Day 14.

PMDA asked the applicant to present distribution of the period from the first dose to an invasive procedure in patients receiving no platelet transfusion in the Japanese phase III study (Study M0631), then explain whether clinically relevant haemorrhage-related adverse events occurred after the invasive procedure, and furthermore justify the study schedule in which the first dose of lusutrombopag was administered between 8 and 13 days before the planned invasive procedure.

The applicant's response:
In the Japanese phase III study (Study M0631), 48 patients who received lusutrombopag to increase platelet count before an invasive procedure did not receive platelet transfusion before the procedure. Of the 48 patients, 8 patients (16.7%) underwent the invasive procedure on Day 9, 2 patients (4.2%) on Day 10, 7 patients (14.6%) on Day 11, 4 patients (8.3%) on Day 12, 10 patients (20.8%) on Day 13, and 7 patients (14.6%) on Day 14. All of the invasive procedure were performed evenly on the days between Days 9 and 14. Of the haemorrhage-related adverse events after the invasive procedure, events that occurred more frequently in the lusutrombopag 3 mg group than in the placebo group were procedural haemorrhage (3 of 48 patients [6.3%] in the 3 mg group, 1 of 48 patients [2.1%] in the placebo group), post procedural contusion, and haemorrhage subcutaneous (1 of 48 patients [2.1%] in the 3 mg group, 0 of 48 patients [0%] in the placebo group for both events), but no clear difference was observed in the incidence between the lusutrombopag 3 mg group and the placebo group. A causal relationship to the study drug was ruled out for all the haemorrhage-related adverse events after the invasive procedure in the lusutrombopag 3 mg group, and these events resolved. All of these adverse events, except for moderate procedural haemorrhage in 1 patient, were mild. The moderate procedural haemorrhage occurred following percutaneous hepatic cancer ablation and resolved on the same day without any treatment. This event, therefore, was not clinically relevant. Based on the above, no clinically relevant haemorrhage-related adverse events occurred following any invasive procedure. Thus it is appropriate to start administration of lusutrombopag 8 to 13 days before the planned date of the invasive procedure. The draft package insert therefore states that the first dose of lusutrombopag should be administered 8 to 13 days before the planned date of the invasive procedure.

PMDA's view on the timing of the first dose and an invasive procedure:

Changes in platelet counts in the Japanese phase III study (Study M0631) are shown in Figure 1. In patients receiving no platelet transfusion in this study, the median maximum platelet count was 87,000/μL in the lusutrombopag group and 62,000/μL in the placebo group, and the median period from the first dose to the maximum count was 14.0 days in the lusutrombopag group and 10.0 days in the placebo group. Based on the percentage of the responders, changes in platelet counts, and other efficacy and safety data in the Japanese phase III study (Study M0631), PMDA considers that the following statement given by the applicant in the "Precautions for Dosage and Administration" section of the draft package insert is appropriate: "The first dose of lusutrombopag should be administered 8 to 13 days before the planned day of an invasive procedure."

Changes in the platelet counts, however, show that some patients maintained a platelet count ≥50,000/μL for several days even ≥14 days after the first dose. PMDA further reviewed the duration of the effect.

The applicant's explanation for the duration of the thrombopoietic effect of lusutrombopag:
In patients receiving no platelet transfusion in the lusutrombopag 3 mg group, the median duration of the platelet count ≥50,000/μL (the reference platelet count not requiring platelet transfusion, according to "Guidelines for Blood Product Use") was 21.0 days in the Japanese phase II dose-ranging study (Study M0626) and 22.1 days in the Japanese phase III study (Study M0631). Thus, the platelet count (≥50,000/μL) requiring no preoperative platelet transfusion was maintained for approximately 20 days by lusutrombopag at 3 mg once daily for 7 days. On the other hand, the median duration of a platelet count ≥50,000/μL in the placebo group receiving platelet transfusion was 1.1 days in the Japanese phase II dose-ranging study (Study M0626) and 3.3 days in the Japanese phase III study (Study M0631).

PMDA's view:
Some patients with chronic liver disease undergo multiple invasive procedures in a short period if residual tumor is found in the post-operative assessment of the radiofrequency ablation (RFA) on hepatic cancer. In clinical studies of lusutrombopag, some patients underwent multiple invasive procedures in a short period as well. Thus some patients potentially undergo multiple invasive procedures in a short period in clinical settings. Using the package insert, etc., the applicant should provide information on the period during which a platelet count ≥50,000/μL is expected to be maintained, to help healthcare professionals schedule additional invasive procedures in clinical practice.

4.(iii).B.(2).3) Re-administration of lusutrombopag
The median duration of the platelet count ≥50,000/μL without platelet transfusion was 22.1 days in the lusutrombopag group in the Japanese phase III study (Study M0631). PMDA asked the applicant to present more specific details about the patients with chronic liver disease who underwent multiple invasive procedures in a short period. PMDA also asked the applicant to explain whether re-administration is recommended before the second or subsequent invasive procedure for patients with a platelet count that has decreased back to <50,000/μL or patients who did not undergo an invasive procedure at the planned time. In addition, PMDA asked the applicant to discuss the efficacy and safety of re-administration as well as an appropriate rest period between the first administration period and re-administration, if re-administration of lusutrombopag is possible.

The applicant's response:
In the studies in patients with thrombocytopenia due to chronic liver disease (Study M0623, Study M0625, Study M0626, Study M0631, Study M061B), 52 of 220 patients (23.6%) underwent multiple invasive procedures during the study period, and 44 of 220 patients (20.0%) underwent an invasive procedure on a different day from the day it was planned. These patients are divided into 4 categories: (a) A different invasive procedure was performed before the invasive procedure scheduled at the time of enrollment (the scheduled procedure); (b) after the first invasive procedure, an additional invasive procedure was performed on the same site; (c) an invasive procedure was performed to treat an adverse event occurring during the study period, or an unplanned invasive procedure was performed during an examination; and (d) an additional invasive procedure was performed for other reasons. In the Japanese phase II studies (Study M0623, Study M0625, Study M0626), the scheduled procedures were either percutaneous RFA or microwave coagulation therapy (MCT) on hepatic cancer. In the Japanese phase III study (Study M0631) and platelet function study (Study M061B), however, the scheduled procedures included other types of procedures as well as percutaneous RFA or MCT on hepatic cancer. A total of 12 patients were classified into the category (a); they underwent transcatheter arterial

chemoembolization (TACE) or lipiodol-transcatheter arterial infusion (Lip-TAI) before the scheduled percutaneous RFA. The period from TACE or Lip-TAI to RFA was 1 to 6 days (median, 3.0 days). Patients to be classified into this category may undergo multiple invasive procedures in a relatively short period when multiple procedures are scheduled as therapeutic strategy. A total of 26 patients were classified into the category (b); the period from the first invasive procedure to the additional procedure was 3 to 23 days (median, 7.0 days). Patients to be classified into this category may undergo an additional invasive procedure due to the insufficient therapeutic effect of the first invasive procedure on hepatic cancer. Potential combinations of invasive procedures are RFA plus RFA; RFA plus percutaneous ethanol injection therapy (PEIT); and RFA plus TACE. A total of 6 patients were classified into the category (c). Patients to be classified into this category may undergo an additional invasive procedure performed accidentally or emergently for a reason different from that of the scheduled invasive procedure. The period from the first invasive procedure to the procedure for the treatment of an adverse event ranged -5 to 14 days (median, 7.0 days). Expected combinations of invasive procedures are RFA plus thoracentesis; TACE plus left patellar open reduction; EIS plus EIS; colonic biopsy plus endoscopic mucosal resection plus EVL; and argon plasma coagulation (APC) plus gastric mucosal biopsy. The combination and timing of invasive procedures vary among patients and are difficult to predict, because they depend on the onset time of an adverse event or timing of examination. Two patients were classified into the category (d); they underwent EIS or tooth extraction after the first invasive procedure. The period from the first invasive procedure to the second procedure ranged 3 to 8 days (median, 4.5 days). Patients to be classified into this category may undergo additional invasive procedures, depending on changes in platelet counts. As described above, patients with chronic liver disease eligible for lusutrombopag therapy are likely to undergo multiple invasive procedures in a short period when multiple invasive procedures are scheduled in advance, or when the first invasive procedure has an insufficient therapeutic effect.

Re-administration of lusutrombopag after a short rest period is expected to have a similar thrombopoietic effect to that of the first dose, because from a pharmacokinetic viewpoint, the platelet increasing effect of lusutrombopag correlates to AUC, and because a drug-interaction study of lusutrombopag (Study M0617) has shown that repeated doses of lusutrombopag are unlikely to induce or inhibit CYP enzymes.

The applicant discussed the efficacy and safety of lusutrombopag re-administered in response to the platelet count decreasing to <50,000/μL, based on changes in platelet counts and adverse events in 1 patient with thrombocytopenia due to chronic liver disease who received re-administration of lusutrombopag at 3 mg and in 33 Japanese healthy adult subjects who received re-administration of lusutrombopag at 2 or 4 mg: One patient received lusutrombopag at 3 mg in the Japanese phase III study (Study M0631) and then received lusutrombopag at 3 mg again in the platelet function study (Study M061B) approximately 2 months after the last dose in the Japanese phase III study (Study M0631). In this patient, changes in platelet counts and adverse events did not largely differ between the first administration (Study M0631) and re-administration (Study M061B). In single-dose crossover studies in Japanese healthy adult subjects (2 mg in Study M0612 and 4 mg in Study M061A, a 12-day washout period in both studies), the maximum platelet counts following the second and subsequent doses were not largely different from that following the first dose in either study, showing no trend of the intensified thrombopoietic effect following re-administration. Adverse events occurred only in 3 subjects in Study M0612 (skin laceration in 1 subject following the second dose, white blood cell count increased and neutrophil percentage increased in 2 subjects following the third dose) and in 1 subject in Study M061A (ALT increased following the third dose). Although it was difficult to compare the incidence of adverse events among the different numbers of doses, the safety profile of the second and subsequent doses did not tend to greatly change from that of the first dose. In both healthy adult subjects and patients with chronic liver disease, the rate of increase in platelet count correlated to the total lusutrombopag exposure in plasma, and the maximum rate of change in platelet count from baseline increased with the increasing total exposure. These similarities suggest that the response to re-administration of lusutrombopag in patients with chronic liver disease can be evaluated based on the response in healthy adult subjects. As described above, in patients receiving re-administration of lusutrombopag due to a platelet count decreasing back to a considerably low level, changes in platelet counts and the safety did not tend to differ largely between the first administration and re-administration. The applicant, therefore, considers that there are only small concerns about the efficacy and safety of lusutrombopag re-administered to patients with a platelet count that has decreased back to <50,000/μL.

In addition, patients undergoing an additional invasive procedure or an invasive procedure on a later date than the scheduled date for some reasons may receive re-administration of lusutrombopag before their platelet count decreases back to <50,000/μL, out of concern for the possibility that platelet count may decrease back to <50,000/μL at the time of such procedures. Such cases have a potential risk of portal vein thrombosis due to an excessively increased platelet count. The currently available clinical data of lusutrombopag in patients with chronic liver disease complicated by thrombocytopenia do not include any subject who has received re-administration of lusutrombopag with a platelet count ≥50,000/μL, and the extent of decreases in platelet count probably differs among the patients. There are, therefore, no data to determine how much the platelet count should be decreased before re-administration. The extent of increases in platelet count following the first dose of lusutrombopag also differs among patients. The applicant selected the proposed dosage and administration and made the wording for the "Precautions for Dosage and Administration" section in the draft package insert for lusutrombopag, on the assumption that platelet count readily increases in some patients. In individual patients receiving re-administration when they have a platelet count ≥50,000/μL, concerns for excessively increased platelet count due to re-administration can be reduced by paying attention to changes in platelet counts following the previous dose(s) and using lusutrombopag in compliance with the precautions in the draft package insert. It is, however, considered difficult to set a certain rest period applicable to all the patients, because increases in platelet count and durations of the increased platelet count differ among patients as found in clinical studies; in patients receiving no platelet transfusion in the lusutrombopag 3 mg group, the duration of the platelet count ≥50,000/μL (minimum to maximum) was 11.6 to 33.6 days in the Japanese phase II dose-ranging study (Study M0626) and 5.7 to 33.5 days in the Japanese phase III study (Study M0631).

PMDA's view:
As explained by the applicant, patients with chronic liver disease are likely to undergo multiple invasive procedures in a short period. Also, there are other cases where an invasive procedure apart from scheduled ones is required because of an unexpected adverse event attributable to complication of chronic liver disease(e.g., rupture of oesophageal varices), or where an invasive procedure (EIS, etc.) is deliberately added to the scheduled procedure before the platelet count decreases back to baseline. However, the necessity of re-administration should be discussed especially in cases where a combination of multiple invasive procedures is planned as a treatment strategy against hepatic cancer associated with chronic liver disease and more than one procedure is performed in a relatively short period. In the Japanese phase III study (Study M0631), the platelet count not requiring preoperative platelet transfusion (≥50,000/μL) was maintained for approximately 20 days on average in patients receiving 3 mg of lusutrombopag. In clinical settings, however, many patients may choose a hepatic cancer treatment strategy to undergo multiple invasive procedures in a period longer than the duration of increased platelet count induced by lusutrombopag therapy. In addition, an additional invasive procedure may be performed to treat hepatic cancer for reasons including insufficient therapeutic effect of the first procedures, or the planned invasive procedure may be delayed due to an accidental circumstance. In these cases, patients may need to increase their platelet count again even after 7-day treatment with lusutrombopag. At present, however, only quite limited information is available on re-administration in patients with a platelet count not decreasing back to baseline after lusutrombopag 3 mg therapy for 7 days (the proposed dosage and administration), as explained by the applicant. In such patients, nothing is known about the efficacy and safety of lusutrombopag, appropriate dose, treatment period, or appropriate measures for platelet count monitoring. In light of a risk of thromboembolism associated with an excessively increased platelet count by lusutrombopag, at present, re-administration of lusutrombopag is not recommended for patients with a platelet count not decreasing back to baseline. Patients who need an additional invasive procedure while platelet count is decreasing after lusutrombopag therapy should receive other treatment such as platelet transfusion where necessary.

The applicant explained the efficacy and safety of lusutrombopag re-administered in response to the platelet count that has decreased back to baseline, using the results in 1 patient with thrombocytopenia due to chronic liver disease who received re-administration of lusutrombopag at 3 mg in the platelet function study (Study M061B) and in 33 Japanese healthy adult subjects who received re-administration of lusutrombopag in the crossover study. The applicant further explained that the response to re-administration of lusutrombopag in patients with chronic liver disease can be discussed based on the results in healthy adult subjects. It is, however, difficult to infer the efficacy and safety of lusutrombopag

re-administered to patients with chronic liver disease complicated by thrombocytopenia from the data of lusutrombopag re-administered to healthy adult subjects, because not only the platelet count at baseline, but also major factors involved in turnover of platelets, such as TPO production ability, and platelet destruction and use in the spleen differ between healthy adult subjects and patients with chronic liver disease. Among patients with chronic liver disease complicated by thrombocytopenia, only 1 patient has received re-administration of lusutrombopag to date. Nothing is thus known about the efficacy and safety of lusutrombopag re-administered to patients with chronic liver disease with a platelet count shown to have decreased back to baseline after lusutrombopag therapy. Re-administration of lusutrombopag after 7-day treatment with lusutrombopag 3 mg is not highly recommended even in the case where the platelet count is judged to have decreased back to baseline. Taking account of a risk of blood preparations, however, re-administration should be allowed in patients with thrombocytopenia with a platelet count that has decreased back to baseline, provided that the patients' conditions and their platelet counts are monitored at least as carefully as the monitoring following the first administration. At present, there is no information at all on the appropriate rest period between the first-administration and re-administration or the efficacy and safety of re-administration (appropriateness of the dosage and administration). The applicant should therefore collect information on the timing of re-administration and the efficacy and safety of re-administration of lusutrombopag after the market launch.

The appropriateness of re-administration of lusutrombopag, appropriate rest period (if re-administration is allowed), appropriate dosage and administration, and details of post-marketing information collection covering the efficacy and safety of lusutrombopag, will be reviewed further, taking account of comments raised in the Expert Discussion.

4.(iii).B.(3) Efficacy of lusutrombopag

4.(iii).B.(3).1) Appropriateness of the primary endpoint

The applicant's explanation on the primary efficacy endpoint in the Japanese phase II dose-ranging study (Study M0626) and Japanese phase III study (Study M0631):

The expected effect of lusutrombopag is to avoid platelet transfusion by increasing the platelet count, prior to an invasive procedure in patients with chronic liver disease complicated by thrombocytopenia. In the Japanese phase II dose-ranging study (Study M0626) and Japanese phase III study (Study M0631), therefore, the primary endpoint was the percentage of patients requiring no platelet transfusion prior to the scheduled invasive procedure (i.e., the percentage of patients requiring no platelet transfusion prior to the first invasive procedure). To ensure appropriate efficacy evaluation, these studies established the criteria for performing platelet transfusion during the study period. In clinical settings, platelet transfusion is performed according to institution-specific criteria, and no standardized criteria are available. Based on the "Guidelines for Blood Product Use," which specifies that a platelet count <50,000/μL requires platelet transfusion, the following criterion was set: Platelet transfusion is always implemented if the platelet count is <50,000/μL at ≥8 days after the initiation of administration and immediately before the invasive procedure (between 2 days before the procedure and the day of the procedure). In addition, platelet transfusion was prohibited between study enrollment and the end of the follow-up period, except for platelet transfusion prior to an invasive procedure (when judged necessary) and platelet transfusion used for rescue treatment.

PMDA's view:

In patients with advanced chronic liver disease, such as hepatic cirrhosis, invasive procedures, are often required to treat complications of oesophageal varices or hepatic cancer. Prior to the invasive procedures, however, a haemorrhagic trend due to decreased platelet count is a clinical problem. The final effect expected for lusutrombopag is to increase platelet count and thereby avoid a critical risk of haemorrhage during the invasive procedure. Platelets are essential for blood coagulation against haemorrhage, and therefore a certain amount of platelets is required to prevent critical haemorrhage before an invasive procedure potentially causing haemorrhage. The blood coagulation mechanism, however, involves factors other than platelets. Patients with hepatic disease complicated by decreased platelet count who are eligible for lusutrombopag therapy are likely to have abnormal coagulation factors as well, and the severity of haemorrhage is thus considered to be affected by not only platelets but also other factors. In addition, the platelet count required before procedure to induce blood coagulation or reduce the risk of haemorrhage varies depending on the type of invasive procedure potentially causing haemorrhage. In clinical settings, therefore, the desirable platelet count or necessity of platelet transfusion will be

determined prior to an invasive procedure based on a comprehensive evaluation of the haemorrhagic risk (e.g., the type of invasive procedure, platelet count, coagulation factor status) in individual patients with chronic hepatic disease. However, the "Guidelines for Blood Product Use" states that "For patients with a platelet count <50,000/μL who are scheduled to undergo open surgery, healthcare professionals should prepare platelet concentrate or determine whether to give platelet transfusion immediately before the surgery, depending on the nature of the surgery. For patients who undergo elective surgery or an invasive procedure such as lumbar puncture, epidural anaesthesia, transbronchial biopsy, and liver biopsy, platelet transfusion is usually not necessary if the platelet count is ≥50,000/μL before surgery or an invasive procedure." In the Japanese phase III study (Study M0631), (1) patients were eligible if they had chronic liver disease complicated by thrombocytopenia and were scheduled to undergo an invasive procedure, excluding "surgery involving laparotomy, thoracotomy, craniotomy, or cardiotomy" or "organ resection or partial resection (other than procedures equivalent to tissue resection)"; (2) platelet transfusion was allowed in patients with a platelet count <50,000/μL; and (3) the primary endpoint was the percentage of patients requiring no platelet transfusion prior to the invasive procedure. PMDA has concluded that this primary endpoint was reasonable to a certain extent, in view of the statements above by the "Guidelines for Blood Product Use," and that the efficacy of lusutrombopag can be evaluated based on the results on the primary endpoint. The efficacy of lusutrombopag should be evaluated based on not only the primary endpoint but also suppression of haemorrhagic symptoms by lusutrombopag (i.e. the thrombopoietic effect of lusutrombopag).

4.(iii).B.(3).2) Thrombopoietic effect

The applicant's explanation on the efficacy data of lusutrombopag:

The results of the primary efficacy endpoint are as follows: In the Japanese phase II dose-ranging study (Study M0626), the percentage of patients requiring no platelet transfusion before a scheduled procedure was significantly higher in the lusutrombopag groups than in the placebo group (multiplicity in the test unadjusted): 80.0% (12 of 15 subjects) in the lusutrombopag 2 mg group, 81.3% (13 of 16 subjects) in the 3 mg group, 93.3% (14 of 15 subjects) in the 4 mg group, and 20.0% (3 of 15 subjects) in the placebo group. In the Japanese phase III study (Study M0631), the percentage of patients requiring no platelet transfusion before an invasive procedure was 79.2% (38 of 48 subjects) in the lusutrombopag 3 mg group, which was significantly higher than that in the placebo group (12.5%, 6 of 48 subjects). The results of the secondary efficacy endpoint were as follows: The percentage of responders during the study period was 66.7% (10 of 15 subjects) in the lusutrombopag 2 mg group, 68.8% (11 of 16 subjects) in the 3 mg group, 80.0% (12 of 15 subjects) in the 4 mg group, and 6.7% (1 of 15 subjects) in the placebo group in the Japanese phase II dose-ranging study (Study M0626); and 77.1% (37 of 48 subjects) in the lusutrombopag 3 mg group and 6.3% (3 of 48 subjects) in the placebo group in the Japanese phase III study (Study M0631). The percentage of responders exceeded 50% on Day 12 and Day 14 in the 2 mg group; on Days 10 to 17 in the 3 mg group; and Days 8 to 17 in the 4 mg group in the Japanese phase II dose-ranging study (Study M0626). The percentage of responders exceeded 50% on Days 10 to 17 in the lusutrombopag 3 mg group in the Japanese phase III study (Study M0631). In the lusutrombopag groups, the maximum percentage of responders was found on Day 12 and Day 14 in the 2 mg group, Day 10 and Day 17 in the 3 mg group, and Day 14 in the 4 mg group in the Japanese phase II dose-ranging study (Study M0626) as well as Day 14 in the 3 mg group in the Japanese phase III study (Study M0631). In both studies, the percentage of responders in the placebo group did not increase or exceed 50% at any time point during the study period.

PMDA considers that the following study data demonstrate the clinically significant thrombopoietic effect of lusutrombopag: (1) The percentage of patients requiring no platelet transfusion was higher in the lusutrombopag group than in the placebo group in both Japanese phase II dose-ranging study (Study M0626) and Japanese phase III study (Study M0631); (2) the percentage of responders, the secondary endpoint, was higher in the lusutrombopag group than in the placebo group; (3) and the percentage of patients showing a platelet count ≥50,000/μL (the reference platelet count required before an invasive procedure according to the "Guidelines for Blood Product Use") after study drug administration was higher in the lusutrombopag group than in the placebo group.

4.(iii).B.(3).3) Suppression of haemorrhagic symptoms by lusutrombopag

The applicant's explanation on haemorrhage-related adverse events:

Combined analysis of the Japanese controlled studies (Studies M0626 and M0631) showed that the incidence of haemorrhage-related adverse events was 18.8% (12 of 64 subjects) in patients receiving lusutrombopag 3 mg and 33.3% (21 of 63 subjects) in patients receiving placebo. Of the observed events, procedural haemorrhage, haemorrhage subcutaneous, and purpura occurred more frequently in the 3 mg group than in the placebo group, but the other events occurred less frequently in the 3 mg group than in the placebo group. Procedural haemorrhage occurred in 2 subjects in the lusutrombopag 3 mg group and 1 subject in the placebo group in the Japanese phase II dose-ranging study (Study M0626); in 3 subjects in the 3 mg group and 1 subject in the placebo group in the Japanese phase III study (Study M0631); and in 1 subject in the 3 mg group in the platelet function study (Study M061B). All procedural haemorrhage occurred after invasive procedure during the follow-up period and were considered by the (sub-)investigator to be attributable to the procedure. The platelet count immediately before the procedural haemorrhage was 63,000/μL, 58,000/μL, 67,000/μL (immediately after blood transfusion), 39,000/μL, 86,000/μL, and 86,000/μL in each patient receiving lusutrombopag; and 40,000/μL and 22,000/μL (immediately after blood transfusion) in each patient receiving placebo, indicating that haemorrhage-related adverse events occurred in not only patients with a platelet count <50,000/μL but also patients with a platelet count ≥50,000/μL. Changes in platelet count up to the day of haemorrhage did not indicate any transient post-dose thrombocytopenia. In 1 subject, platelet transfusion was performed to treat a haemorrhage-related adverse event (a serious adverse event of pleural haemorrhage, 10 units of blood transfusion) in the lusutrombopag 0.5 mg group in the Japanese phase II dose-finding study (Study M0623); 1 subject (due to a serious adverse event of incision site haemorrhage, 20 units of blood transfusion) in the lusutrombopag 3 mg group in the Japanese phase II dose-ranging study (Study M0626); and 1 subject (due to a serious adverse event of oesophageal varices haemorrhage, 10 units of blood transfusion) in the placebo group in the Japanese phase III study (Study M0631).

PMDA's view:
In the Japanese phase III study (Study M0631) and Japanese phase II dose-ranging study (Study M0626), haemorrhage-related adverse events did not tend to occur more frequently in the lusutrombopag group than in the placebo group. This suggests that, in patients achieving a target platelet count following lusutrombopag therapy before an invasive procedure, the perioperative risk of haemorrhagic symptoms is expected to be reduced to an extent equivalent to that following platelet transfusion intended to maintain a platelet count ≥50,000/μL.

4.(iii).B.(3).4) Efficacy in patients with a baseline platelet count <35,000/μL
Combined analysis of the Japanese controlled studies (Studies M0626 and M0631) showed that in the population receiving lusutrombopag 3 mg, the percentage of patients requiring no platelet transfusion was lower in patients with a baseline platelet count <35,000/μL than in patients with a baseline platelet count ≥35,000/μL (<35,000, 40.0% [4 of 10 subjects]; ≥35,000, 87.0% [47 of 54 subjects]). Based on the above finding, PMDA asked the applicant to explain whether lusutrombopag should be recommended to patients with a baseline platelet count <35,000/μL.

The applicant's response:
Combined analysis of the Japanese controlled studies (Study M0626, Study M0631) showed that, in the population receiving lusutrombopag 3 mg without platelet transfusion, platelet count remained lower in patients with a baseline platelet count <35,000/μL than in patients with a baseline platelet count ≥35,000/μL. In patients with a baseline platelet count <35,000/μL, the median platelet count from Day 8 to Day 17 was ≥50,000/μL; the platelet count from Day 8 to Day 17 in these patients stayed higher than that in patients with a baseline platelet count ≥35,000/μL who received placebo and platelet transfusion. In patients receiving lusutrombopag 3 mg with a baseline platelet count <35,000/μL, the maximum percentage of responders was 40.0% (4 of 10 subjects), being lower than that in patients receiving lusutrombopag 3 mg with a baseline platelet count ≥35,000/μL but higher than that in patients receiving placebo with a baseline platelet count ≥35,000/μL (4.1%, 2 of 49 subjects). At almost all time points, the percentage of responders was higher in patients receiving lusutrombopag 3 mg with a baseline platelet count <35,000/μL than in patients receiving placebo with a baseline platelet count ≥35,000/μL. The findings above suggest that lusutrombopag at 3 mg is effective even in patients with a baseline platelet count <35,000/μL. Combined analysis of the Japanese controlled studies (Study M0626, Study M0631) showed that, in the lusutrombopag 3 mg group, the percentage of patients requiring no platelet transfusion before an invasive procedure was 40.0% (4 of 10 subjects) in the population with a baseline

platelet count <35,000/μL, lower than 87.0% (47 of 54 subjects) in the population with a baseline platelet count ≥35,000/μL. The concerned difference was caused by the low percentage of patients requiring no platelet transfusion before an invasive procedure (0% [0 of 3]) in patients with a baseline platelet count <35,000/μL in the lusutrombopag 3 mg group in the Japanese phase II dose-ranging study (Study M0626). On the other hand, the percentage of patients requiring no platelet transfusion in patients with a baseline platelet count <35,000/μL was ≥50.0% in the lusutrombopag 2 and 4 mg groups in the Japanese phase II dose-ranging study (Study M0626) and the lusutrombopag 3 mg group in the Japanese phase III study (Study M0631) (50.0% [2 of 4] of patients receiving 2 mg in Study M0626; 75.0% [3 of 4] of patients receiving 4 mg in Study M0626; and 57.1% [4 of 7] of patients receiving 3 mg in Study M0631). These findings suggest that the low percentage (0%) in the lusutrombopag 3 mg group in the Japanese phase II dose-ranging study (Study M0626) is considered to fall within a range of variations due to the limited number of patients. Thus approximately 50% of patients with a baseline platelet count <35,000/μL are expected to be able to avoid platelet transfusion following lusutrombopag 3 mg therapy.

In addition, combined analysis of the Japanese controlled studies (Studies M0626 and M0631) showed that haemorrhage-related adverse events occurred in 2 of 10 patients (20.0%) with a baseline platelet count <35,000/μL and 10 of 54 patients (18.5%) with a baseline platelet count ≥35,000/μL in the lusutrombopag 3 mg group; and in 6 of 14 patients (42.9%) with a baseline platelet count <35,000/μL and 15 of 49 patients (30.6%) with a baseline platelet count ≥35,000/μL in the placebo group. Although some variations were observed due to the limited number of haemorrhage-related adverse events, there was no relationship between baseline platelet count and the incidence of haemorrhage-related adverse events. Based on the above, the applicant considers lusutrombopag can be used irrespective of baseline platelet count (either <35,000/μL or ≥35,000/μL).

PMDA's view:
The Japanese clinical studies suggest that lusutrombopag exerts a thrombopoietic effect irrespective of baseline platelet count, although the percentage of patients not achieving an increased platelet count required for an invasive procedure following lusutrombopag therapy tended to be higher in the subgroup with a baseline platelet count <35,000/μL than in the subgroup with a baseline platelet count ≥35,000/μL. In addition, patients with a lower baseline platelet count have a higher haemorrhagic risk, indicating that the increase in platelet count has a considerable clinical significance. It is therefore important to make lusutrombopag available in clinical practice as a therapeutic option prior to an invasive procedure for avoidance of haemorrhage, in addition to platelet transfusion. Lusutrombopag thus should be made available also to patients with chronic liver disease with a baseline platelet count <35,000/μL. The package insert, however, should provide the following information: (1) lusutrombopag is often less effective in patients with lower baseline platelet count than in those with higher baseline platelet count; (2) lusutrombopag has not been used in patients with a platelet count <20,000/μL; and (3) for patients with an inadequate response to 7-day treatment with lusutrombopag 3 mg, appropriate measures such as platelet transfusion should be prepared prior to an invasive procedure.

4.(iii).B.(3).5) Patient population with an inadequate response to lusutrombopag
PMDA asked the applicant to examine whether patient characteristics or disease profile at baseline differ between non-responders and responders (patients achieving a platelet count ≥50,000/μL as a result of a ≥20,000/μL increase from baseline during the study period) among patients receiving lusutrombopag 3 mg in the Japanese controlled studies (Study M0626, Study M0631), and to discuss whether lusutrombopag should be recommended to patients with patient characteristics or disease profile, if any, that affect response rate.

The applicant's response:
In the lusutrombopag 3 mg group, there were no large differences between the responders and non-responders in any of the demographic characteristics, reference data, or background factors of the chronic liver disease, except for ascites and baseline platelet count (<35,000/μL or ≥35,000/μL). In the lusutrombopag 3 mg group, 16.7% (8 of 48) of responders and 43.8% (7 of 16) of non-responders had ascites, and 8.3% (4 of 48) of responders and 37.5% (6 of 16) of non-responders had a baseline platelet count <35,000/μL. Both "the percentage of patients with ascites" and "the percentage of patients with a baseline platelet count <35,000/μL" tended to be higher in non-responders than in responders. As described in "4.(iii).B.(3).4) Efficacy in patients with a baseline platelet count <35,000/μL,"

lusutrombopag can be administered to patients irrespective of baseline platelet count (either <35,000/μL or ≥35,000/μL). In the lusutrombopag 3 mg group, the percentage of patients requiring no platelet transfusion prior to the first invasive procedure was slightly higher in patients without ascites (85.7% [42 of 49 patients]) than in patients with ascites (60.0% [9 of 15]), but changes in platelet counts in patients receiving no platelet transfusion in the lusutrombopag 3 mg group were almost the same irrespective of ascites. At each time point, the percentage of responders in patients receiving lusutrombopag 3 mg with ascites (0.0%-53.3%) tended to be slightly lower than that in patients receiving lusutrombopag 3 mg without ascites (4.2%-71.4%), but tended to be considerably higher than that in patients receiving placebo without ascites (0.0%-4.8%). There were no large differences in the percentage of the patients with a baseline platelet count <35,000/μL between patients with and without ascites in the lusutrombopag 3 mg group. Furthermore, the impact of ascites on pharmacokinetics of lusutrombopag was investigated using the plasma drug concentration data in the lusutrombopag 3 mg group in the Japanese controlled studies (Study M0626, Study M0631). As a result, the distribution of plasma lusutrombopag concentrations in patients with ascites fell within that in patients without ascites, demonstrating no large differences in plasma concentration between patients with and without ascites. The findings above suggest that ascites is unlikely to affect the efficacy of lusutrombopag considerably, allowing the use of lusutrombopag irrespective of ascites.

PMDA's view:
Although lusutrombopag tended to be less effective in patients with ascites than in patients without ascites, the reason for the different efficacy between these patients remains unknown, as patients with ascites did not tend to have severer hepatic impairment or lower platelet count at baseline than patients without ascites. The pharmacokinetic investigation also failed to identify the reason. Even in patients with ascites, however, the percentage of responders at each time point was adequately higher in the lusutrombopag group than in the placebo group, and in patients receiving no platelet transfusion in the lusutrombopag 3 mg group, changes in platelet counts did not differ largely between patients with and without ascites. Lusutrombopag is expected to have a clinically significant thrombopoietic effect in patients with ascites as well. The use of lusutrombopag thus need not be restricted based on the presence or absence of ascites. The applicant, nevertheless, should inform healthcare professionals that, compared with patients without ascites, patients with ascites are often unable to achieve a platelet count sufficient enough to avoid platelet transfusion. Some patients without ascites who had relatively mild thrombocytopenia (baseline platelet count ≥35,000/μL), on the other hand, were identified as non-responders. The package insert should therefore include the following cautionary statement: Lusutrombopag may not increase the platelet count to the level sufficient for an invasive procedure in some patients, and for patients with an inadequate response to lusutrombopag, appropriate measures such as platelet transfusion should be prepared prior to the invasive procedure.

4.(iii).B.(4) Target population and indications of lusutrombopag
4.(iii).B.(4).1) Target population and indications of lusutrombopag
PMDA asked the applicant to explain characteristics of patients with chronic liver disease who need to increase the platelet count prior to an invasive procedure.

The applicant's response:
Despite the decreased platelet count in peripheral blood, patients with advanced chronic liver disease frequently undergo invasive examinations, procedures, or surgery that potentially cause haemorrhage for diagnosis of liver disease and treatment of complications or hepatic cancer. More specifically, laparoscopy or laparoscopic or ultrasound guided liver biopsy is performed for diagnosis of hepatic fibrosis stage and hepatocellular carcinoma; EVL, EIS, balloon-occluded retrograde transvenous obliteration, transjugular intrahepatic portosystemic shunt, various paracenteses, or peritoneo-subclavian shunt is performed for diagnosis and treatment of the complications of chronic liver disease (gastrooesophageal varices, ascites, hepatic encephalopathy); hepatectomy (including laparoscopic procedure), local puncture therapy, transcatheter intra-arterial treatment, or liver transplantation is performed for the therapy of hepatic cancer. The platelet count has to be increased prior to these invasive procedures.

PMDA asked the applicant to present details of "invasive procedures" performed in the Japanese phase III study (Study M0631) and then explain differences in the efficacy and safety of lusutrombopag among the invasive procedures.

The applicant's response:
Invasive procedures performed in the Japanese phase III study (Study M0631) were percutaneous hepatic cancer ablation (percutaneous RFA or MCT) in 21 of 48 subjects (43.8%) in the lusutrombopag 3 mg group and 20 of 48 subjects (41.7%) in the placebo group, and procedures other than percutaneous hepatic cancer ablation (percutaneous RFA or MCT) in 27 of 48 subjects (56.3%) in the 3 mg group and 27 of 48 subjects (56.3%) in the placebo group. The invasive procedures other than percutaneous RFA or MCT were EVL in 6 of 48 subjects (12.5%) in the 3 mg group and 8 of 48 subjects (16.7%) in the placebo group; EIS in 2 of 48 subjects (4.2%) in the 3 mg group and 2 of 48 subjects (4.2%) in the placebo group; TACE in 13 of 48 subjects (27.1%) in the 3 mg group and 11 of 48 subjects (22.9%) in the placebo group; APC in 2 of 48 subjects (4.2%) in the 3 mg group and 4 of 48 subjects (8.3%) in the placebo group; liver biopsy in 3 of 48 subjects (6.3%) in the 3 mg group and 2 of 48 subjects (4.2%) in the placebo group; and PEIT in 1 of 48 subjects (2.1%) in the 3 mg group and 0 of 48 subjects (0%) in the placebo group. No platelet transfusion was required before an invasive procedure in 71.4% (15 of 21) of subjects in the 3 mg group and 15.0% (3 of 20) of subjects in the placebo group who underwent percutaneous hepatic cancer ablation (percutaneous RFA or MCT); and 85.2% (23 of 27) of subjects in the 3 mg group and 11.1% (3 of 27) of subjects in the placebo group who underwent procedures other than percutaneous hepatic cancer ablation (percutaneous RFA or MCT). In the 3 mg group, no clear difference was observed between percutaneous hepatic cancer ablation (percutaneous RFA or MCT) and the other procedures. In the lusutrombopag group, no platelet transfusion was required before an invasive procedure in 100.0% (6 of 6) of subjects undergoing EVL, 50.0% (1 of 2) of subjects undergoing EIS, 84.6% (11 of 13) of subjects undergoing TACE, and 83.3% (5 of 6) of subjects undergoing other procedures (excluding percutaneous hepatic cancer ablation [percutaneous RFA or MCT]). No clear differences were observed in efficacy among these invasive procedures. Although it is difficult to compare the adverse events because of the limited number of patients undergoing endoscopic gastrooesophageal variceal therapy (EVL or EIS) or other invasive procedures, AST increased and ALT increased tended to occur more frequently in the patients undergoing percutaneous hepatic cancer ablation (percutaneous RFA or MCT) or TACE than in patients undergoing the other procedures in the 3 mg group. This trend, however, was observed in the placebo group as well and thus was considered to be a consequence of these invasive procedures in the liver against hepatic cancer. Based on the above, the applicant considered that the efficacy and safety of lusutrombopag did not differ among these types of invasive procedures.

PMDA asked the applicant to list invasive procedures which potentially require administration of lusutrombopag, including procedures not directly related to liver diseases, other than procedures performed in the clinical studies, and then discuss the expected efficacy and safety of lusutrombopag administered prior to such procedures.

The applicant's response:
Lusutrombopag is expected to be used in patients prior to various invasive procedures, other than surgery involving laparotomy, thoracotomy, cardiotomy, craniotomy, or organ resection. Such procedures include percutaneous needle electrode insertion, percutaneous catheterization, laparoscopy, and endoscopy. Some of these procedures are directly related to liver diseases (e.g., treatment of hepatocellular carcinoma and oesophageal varices, laparoscopic liver biopsy, and peritoneo-subclavian shunt); or not directly related to liver diseases (e.g., treatment of biliopancreatic disease [endoscopic sphincterotomy, etc.], gastrointestinal tract [endoscopic polypectomy, endoscopic mucosal resection, etc.], and urinary tract [transurethral resection of the bladder tumor, transurethral lithotripsy); or related to the diagnosis of liver diseases (e.g., percutaneous needle biopsy and laparoscopic biopsy). All these invasive procedures are considered to meet the following criteria in the "Guidelines for Blood Product Use": "For patients who undergo an elective surgery or an invasive procedure such as lumbar puncture, epidural anaesthesia, transbronchial biopsy, and liver biopsy, platelet transfusion is usually not necessary if the platelet count is ≥50,000/μL before surgery or an invasive procedure." Lusutrombopag can be administered to patients prior to the invasive procedures presented above, because these procedures are considered to have an equivalent or lower risk of invasiveness and haemorrhage compared with

percutaneous hepatic cancer ablation (percutaneous RFA or MCT), which was performed in more than half of the patients in the clinical studies of lusutrombopag; the reasons are listed below.

- The incision size is approximately 2 to 10 mm.

- Among the procedures listed above, the procedures for tumor resection are recommended for superficial or submucosal tumors ≤3 cm in size. This indication is equivalent to that of percutaneous RFA: hepatic tumors up to 3 cm in diameter. The extent of the tissue injury due to tissue resection is also similar to that due to percutaneous RFA.

- None of the procedures listed above are likely to require blood preparations (e.g., erythrocyte preparation and fresh frozen human plasma) other than platelet preparations during or after surgery. These procedures cause only a limited amount of haemorrhage with a limited area requiring hemostasis. In addition, relatively easy methods of hemostasis are used in these procedures.

The expected efficacy of lusutrombopag administered prior to the above invasive procedures is unlikely to be affected by the type of procedure, because no clear difference was observed in the efficacy of lusutrombopag among different invasive procedures in the Japanese phase III study (Study M0631), and because lusutrombopag is administered prior to an invasive procedure to enhance thrombopoiesis. Any of the invasive procedures above is considered to have little impact on the safety of lusutrombopag. The reason for the limited impact is that preoperative platelet transfusion is performed to prevent haemorrhage in the area to be invaded by the procedure, and a threshold platelet count that triggers platelet transfusion prior to a procedure reflects the invasiveness and haemorrhage risk of the procedure. When platelet transfusion is triggered by a threshold platelet count of 50,000/μL before a procedure, the procedure is considered to have equivalent or lower risk of invasiveness and haemorrhage, compared with the invasive procedures performed in the Japanese phase III study (Study M0631). The impact of these procedures on the safety of lusutrombopag is therefore limited.

PMDA asked the applicant to consider the necessity of providing more specific information about the "invasive procedures" allowed following lusutrombopag therapy.

The applicant's response:
Progress in science will probably lead to the development of new procedures not requiring laparotomy. The applicant therefore considered it appropriate to list the invasive procedures that must not be performed following lusutrombopag therapy, rather than procedures allowed to be performed. The Japanese phase III study (Study M0631) thus excluded "surgery involving laparotomy, thoracotomy, cardiotomy, craniotomy, and organ resection," and demonstrated that the efficacy and safety of lusutrombopag did not differ among different invasive procedures performed in this study. Healthcare professionals who will use lusutrombopag should be informed of procedure criteria equivalent to those used in the Japanese phase III study (Study M0631). Thus the "Precautions for Indications" section in the draft package insert will include the following statement: "The efficacy and safety of lusutrombopag administered prior to the invasive procedures involving laparotomy, thoracotomy, cardiotomy, craniotomy, or organ resection have not been established. [No experience in clinical studies]."

PMDA's view:
Only extremely number of patients underwent each of the invasive procedures including percutaneous hepatic cancer ablation (percutaneous RFA or MCT), EVL, EIS, TACE, and other local invasive procedures in the liver. Although rigorous comparison is difficult, there were no clear differences in the efficacy and safety of lusutrombopag among the invasive procedures performed in the Japanese phase III study (Study M0631). The applicant explained that the invasive procedures for treatment and examination by percutaneous needle electrode insertion, percutaneous catheterization, laparoscopy, and endoscopy are expected to be performed following lusutrombopag therapy, although they were not performed in the clinical studies of lusutrombopag. In addition to these procedures, the following procedures should be allowed following lusutrombopag therapy because they are unlikely to have a remarkably high haemorrhagic risk compared with the procedures performed in the Japanese clinical studies: elective surgery or invasive procedures such as lumbar puncture, epidural anaesthesia, transbronchial biopsy, and liver biopsy; and ones for which, "platelet transfusion is usually not necessary

if the platelet count is ≥50,000/μL before surgery or an invasive procedure" as defined in the "Guidelines for Blood Product Use."

The "Guidelines for Blood Product Use," on the other hand, indicates that "the preoperative platelet count exceeding 70,000 to 100,000/μL is desirable prior to the surgery in particular fields such as intracranial surgery in which local blood coagulation is difficult." The invasive procedures involving laparotomy, thoracotomy, cardiotomy, craniotomy, or organ resection, which were excluded in the clinical studies of lusutrombopag, have a higher haemorrhagic risk than the procedures performed in the studies; thus prior to these procedures, the platelet count has to be maintained at a high level. The invasive procedures involving laparotomy etc. should be excluded from the indications of lusutrombopag at present, because whether the haemorrhagic risk associated with the procedures can be adequately avoided remains unknown. Furthermore, emergency surgery should not be performed following lusutrombopag therapy, because after the first dose of lusutrombopag, it takes several days for the platelet count to increase to a level requiring no platelet transfusion.

The specific platelet count that should trigger administration of lusutrombopag is <50,000/μL, because the "Guidelines for Blood Product Use" state that platelet transfusion is usually not necessary if the platelet count is ≥50,000/μL before an invasive procedure, and because the clinical studies of lusutrombopag included only patients with a platelet count <50,000/μL at screening.

Based on the above, PMDA considers that the indication should be "Improvement of thrombocytopenia associated with chronic liver disease in patients prior to elective invasive procedures," and the "Precautions for Indications" section should include a cautionary statement that "lusutrombopag should be used in patients assessed to have a high haemorrhagic risk based on laboratory values, such as the platelet count, clinical symptoms, and type of the invasive procedure scheduled" and that "lusutrombopag should not be used before an invasive procedure involving laparotomy, thoracotomy, cardiotomy, craniotomy, or organ resection." In addition, the "Clinical Studies" section in the package insert should provide information on the platelet counts at screening in the patients included in the clinical studies of lusutrombopag, because the inclusion criteria of the Japanese phase III study (Study M0631) required a platelet count <50,000/μL at screening. Furthermore, the "Clinical Studies" section in the package insert should provide information on the invasive procedures actually performed in the Japanese phase III study more specifically (i.e., percutaneous hepatic cancer ablation [percutaneous RFA or MCT], EVL, EIS, TACE, APC, liver biopsy, and PEIT), because the efficacy and safety of lusutrombopag were evaluated based on these procedures. The target population for lusutrombopag, indications, and the wording in the "Precautions for Indications" section will be reviewed further, taking account of comments raised in the Expert Discussion.

4.(iii).B.(4).2) Use of lusutrombopag in patients with splenectomy

PMDA asked the applicant to explain the reason "patients who had undergone splenectomy" were excluded from the Japanese phase II and phase III studies (Study M0623, Study M0625, Study M0626, Study M0631), and discuss whether lusutrombopag should be recommended to patients who had undergone splenectomy.

The applicant's response:

The reason the "patients who had undergone splenectomy" were excluded from the Japanese phase II and phase III studies (Study M0623, Study M0625, Study M0626, Study M0631) was as follows: Patients who had undergone splenectomy are known to maintain an increased platelet count for a long period (at least several years) (Tomikawa M et al. *J Gastroenterol Hepatol.* 2002;17:77-80), and thus unlikely to become eligible for lusutrombopag therapy because their platelet count is unlikely to decrease again. Once the spleen serving as storage of platelets was removed, changes in platelet count may be unpredictable. Patients who had undergone splenectomy were, therefore, considered to be ineligible for the clinical studies.

To discuss differences in the efficacy of a TPO receptor agonist between patients with and without splenectomy, the applicant reviewed a clinical study of eltrombopag, a drug in the same class, in patients with chronic idiopathic thrombocytopenic purpura (cITP) (Cheng G et al. *Lancet.* 2011;377:393-402). The post-hoc analysis of this study showed that the continued response rate (the percentage of patients who maintained a platelet count ≥50,000/μL without rescue therapy for ≥6 weeks of the last 8 weeks of

the 26-week treatment period in patients who completed the 26-week treatment) did not differ largely between patients with and without splenectomy: 51.4% (19 of 37) of patients with splenectomy and 65.5% (38 of 58) of patients without splenectomy. Most patients with splenectomy who require lusutrombopag probably have a recurrence of thrombocytopenia. Recurrence of cITP after splenectomy is potentially caused by platelet destruction enhanced by accessory spleens, instead of the spleen, that have swollen after splenectomy (Ambriz P et al. *Radiology.* 1985;155:793-796, Facon T et al. *Am J Hematol.* 1992;41:184-189, Morris KT et al. *Surg Endosc.* 1999;13:520-522); or by enhanced platelet destruction due to phagocytosis of reticuloendothelial cells in the liver or bone marrow other than the spleen, as a result of anti-platelet autoantibodies produced in the bone marrow, etc. other than the spleen after splenectomy (Lightsey AL Jr et al. *J Pediatr.* 1976;88:415-418). In the former case, the pathological condition is similar to that before the splenectomy, while in the latter case, the production of anti-platelet autoantibodies has already been enhanced in other regions than the spleen. Although the study of eltrombopag included both cases, it demonstrated the efficacy of eltrombopag irrespective of a history of the splenectomy. The causes of thrombocytopenia in patients with cITP mostly remain to be identified, but the mechanism is considered to involve increased platelet destruction, decreased thrombopoiesis due to defective or impaired megakaryocyte maturation, and reduced platelet lifespan due to autoantibodies (McMillan R et al. *Blood.* 2004;103:1364-1369; Japan Intractable Diseases Information Center. Idiopathic thrombocytopenic purpura [http://www.nanbyou.or.jp/entry/303]). Thrombocytopenia caused by chronic liver disease is also considered to be a consequence of decreased thrombopoiesis and reduced platelet lifespan (Afdhal N et al. *J Hepatol.* 2008;48:1000-1007, Imawari M et al. *Hepatology.* 2006;189-194, Violi F et al. *J Hepatol.* 2011;55:1415-1427, Hayashi H et al. *World J Gastroenterol.* 2014;20:2595-2605), having a similar mechanism to that of cITP. The mechanism of thrombocytopenia is basically similar in patients with cITP and patients with chronic liver disease, although, in contrast to patients with chronic liver disease, patients with cITP do not show extensive splenomegaly or decreased endogenous TPO production. The fact that eltrombopag was shown to be effective in patients with cITP irrespective of splenectomy in a clinical study suggests that lusutrombopag is also expected to be effective in patients with chronic liver disease who have undergone splenectomy. Eltrombopag has been approved for the indication of the “treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy” irrespective of a history of splenectomy, in addition to patients with cITP in the US and EU. The thrombopoietic effect of a TPO receptor agonist has thus been demonstrated in both patients with cITP and with chronic liver disease irrespective of splenectomy. Lusutrombopag has never been administered to patients who had underwent splenectomy. The discussion above, however, indicates that lusutrombopag can be administered to patients with splenectomy as safely as to patients without splenectomy, as long as lusutrombopag is used in compliance with the “Precautions for Dosage and Administration” section in the package insert (draft) and platelet count is controlled and prevented from excessively increasing.

PMDA’s view:
Splenectomy has been recently performed in an increasing number of patients not only to resolve thrombocytopenia caused by hypersplenism but also to optimize the interferon therapy for hepatitis C and hepatic cancer therapy and to resolve portal hypertension. Patients with chronic liver disease scheduled to undergo invasive procedures who are potentially eligible for lusutrombopag therapy may have a history of splenectomy. The applicant inferred the efficacy and safety of lusutrombopag based on the efficacy and safety data for another TPO receptor agonist; this inference is not appropriate, because such data are not necessarily applied to the analysis of lusutrombopag. In contrast to the target patients of lusutrombopag, patients with cITP tend to receive a long-term treatment with a drug at doses adjusted according to requirements of individual patients. However, taking into account that a drug in the same class is allowed to be administered to patients with cITP irrespective of splenectomy, patients with a history of splenectomy need not be excluded from the population eligible for lusutrombopag, provided that the platelet count is carefully monitored. In patients with a history of splenectomy, the platelet count decreases differently from that in patients without splenectomy and lusutrombopag has never been administered to patients who had undergone splenectomy. It is, thus, essential to collect post-marketing information on the efficacy and safety of lusutrombopag administered to patients who have a history of splenectomy. Taking account of comments raised in the Expert Discussion, PMDA will further review the appropriateness of administration of lusutrombopag to patients with splenectomy, the necessity of the cautionary statements regarding such patients in the package insert, and the details of collection of the post-marketing information.

4.(iii).B.(5) Safety of lusutrombopag

4.(iii).B.(5).1) Risk of thromboembolism

(a) Risk of thromboembolism during lusutrombopag therapy

The applicant's explanation on thromboembolic adverse events:

Combined analysis of the Japanese controlled studies (Study M0626, Study M0631) showed that the incidence of thromboembolic adverse events was 1.6% (1 of 64 subjects) in the 3 mg group and 3.2% (2 of 63 subjects) in the placebo group. Combined analysis of the studies in patients with thrombocytopenia due to chronic liver disease (Study M0623, Study M0625, Study M0626, Study M0631, Study M061B) showed that thromboembolic adverse events occurred in 5.1% (2 of 39 subjects) in the 1.5 to 2.5 mg groups, 1.3% (1 of 79 subjects) in the 3 mg group, 8.7% (2 of 23 subjects) in the 4 mg group, and 3.2% (2 of 63 subjects) in the placebo group. Thromboembolic adverse events occurred in 1 subject (hepatic infarction) in the 2 mg group in the Japanese phase II dose-finding study (Study M0623); 1 subject (hepatic infarction and portal vein thrombosis) in the 2 mg group, 2 subjects (mesenteric vein thrombosis, portal vein thrombosis [1 subject each]) in the 4 mg group, and 1 subject (mesenteric vein thrombosis) in the placebo group in the Japanese phase II dose-ranging study (Study M0626); and 1 subject (portal vein thrombosis) in the 3 mg group and 1 subject (mesenteric vein thrombosis) in the placebo group in the Japanese phase III study (Study M0631). All the events were moderate or severe. Hepatic infarction in the 2 mg group in the Japanese phase II dose-finding study (Study M0623) occurred immediately after an invasive procedure (percutaneous RFA), and hepatic infarction in the 2 mg group in the Japanese phase II dose-ranging study (Study M0626) occurred 5 days after an invasive procedure (percutaneous RFA). Both events were assessed to be associated with the invasive procedure and unrelated to the study drug. Hepatic infarction and portal vein thrombosis in the 2 mg group and portal vein thrombosis in the 4 mg group in the Japanese phase II dose-ranging study (Study M0626) and mesenteric vein thrombosis in the placebo group in the Japanese phase III study (Study M0631) remained unresolved and the follow-up was terminated, because the patients' clinical courses were expected to be adequately followed in routine clinical practice, and portal blood flow was maintained; these patients showed no severe symptoms or sings resulting in sequelae. Serious events were hepatic infarction in 1 subject in the 2 mg group in the Japanese phase II dose-finding study (Study M0623) and portal vein thrombosis in 1 subject in the 3 mg group in the Japanese phase III study (Study M0631), but all of the other events were non-serious. A causal relationship to the study drug was assessed as "possible" for mesenteric vein thrombosis and portal vein thrombosis in the 4 mg group in the Japanese phase II dose-ranging study (Study M0626) and as "probable" for portal vein thrombosis in the 3 mg group in the Japanese phase III study (Study M0631). Table 13 shows the onset time of portal thrombosis, timing of the invasive procedure, platelet count immediately before the onset of thrombosis, and the maximum platelet count in patients experiencing portal thrombosis.

Table 13. Timing of the invasive procedure and platelet count in patients with portal thrombosis (modified excerpt from the submitted data)

Study	Japanese phase II dose-ranging study (Study M0626)				Japanese phase III study (Study M0631)	
Dose group	2 mg	4 mg	4 mg	Placebo	3 mg	Placebo
Event term	Portal vein thrombosis	Mesenteric vein thrombosis	Portal vein thrombosis	Mesenteric vein thrombosis	Portal vein thrombosis	Mesenteric vein thrombosis
Date of onset[a)]	18	14	18	19	14	20
Invasive procedure (date of conduct[a)])	RFA (Day 13)	TACE (Day 8) RFA (Day 11)	RFA and PEIT (Day 13)	RFA (Days 9, 16, 23)	TACE (Day 10)	TACE (Day 13)
Platelet count immediately before the onset (10,000/μL)	3.7	9.1	8.5	6.2	7.7	4.6
Maximum platelet count (10,000/μL)	5.4	9.1	12.7	6.2	7.7	5.6

[a)] Day of the first dose = Day 1.

Portal thrombosis was found by imaging diagnosis (computerized tomography [CT] or magnetic resonance imaging [MRI]) performed to evaluate portal vein thrombosis 3 to 10 days after the invasive

procedure. Ultrasound diagnosis showed that all patients with portal thrombosis maintained hepatopetal portal blood flow requiring no surgical treatment.
Most of the patients with chronic liver disease with a platelet count decreasing to <50,000/μL have a pathological condition progressed to hepatic cirrhosis and thus are predisposed to portal vein thrombosis due to the activated blood coagulation system, abnormal portal blood flow, altered portal wall condition, and spreading periportal inflammation (Matsutani S et al. *Kan-Tan-Sui*. 2010;61:259-268, Tsochatzis EA et al. *Aliment Pharmacol Ther.* 2010;31:366-374). Portal vein thrombosis, therefore, is known to frequently occur in patients with hepatic cirrhosis and malignant tumour such as primary hepatic cancer. A retrospective study reported that 10% to 25% of patients with hepatic cirrhosis experienced portal vein thrombosis (Tsochatzis EA et al. *Aliment Pharmacol Ther.* 2010;31:366-374). In addition, portal vein thrombosis is recognized to develop in response to periportal inflammation induced by an invasive procedure on the liver, based on clinical experience. Previously, a clinical study of a drug in the same class was conducted in patients with thrombocytopenia due to chronic liver disease who were scheduled to undergo invasive procedures. The study, however, was discontinued, because the incidence of thromboembolic adverse events in the active drug group was higher than that in the placebo group (1.4% [2 of 145 subjects] in the placebo group, 4.2% [6 of 143 subjects] in the active drug group), and most of the thromboembolic adverse events involved the portal system. (Portal thrombosis occurred in 0.7% [1 of 145 subjects] in the placebo group and 4.2% [6 of 143 subjects] in the active drug group.) (Afdhal NH et al. *N Engl J Med*. 2012;367:716-724). Combined analysis of the Japanese controlled studies (Study M0626, Study M0631) showed that the incidence of portal thrombosis (portal vein thrombosis, mesenteric vein thrombosis) was similar in the lusutrombopag 3 mg group (1.6% [1 of 64 subjects]) and the placebo group (3.2% [2 of 63 subjects]). Combined analysis of the studies in patients with thrombocytopenia due to chronic liver disease (Study M0623, Study M0625, Study M0626, Study M0631, Study M061B) showed that the incidence of portal thrombosis was similar in different lusutrombopag dose groups: 2.6% (1 of 39 subjects) in the 1.5 to 2.5 mg groups; 1.3% (1 of 79 subjects) in the 3 mg group; 8.7% (2 of 23 subjects) in the 4 mg group; and 3.2% (2 of 63 subjects) in the placebo group. In the previous clinical study of a drug in the same class in patients with thrombocytopenia due to chronic liver disease who were scheduled to undergo invasive procedures, 5 of 6 subjects with portal thrombosis in the active drug group had a platelet count >200,000/μL at the onset; this suggested that excessively increased platelet contributed to the onset of portal thrombosis. In patients experiencing thrombi in clinical studies of lusutrombopag, the maximum platelet count before the onset of thrombi ranged 54,000 to 127,000/μL; and the platelet count immediately before the onset ranged 37,000 to 91,000/μL. Neither the maximum platelet count nor the platelet count immediately before the onset increased excessively to >200,000/μL. As described above, patients with thrombocytopenia due to chronic liver disease are predisposed to portal thrombosis and thus potentially experience thrombosis as a consequence of an invasive procedure in the liver. The risk of emboli and thrombi can therefore be suppressed by controlling thrombopoiesis induced by lusutrombopag so as not to increase the platelet count excessively.

PMDA asked the applicant to discuss the reason portal thrombosis occurred even in patients with a platelet count ≤200,000/μL immediately before the onset in the lusutrombopag group in the Japanese clinical studies (Study M0626, Study M0631).

The applicant's response:
The events of portal thrombosis in the Japanese clinical studies are considered attributable to the invasive procedure performed on patients with chronic liver disease at a high thrombus risk and to patient characteristics such as treatment history. In clinical studies of lusutrombopag in patients with thrombocytopenia due to chronic liver disease (Study M0623, Study M0625, Study M0626, Study M0631, Study M061B), the incidence of portal thrombosis was 2.5% (4 of 157 subjects) in the lusutrombopag group and 3.2% (2 of 63 subjects) in the placebo group, showing no difference between these groups. In the Japanese controlled studies (Study M0626, Study M0631), the safety evaluation committee and imaging evaluation committee consisting of hepatologists and hematologists assessed the presence or absence of portal thrombi and reviewed the safety in individual patients under blinded conditions. The evaluation committee determined that thrombi were not attributable to the increase in the platelet count, but due to the number of procedures on hepatic cancer, perivascular procedural invasion, and concurrent multiple procedures, because no correlation was observed between the onset of portal thrombosis and the platelet count. In addition, patients' treatment history of hepatic cancer was

assessed to have a potential impact on the onset of thrombi. Furthermore, in a clinical study of eltrombopag, a drug in the same class, in patients with thrombocytopenia due to chronic liver disease who were scheduled to undergo an invasive procedure (Study ELEVATE), the protocol specified that imaging evaluation (Doppler ultrasonography, MRI, CT, etc.) should be performed only when an thromboembolic event was suggested by symptoms or signs. On the other hand, the protocols of the clinical studies of lusutrombopag specified that imaging evaluation (MRI, CT) must be performed prospectively even if there was no symptoms or signs. The clinical studies of lusutrombopag had more sensitivity to detect portal thrombosis than Study ELEVATE. Thus, portal thrombosis was observed in the Japanese phase II study (Study M0626) and Japanese phase III study (Study M0631), although the platelet count >200,000/μL was not observed in any subject in the clinical studies of lusutrombopag in patients with thrombocytopenia due to chronic liver disease (Study M0623, Study M0625, Study M0626, Study M0631, Study M061B).

PMDA's view:
Basically, data on a drug in the same class should not be used directly to evaluate the safety lusutrombopag. Nevertheless, excessively increased platelet count is assumed to pose a risk of thromboembolism in the treatment with lusutrombopag as well. The target platelet count in the treatment with lusutrombopag should be the minimum level required to ensure blood coagulation following an invasive procedure. During the treatment with lusutrombopag, therefore, the platelet count should be carefully monitored to avoid an excessive increase in platelet count, and appropriate measures, such as discontinuation of treatment, should be taken when the platelet count reaches a higher than necessary level. Patients with hepatic cirrhosis may present with not only thrombocytopenia but also bleeding tendency due to depletion of the blood coagulation factors. For the reasons explained by the applicant, patients with hepatic cirrhosis are also known to be predisposed to thromboembolism. In particular, these patients are susceptible to portal vein thrombosis due to hepatic cancer and increased portal pressure associated with hepatic cirrhosis. Thromboembolism occurring in patients receiving lusutrombopag in the clinical studies is therefore considered attributable to not only lusutrombopag but also hepatic cirrhosis, the primary disease of the patients. In the clinical studies of lusutrombopag, thromboembolism also occurred in the placebo group. The incidence of thromboembolism did not largely differ between the lusutrombopag and placebo groups. However, thromboembolism occurred in the lusutrombopag group 4 to 6 days after an invasive procedure even in the patients with a platelet count not excessively high (the maximum platelet count, 54,000-127,000/μL). Adequate attention should therefore be paid to the risk of thromboembolism in patients treated with lusutrombopag especially after an invasive procedure. At present, much remains unknown about the level of platelet count (or the amount of increase in platelet count following lusutrombopag therapy) that would sharply increase the risk of thromboembolic adverse events in patients with chronic liver disease. The target platelet count following lusutrombopag therapy should be the minimum required level that would not pose haemorrhagic risk associated with an invasive procedure, because patients with chronic liver disease are predisposed to thromboembolism such as portal vein thrombosis due to the primary disease, and because invasive procedures increase the risk of thromboembolism [see "4.(iii).B.(5).1).(b) Measures against the risk of thromboembolism during lusutrombopag therapy"]. In addition, the applicant should continue to collect information on thromboembolic adverse events and the platelet count at the onset via post-marketing surveillance and then disseminate the information appropriately.

(b) Measures against the risk of thromboembolism during lusutrombopag therapy
The inclusion criteria of the Japanese phase II and phase III studies (Study M0623, Study M0625, Study M0626, Study M0631) required that only patients with hepatopetal portal blood flow confirmed by imaging at screening be eligible. PMDA asked the applicant to explain the reasons this criterion was set, and whether hepatopetal portal blood flow should be confirmed before administration of lusutrombopag.

The applicant's response:
In patients with chronic liver disease, the risk of portal vein thrombosis increases with decreasing hepatic function (DeLeve LD et al. *Hepatology.* 2009;49:1729-1764). In patients with chronic liver disease, hepatofugal portal blood flow poses a greater risk of portal vein thrombosis than hepatopetal portal blood flow (Gaiani S et al. *Gastroenterology.* 1991;100:160-167). In consideration of these findings, the protocols specified that only patients with hepatopetal portal blood flow were eligible for the clinical studies of lusutrombopag, in order to ensure subject safety by excluding patients with disease

characteristics that would increase the risk of thrombi. Other than portal blood flow, however, the known factors causing portal vein thrombosis include the severity of hepatic impairment, the presence or absence of hepatic cancer, portal blood flow rate, and congenital and acquired coagulation disorder (Chen H et al. *Indian J Med Res.* 2014;139:260-266, DeLeve LD et al. *Hepatology.* 2009;49:1729-1764, Kumar A et al. *Aliment Pharmacol Ther.* 2014;41:276-292). The onset of thrombus therefore cannot be predicted based solely on portal blood flow direction. It is desirable to identify patients with an increased risk of thrombi by comprehensively assessing the factors potentially involved in the onset of thrombus in individual patients, and then to monitor the identified patients carefully in accordance with the precautions in the package insert (draft), but the examination of portal blood flow direction is not essential.

PMDA's view:
It is understandable that only patients with hepatopetal portal blood flow were included in the clinical studies so that patients with disease characteristics leading to an increased risk of thrombi were excluded, to ensure the safety of subjects. This criterion was appropriate to ensure the proper safety evaluation of lusutrombopag in comparison with placebo. In clinical settings, however, the use of lusutrombopag should be considered based on a comprehensive assessment of the details of the invasive procedure scheduled for individual patients (diagnosis or treatment), the haemorrhagic risk associated with the procedure, benefits of lusutrombopag, the risk of thromboembolism attributable to the patient characteristics, and other information. The screening of portal blood flow by imaging before administration of lusutrombopag is therefore not essential. The following information should be provided via the package insert: The clinical studies of lusutrombopag included only patients with hepatopetal portal blood flow confirmed by imaging evaluation at the screening; and the risk of portal vein thrombosis is generally higher in patients with hepatofugal portal blood flow than in patients with hepatopetal portal blood flow. PMDA considers that portal blood flow should be examined by imaging where necessary based on the condition of chronic liver disease in individual patients, but will make a final decision on this matter taking account of comments raised in the Expert Discussion.

In the Japanese phase II and phase III studies (Study M0623, Study M0625, Study M0626, Study M0631), patients with current or past thrombosis were excluded as a result of imaging assessment of thrombosis performed at 3 time points (2 time points in the Studies M0623, M0625, and M0626): (1) at screening; (2) between Day 8 and immediately before an invasive procedure (only Study M0631); and (3) within 3 days after an invasive procedure or between 3 and 10 days after the invasive procedure. PMDA asked the applicant to explain the necessity of imaging evaluation for thrombosis before and after administration of lusutrombopag (or immediately before an invasive procedure) and after an invasive procedure.

The applicant's response:
As described above, portal thrombosis may be likely to develop after a procedure on hepatic cancer. In general, patients with hepatic cancer undergo imaging (CT or MRI) for diagnosis of hepatic cancer before an invasive procedure, and again undergo the same imaging approximately 1 week after the procedure to assess its therapeutic effect. In consideration of the burden on patients, additional imaging should not be performed for the sole purpose of assessing thrombosis. Instead, thrombosis should be assessed by imaging performed to diagnose hepatic cancer before an invasive procedure or to assess the therapeutic effect of the procedure. In addition, it is not essential to assess thrombosis by imaging before and after administration of lusutrombopag (or immediately before an invasive procedure), because all the events of portal thrombosis in the Japanese phase II and phase III studies (Study M0626, Study M0631) occurred after an invasive procedure. Although it is desirable to assess thrombosis by monitoring the patient carefully after an invasive procedure, the safety of patients receiving lusutrombopag can be ensured by following the precautions in the package insert (draft), because thrombosis can be assessed by imaging performed to evaluate the therapeutic effect of an invasive procedure, as described above.

PMDA's view:
Patients with chronic liver disease complicated by thrombocytopenia who are potentially eligible for lusutrombopag experience portal thrombosis frequently irrespective of lusutrombopag therapy, and as shown in the clinical studies of lusutrombopag, portal thrombosis tend to occur in particular immediately

after an invasive procedure. Therefore, adequate attention should be paid to thromboembolism. Imaging such as abdominal echography, CT, and MRI are useful to evaluate hepatic blood flow and diagnose portal thrombosis, and should be performed as necessary in patients receiving lusutrombopag for the above reasons. In patients with chronic liver disease who undergo therapeutic procedure for the treatment of hepatic cancer, hepatic blood flow and portal thrombosis can be evaluated by imaging performed to assess the therapeutic effect on hepatic cancer, as explained by the applicant. In patients undergoing other invasive procedures, thromboembolism can be managed by adequately monitoring patients with special attention to thrombosis after the completion of lusutrombopag therapy (including the period after an invasive procedure) and by performing imaging, as necessary, in the event of abdominal pain or a change in pathological conditions, such as deteriorated symptom associated with increased portal pressure. Accordingly, the applicant need not mandate the assessment of thrombosis by imaging before and after the administration of lusutrombopag (or immediately before an invasive procedure) and after an invasive procedure. The package insert, however, should include a cautionary statement that attention should be paid to thromboembolism such as portal vein thrombosis during treatment with lusutrombopag, and healthcare professionals should assess thrombosis by imaging when clinically necessary.

4.(iii).B.(5).2) Measures to prevent excessive increases in platelet count

In Japanese clinical studies (Study M0623, Study M0626, Study M0631), the platelet count was measured before administration of lusutrombopag on Day 5 and thereafter to avoid a risk of thrombogenesis due to an excessively increased platelet count. In the studies, lusutrombopag was discontinued "when the platelet count reached ≥50,000/μL as a result of a ≥20,000/μL increase from baseline." PMDA asked the applicant whether a cautionary statement should be issued to ensure that healthcare professionals take measures to prevent an excessive increase in platelet count, for example, by measuring platelet count before each administration of lusutrombopag from Day 5 to Day 7.

The applicant's response:

Using the PPK/PD model constructed from the plasma drug concentration data and platelet count data in the Japanese phase II studies (Study M0623, Study M0625, Study M0626), changes in platelet counts in patients with thrombocytopenia due to chronic liver disease who received lusutrombopag 3 mg were simulated. From the simulated platelet count, the probability of the platelet count exceeding 200,000/μL by Day 30 ("the probability") was calculated for each of the days on which the discontinuation criteria were met. The results are shown in Table 14.

Table 14. Probability of the platelet count exceeding 200,000/μL by Day 30 of lusutrombopag 3 mg (modified excerpt from the submitted data)

Day meeting the discontinuation criteria	Maximum platelet count (×10,000/μL) (median [90% prediction interval])	Probability of the platelet count exceeding 200,000/μL until Day 30
None (fixed dose for 7 days)	7.03 [4.29-13.79]	0.99%
Discontinuation on Day 5, Day 6, and Day 7	6.94 [4.29-12.01]	0.24% (0.00%*)
Discontinuation on Day 5 and Day 6	6.98 [4.29-12.31]	0.28%
Discontinuation on Day 5 and Day 7	6.96 [4.29-12.40]	0.34%
Discontinuation on Day 6 and Day 7	6.95 [4.29-12.33]	0.37%
Discontinuation on Day 5	7.01 [4.29-13.02]	0.49%
Discontinuation on Day 6	6.99 [4.29-12.64]	0.42%
Discontinuation on Day 7	6.98 [4.29-12.95]	0.62%

*: Actual percentage in the Japanese phase III study (Study M0631)

Based on the data on the characteristics of 101 individual patients in Study M0623, Study M0625, and Study M0626 (body weight, age, sex, Child Pugh class), simulation was repeated 200 times for different conditions (by day meeting the discontinuation criteria). The constructed PPK/PD model was verified, as it could explain the plasma drug concentration data and platelet count data in the Japanese phase III study (Study M0631). In this model, the probability of the platelet count exceeding 200,000/μL by Day 30 was calculated to be <1%, even in the case where lusutrombopag was administered at a fixed dose for 7 days without the discontinuation criteria. The risk of an excessively increased platelet count is therefore low even without discontinuation criteria. In the above simulation, the probability decreased

to a range of 0.28% to 0.37% when discontinuation criteria were set for 2 days between Days 5 and 7 and to a range of 0.42% to 0.62% when discontinuation criteria were set for only 1 day. These results suggest that the probability (i.e., the risk of a platelet count exceeding 200,000/μL by Day 30) can by reduced by defining discontinuation criteria for lusutrombopag therapy. In patients with intra-individual variability in platelet count and patients meeting the criteria provided in "Careful Administration" in the draft package insert (i.e., patients at a high risk of thrombosis or thromboembolism and patients with severe hepatic impairment), it is appropriate to use lusutrombopag while monitoring the platelet count during treatment with reference to the discontinuation criteria included in the "Precautions for Dosage and Administration" section of the package insert (draft). In the simulation, the probability was similar regardless of the day for which the discontinuation criteria were set (Day 5, 6, or 7), giving no grounds for fixing the day(s) of platelet count monitoring based on discontinuation criteria. In addition, fixing the day(s) of platelet count monitoring compromises convenience, because patients recommended for lusutrombopag therapy undergo elective invasive procedures scheduled in advance and are thus very likely to receive outpatient treatment with lusutrombopag (from 8 to 13 days before the procedure). In the clinical studies, the platelet count was frequently monitored wherever possible to clarify the platelet count increasing profile of lusutrombopag. The package insert, however, need not provide additional cautionary statements against the excessively increased platelet count, because (1) the risk of an excessively increased platelet count is very low, even if the platelet count is not monitored on Day 5, Day 6, or Day 7, and because (2) the preventive effect against the excessively increased platelet count does not differ among the different days of the monitoring, indicating that the day(s) of monitoring need not be specified. Thus, the proposed cautionary statements in the draft package insert are appropriate.

PMDA's view:
The target platelet count following lusutrombopag therapy should be a level posing no risk of haemorrhage during an invasive procedure (slightly more than 50,000/μL), because an excessively increased platelet count may increase the risk of thromboembolism. Measures to prevent an excessively increased platelet count should be adequately taken. In addition, the platelet count must be monitored in routine clinical use of lusutrombopag, and it is desirable to specify a monitoring schedule of platelet count equivalent to the schedule used in the Japanese clinical studies, for the following reasons: (1) In clinical studies of lusutrombopag, the platelet count was monitored before dosing of lusutrombopag from Day 5 to Day 7, and lusutrombopag was discontinued when the platelet count reached ≥50,000/μL as a result of a ≥20,000/μL increase from baseline, and as a result, the safety was clinically acceptable. (2) Among 79 patients with thrombocytopenia due to chronic liver disease who received lusutrombopag 3 mg in clinical studies (Studies M0625, M0626, M0631, and M061B), 4 subjects (5.1%) discontinued the study treatment on Day 4, 4 subjects (5.1%) on Day 5, and 5 subjects (6.3%) on Day 6, according to the discontinuation criteria. Using the simulation results, the applicant explained that the risk of an excessively increased platelet count was very low, even without platelet count monitoring on Day 5, Day 6, or Day 7, and that the preventive effect against an excessively increased platelet count was similar regardless of the day(s) of monitoring, claiming that the day(s) of monitoring need not be specified. In a simulation where the discontinuation criteria was set for Day 5, Day 6, or Day 7, as in the clinical studies, however, the risk of an excessively increased platelet count was lower than that in the other settings, although the difference was not remarkable. In addition, the target populations for lusutrombopag therapy include patients with large intra-individual variability in platelet count and patients at a high risk of thromboembolism, and these patients are difficult to identify correctly. In consideration of the above, speculation based on the simulation has its limitations. The applicant's claim that fixing the day(s) of platelet count monitoring compromises convenience is, however, understandable, because patients recommended for lusutrombopag therapy undergo elective invasive procedures scheduled in advance and are thus very likely to receive outpatient treatment with lusutrombopag (from 8 to 13 days before the procedure). In consideration of the burden and convenience for patients, the platelet count should be monitored at least once between Day 5 and Day 7. Accordingly, platelet count should be measured basically on Day 5, and actions to be taken should be decided based on the measured platelet count (e.g., whether to administer lusutrombopag on Day 5; whether to monitor platelet count or administer lusutrombopag from Day 6 onward); this monitoring rule should be implemented. As there are no actual data indicating what degree of safety can be ensured by this monitoring rule, the simulation results above should be interpreted carefully. This monitoring rule, nevertheless, is likely to prevent platelet count from increasing to a clinically unacceptable level. As with the protocol of the clinical studies, the package insert should include a cautionary statement that

appropriate measures such as discontinuation of lusutrombopag should be taken if the platelet count reaches ≥50,000/μL as a result of a ≥20,000/μL increase from baseline. PMDA will review the following matters, taking account of comments raised in the Expert Discussion: the platelet count monitoring schedule; the criteria for the platelet count requiring discontinuation of lusutrombopag; actions to be taken for patients with a platelet count exceeding the lusutrombopag discontinuation criteria before Day 7; and details of the cautionary statements in the package insert.

4.(iii).B.(5).3) Safety of lusutrombopag by liver functional reserve

(a) Safety according to Child Pugh class (A or B)

PMDA asked the applicant to:

(1) Present the safety profile in patients with different liver functional reserve (Child Pugh class A or B) in the lusutrombopag 3 mg and placebo groups in patients with thrombocytopenia due to chronic liver disease in the Japanese clinical studies (Study M0625, Study M0626, Study M0631, Study M061B); (2) Present the adverse events with a ≥5% difference in incidence between patients with the liver function of Child Pugh class A and B in the lusutrombopag 3 mg and placebo groups in the Japanese clinical studies in the patients with thrombocytopenia due to chronic liver disease, and discuss the reasons for the difference, if any; and (3) Consider the necessity of a cautionary statement concerning hepatic function status in the package insert.

The applicant's response:

Table 15 shows the safety profiles according to the liver functional reserve (Child Pugh class A or B) in the lusutrombopag 3 mg and placebo groups in patients with thrombocytopenia due to chronic liver disease in Studies M0625, M0626, M0631, and M061B.

Table 15. Safety profiles according to liver functional reserve (Child Pugh class A or B) in the Japanese clinical studies (based on the combined data of Studies M0625, M0626, M0631, and M061B) (modified excerpt from submitted data)

	Lusutrombopag 3 mg		Placebo	
	Class A (N = 41)	Class B (N = 38)	Class A (N = 31)	Class B (N = 32)
All adverse events	39 (95.1)	37 (97.4)	31 (100.0)	32 (100.0)
Severe adverse events	22 (53.7)	17 (44.7)	15 (48.4)	18 (56.3)
Serious adverse events	1 (2.4)	1 (2.6)	2 (6.5)	3 (9.4)
Adverse events resulting in death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse events leading to study drug discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse drug reactions	1 (2.4)	7 (18.4)	1 (3.2)	0 (0.0)

n (%); Class A= Child Pugh class A; Class B=Child Pugh class B

Combined analysis of the studies in patients with thrombocytopenia due to chronic liver disease (Study M0625, Study M0626, Study M0631, Study M061B) identified adverse events with a ≥5% higher incidence in patients with Child Pugh class B than in patients with Child Pugh class A in the lusutrombopag 3 mg group, as shown in Table 16.

Table 16. Adverse events with a ≥5% higher incidence in patients with Child Pugh class B than in patients with Child Pugh class A in the lusutrombopag 3 mg group in the Japanese clinical studies (combined data of Studies M0625, M0626, M0631, M061B) (modified excerpt from submitted data)

MedDRA (ver 17.0)	Lusutrombopag 3 mg		Placebo	
System Organ Class Preferred term	Class A (N = 41)	Class B (N = 38)	Class A (N = 31)	Class B (N = 32)
Gastrointestinal disorders				
Constipation	2 (4.9)	4 (10.5)	3 (9.7)	3 (9.4)
General disorders and administration site conditions				
Pyrexia	1 (2.4)	7 (18.4)	1 (3.2)	3 (9.4)
Malaise	0 (0.0)	3 (7.9)	1 (3.2)	1 (3.1)
Oedema peripheral	0 (0.0)	3 (7.9)	1 (3.2)	0 (0.0)
Pain	0 (0.0)	2 (5.3)	0 (0.0)	0 (0.0)
Infections and infestations				
Nasopharyngitis	2 (4.9)	4 (10.5)	4 (12.9)	3 (9.4)
Injury, poisoning and procedural complications				
Procedural pain	15 (36.6)	18 (47.4)	16 (51.6)	11 (34.4)
Post procedural contusion	0 (0.0)	2 (5.3)	1 (3.2)	0 (0.0)
Investigations				
AST increased	11 (26.8)	13 (34.2)	9 (29.0)	9 (28.1)
Antithrombin III decreased	0 (0.0)	2 (5.3)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain	1 (2.4)	3 (7.9)	1 (3.2)	0 (0.0)
Periarthritis	0 (0.0)	2 (5.3)	0 (0.0)	0 (0.0)
Psychiatric disorders				
Insomnia	0 (0.0)	5 (13.2)	3 (9.7)	2 (6.3)
Skin and subcutaneous tissue disorders				
Pruritus	1 (2.4)	3 (7.9)	2 (6.5)	1 (3.1)
Erythema	0 (0.0)	2 (5.3)	1 (3.2)	1 (3.1)

n (%); Class A= Child Pugh class A; Class B= Child Pugh class B

Of the events listed in Table 16, pyrexia, pain, AST increased, antithrombin III decreased, and periarthritis showed a ≥5% higher incidence in patients with Child Pugh class B who received lusutrombopag 3 mg than in patients receiving placebo with Child Pugh class A or B. Pain, antithrombin III decreased, and periarthritis occurred in only 2 of 38 patients with the Child Pugh class B who received lusutrombopag 3 mg, and these events are considered likely to have an incidental bias. In patients with AST increased who received lusutrombopag 3 mg, other liver function parameters (e.g., ALT and bilirubin) did not tend to be higher in those with the Child Pugh class B than in those with the Child Pugh class A; this suggests that the events of AST increased do not have a clinically significant bias. In the lusutrombopag 4 mg group, the incidence of pyrexia was higher in patients with Child Pugh class A (5 of 16 subjects, 31.3%) than in patients with Child Pugh class B (1 of 7 subjects, 14.3%); this suggests that the higher incidence of pyrexia in patients with Child Pugh class B who received lusutrombopag 3 mg does not have a clinically significant bias. Thus, there were no differences in the safety profile between patients with different hepatic functional reserve (Child Pugh classes A and B), and the incidence of adverse events in the lusutrombopag group is unlikely to differ among such subgroups. It is therefore unnecessary to provide cautionary statements according to the hepatic functional reserve.

PMDA's view:
Adverse events showed no clear tendency to occur more frequently in patients with Child Pugh class B than in patients with Child Pugh class A, although this subgroup analysis has limitations because of the limited number of subjects. Therefore, at present, the package insert need not provide cautionary statements according to the hepatic functional reserve for patients with Child Pugh class A or B.

(b) Use of lusutrombopag in patients with severe hepatic impairment (Child Pugh class C)
PMDA asked the applicant to explain a potential use of lusutrombopag in patients with severe hepatic impairment (Child Pugh class C) prior to an invasive procedure in clinical practice, by presenting the applicable cases more specifically, to discuss the efficacy and safety of lusutrombopag in these patients, and then to explain whether lusutrombopag should be recommended to patients with severe hepatic impairment (Child Pugh class C).

The applicant's response:
In patients with chronic liver disease, the incidences of hepatic cancer and varices oesophageal increase with the progression of hepatic impairment. Patients with Child Pugh class C, thus, may receive local treatment for hepatic cancer or treatment of varices oesophageal, although less frequently than patients with Child Pugh class A and B. EIS, a treatment of varices, is contraindicated for patients with severe hepatic impairment assessed as Child Pugh class C, etc., and thus patients ineligible for EIS undergo EVL, a procedure that has very little effect on hepatic function (Obara K. *Japanese Journal of Portal Hypertension.* 2011;17:43-51). These patients experience complications such as intractable ascites and hepatic encephalopathy associated with the progression of hepatic impairment, and thus may undergo invasive procedures for the treatment of these complications (balloon-occluded retrograde transvenous obliteration, transjugular intrahepatic portosystemic shunt, peritoneo-subclavian shunt, etc.). The Treatment Algorithms for Hepatocellular Carcinoma of the Japan Society of Hepatology, a consensus-based practice guideline 2010 (The Japan Society of Hepatology. *Clinical Management Manual for Hepatic Cancer*, version 2. 23:2010) recommend that hepatic cancer be treated based on the number of hepatic cancer masses and their size as well as Child Pugh class grade, and recommend liver transplantation or palliative care for patients with Child Pugh class C. The Treatment Algorithms for Hepatocellular Carcinoma 2010 also state that patients with Child Pugh class C "may undergo local therapy or subsegmental TAE in a clinical study" if the patient has total bilirubin <3.0 mg/dL but no hepatic encephalopathy or intractable ascites (Child Pugh class C close to class B). These patients therefore may undergo local invasive procedures, such as percutaneous hepatic cancer ablation (percutaneous RFA or MCT) and subsegmental TAE, after treatment with lusutrombopag. As described above, even patients with Child Pugh class C may undergo invasive procedures following lusutrombopag therapy, depending on the severity of hepatic impairment. However, there are no data on pharmacokinetics of lusutrombopag and platelet count in these patients, and the efficacy and safety of lusutrombopag in patients with Child Pugh class C remain unknown. Since no information is available on the difference in the increase in platelet count between patients with Child Pugh class C and patients with Child Pugh class A or B, the platelet count in patients with Child Pugh class C is difficult to predict from the available data in patients with Child Pugh class A or B. In the population with thrombocytopenia due to chronic liver disease who received lusutrombopag 3 mg in clinical studies (Study M0625, Study M0626, Study M0631, Study M061B), the percentage of patients with adverse events was not clinically significantly higher in the subgroup with Child Pugh class B than in the subgroup with Child Pugh class A. The incidence of adverse events other than events related to the thrombopoietic effect is therefore unlikely to increase in the subgroup with Child Pugh class C. As described above, there are no data on pharmacokinetics and pharmacodynamics of lusutrombopag in patients with Child Pugh class C, making it difficult to predict the efficacy and safety of lusutrombopag in such patients. Lusutrombopag should be carefully administered to patients with severe hepatic impairment (Child Pugh class C) as described in the "Careful Administration" section of the draft package insert. In addition, the Child Pugh class grade is determined by the sum of the severity scores on encephalopathy, ascites, serum bilirubin, serum albumin, and prothrombin time, and the scores may change depending on the pathological condition of the patient. Lusutrombopag should not be contraindicated in patients with Child Pugh class C, but these patients should be subject to careful administration, because the cautionary statement in the "Precautions for Dosage and Administration" section in the draft package insert is intended for patients likely to have an excessively increased platelet count.

PMDA's view:
The usefulness of lusutrombopag in patients with Child Pugh class C is difficult to estimate by extrapolating data on the thrombopoietic effect and safety of lusutrombopag in patients with Child Pugh class A and B. The thrombopoietic effect and safety of lusutrombopag in patients with Child Pugh class C remain unknown at present, because the drug has never been administered to these patients. Use of lusutrombopag in patients with Child Pugh class C should be carefully decided, because (1) the risk of portal vein thrombosis may be higher in patients with Child Pugh class C than in patients with Child Pugh class A or B, and because (2) patients with severe hepatic impairment (e.g., Child Pugh class C) may have a higher risk of adverse events (e.g., excessively increased platelet count) resulting from increased exposure to lusutrombopag, since lusutrombopag is metabolized in the liver. Based on the mechanism of action, lusutrombopag is expected to have a thrombopoietic effect even in patients with

Child Pugh class C. According to the Treatment Algorithms for Hepatocellular Carcinoma 2010, patients with Child Pugh class C potentially undergo an invasive procedure for which administration of lusutrombopag is indicated, for instance, a procedure for the treatment of oesophageal varices, although the invasive local treatment is unlikely to be required for the complication such as hepatic cancer. Based on the above, lusutrombopag should be made available to patients with Child Pugh class C, provided that the efficacy and safety of lusutrombopag are monitored by healthcare professionals who have been fully informed that (1) lusutrombopag exposure and thromboembolic risk may be increased in patients with Child Pugh class C and that (2) lusutrombopag has never been used in patients with Child Pugh class C. The applicant should collect information on the increase in platelet counts over time, the degree of increase in platelet counts, and the safety in patients with Child Pugh class C after the market launch. The appropriateness of administration of lusutrombopag to patients with Child Pugh class C, the details of the cautions in the package insert, and the details of collection of the post-marketing information will be reviewed, taking account of comments raised in the Expert Discussion.

4.(iii).B.(5).4) Risk of bone marrow reticulin increased and fibrosis

The applicant's explanation on the risk of bone marrow reticulin increased and fibrosis due to lusutrombopag:

TPO receptor agonists have been known to potentially facilitate formation of reticulin fibers and fibrillization in the bone marrow. In a foreign extension study of lusutrombopag in cITP patients (Study M0622), moderate bone marrow reticulin fibrosis occurred in 1 subject, but whether this event is attributable to lusutrombopag remains unknown, because this patient had received romiplostim (genetical recombination), another TPO receptor agonist, prior to the first dose of lusutrombopag. In the clinical studies in patients with thrombocytopenia due to chronic liver disease (Study M0623, Study M0625, Study M0626, Study M0631, Study M061B), no adverse events involving bone marrow occurred. The long-term safety of lusutrombopag has not been evaluated in the clinical studies in patients with chronic liver disease; lusutrombopag thus has a potential risk of bone marrow reticulin increased and fibrosis. In the clinical studies in patients with thrombocytopenia due to chronic liver disease, no adverse events involving bone marrow occurred, and at present, there is no information on appropriate measures for reducing the risk of bone marrow reticulin increased and fibrosis during the treatment with lusutrombopag. The package insert therefore will provide a cautionary statement that bone marrow reticulin fibrosis occurred in a foreign extension study in cITP patients (Study M0622).

PMDA's view:

Short-term clinical studies in patients with chronic liver disease did not suggest that lusutrombopag causes clinically significant development of reticulin and collagen fibers and fibrosis in the bone marrow. The risk of bone marrow reticulin increased and fibrosis during the short-term treatment of lusutrombopag remains unknown at present. A possibility of development of bone marrow reticulin and fibrosis cannot be excluded in patients with chronic liver disease treated with lusutrombopag for as short as 7 days, because bone marrow reticulin fibrosis occurred in a foreign clinical study of lusutrombopag in cITP patients, although the target patients and treatment period were different. In this clinical development program in patients with chronic liver disease, the observation period for each patient was very short, and the long-term risk remains unknown. Based on the currently available information, the package insert should include a cautionary statement that bone marrow reticulin fibrosis occurred in a foreign clinical study of lusutrombopag in cITP patients. The applicant should pay attention to the long-term development of bone marrow reticulin and fibrosis in patients treated with lusutrombopag and collect relevant information after the market launch.

4.(iii).B.(5).5) Progression risk of hematological malignancy such as myelodysplastic syndrome

The applicant's explanation on lusutrombopag-related risk of progression of hematological malignancy such as myelodysplastic syndrome:

TPO receptor agonists are known to potentially cause the progression of existing hematological malignancy such as myelodysplastic syndrome. In clinical studies of lusutrombopag, adverse events involving hematological malignancy have not been reported. Patients with hematologic diseases such as hematopoietic malignancy and myelodysplastic syndrome were excluded from the clinical studies in patients with thrombocytopenia due to chronic liver disease (Study M0623, Study M0625, Study M0626, Study M0631, Study M061B). Lusutrombopag has a potential risk of causing progression of hematological malignancy such as myelodysplastic syndrome for the following reasons: The risk of

diseases such as hematopoietic malignancy and myelodysplastic syndrome has not been evaluated in non-clinical studies of lusutrombopag; lusutrombopag has not been administered to patients with the above diseases; and the long-term safety has not been evaluated. In the clinical studies in patients with thrombocytopenia due to chronic liver disease (Study M0623, Study M0625, Study M0626, Study M0631, Study M061B), progression of hematological malignancy was not observed, and at present, there is no information on appropriate measures for reducing the risk during lusutrombopag therapy. The package insert will state that progression of hematological malignancy is a potential risk of TPO receptor agonist, to raise awareness of the risk.

PMDA's view:
Although the progression risk of diseases such as hematopoietic malignancy and myelodysplastic syndrome has not been evaluated in non-clinical studies of lusutrombopag, it has been suggested that other TPO receptor agonists, drugs in the same class, cause the progression of existing hematological malignancy such as myelodysplastic syndrome. The lusutrombopag-related risk of progression of existing hematological malignancy (e.g., myelodysplastic syndrome) cannot be denied even in short-term treatment, because only a limited number of subjects were treated with lusutrombopag in clinical studies. At present, the package insert should include the cautionary statement that TPO receptor agonists potentially cause the progression of existing hematological malignancy such as myelodysplastic syndrome. The post-marketing information on the incidence of hematological malignancy in routine clinical use of lusutrombopag should be collected and be provided to healthcare professionals appropriately.

4.(iii).B.(6) Others

4.(iii).B.(6).1) Function of platelets produced in response to lusutrombopag

The applicant's explanation on functions of platelets produced in response to lusutrombopag:
In the Japanese single dose study (Study M0611) and Japanese multiple dose study (Study M0613), simple platelet aggregation tests demonstrated normal aggregation of the produced platelets. In the platelet function study (Study M061B), no abnormalities were observed in platelet aggregation (the maximum aggregation rate in the presence of ADP or collagen, platelet aggregation inducers, at multiple concentrations; the presence or absence of secondary aggregation) or in platelet release (the expression rate of P-selectin, a parameter of platelet activation, in the presence or absence of ADP, a platelet aggregation inducer), and no trend of increase in platelet morphological abnormalities after treatment with lusutrombopag was observed, either. These findings suggest that the aggregation and activation of platelets produced in response to lusutrombopag were not largely different from those before the administration.

PMDA considers that functions of platelets produced in response to lusutrombopag are acceptable.

4.(iii).B.(6).2) Changes in platelet counts after the completion or discontinuation of lusutrombopag therapy

The applicant's explanation on changes in platelet counts after the completion or discontinuation of lusutrombopag therapy and adverse events associated with haemorrhage:
As for the adverse events occurring during the follow-up period (after the completion or discontinuation of lusutrombopag therapy) in the controlled studies in patients with thrombocytopenia due to chronic liver disease (combined data from Study M0626 and Study M0631), the percentage of patients with these events did not tend to largely differ between the lusutrombopag 3 mg and placebo groups. During the follow-up period, the following haemorrhage-related adverse events occurred more frequently in the 3 mg group than in the placebo group: procedural haemorrhage (7.8% [5 of 64 subjects] in the 3 mg group, 3.2% [2 of 63 subjects] in the placebo group), haemorrhage subcutaneous (3.1% [2 of 64 subjects] in the 3 mg group, 1.6% [1 of 63 subjects] in the placebo group), and purpura (1.6% [1 of 64 subjects] in the 3 mg group, 0% [0 of 63 subjects] in the placebo group). Changes in platelet count until the day of onset of adverse events showed that transient platelets decreased did not occur after the completion of administration. Following the completion or discontinuation of lusutrombopag therapy, the percentage of patients with a platelet count decreasing below baseline was lower in the 3 mg group (60.9% [39 of 64 patients]) than in the placebo group (87.3% [55 of 63 patients]). This suggests that the risk of transient decrease in platelet count or haemorrhage is unlikely to increase after the completion or discontinuation of lusutrombopag therapy.

PMDA's view:
In the clinical studies, lusutrombopag did not show the possibility of reducing platelet count below baseline more frequently with clearly increased bleeding tendency than placebo, after the completion or discontinuation of lusutrombopag therapy. However, lusutrombopag should be carefully used with attention to the risk of haemorrhage, which more gradually increases after the completion or discontinuation of lusutrombopag therapy than during the therapy, for the following reasons. (1) The number of subjects treated with lusutrombopag in the clinical studies was extremely limited. (2) Albeit different target patients and treatment period, the studies of another TPO receptor agonist in cITP patients suggested an increased risk of haemorrhage due to the decreased platelet count after discontinuation of treatment. (3) The platelet count decreases after a certain period following the completion or discontinuation of lusutrombopag therapy, although it does not fall below baseline. The applicant should therefore provide information on changes in platelet counts after the completion or discontinuation of lusutrombopag therapy in the package insert. The applicant should also discuss the necessity of informing healthcare professionals about the haemorrhagic risk after the completion or discontinuation of treatment. Information on platelet count and haemorrhagic adverse events after the completion or discontinuation of treatment should be collected via post-marketing surveillance.

4.(iii).B.(7) Post-marketing investigations
The applicant's explanation on the post-marketing surveillance for lusutrombopag:
The applicant plans to conduct a drug use-results survey for 2 years and 2 months after the end of the early post-marketing phase vigilance in order to evaluate the safety and efficacy of lusutrombopag in patients with chronic liver disease complicated by thrombocytopenia prior to an elective invasive procedure in routine clinical use. In this survey, thrombosis and thromboembolism will be the priority investigation items and the observation period will be from the first dose of lusutrombopag to 4 weeks after the first invasive procedure. The incidence of adverse drug reactions of thrombosis and thromboembolism (i.e., the priority investigation items in this survey) in the Japanese clinical studies was 1.9% (3 of 157 subjects). Approximately 158 patients should be included to detect the adverse drug reactions at an incidence of ≥1.9% with 95% probability. The target sample size in this survey was, however, set as 300 patients, because invasive procedures performed after lusutrombopag therapy may confound the risk of thrombogenesis.

PMDA's view:
The priority investigation items in the drug use-results survey proposed by the applicant are generally acceptable, but the survey should be conducted for an extended period in patients with chronic liver disease complicated by thrombocytopenia who have received lusutrombopag prior to an elective invasive procedure, because lusutrombopag has been administered to extremely limited number of patients with a short observation period. In particular in patients with a low baseline platelet count (<35,000/μL, etc.), the applicant should collect information on the efficacy and safety of lusutrombopag and development of thromboembolism and examine the appropriateness of the timing and frequency of platelet count monitoring defined at the time of approval. The proposed observation period for the priority investigation items is from the first dose of lusutrombopag to 4 weeks after the first invasive procedure. PMDA, however, considers that the observation period should be changed to at least 3 to 4 months, in order to collect information on re-administration of lusutrombopag and changes in platelet counts after the completion of lusutrombopag therapy (changes from baseline and 50,000/μL). The applicant should also collect information on bone marrow reticulin increased and fibrosis and progression of hematological malignancy such as myelodysplastic syndrome as well as the safety and efficacy in patients with Child Pugh class C and in patients who had undergone splenectomy. In addition, the applicant should reconsider the target sample size in this survey so as to collect information on various matters that have not been thoroughly investigated in the Japanese clinical studies because of the limited scale and plan. The details of the post-marketing surveillance will be finalized, taking account of comments raised in the Expert Discussion.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

The compliance assessment is currently ongoing, and the results and conclusion by PMDA will be reported in the Review Report (2).

IV. Overall Evaluation

As a result of the reviews presented above and based on the submitted data, PMDA has concluded that lusutrombopag has been shown to have efficacy in the treatment of thrombocytopenia in patients with chronic liver disease complicated by thrombocytopenia prior to an elective invasive procedure, and that the safety of lusutrombopag is acceptable in view of its observed benefits. Lusutrombopag is considered to be a clinically significant drug used to increase the platelet count prior to an elective invasive procedure in patients with chronic liver disease complicated by thrombocytopenia. PMDA considers it necessary to further review the appropriateness of the indication, dosage and administration, and cautionary statements as well as post-marketing investigations.

PMDA considers that lusutrombopag may be approved if the drug is considered to have no particular problems based on comments from the Expert Discussion.

Review Report (2)

August 7, 2015

I. Product Submitted for Registration

[Brand name]	Mulpleta Tablets 3 mg
[Non-proprietary name]	Lusutrombopag
[Applicant]	Shionogi & Co., Ltd.
[Date of application]	December 17, 2014

II. Content of the Review

The comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by the Pharmaceuticals and Medical Devices Agency" (PMDA Administration Rule No. 8/2008 dated December 25, 2008).

1. Clinical positioning of lusutrombopag

In patients with chronic liver disease, invasive procedures are frequently required to treat hepatocellular carcinoma despite the presence of thrombocytopenia caused by decreased production of endogenous thrombopoietin (TPO) associated with the progression of chronic liver disease. In a Japanese phase III study (Study M0631), lusutrombopag has been demonstrated to maintain adequate platelet counts required to perform an invasive procedure, with acceptable safety. PMDA therefore has concluded that lusutrombopag is significant enough to be used in clinical practice. This conclusion by PMDA was supported by the expert advisors. The following comments were raised from the expert advisors: (1) Deciding the initiation of lusutrombopag therapy based solely on the platelet count may be inappropriate, because the haemorrhagic trend is affected by not only the platelet count but also decreased activities of the coagulation factors due to chronic liver disease. (2) The international normalized ratio of prothrombin time, which is generally used as an indicator of the haemorrhagic trend, should be used as a criterion to initiate treatment in addition to platelet count. In response these comments, PMDA explained the following: (1) Lusutrombopag is to be used in rescue therapy for a low platelet count, one of the factors affecting haemorrhagic risk. (2) At present, platelet count (<50,000/μL) is used as a criterion to initiate platelet transfusion prior to an elective invasive procedure, as specified in the "Guidelines for the Use of Blood Product" (Blood and Blood Products Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated September 2005 [revised in 2012]) (Guidelines for Blood Product Use), but there is no evidence to define the cut-off value for any coagulation marker. (3) The applicant will advise that the use of lusutrombopag be decided based on not only the platelet count but also individual patients' conditions. For example, the "Precautions for Indications" section in the package insert states, "Lusutrombopag should be used in patients assessed to have a high haemorrhagic risk based on laboratory values, such as the platelet count, clinical symptoms, and type of the invasive procedure scheduled." The criteria to initiate treatment presented by PMDA were supported by the expert advisors.

2. Efficacy and dosage and administration

1) Efficacy and dosage and administration of lusutrombopag

The expert advisers discussed the following conclusions by PMDA: (1) The efficacy of lusutrombopag can be evaluated based on the percentage of patients requiring no platelet transfusion prior to an invasive procedure in a Japanese phase III study (Study M0631) conducted in patients with chronic liver disease complicated by thrombocytopenia who are scheduled to undergo an elective invasive procedure. In the study, patients with a platelet count <50,000/μL received platelet transfusion. (2) "Lusutrombopag 3 mg once daily for 7 days" was shown to have a clinically significant thrombopoietic effect, based on the percentage of patients requiring no platelet transfusion prior to the invasive procedure and the percentage of responders, the secondary endpoint, in the Japanese phase II dose-ranging study (Study M0626) and

Japanese phase III study (Study M0631). (3) The proposed dosage and administration of lusutrombopag are appropriate. The expert advisors commented that the conclusions by PMDA are acceptable, and that it remains uncertain whether the dose of lusutrombopag should be adjusted according to body weight. PMDA explained that doses of lusutrombopag need not be adjusted according to body weight for the following reasons: (1) Population pharmacokinetic and pharmacodynamic analysis based on pharmacokinetic data and platelet counts in Japanese healthy adult subjects and patients with chronic liver disease showed that body weight was not a significant covariate to the drug effect parameter corresponding to the slope in the effect-concentration plot; The platelet count simulation following lusutrombopag 3 mg once daily for 7 days showed that either "the probability of a platelet count exceeding 200,000/μL during the treatment period" or "the probability of a platelet count exceeding 50,000/μL between Day 9 and Day 14" did not largely differ among subgroups defined by body weight. (2) Combined analysis of the Japanese controlled studies (Study M0626, Study M0631) showed no large differences among subgroups defined by body weight in the percentages of patients requiring no platelet transfusion prior to an invasive procedure or incidences of overall adverse events. This conclusion by PMDA was supported by the expert advisors.

Based on the above review, PMDA has concluded that the appropriate dosage and administration are as shown below.

[Dosage and administration]
The usual adult dosage is 3 mg of lusutrombopag orally administered once daily for 7 days.

2) Re-administration of lusutrombopag

The expert advisers discussed the following conclusions by PMDA: (1) At present, re-administration of lusutrombopag is not recommended for patients with a platelet count that has not adequately decreased back to baseline, because much remains unknown about the efficacy, safety, appropriate dose, number of dosing days, and appropriate method of platelet count monitoring in these patients; Platelet transfusion or other treatment should be administered, as necessary, to patients requiring an additional invasive procedure who presents with decreasing platelet count after lusutrombopag therapy. (2) Re-administration of lusutrombopag is not highly recommended for patients with a platelet count that has decreased to baseline, because the efficacy and safety of re-administration in such patients remain unknown. However, re-administration to such patients is acceptable if platelet counts and the condition of patients are monitored at least as carefully as monitoring following the first administration. Several comments were raised from the expert advisors: (1) The conclusions by PMDA are acceptable. (2) An additional study of re-administration should be conducted to collect information, because the clinical benefits of lusutrombopag is undermined if platelet transfusion or other treatment is administered to patients who require re-administration of lusutrombopag in clinical practice. (3) The applicant should make an appropriate plan for how to collect data from patients receiving re-administration and how to evaluate such patients in the post-marketing surveillance. PMDA explained that re-administration is not highly recommended at present, since how the effect of lusutrombopag changes following re-administration is a matter for speculation because of a lack of evaluable data, but the applicant plans to design the surveillance so as to collect the efficacy and safety data on re-administration and further collect and evaluate information in the post-marketing settings. These provisional conclusions by PMDA were supported by the expert advisors.

In consideration of the above, PMDA requested the applicant to include the following cautionary statement in the "Precautions for Dosage and Administration" section in the package insert: "The efficacy and safety of re-administration of lusutrombopag have not been studied. Other treatment options should be chosen especially for patients with a platelet count that has not decreased back to baseline." The applicant took an appropriate action in response to this request. PMDA also instructed the applicant to design the post-marketing surveillance to ensure appropriate collection and evaluation of the efficacy and safety data on re-administration. The applicant took appropriate actions.

3. Patient populations and indications of lusutrombopag

The following conclusions by PMDA were supported by the expert advisors: (1) The invasive procedures allowed following lusutrombopag therapy are the invasive procedures performed in the Japanese phase III study of lusutrombopag (Study M0631) and other invasive procedures before which

"platelet transfusion is usually not necessary if the platelet count is ≥50,000/μL," as defined in the "Guidelines for Blood Product Use." (2) Invasive procedures involving laparotomy, thoracotomy, cardiotomy, craniotomy, or organ resection should not be performed following lusutrombopag therapy. (3) Patients requiring an urgent operation are ineligible for lusutrombopag therapy.

In addition, the following conclusion by PMDA was also supported by the expert advisors: The "Clinical Studies" section in the package insert should state that "platelet count <50,000/μL at screening" was an inclusion criterion in the clinical studies of lusutrombopag. The section should also provide the list of the invasive procedures performed in the Japanese phase III study (Study M0631).

PMDA concluded that patients with splenectomy should be allowed to use lusutrombopag, provided that the drug is administered carefully with adequate attention to changes in platelet count, although lusutrombopag has never been administered to patients with splenectomy. The expert advisors made several comments: (1) This conclusion by PMDA is acceptable. (2) Patients with splenectomy need not be excluded from receiving lusutrombopag, but the safety in these patients should be investigated via the post-marketing surveillance. (3) Patients with splenectomy should be shown to have no factors leading to low platelet count, other than decreased TPO activity, before receiving lusutrombopag. PMDA explained the following: (1) Not many patients will require lusutrombopag after splenectomy, therefore the applicant plans to collect information from all patients with splenectomy who have received lusutrombopag and provide cautions or conduct additional surveys where necessary. (2) Healthcare professionals should be advised to carefully assess the eligibility of not only patients with splenectomy but also all patients potentially treated with lusutrombopag. This explanation by PMDA was supported by the expert advisors.

Based on the above, PMDA has concluded that the indication should be "Improvement of thrombocytopenia associated with chronic liver disease in patients prior to elective invasive procedures."

PMDA instructed the applicant to include the following cautionary statements in the "Precautions for Indications" in the package insert: "Lusutrombopag should be used in patients assessed to have a high haemorrhagic risk based on laboratory values, such as the platelet count, clinical symptoms, and type of the invasive procedure scheduled. (In the clinical studies, patients with a platelet count <50,000/μL were included [see the "Clinical Studies" section].)"; and "Lusutrombopag should not be used prior to invasive procedure involving laparotomy, thoracotomy, cardiotomy, craniotomy, or organ resection. (The efficacy and safety have not been established in patients undergoing these procedures.)" Furthermore, PMDA instructed the applicant to add the baseline platelet counts and the invasive procedures performed in the Japanese phase III study in the "Clinical Studies" section. The applicant took appropriate actions.

4. Safety of lusutrombopag

1) Measures against the risk of thromboembolism during lusutrombopag therapy

The following conclusions by PMDA were supported by the expert advisors: (1) In clinical practice, the use of lusutrombopag should be determined for individual patients based on a comprehensive assessment of the details of the invasive procedure scheduled, the haemorrhagic risk associated with the procedure, benefits of lusutrombopag, and the risk of thromboembolism attributable to the patient characteristics. (2) The screening of portal blood flow before administration of lusutrombopag is not essential but should be implemented where necessary, although the "Careful Administration" section in the package insert should state that the clinical studies of lusutrombopag included only patients with hepatopetal portal blood flow, and that patients with hepatofugal portal blood flow generally have a higher risk of portal vein thrombosis than patients with hepatopetal portal blood flow. The following conclusion by PMDA was also supported by the expert advisors: The package insert should include a cautionary statement that patients should be monitored or tested with attention to thromboembolism such as portal vein thrombosis during lusutrombopag therapy, because portal thrombosis frequently occurs, particularly immediately after an invasive procedure, in patients with chronic liver disease complicated by thrombocytopenia, who are potentially eligible for lusutrombopag therapy, irrespective of lusutrombopag therapy. The expert advisors commented that specific measures for patients with thrombi should be considered. The expert advisers agreed that (1) patients with thrombi should be listed in the "Careful Administration" section, because lusutrombopag may increase the risk of thrombi, and

that (2) the post-marketing safety data in these patients should be provided to healthcare professionals when adequate information become available, because patients with current or past thrombi were excluded from the clinical studies.

Based on the above discussion, PMDA requested the applicant to include "patients with hepatofugal portal blood flow" and "patients with thrombosis" in the "Careful Administration" section, and to design the post-marketing surveillance to appropriately collect safety data in patients with current or past thrombosis or thromboembolism, and to construct a system so that useful post-marketing information, when it becomes available, can be provided to healthcare professionals as appropriate. The applicant took appropriate actions.

2) Measures to prevent excessive increases in platelet count

PMDA concluded that (1) platelet counts in patients receiving lusutrombopag must be monitored in routine clinical practice, because lusutrombopag was shown to have clinically acceptable safety in patients undergoing platelet count monitoring performed in compliance with the predefined schedule in the clinical studies, and that (2) platelet count should be measured on Day 5 basically, in accordance with the schedule in the Japanese clinical studies, and actions to be taken should be decided based on the measured platelet count (e.g., whether to administer lusutrombopag on Day 5; whether to monitor platelet count or administer lusutrombopag from Day 6 onward). In addition, PMDA concluded that appropriate measures (e.g., discontinuation of lusutrombopag) should be taken in cases where the platelet count has reached ≥50,000/μL as a result of a ≥20,000/μL increase from baseline. The expert advisors supported these conclusions by PMDA. Some expert advisers, however, comment that the criterion "discontinue lusutrombopag when the platelet count reaches ≥50,000/μL" alone may be sufficient for discontinuation (efficacy) criteria (i.e. the wording "as a result of a ≥20,000/μL increase from baseline" is unnecessary). PMDA explained that no data have shown whether patients who have discontinued lusutrombopag immediately after achieving a platelet count ≥50,000/μL (irrespective of the degree of increase from baseline) can maintain a platelet count ≥50,000/μL for a certain period after the discontinuation. The conclusions by PMDA were supported by the expert advisors.

PMDA requested the applicant to include the following cautionary statement in the "Precautions for Dosage and Administration" in the package insert: "Attention should be paid to the platelet count during the treatment with lusutrombopag. The platelet count should be measured at least once approximately 5 days after the first dose and as necessary thereafter. Appropriate measures such as discontinuation of lusutrombopag should be taken if the platelet count reaches ≥50,000/μL as a result of a ≥20,000/μL increase from baseline." The applicant took appropriate actions.

3) Use of lusutrombopag in patients with severe hepatic impairment (Child Pugh class C)

Lusutrombopag has never been administered to patients with Child Pugh class C, thus the efficacy and safety in such patients remain unclear at present. These patients may have a higher risk of portal vein thrombosis than patients with Child Pugh class A or B, and may present with increased exposure to lusutrombopag. PMDA, however, concluded that lusutrombopag should be made available to patients with Child Pugh class C, provided that healthcare professionals are advised to carefully monitor the patients, through the package insert, because the mechanism of action of lusutrombopag suggests that the drug has thrombopoietic effect even in these patients. The expert advisors found this conclusion acceptable, but made the following comments: (1) Since platelet transfusion is available for a wider range of patients, lusutrombopag need not be selected for patients with Child Pugh class C, for the following reasons: (a) The extent of increase in the risk of thrombosis remains unclear in patients with Child Pugh class C; (b) The efficacy, safety, and appropriate dosage regimen of lusutrombopag remain unclear in patients with Child Pugh class C, because lusutrombopag has never been administered to these patients in clinical studies, although these patients have a risk of increased exposure to lusutrombopag as it is metabolized in the liver. (2) In clinical practice, contraindicating lusutrombopag in patients with Child Pugh class C will provide more benefits than allowing these patients to use the drug, because the risk and benefit of lusutrombopag in these patients are unclear. Taking account of these comments raised in the Expert Discussion, PMDA has concluded that lusutrombopag should be contraindicated in patients with severe hepatic impairment (Child Pugh class C). This conclusion by PMDA was supported by the expert advisors.

PMDA requested the applicant to contraindicate lusutrombopag in "patients with severe hepatic impairment (Child Pugh class C)." The applicant took appropriate action regarding the above request.

5. Risk management plan (draft)

Based on the results of the review in "4.(iii).B.(7) Post-marketing investigations" of the Review Report (1) and the comments raised by expert advisors at the Expert Discussion, PMDA considers that the following items should be added to the post-marketing surveillance.

- Incidence of thromboembolism-related events, types of the events (portal vein thrombosis, etc.), severity, characteristics of the patients experiencing thromboembolism-related events, platelet count, and timing and frequency of platelet count monitoring
- Efficacy and safety in patients with a low baseline platelet count (e.g., <35,000/μL)
- Changes in platelet counts after the completion or discontinuation of lusutrombopag therapy (changes from baseline and 50,000/μL)
- Safety and efficacy of re-administration (e.g., period from the completion of first administration to the start of re-administration, platelet count at the start of re-administration, changes in platelet counts after the initiation of the re-administration)
- Safety and efficacy in patients who had undergone splenectomy
- Safety in patients with thrombosis
- Details of the invasive procedure for which lusutrombopag is indicated, details of the invasive procedure actually performed after lusutrombopag therapy, and efficacy (e.g., whether the patient received platelet transfusion prior to the invasive procedure)
- Risks of bone marrow reticulin increased and bone marrow fibrosis
- Progression risk of hematological malignancy such as myelodysplastic syndrome

PMDA instructed the applicant to investigate these items in the post-marketing surveillance. The applicant submitted the post-marketing surveillance plan (draft) shown in Table 17.

Table 17. Outline of the drug use-results survey (draft)

Objective	Collection of information regarding the safety and efficacy of lusutrombopag in routine clinical use
Method	Central registration system
Population	Patients with thrombocytopenia due to chronic liver disease prior to an elective invasive procedure
Observation period	Two months after the first dose of lusutrombopag (if re-administration is started within 6 months after the first dose, the observation is performed for another 2 months after the start of re-administration)
Target sample size	1000 patients
Priority investigation item	Thrombosis and thromboembolism
Major investigation items	• Patient characteristics • Use status of lusutrombopag • Invasive procedure • Drugs used other than lusutrombopag • Platelet transfusion during the observation period • Adverse events

Based on the above discussion, PMDA has concluded that the draft risk management plan of lusutrombopag should include the safety and efficacy specifications shown in Table 18 and additional pharmacovigilance activities and risk minimization actions shown in Table 19. The applicant submitted a draft risk management plan developed based on Tables 18 and 19.

Table 18. Safety and efficacy specifications in the risk management plan

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Thrombosis and thromboembolism	• Bone marrow reticulin increased and fibrosis • Progression of hematological malignancy such as myelodysplastic syndrome	• Safety of re-administration
Efficacy specification		
• Efficacy in routine clinical use		

Table 19. Summary of additional pharmacovigilance activities and risk minimization actions in the risk management plan

Additional pharmacovigilance activities	Additional risk minimization actions
• Early post-marketing phase vigilance • Drug use-results survey	• Information provision through the early post-marketing phase vigilance • Preparation and distribution of materials for healthcare professionals

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

PMDA conducted a document-based compliance inspection and data integrity assessment of the data submitted in the new drug application, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

PMDA conducted GCP on-site inspection of the data submitted in the new drug application (5.3.5.1-02, 5.3.5.1-03, 5.3.5.1-04), in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

As a result of the above review, PMDA concludes that the product may be approved for the indication and dosage and administration shown below, with the following conditions. As lusutrombopag is a drug with a new active ingredient, the appropriate re-examination period is 8 years. Neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug. The product is not classified as a biological product or a specified biological product.

[Indication]	Improvement of thrombocytopenia associated with chronic liver disease in patients prior to elective invasive procedures
[Dosage and administration]	The usual adult dosage is 3 mg of Lusutrombopag orally administered once daily for 7 days.
[Conditions for approval]	The applicant is required to develop and appropriately implement a risk management plan.