Report on the Deliberation Results

September 2, 2010

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

[Brand name]	Revolade Tablets 12.5 mg and 25 mg
[Nonproprietary name]	Eltrombopag Olamine (JAN*)
[Applicant]	GlaxoSmithKline K.K.
[Date of application]	September 30, 2009

[Results of deliberation]
In the meeting held on August 26, 2010, 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 product is not classified as a biological product or a specified biological product, the re-examination period is 10 years, and both the drug substance and the drug product are classified as powerful drugs.

[Conditions for approval]
Since the product has been studied in only a limited number of patients in Japan, the applicant is required to conduct a drug use-results survey involving all patients treated with the product after market launch until data from a certain number of patients have been accumulated in order to understand the characteristics of the patients treated. At the same time, safety and efficacy data on the product should be collected without delay and necessary measures should be taken to facilitate the proper use of the product.

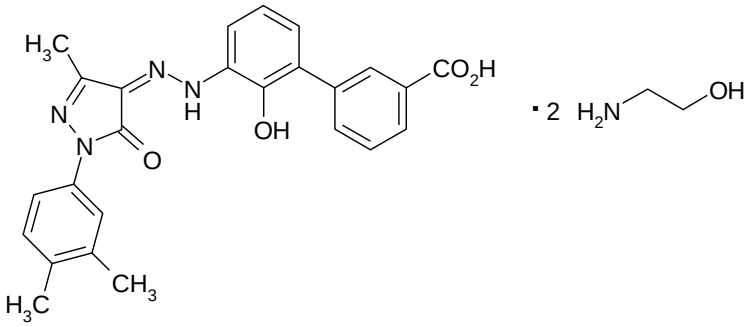
**Japanese Accepted Name (modified INN)*

Review Report

August 17, 2010
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]	Revolade Tablets 12.5 mg and 25 mg
[Non-proprietary name]	Eltrombopag Olamine
[Applicant]	GlaxoSmithKline K.K.
[Date of application]	September 30, 2009
[Dosage form/Strength]	Film-coated tablets: Each tablet contains 12.5 mg or 25 mg of Eltrombopag
[Application classification]	Prescription drug (1) Drug with a new active ingredient
[Chemical structure]	



Molecular formula:	$C_{25}H_{22}N_4O_4 \cdot 2\ (C_2H_7NO)$
Molecular weight:	564.63
Chemical name:	3'-{(2*Z*)-2-[1-(3,4-Dimethylphenyl)-3-methyl-5-oxo-1,5-dihydro-4*H*-pyrazol-4-ylidene]hydrazino}-2'-hydroxybiphenyl-3-carboxylic acid bis(2-aminoethanol)

[Items warranting special mention]
Orphan drug (Notification No. 0323003 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated March 23, 2007)

[Reviewing office] Office of New Drug I

Review Results

August 17, 2010

[Brand name]	Revolade Tablets 12.5 mg and 25 mg
[Non-proprietary name]	Eltrombopag Olamine
[Applicant]	GlaxoSmithKline K.K.
[Date of application]	September 30, 2009

[Results of review]
Based on the submitted data, it is concluded that the efficacy of Revolade Tablets 12.5 mg and 25 mg in patients with chronic idiopathic thrombocytopenic purpura has been demonstrated and the safety is acceptable in view of its observed benefits. Concerning the safety and efficacy of, and thromboembolic events associated with, the long-term use of the product in routine clinical practice, it is considered important to collect the information via post-marketing surveillance.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the indication and dosage and administration as described below, with the following conditions.

[Indication]	Chronic idiopathic thrombocytopenic purpura
[Dosage and administration]	The usual initial adult dosage of eltrombopag is 12.5 mg once daily administered orally on an empty stomach (>2 hours before or after a meal). The dose may be adjusted according to the patient's platelet count and condition. The maximum daily dose is 50 mg.
[Conditions for approval]	Since the product has been studied in only a limited number of patients in Japan, the applicant is required to conduct a drug use-results survey involving all patients treated the product after market launch until data from a certain number of patients have been accumulated in order to understand the characteristics of the patients treated. At the same time, safety and efficacy data on the product should be collected without delay and necessary measures should be taken to facilitate the proper use of the product.

Review Report (1)

July 21, 2010

I. Product Submitted for Registration

[Brand name] Revolade Tablets 12.5 mg and 25 mg
[Non-proprietary name] Eltrombopag Olamine
[Name of applicant] GlaxoSmithKline K.K.
[Date of application] September 30, 2009
[Dosage form/Strength] Film-coated tablets: Each tablet contains 12.5 mg or 25 mg of Eltrombopag
[Proposed indication] Idiopathic thrombocytopenic purpura
[Proposed dosage and administration]
The usual initial adult dosage of eltrombopag is 12.5 mg administered orally once daily. The dose may be adjusted according to the patient's platelet count and condition. The maximum daily dose is 50 mg.
[Items warranting special mention]
Orphan drug (Notification No. 0323003 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated March 23, 2007)

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

A summary of the submitted data in this application and an outline of the review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

Eltrombopag olamine is an orally available low molecular weight thrombopoietin (TPO) receptor (TPO-R) agonist developed by GlaxoSmithKline plc. (UK). Eltrombopag partially activates the TPO signal transduction pathway through activation of the TPO-R, enhancing cellular proliferation and differentiation in a process from the bone-marrow precursor cells into megakaryocytes and consequently increasing the platelet count.

Overseas, the development of eltrombopag olamine was initiated in 19[redacted] by GlaxoSmithKline plc. (UK), and in November 2008, it was first approved for the indication of "the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura who have had an insufficient response to corticosteroids, immunoglobulin, or splenectomy," in the US. As of June 2010, it has been approved in 39 countries.

In Japan, its development was initiated by GlaxoSmithKline K.K. in 20[redacted], and an application for marketing approval has been recently submitted based on Japanese and foreign clinical data, etc. During the review, the initially submitted CTD Module 5 was replaced with the revised data as it was found to be defective. In Japan, eltrombopag was designated as an orphan drug in March 2007.

2. Data relating to quality

2.A Summary of the submitted data

Eltrombopag 12.5 and 25 mg in tablet form (collectively referred to as "the drug product") are

supplied as film-coated tablets. Each tablet contains 15.9 or 31.9 mg of eltrombopag olamine (molecular formula, $C_{25}H_{22}N_4O_4 \cdot 2[C_2H_7NO]$; molecular weight, 564.63) (12.5 and 25 mg as eltrombopag), respectively, per tablet.

2.A.(1) Drug substance
2.A.(1).1) Characterization
(a) Structure
The drug substance is a bis 2-aminoethanol salt of eltrombopag, having a hydrazone structure. It is in a Z-configuration with an intramolecular hydrogen bond. The chemical structure of the drug substance has been elucidated by elementary analysis, mass spectrometry, ultraviolet-visible spectrophotometry, infrared spectrophotometry (IR), hydrogen nuclear magnetic resonance spectrometry (^{1}H-NMR), carbon nuclear magnetic resonance spectrometry, single-crystal X-ray crystallography, carbon solid-state nuclear magnetic resonance spectroscopy, and X-ray powder diffraction.

(b) General properties
The determined general properties of the drug substance include description, solubility, hygroscopicity, thermal analysis, dissociation constant (pKa), partition coefficient, crystalline polymorphism, optical rotation, and particle size. The drug substance is a red to brown powder. It is sparingly soluble in water, slightly soluble in methanol and in ethanol (99.5), and practically insoluble in 0.1 mol/L hydrochloric acid. It is non-hygroscopic and remains thermodynamically stable at up to 125°C. At a higher temperature, an endothermic reaction associated with its degradation occurs. The pKa of the carboxyl group, phenolic hydroxyl group, and hydrazone are 4.06, 9.57, and 11.88, respectively, and the partition coefficient (1-octanol/water) is 4.05. Investigations under various crystallization conditions have demonstrated that only one crystal form of the drug substance has been identified. The drug substance has no optical rotation, and the particle size ([redacted]) consistent with [redacted]% cumulative distribution ranges from [redacted] to [redacted] μm.

2.A.(1).2) Manufacturing process
The drug substance is manufactured using the following 5 steps.
Step 1: [redacted]

Step 2: [redacted]

Step 3: [redacted]

Step 4: Eltrombopag olamine is pulverized.

Step 5: Pulverized eltrombopag olamine is placed in a polyethylene bag.

2.A.(1).3) Control of critical process steps
Step [redacted] and Step [redacted] are defined as the critical process steps. The process control parameters include the amount of gsk002, an impurity, in Step [redacted] as well as the amount of gsk001 and the specification for eltrombopag, a critical intermediate, in Step 2.

2.A.(1).4) Control of drug substance
[redacted]

2.A.(1).5) Stability of drug substance
The stability study has consisted of the following tests using the batches manufactured on a commercial production scale.

(a) Long-term testing (30°C/65%RH, polyethylene bottle, 24 months)
(b) Accelerated testing (40°C/75%RH, polyethylene bottle, 6 months)

Using the batches manufactured on a pilot scale, the following tests were conducted.

(c) Stress testing; Stability against temperature (50°C, polyethylene bag/cardboard carton, 3 months)
(d) Stress testing; Photostability (approximately 25°C, cool white fluorescent lamp [overall illumination of ≥1.20 million lx·h] and near ultraviolet lamp [integrated near ultraviolet energy of ≥200 W·h/m^2], exposed sample).

[redacted]

Under all storage conditions, no change over time was observed in the description, related substances, or content. [redacted]

[redacted] In addition, the description failed to meet the specification in the above batches after 24 months of storage and in samples stored for 30 months in the currently ongoing long-term testing. [redacted]

Based on the above results, a retest period of 12 months has been proposed for the drug substance when stored in an airtight container at room temperature, in consideration of the duration in which no changes were observed even in [redacted]3044.

2.A.(2) Reference material
The proposed specifications for the reference material of the drug substance include description (visual observation), identification (IR, ^{1}H-NMR), purity (related substances [HPLC], residual

solvents [GC]), water content, residue on ignition, and purity.

2.A.(3)Drug product
2.A.(3).1)Description and composition of the drug product

[redacted]

2.A.(3).2) Formulation development

[redacted]

2.A.(3).3) Manufacturing process
The drug product is produced through the manufacturing process comprising the following 11 steps.

Step 1 ([redacted] process): [redacted]

Step 2 (granulation process): [redacted]

Step 3 (grinding process): [redacted]

Step 4 (drying process): [redacted]

Step 5 (sizing process): [redacted]

Step 6 (blending process): [redacted]

Step 7 (tableting process): [redacted]

Step 8 (coating process): [redacted]

Step 9 (storage process): The film-coated tablets are stored.

Step 10 (primary packaging process): With a Press Through Pack (PTP) package machine, the film-coated tablets are placed in an aluminum sheet and heat-sealed with aluminum foil, and PTP sheets are cut.

Step 11 (secondary packaging process, labeling, storage): The PTP sheets are packaged in a paper carton and stored.

2.A.(3).4) Control of critical process steps
Step [redacted] ([redacted] process) is defined as a critical process step. Step [redacted] ([redacted] process) and Step [redacted] ([redacted] process) have their design spaces set, and Step [redacted] ([redacted] process) and Step [redacted] ([redacted] process) have the process control parameters and in-process controls set.

2.A.(3).5) Control of drug product
The proposed specifications for the drug product include description (visual observation), identification (IR), uniformity of dosage units (content uniformity [HPLC]), dissolution (paddle

method, ultraviolet-visible spectrophotometry), and content (HPLC).

2.A.(3).6) Stability of drug product
Using the batches manufactured on a commercial production scale, the following tests were conducted.

(a) Long-term testing (30°C/65%RH, double aluminum PTP sheet, 12.5 mg tablets for 24 months, 25 mg tablets for 48 months)
(b) Accelerated testing (40°C/75%RH, double aluminum PTP sheet, 6 months)
(c) Stress testing; stability against temperature (50°C, double aluminum PTP sheet, 3 months)
(d) Stress testing; photostability (25°C, cool white fluorescent lamp [overall illumination of ≥1.20 million lx·h] and near ultraviolet lamp [integrated near ultraviolet energy of ≥200 W·h/m^2])

The description, content, related substances, and dissolution were measured at all time points in all tests.

Under all storage conditions, no change over time was observed in the description, content, related substances, or dissolution.

Based on the above results, a shelf life of 36 months has been proposed for the 12.5 mg tablet formulation of the drug product and a shelf life of 48 months has been proposed for the 25 mg tablet formulation of the drug product, in accordance with the "Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003). The long-term testing of 12.5 mg tablets is planned to be continued for up to [redacted] months.

2.B Outline of the review by PMDA

2.B.1) Stability of drug substance

[redacted]

The applicant explained as follows:

[redacted]

PMDA has accepted the applicant's explanation that the storage condition at room temperature using a well-closed container would not be changed as long as 1 year of the retest period is set.

2.B.2) Design space in the manufacturing process of drug product

[redacted]

[redacted] As described above, because the design space in the concerned process would be affected by the scale, it is difficult to estimate the non-conformity range at a commercial production scale only based on the data at the pilot scale. [redacted]

[redacted]

The applicant changed to include the above PAR to the partial change approval application item.

PMDA accepted the applicant's action and has concluded that there are no particular problems with the quality of the drug product.

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 Stimulation of platelet production
(a) Effects on growth of megakaryocytic cell strain (Attached document 4.2.1.1.1, 4.2.1.1.2)
Human megakaryocytic leukemia cell strain (N2C-TPO cell) endogenously expressing TPO-R was added with eltrombopag disodium salt (0.001, 0.003, 0.01, 0.03, 0.1, 0.3, 1, 3, 10 μM as eltrombopag), human recombinant TPO (rhTPO) (5, 10, 50, 100, 200 ng/mL), or vehicle and then incubated for 68 hours, and ^{3}H-thymidine was added. The cellular intake of ^{3}H-thymidine for 4 hours after addition of ^{3}H-thymidine increased in an eltrombopag or rhTPO concentration-dependent manner and the 50% effective concentration (EC_{50}) was 0.3 μM and 30 ng/mL, respectively. N2C-TPO cells were added with eltrombopag monosodium salt (0.0001, 0.0003, 0.001, 0.003, 0.01, 0.03, 0.1, 0.3, 1, 3, 10 μM as eltrombopag) or rhTPO (75 ng/mL) and then incubated for 44 hours, and 5-bromo-2'-deoxyuridine (BrdU) was added. The cellular intake of BrdU for 4 hours after addition of BrdU increased in an eltrombopag concentration-dependent manner in the range from 0.01 to 3 μM, and the EC_{50} was 0.03 μM. The BrdU uptake at the eltrombopag concentration of 3 μM was greater than that at the rhTPO concentration of 75 ng/mL.

(b) Effect of TPO on N2C-TPO cell growth stimulation (Attached document 4.2.1.1.3)
N2C-TPO cells were added with eltrombopag olamine (0, 0.003, 0.01, 0.03, 0.1, 0.3, 1, 3 μM as eltrombopag) or rhTPO (0, 1, 3, 10, 30, 100 ng/mL), or in all combinations at each concentration of eltrombopag and rhTPO and then incubated for 68 hours and ^{3}H-thymidine was added. The cellular intake of ^{3}H-thymidine for 4 hours after addition of ^{3}H-thymidine increased in an eltrombopag and rhTPO concentration-dependent manner at ≥0.03 μM and ≥3 ng/mL, respectively. At any eltrombopag concentration, rhTPO enhanced the intake of ^{3}H-thymidine concentration-dependently, and at any concentration of rhTPO, eltrombopag enhanced that of ^{3}H-

thymidine concentration-dependently.

(c) Effects on differentiation of bone-marrow precursor cells (Attached document 4.2.1.1.1, 4.2.1.1.2)

CD34 positive cells isolated from normal human bone marrow were incubated in a medium containing eltrombopag (0.003, 0.01, 0.03, 0.1, 0.3, 1, 3 μM), rhTPO (1, 10, 100 ng/mL), or a vehicle in addition to human recombinant stem cell factor (rhSCF) at 100 ng/mL for 10 days. Then, the ratio of CD41 positive cell count with respect to the total cell count (difference in the ratio with and without the test drug) was calculated. Differentiation was assessed based on the proportion (%) of CD41 positive cell count in the presence of eltrombopag relative to that in the presence of rhTPO. The relative proportion of CD41 positive cell count increased in an eltrombopag concentration-dependent manner, and the EC_{50} was 0.1 μM. Differentiation stimulated by eltrombopag reached the peak at 1 μM (relative value, approximately 150%).

(d) Anti-apoptosis effect in N2C-TPO cells (Attached document 4.2.1.1.3)

N2C-TPO cells were added with eltrombopag olamine (0, 0.003, 0.01, 0.03, 0.1, 0.3, 1, 3 μM as eltrombopag) or rhTPO (0, 1, 3, 10, 30, 100 ng/mL), or in all combinations at the concentrations of eltrombopag and rhTPO and then incubated for 72 hours and Caspase-Glo™ reagent (Promega Corporation) was added followed by additional incubation at room temperature for 90 minutes. The production of luminescent signal, which is proportional to caspase-3/-7 activity, suggested that eltrombopag and rhTPO would have an anti-apoptosis effect at ≥0.03 μM and ≥10 ng/mL, respectively. Eltrombopag and rhTPO did not inhibit each other's anti-apoptotic effect.

(e) Effects on platelet count in normal chimpanzees (Attached document 4.2.1.1.4)

Eltrombopag olamine (10 mg/kg as eltrombopag) or vehicle was orally administered to female chimpanzees (7-8 years of age, n = 2-3) for 5 days. The platelet count (mean) 11, 15, and 22 days after the first dose was 1.6, 1.7, and 1.3 times that at the baseline, respectively, while the reticulated platelet count (mean) was 2.2, 1.5, and 0.91 times that at the baseline, respectively. Repeated oral dose of 10 mg/kg of eltrombopag for 5 days did not affect the general conditions, body weight, or the hematology or clinical chemistry parameters except for coagulation parameters and platelet count.

3.(i).A.(1).2) Effects on TPO signal transduction

(a) Activation of signal transducer and activator of transcription in mouse lymphocytic leukemia cells with interferon regulatory factor-1 promoter introduced (Attached document 4.2.1.1.5, 4.2.1.1.6)

Mouse lymphocytic leukemia cell strains (BAF3-TPO cells) expressing interferon regulatory factor-1 (IRF-1) promoter connected with human recombinant TPO-R gene and luciferase gene were added with, eltrombopag (0.006, 0.012, 0.024, 0.049, 0.10, 0.20, 0.39, 0.78, 1.6, 3.1, 6.3, 12.5, 25 μM) or rhTPO (100 ng/mL) and incubated for 4 hours. The luminescence, which depends on the level of intracellular luciferase as an indicator of the activation of signal transducer and activator of transcription (STAT), increased in an eltrombopag concentration-dependent manner (EC_{50}, 0.27 μM), and its maximum (eltrombopag at 25 μM) was approximately 95% of the luminescence for rhTPO at 100 ng/mL. In addition, BAF3-TPO cells were added with eltrombopag (0.0003, 0.001, 0.003, 0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30 μM) and incubated with and without rhTPO (3 ng/mL) for 7 hours. The luminescence of eltrombopag with rhTPO was greater than that without rhTPO.

(b) STAT5 activation in N2C-TPO cells (Attached document 4.2.1.1.5)

N2C-TPO cells were added with eltrombopag (10 μM) or rhTPO (100 ng/mL) and incubated for 60 minutes. Phosphorylation of STAT5, which indicates STAT5 activation, was detected at 5 minutes after the addition of eltrombopag and reached the peak at 10 minutes of incubation, followed by a decrease, but still remained detectable at 60 minutes of incubation. At 5 minutes

after addition of rhTPO, phosphorylation of STAT5 was detected, and then remained detectable even at 60 minutes of incubation.

(c) STAT activation in washed human platelets (Attached document 4.2.1.1.7)
Washed human platelets were added with eltrombopag olamine (1, 2.5, 5, 7.5, 10, 15 μM), rhTPO (100 ng/mL), or vehicle and incubated for 15 minutes. Effects of the test drugs were evaluated based on phosphorylation of STAT1, 3, and 5. Although eltrombopag (1-15 μM) and rhTPO phosphorylated STAT1, 3, and 5, the phosphorylation of STAT1 by eltrombopag was mild.

(d) Effects on MAPK activation (Attached document 4.2.1.1.5)
N2C-TPO cells were added with eltrombopag (10 μM) or rhTPO (50 ng/mL) and incubated for 60 minutes. Phosphorylation of p44/42 mitogen activation protein kinase (MAPK), which indicates MAPK activation, was observed at 5 minutes after addition of eltrombopag and rhTPO and remained detectable at 60 minutes.

(e) Effects on Akt activation (Attached document 4.2.1.1.7)
Washed human platelets were added with eltrombopag olamine (10 μM), rhTPO (100 ng/mL), or vehicle and incubated with or without ADP (final concentration, 1 μM; added at 13 minutes after addition of the test drug) for 15 minutes. Phosphorylation of protein kinase B (Akt), which indicates Akt activation, was not observed following addition of eltrombopag irrespective of the presence or absence of ADP. On the other hand, following addition of rhTPO, phosphorylation of Akt was observed even in the absence of ADP and further intensified in the presence of ADP.

(f) Effects on megakaryocyte-specific promoter activation (Attached document4.2.1.1.5)
Mouse bone marrow cells (32D-mpl cells) expressing membrane glycoprotein IIb (gpIIb) promoter, megakaryocyte-specific promoter, which is connected with human recombinant TPO-R gene and luciferase gene, were added with eltrombopag (0.01, 0.03, 0.1, 0.3, 1, 3, 10 μM) or rhTPO (0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30 ng/mL) and incubated for 5 hours. The luminescence, which depends on the level of intracellular luciferase as an indicator of the gpIIb promoter activation mediated by the test drug, reached the peak at the eltrombopag concentration of 3 μM, and the peak was comparable to that at the rhTPO concentration of 30 ng/mL. The EC_{50} of eltrombopag based on the concentration-luminescence reaction curve was 0.1 μM.

(g) Effects on expression of early response genes (Attached document 4.2.1.1.5)
N2C-TPO cells were added with eltrombopag (30 μM) or rhTPO (75 ng/mL) and incubated for 120 minutes. Eltrombopag enhanced the expression of Fos, early growth response protein 1 (EGR-1), and thyroid-like receptor 3 (TR3) mRNA.

3.(i).A.(1).3) Selectivity to TPO-R
(a) Effects on cells expressing various cytokine receptors (Attached document 4.2.1.1.8)
Mouse lymphocytic leukemia cell strain expressing human granulocyte colony-stimulating factor (G-CSF) receptor (BAF3-GCSFR cells) and human megakaryoblastic leukemia cell strain endogenously expressing erythropoietin (Epo) receptor (UT7-Epo cells) were added with eltrombopag (0.01, 0.03, 0.1, 0.3, 1, 3, 10, 30 μM for BAF3-GCSFR cells; 0.03, 0.1, 0.3, 1, 3, 10, 30 μM for UT7-Epo cells) or rhTPO (100 ng/mL). The test drugs did not increase BrdU intake. BAF3 cells endogenously expressing IL-3 receptor and HepG2 cells in which STATs are activated by IFN-α and -γ were added with eltrombopag (0.03, 0.1, 0.3, 1, 3, and 10 μM for BAF3 cells; 10 μM for HepG2 cells) or rhTPO (100 ng/mL for BAF3 cells, 50 ng/mL for HepG2 cells). The test drugs did not affect STAT activation as assessed by reporter gene assay or gel shift assay.

(b) Effects on differentiation of non-megakaryocytic hematopoietic progenitor cells (Attached document 4.2.1.1.9)

Normal human bone marrow cells were added with eltrombopag olamine (0.01, 0.03, 0.1, 0.3, 1, 3 μg/mL [0.02, 0.07, 0.2, 0.7, 2, 7 μM] as eltrombopag), stem cell factor (SCF) at 50 ng/mL, G-CSF (positive control for colony forming unit-granulocyte/macrophage [CFU-GM]) at 50 ng/mL, granulocyte-macrophage colony-stimulating factor (GM-CSF) (positive control for CFU-GM) at 25 ng/mL, Epo (positive control for burst-forming unit-erythroid [BFU-E]) at 2 U/mL, or rhTPO at 100 ng/mL and incubated for 14 days. The increased colony count was observed for CFU-GM in the presence of G-CSF and GM-CSF and for BFU-E in the presence of Epo, but no colonies of CFU-GM or BFU-E were observed in the presence of eltrombopag or rhTPO. Normal human bone marrow cells were incubated with eltrombopag olamine (0.01, 0.03, 0.1, 0.3, 1, 3 μg/mL as eltrombopag) or rhTPO at 100 ng/mL in addition to SCF at 50 ng/mL for 14 days. No colonies of BFU-E were observed, and neither eltrombopag nor rhTPO affected the SCF, which increases the colony count of CFU-GM.

3.(i).A.(1).4) Species specificity

(a) Species specificity of STAT activation effect (Attached document 4.2.1.1.10)

Platelets from mice, cotton rats, cats, pigs, cynomolgus monkeys, ferrets, tree shrews, chimpanzees, and humans were treated with eltrombopag at 0.3, 1, 3, 10, and 30 μM or rhTPO at 100 ng/mL for 20 minutes, solubilized, and then subjected to reaction with ^{32}P-labeled IRF-1 DNA probe (for ferrets, ^{32}P-labeled TTCCIC DNA probe) at room temperature for 20 minutes. Eltrombopag phosphorylated STATs in platelets from humans and chimpanzees in a concentration-dependent manner (human EC_{50}, 3 μM), but did not phosphorylate STATs in platelets from the other animals. On the other hand, rhTPO phosphorylated STATs in platelets from all animal species.

(b) Amino acid residues in human TPO-R involved in activity expression

i) Comparison of human TPO-R amino acid sequence with those in various animal species (Attached document 4.2.1.1.11, 4.2.1.1.12)

TPO-R cDNA was cloned from rats, dogs, baboons, and cynomolgus monkeys, and amino acid consensus sequences in the transmembrane and juxtamembrane domains of human TPO-R were compared with those from various animals (chimpanzees, rhesus monkeys, squirrel monkeys, marmosets, mice, guinea pigs, cattle) using the National Center for Biotechnology Information (NCBI) gene database (GenBank, US). The amino acid sequence of the transmembrane domain (positions 492-513 amino acid residues from the N-terminal, aa 492-513) was found identical between humans and chimpanzees having histidine at aa 499, while aa 499 in the cynomolgus monkeys, baboons, dogs, rats, mice, and cattle was leucine, and that in rhesus monkeys, squirrel monkeys, marmosets, and guinea pigs was phenylalanine. In humans, chimpanzees, cynomolgus monkeys, and baboons, aa 507 was valine, but that in the other animal species was leucine. The amino acid residues in dogs, mice, rats, and cattle were found to have 2 to 3 additional differences from that in humans. In the amino acid sequence of the juxtamembrane domain (aa 479-491), aa 481 in humans was threonine, while that in the other animal species was alanine or valine.

ii) Effects on mutated mouse G-CSF receptor resembled to TPO-R transmembrane domain (Attached document 4.2.1.1.13)

HepG2 cells expressing IRF-1 promoter connected with mutated G-CSF receptor gene and luciferase gene were added with eltrombopag at 10 or 30 μM or G-CSF at 50 ng/mL and incubated for 5 hours. The mutated G-CSF receptor gene was prepared by amino acid substitutions in mouse wild-type G-CSF receptor from amino acid residues corresponding to histidine 499 or histidine 499 and threonine 496 in the transmembrane domain of human TPO-R into histidine 499 or histidine 499 and threonine 496. The luminescence, which depends on the level of intracellular luciferase as an indicator of the STAT activation induced by the test drug, was increased by eltrombopag at 10 and 30 μM in HepG2 cells expressing either mutated G-CSF receptor in a concentration-dependent manner. The luminescence was greater in the cells substituted with histidine 499 and threonine 496 than that in the cells substituted with histidine 499 alone. G-CSF

remarkably increased the luminescence in HepG2 cells expressing any of the wild-type and mutated G-CSF receptors, while eltrombopag did not produce luciferase in HepG2 cells expressing the wild-type G-CSF receptor.

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

3.(i).A.(2).1) Effects on various receptors and enzymes (Attached document 4.2.1.2.1, 4.2.1.2.2)

Of 30 kinds of animal- and human-origin neurotransmitters, hormone receptors and ion channels, adrenaline α_{2B}, imidazoline I_2, and estrogen receptors α and β were inhibited in terms of ligand-binding by eltrombopag (50% inhibitory concentration [IC_{50}]; 15.5, 1.71, 0.344, 1.94 μM), while the remaining 26 kinds were hardly inhibited in terms of binding by eltrombopag even at 1 μM (approximately ≥37 times the maximum plasma concentration [C_{max}] of plasma protein unbound unchanged eltrombopag [estimated to be <0.027 μM] in humans receiving multiple doses of eltrombopag at 50 mg) (binding inhibition rate, ≤20%). Inhibitory effects of eltrombopag on various enzymes were investigated, but any of 11 enzymes investigated was hardly inhibited by eltrombopag at 1 μM (inhibitory rate, ≤20%).

3.(i).A.(2).2) Effects on normal platelet functions

(a) Effects on P-selectin expression in human whole blood (Attached document 4.2.1.2.3)

Citrated human blood samples from healthy adult subjects were treated with eltrombopag olamine (0.1, 0.3, 1.0, 3.0, 10 μM as eltrombopag), rhTPO at 150 ng/mL or a vehicle, for 5 minutes. Eltrombopag did not induce expression of P-selectin on the platelet membrane; however, the proportion of P-selectin positive platelets in the rhTPO-treated samples increased to approximately twice that in the vehicle-treated samples.

(b) Effects on P-selectin expression in human platelet-rich plasma (Attached document 4.2.1.2.4)

Human platelet-rich plasma was added with eltrombopag olamine at 1, 3, 10, 30, 100 μM, or rhTPO at 100 ng/mL, allowed to stand at room temperature for 15 minutes, and then further allowed to stand at room temperature for 5 minutes with or without ADP at 1 μM. Eltrombopag hardly affected P-selectin expression on the platelet membrane irrespective of the presence or absence of ADP. On the other hand, rhTPO hardly affected P-selectin expression without ADP, but increased with ADP.

(c) Effects on agonist-induced platelet aggregation (Attached document 4.2.1.2.4)

Washed human platelets or platelet-rich plasma were treated with eltrombopag olamine at 1, 3, 10, 30, or 100 μM, or rhTPO at 100 ng/mL, or vehicle for 15 minutes. After ADP or collagen was added, platelet aggregation was assessed. In the washed human platelets, eltrombopag at 10 μM did not affect ADP (0.25 μM)-induced platelet aggregation; eltrombopag did not induce aggregation of the platelets that had not been aggregated in the presence of collagen at below the threshold concentration (0.0625-0.25 μg/mL depending on the donor). In the platelet-rich plasma, eltrombopag did not affect ADP (1.5 μM)-induced platelet aggregation at up to 100 μM; eltrombopag did not induce aggregation of the platelets that had been hardly aggregated in the presence of collagen at below the threshold concentration. On the other hand, rhTPO intensified ADP-induced platelet aggregation to the maximum in both washed platelets and platelet-rich plasma; rhTPO maximized aggregation of the platelets that had not been or been hardly aggregated in the presence of collagen at below the threshold concentration.

3.(i).A.(2).3) Effects on growth of various cancer cell strains (Attached document4.2.1.2.5 to 4.2.1.2.9)

A total of 17 kinds of human leukemia cell strains and 10 kinds of human solid cancer cell strains (liver, lung, ovarian and prostate cancer) were added with eltrombopag olamine at 0.1 to 100 μg/mL (0.2-226 μM) or rhTPO at 100 ng/mL (6 kinds of human leukemia cell strains were treated

with rhTPO) and incubated for 54 or 72 hours. Eltrombopag enhanced the growth of 2 kinds of leukemia cell strains expressing TPO-R and megakaryocyte markers (CD41, CD61), N2C-TPO and HEL92.1.7, in a concentration range from 0.006 to 1.7 μg/mL (0.01-3.8 μM) and 0.1 to 1 μg/mL (0.2-2 μM), respectively (the maximum growth rate; 350%, 110%-120%), but at the concentrations above the range, inhibited their growth (IC_{50}, 20.7 and 2.3 μg/mL [46.8 and 5.2 μM]). Eltrombopag inhibited the growth of leukemia cell strains, OCI-M1, and ovarian cancer cell strains, SKOV-3, but the effects were weak (IC_{50}, >40 μg/mL [90 μM]). The growth of leukemia cell strains, NOMO-1, was not affected by eltrombopag. Eltrombopag inhibited the growth of other leukemia (13 strains), liver cancer (1 strain), lung cancer (4 strains), ovarian cancer (2 strains), and prostate cancer (2 strains) cell strains (IC_{50}, 0.56-15.4 μg/mL [1.3-34.8 μM]). On the other hand, rhTPO did not inhibit the growth of 6 leukemia cell strains (K562, CCRF-CEM, HL-60, MOLT-4, RPMI-8226, SR) and 10 solid cancer cell strains. In addition, rhTPO slightly enhanced the growth of CCRF-CEM and RPMI-8226 cells (compared with the growth in the absence of rhTPO, 106% and 111%, respectively). Eltrombopag inhibited the growth of 3 acute bone marrow leukemia cell strains, OCI-AML2, OCI-AML3, and ML-2, of which OCI-AML2 and ML-2 presented mild apoptosis (up to 18%), but no concentration-dependency was observed. In all cell strains, eltrombopag at 4 to 40 μg/mL (9-90 μM) decreased the viable cell count and increased the dead cell count in a concentration-dependent manner.

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

3.(i).A.(3).1) Effects on the central nervous system (Attached document 4.2.1.3.1)

Following single oral dose of eltrombopag olamine (3, 10, 40 mg/kg as eltrombopag) or vehicle to male SD rats (83 days of age, n = 10), none of the general conditions, body weight, and behavior were affected until 48 hours after administration.

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

(a) Effects on blood pressure, heart rate, and electrocardiogram (Attached document 4.2.1.3.2)

Following single oral dose of eltrombopag olamine (3, 10, 30 mg/kg as eltrombopag) or vehicle to conscious, unrestrained male dogs (2-4 years of age, n = 3-4), the mean arterial pressure and diastolic blood pressure increased in the 10 mg/kg eltrombopag group 2 hours after administration, and the mean arterial pressure and systolic and diastolic blood pressure decreased in the 30 mg/kg eltrombopag group 3 hours after administration. In the 3, 10, and 30 mg/kg eltrombopag groups, shortening of QRS, QT, and QTc intervals occurred at ≥18 hours after administration.

(b) Effects on isolated dog Purkinje fibers (Attached document 4.2.1.3.3)

Eltrombopag olamine at 10 and 25 μM did not affect the resting membrane potential or 30% repolarization action potential duration (APD) (APD_{30}) in Purkinje fibers isolated from male dogs (235-326 days of age), but significantly shortened APD_{60} by 8%-12% and 14%-18%, respectively, and APD_{90} by 6%-10% and 11%-16%, respectively. Eltrombopag at 10 and 25 μM mildly shortened the maximum rate of depolarization (MRD) (14%-24%). Furthermore, eltrombopag did not affect the upstroke amplitude (UA) at the stimulation frequency of 0.5 Hz, but significantly decreased the UA at the stimulation frequency of 1 Hz (decreased by 3 and 5 mV at 10 and 25 μM, respectively). The eltrombopag concentration (4.4 μg/mL) at which isolated Purkinje fibers were electrophysiologically affected would be ≥370 times C_{max} (<0.012 μg/mL) of unbound unchanged eltrombopag estimated from C_{max} (11.9 μg/mL) in Japanese patients with chronic idiopathic thrombocytopenic purpura (ITP) who received eltrombopag at the maximum recommended clinical dose of 50 mg once daily.

(c) Effects on hERG current (Attached document 4.2.1.3.4)

In HEK293 cells expressing human ether-a-go-go-related gene (hERG), eltrombopag inhibited the tail current in a concentration-dependent manner, and IC_{50} was 0.69 μM (0.31 μg/mL).

3.(i).A.(3).3) Effects on the respiratory system (Attached document 4.2.1.3.5)
Following a single oral dose of eltrombopag olamine (3, 10, 40 mg/kg as eltrombopag) or vehicle to male SD rats (366-398 g, n = 4), no effects were observed on the tidal volume, respiratory rate, minute ventilation, or airway resistance at 1 and 4 hours after administration (around the time to reach the maximum plasma concentration [t_{max}]) or 24 and 48 hours after administration.

3.(i).A.(4) Pharmacodynamic drug interactions
No data were submitted.

3.(i).B Outline of the review by PMDA
PMDA asked the applicant to explain whether or not eltrombopag could induce biological reactions different from those by endogenous TPO, taking differences in TPO-R signal transduction between TPO and eltrombopag into account.

The applicant responded as follows:
In a study using human bone marrow cells, eltrombopag did not induce the differentiation into either monocytic or erythroblastic lineage in the concentration range (0.01-3 μM) at which differentiation into megakaryocytic cells could occur as with rhTPO (100 ng/mL). Even in the presence of SCF, eltrombopag did not produce BFU-E colonies or affect the CFU-GM colony increase effect in the presence of SCF as with rhTPO. As described above, eltrombopag has the same effects on human bone marrow cells as with TPO and is considered unlikely to differentiate human bone-marrow precursor cells into non-megakaryocytic cells. On the other hand, eltrombopag may not activate PI3K-AKT, one of the 3 signal transduction pathways which is stimulated through activation of the TPO-R (i.e., JAK-STAT, Ras-MAPK, and PI3K-AKT pathways), and may enhance the differentiation and growth of megakaryocytic cells mediated by a part of the TPO-R signal transduction pathway unlike TPO. The applicant considered it unlikely that eltrombopag could induce reactions different from those by endogenous TPO including the differentiation of human bone-marrow precursor cells into non-megakaryocytic cells biologically, because eltrombopag induced the differentiation into megakaryocytic cells only as with TPO *in vitro*; it did not affect hematology parameters in normal chimpanzees; no clinically significant changes occurred in various blood total counts and percentages in clinical studies.

PMDA asked the applicant to explain the appropriateness of the safety pharmacology studies of eltrombopag, which used animal species not pharmacologically responding to eltrombopag.

The applicant responded as follows:
Eltrombopag did not activate TPO-R of all animal species except for human and chimpanzee, therefore, the pharmacological reactions attributable to TPO-R agonist effects of eltrombopag could not be evaluated in the core-battery studies for the central nervous system, cardiovascular system, and respiratory system in rats and dogs. However, these studies could detect the off-target effect of eltrombopag. The effects of eltrombopag on platelet count also were evaluated in a pharmacology study for effects on platelet count in chimpanzees as well as those on general conditions, body weight, hematology/clinical chemistry parameters, and coagulation system parameters, which were considered relevant from a safety pharmacological viewpoint. Based on the above, the applicant considered it appropriate to evaluate the safety pharmacological characteristics of eltrombopag in these studies.

PMDA considers as follows:
Regarding the primary pharmacodynamics of eltrombopag, eltrombopag can be expected to increase platelet count in humans based on submitted *in vitro* pharmacology data obtained from human cells and cell strains and cells expressing human receptors as well as *in vivo* pharmacological data in chimpanzees. On the other hand, the safety pharmacology attributable to the on-target effect of eltrombopag cannot be evaluated in the safety pharmacology studies in

animal species not pharmacologically responding to eltrombopag as the applicant explained, while the feasibility of the safety pharmacology studies in animal species in which the on-target effect of eltrombopag can be detected (chimpanzees) could be limited, making the evaluation difficult. In addition, in consideration that endogenous TPO and eltrombopag differently involve the signal transduction pathways after the receptor binding, it is necessary to pay attention to adverse drug reactions attributable to the on-target effect of eltrombopag.

3.(ii) Summary of pharmacokinetic studies

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

As an eltrombopag-metabolite with hydrazine linkage cleavaged was detected in a metabolism study, eltrombopag with ^{14}C-labeled pyrazole ring (^{14}C-labeled eltrombopag [pyrazole ring]) and eltrombopag with ^{14}C-labeled benzoic acid (^{14}C-labeled eltrombopag [benzoic acid]) were used to investigate the pharmacokinetics.

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

3.(ii).A.(1).1) Oral administration

(a) Single-dose studies (Attached document 4.2.2.2.1, 4.2.2.2.3, 4.2.2.2.9, 4.2.2.2.12, 4.2.2.2.13)

Following a single oral dose of eltrombopag olamine (75, 150, 300 mg/kg as eltrombopag) to female mice, the t_{max} of unchanged eltrombopag was 4 hours in all groups, the C_{max} was 91.3, 172, and 213 μg/mL, respectively, and the area under the plasma concentration time curve from zero to the last measurable time point (AUC_{0-t}) was 846, 1779, and 3427 μg·h/mL, respectively (n = 3/time point).

Following a single oral dose of eltrombopag (in solution) to male rats, male dogs, and male cynomolgus monkeys at 6.05, 3.60, and 4.54 mg/kg, the t_{max} was approximately 1.7, 1.4, and 4.3 hours, respectively, and the bioavailability (F) was 26.1%, 83.0%, and 88.7%, respectively (n = 3 for rats, n = 4 for dogs, n = 4 for cynomolgus monkeys).

Following a single oral dose of eltrombopag olamine (0.3, 1, 3, 10 mg/kg as eltrombopag) to female chimpanzees, the C_{max} was 0.110, 0.284, 2.081, and 0.525 μg/mL, and the AUC_{0-t} was 1.42, 6.27, 19.3, and 12.1 μg·h/mL, respectively. Plasma unchanged eltrombopag concentrations in the 0.3 and 10 mg/kg groups remained measurable only at several time points (n = 1).

(b) Repeat-dose studies (Attached document 4.2.2.2.2, 4.2.2.2.5, 4.2.2.2.8, 4.2.2.2.11)

Following repeated oral doses of eltrombopag olamine (10, 60, 100 mg/kg as eltrombopag) to male and female mice for 13 weeks, the eltrombopag exposure dose-dependently increased but no gender-related differences were found. The C_{max} and the area under the plasma concentration time curve from 0 to 24 hours (AUC_{0-24}) in the 100 mg/kg group were approximately 40 and 33 times, respectively, those in the 10 mg/kg group (n = 2-3/sex/time point).

Following repeated oral doses of eltrombopag olamine (3, 10, 40 mg/kg as eltrombopag) to male and female rats for 14 days, the C_{max} and AUC_{0-24} on Day 14 were ≤2.3 times those on Day 1 (n = 3/sex). Following repeated oral doses of eltrombopag olamine (3, 10, 30, 60 mg/kg as eltrombopag) to male and female rats for 28 weeks, the AUC_{1-4} in males in the 30 mg/kg group was approximately 31 times that in the 3 mg/kg group, and the AUC_{0-t} in females of the 60 mg/kg group was approximately 37 times that in the 3 mg/kg group (n = 2-3/sex/time point). Male rats died at the dose of 60 mg/kg and the pharmacokinetics was not evaluated at this dose.

Following repeated oral doses of eltrombopag olamine (3, 10, 30 mg/kg as eltrombopag) to male and female dogs for 52 weeks, the exposure to eltrombopag tended to increase in both males and females in the 3 mg/kg group with increasing treatment duration. In the 10 and 30 mg/kg groups,

the exposure was higher (1.7-3.7 times) at Week 4 than that on Day 1 but remained almost constant thereafter until Week 52 (n = 4/sex).

3.(ii).A.(1).2) Intravenous administration (Attached document 4.2.2.2.3, 4.2.2.2.9, 4.2.2.2.12)
Following 1-hour continuous intravenous administration of eltrombopag olamine to male rats male dogs, and male monkeys at 0.935, 1.44, and 0.90 mg/kg, respectively, the area under the plasma concentration time curve from zero to infinity ($AUC_{0-\infty}$) was 35.3, 62.2, and 4.7 μg·h/mL, respectively; the elimination half-life ($t_{1/2}$) was 11.8, 13.9, and 7.7 hours, respectively; the plasma clearance (CLp) was 27, 26.4, and 200.4 mL/h/kg, respectively; and the distribution volume at steady state (Vss) was 0.196, 0.47, and 1.39 L/kg, respectively (n = 3 for rats, n = 4 for dogs, n = 4 for monkeys).

3.(ii).A.(2) Distribution
3.(ii).A.(2).1) Single-dose studies (Attached document 4.2.2.3.1 to 4.2.2.3.3)
Following a single oral dose of ^{14}C-labeled eltrombopag olamine (pyrazole ring) to female albino mice at 25 or 150 mg/kg as eltrombopag and to female pigmented mice at 25 or 100 mg/kg as eltrombopag, the radioactivity was immediately and extensively distributed and reached the maximum concentration in most of the tissues by 4 hours after administration. The maximum concentration of the radioactivity was high in the bile, gallbladder, liver, and kidney (cortex, medulla) (n = 1/sex/time point).

Following a single oral dose of ^{14}C-labeled eltrombopag olamine (benzoic acid) (10 mg/kg as eltrombopag) to male pigmented rats, the radioactivity reached the maximum concentration in most of the tissues 4 or 8 hours after administration. The radioactivity was higher in the liver, kidneys (cortex), and colon content than that in the blood, but decreased to below the limit of quantitation (0.089 μg eq./g) in other tissues 7 days after administration (n = 1/time point). Following single intravenous administration of ^{14}C-labeled eltrombopag olamine (pyrazole ring) (1 mg/kg as eltrombopag) to male pigmented rats, the radioactivity reached the maximum concentration in most of the tissues 0.25 or 1 hour after administration and was gradually eliminated from the body. The radioactivity decreased to below the limit of quantitation (0.014 μg eq./g) in most of the tissues by Day 7 (n = 1/time point).

3.(ii).A.(2).2) Repeat-dose studies (Attached document 4.2.2.3.1, 4.2.2.3.4)
Following repeated oral doses of ^{14}C-labeled eltrombopag olamine (pyrazole ring) to female albino mice at 25 or 150 mg/kg as eltrombopag and to female pigmented mice at 25 or 100 mg/kg as eltrombopag for 14 days, the tissue distribution of the radioactivity was similar to that after the single dose. In addition, eltrombopag-related substances did not accumulate in the melanin-contained tissues (eyes, skin) of pigmented mice, suggesting that drug-related substances would not bind to melanin (n = 1/group/time point).

Following repeated oral doses of ^{14}C-labeled eltrombopag olamine (benzoic acid) (10 mg/kg as eltrombopag) to male pigmented rats for 14 days, the radioactivity was immediately absorbed in the body as with the single dose and reached the maximum concentration in most of the tissues at 2 hours after administration. The radioactivity was higher in the liver, renal cortex, and gastrointestinal tract than that in the blood. Following the repeat-dose administration, the radioactivity was gradually eliminated from the body but still detected in several tissues (renal cortex, spleen, meninges, liver, etc.) even at 28 days after administration (n = 1/time point).

3.(ii).A.(2).3) Intraocular distribution (Attached document 4.2.2.3.5)
Following a single oral dose of ^{14}C-labeled eltrombopag olamine (pyrazole ring) to female CD-1 (albino) mice (7 weeks of age) at 25 or 150 mg/kg as eltrombopag or repeated oral doses at the same doses for 14 days, the radioactivity in the eyes was approximately one-twentieth to one-tenth of that in the plasma. The radioactivity did not accumulate in the plasma or eyes following

the repeat-dose administration (n = 5/group/time point).

3.(ii).A.(2).4) Plasma protein binding and distribution in blood cells (Attached document 4.2.2.3.7, 4.2.2.3.8)

The plasma protein binding rate of eltrombopag was ≥99.7% in mice and ≥99.9% in rats, rabbits, and dogs and found constant in the eltrombopag concentration range from 2 to 100 μg/mL. Blood samples from rats, dogs, and monkeys were added with eltrombopag at 2 and 6 μg/mL and incubated at 37°C for 30 minutes. As a result, the ratio of the radioactivity in blood to that in plasma was 0.621 to 0.749 at 2 μg/mL eltrombopag and 0.813 to 0.988 at 6 μg/mL eltrombopag.

3.(ii).A.(3) Metabolism

3.(ii).A.(3).1) *In vitro* study (Attached document 4.2.2.4.1 to 4.2.2.4.3, 4.2.2.4.5 to 4.2.2.4.8)

After ^{14}C-labeled eltrombopag olamine (pyrazole ring) was added to hepatocytes from rat, dog and monkey, eltrombopag was mainly metabolized to the cysteine conjugates, or glucuronide conjugates, and after ^{14}C-labeled eltrombopag olamine (benzoic acid) was added to hepatocytes from mouse, rat, rabbit, dog and monkey, eltrombopag was mainly metabolized to mono-oxygenated eltrombopag, cysteine conjugates, glucuronide conjugates, and carboxylated eltrombopag in which a methyl was oxidized to a carbonic acid. When the liver isolated from male rats was perfused with ^{14}C-labeled eltrombopag olamine (pyrazole ring), the bile mainly contained unchanged eltrombopag and glutathione conjugates. When the kidney isolated from male rats was perfused with ^{14}C-labeled eltrombopag olamine (pyrazole ring or benzoic acid) followed by urine sampling, the percentage of the radioactivity collected in the urine was 0.140%. The main component in urine was unchanged eltrombopag, but several metabolites were detected. When cecal contents from mice and rats were incubated with ^{14}C-labeled eltrombopag olamine (benzoic acid) under anaerobic conditions at 37°C for 24 hours, N-acetyl biphenyl moiety and unidentified compounds were detected. The metabolites found in the gastrointestinal tract following incubation of cecal contents from rats and mice with ^{14}C-labeled eltrombopag olamine (benzoic acid) under aerobic or anaerobic condition (with or without antibiotics) at 37°C for 24 hours suggested that the eltrombopag-metabolite with hydrazine linkage cleavage might be generated under anaerobic conditions by enzymes or enteric bacteria in the gastrointestinal tract.

3.(ii).A.(3).2) *In vivo* study (Attached document 4.2.2.4.3, 4.2.2.4.10 to 4.2.2.4.16)

Following single oral doses of ^{14}C-labeled eltrombopag olamine (pyrazole ring) (10 mg/kg as eltrombopag) to male and female mice, rats, and dogs, unchanged eltrombopag was mainly found in the plasma and feces. In addition, small amounts of the monoxide and glucuronide conjugates were detected in the plasma, and small amounts of the glucuronide conjugates and oxide in the feces. In the bile, the unchanged eltrombopag, oxides, and glutathione conjugates were detected. Following single oral doses of SB-611855, eltrombopag-metabolite with hydrazine linkage cleavage, to mice, the metabolite was absorbed in the gastrointestinal tract, and a part of the absorbed metabolite then partially underwent N-acetylation and glucuronidation and was excreted in urine (n = 4-24/sex for mice, n = 2-12/sex for rats, n = 2-3/sex for dogs).

3.(ii).A.(3).3) Effects on hepatic metabolic enzymes (Attached document 4.2.2.4.17 to 4.2.2.4.20, Reference data, 4.2.2.4.18)

The induction of cytochrome P450 (CYP) 3A by eltrombopag in rats was 3% of that by pregnenolone 16α-carbonitrile, which served as a control. Following repeated oral doses of eltrombopag to female rats and male and female dogs for 14 days, no changes occurred in protein concentration of the liver microsome, or CYP concentration or activity 24 hours after administration (n = 2-3 for rats, n = 3/sex for dogs).

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

3.(ii).A.(4).1) Excretion in urine and feces (Attached document 4.2.2.5.1 to 4.2.2.5.3)

Following single oral doses of ^{14}C-labeled eltrombopag olamine (pyrazole ring) (10 mg/kg as

eltrombopag) to male and female mice, rats, and dogs, the radioactivity was almost eliminated by 48, 72, and 96 hours after administration, respectively. In mice, ≥70% and approximately 14% of the radioactivity administered were excreted in feces and urine, respectively. In rats and dogs, approximately 90% of the radioactivity administered was excreted in feces (n = 4/sex for mice, n = 3/sex for rats, n = 3/sex for dogs).

3.(ii).A.(4).2) Excretion into bile (Attached document 4.2.2.5.1 to 4.2.2.5.4)
Following single oral doses of ^{14}C-labeled eltrombopag olamine (pyrazole ring) (10 mg/kg as eltrombopag) to male mice, rats, and dogs, 21.1%, 42.7%, and 6.7% of the radioactivity administered were excreted in the bile, and the excretion rate in urine was 4.3%, 8.9%, and 0.3%, respectively (n = 4 for mice, n = 3 for rats, n = 3 for dogs). Following single intravenous doses of ^{14}C-labeled eltrombopag olamine (pyrazole ring) (0.5 mg/kg as eltrombopag) to male dogs, the excretion rate in bile calculated from the total radioactivity in the bile recovered by bile-duct cannulation was 58.7%. The excretion rate in feces after the total bile recovery was 9.6% (n = 2).

3.(ii).A.(5) Pharmacokinetic drug interactions (Attached document 4.2.2.6.1)
When rat hepatocytes were added with ^{14}C-labeled eltrombopag olamine (benzoic acid), the cellular intake was completed within 20 seconds irrespective of the presence or absence of rifamycin (rOatp1 and rOatp2 inhibitors). The intake of ^{14}C-labeled eltrombopag olamine (benzoic acid) into rat hepatocytes was not changed in the presence of rifamycin, cyclosporine A (rOatp1 and rOatp2 inhibitors), taurocholate (rOatp4 inhibitor), estradiol 17β-D-glucuronide (rOatp1, rOatp2, and rOatp4 inhibitors), indomethacin (rOat2 inhibitor), and probenecid (hOAT inhibitor).

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

3.(ii).B.1) Inter-individual variability of eltrombopag absorption
PMDA asked the applicant for the reason why the exposure tended to increase in the 3 mg/kg groups with increasing treatment duration following repeated oral doses of eltrombopag olamine at 3, 10, and 30 mg/kg to male and female dogs for 52 weeks.

The applicant explained as follows:
The exposure profiles (C_{max}, AUC) with the treatment period in the 3 mg/kg groups varied inter-individually. The inter-individual variability of the exposure at Week 13 and Week 52 were greater than those on Day 1, and at Week 4 and Week 26, and especially, the exposure in 3 animals was higher than that in the remaining 5 animals at Week 52. However, in the 10 and 30 mg/kg groups, the exposure did not clearly increase with increasing treatment duration. Based on the above, the inter-individual variability in the 3 mg/kg group might have caused the increasing trend of the exposure with increasing treatment duration. The reason why the exposure in 3 animals was high at Week 52 remains unknown.

PMDA asked the applicant to explain why the concentration of unchanged eltrombopag was unmeasurable at several time points in the 10 mg/kg groups although that in the 1 and 3 mg/kg groups was measurable at all time points following single oral doses of eltrombopag to chimpanzees.

The applicant explained as follows:
In the chimpanzees that received a single oral dose of eltrombopag at 10 mg/kg, the plasma unchanged eltrombopag concentration was not quantitated until 2.5 hours. The plasma concentration reached the peak at approximately 24 hours after administration in the 1 and 10 mg/kg groups and at 6.60 hours after administration in the 3 mg/kg group. Coefficient of variation (CV) of C_{max} in rats and dogs that received a single oral dose was as large as 36% to 70%, suggesting that the inter-individual variability in plasma eltrombopag concentrations would be large. Accordingly, the plasma unchanged eltrombopag concentrations in chimpanzees may vary

largely. Because each dose level was assigned to 1 animal in this study, absorption in the animal assigned to the dose of 10 mg/kg might be low. This would be the reason why the plasma concentration of unchanged eltrombopag at 10 mg/kg was measurable only at a few time points.

PMDA asked the applicant to explain whether or not the delayed absorption and large inter-individual variability in plasma concentration could raise safety issues in clinical practice based on the fact that plasma concentration of unchanged eltrombopag reached the C_{max} 24 hours after administration in the chimpanzee in the 10 mg/kg group, in which the plasma concentration was not quantitated until 2.5 hours after administration, and the applicant explained that the inter-individual variability in plasma eltrombopag concentrations was large not only in chimpanzees but also in rats and dogs, potentially leading to the substantial differences in t_{max} among groups (individuals).

The applicant explained as follows:
No events of delayed absorption which was observed in a chimpanzee in the 10 mg/kg group were observed in Japanese healthy adult male subjects of the Japanese Study TRA104603 where eltrombopag was orally administered at a single dose of 30 to 100 mg or in the Japanese Study TRA105580 where eltrombopag were administered at a single dose of or 10-day multiple doses of 25 to 75 mg, or in Japanese patients with chronic ITP in the Japanese Study TRA108109 where eltrombopag was administered at multiple doses of 12.5 to 50 mg. The CV of C_{max} in the Japanese Study TRA105580 and Japanese Study TRA108109 (23.4%-42.9%, 31.8%-42.9%) was smaller than that in the animal studies. Accordingly, the applicant considered that the inter-individual variability in plasma concentrations might not raise substantial safety issues in clinical practice.

PMDA considers as follows:
The increase in exposure to eltrombopag with increasing treatment duration and large inter-individual variability in plasma eltrombopag concentrations including the presence of individuals with substantially reduced absorption were remarkable in animals compared with those in humans; however, these findings may be pharmacokinetic characteristics of eltrombopag. Therefore, clinical data should be evaluated considering the possible characteristics of eltrombopag.

3.(ii).B.2) Distribution of eltrombopag in the eyes
Eltrombopag was administered in a single dose and repeated doses to CD-1 mice (albino) to investigate the distribution of eltrombopag in the eyes. PMDA considers it possible to conclude that eltrombopag is neither distributed nor accumulated in the eyes based on the results in albino animals for the following reasons: CD-1 mice were used in a carcinogenicity study where cataract occurred in a dose- and time-dependent manner; and eltrombopag hardly binds to melanin. In addition, given the fact that cataract was observed in mice at the age of 6 weeks but not in those at the age of 26 weeks in the carcinogenicity study, it should be noted that mice aged 7 weeks were used to investigate the tissue and intraocular distributions of the radioactivity.

The mechanism of cataract development associated with eltrombopag will be reviewed in the toxicity section.

3.(iii) Summary of the toxicology studies
3.(iii).A Summary of the submitted data
The toxicity studies conducted include single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, and immunotoxicity studies as well as studies for safety of the impurities, development of cataract and nephrotoxicity, and photosafety (phototoxicity, photogenotoxicity). Although eltrombopag has been known to exert its pharmacological action (TPO-R activation) only in chimpanzees but not in other animals, mice, rats, and dogs were used in the toxicity studies because these animal species have ample historical

data, and chimpanzees are usually unavailable for such studies.

3.(iii).A.(1) Single-dose toxicity

3.(iii).A.(1).1) Dose-escalating oral dose toxicity study in dogs (Attached document4.2.3.1.2, non-GLP)

Male and female beagle dogs (n = 1/sex) orally received eltrombopag olamine at 100 mg/kg and then 7 days later at 300 mg/kg. No death occurred. The approximate lethal dose in this study was thus determined to be >300 mg/kg. Following the dose at 100 mg/kg, decreased food consumption was observed in males and females, and following the dose at 300 mg/kg, decreased body weight, vomiting, abnormal feces, decreased spontaneous motor activity were observed in males.

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

3.(iii).A.(2).1) Four-day oral toxicity study in rats (Attached document4.2.3.1.1, non-GLP)

Eltrombopag was orally administered to male and female SD rats (n = 3/sex) at 100, 300, and 1000 mg/kg for 4 days. Deaths occurred in the 1000 mg/kg group. The approximate lethal dose was thus determined to be 1000 mg/kg. Findings in surviving animals included decreased spontaneous locomotor activity, prone position, discolored stool, and decreased stool volume in males and females at ≥300 mg/kg as well as body weight loss in males, and changes in hematology parameter values (decreased platelet, decreased reticulocyte counts, increased neutrophil count) in males and females at 1000 mg/kg. In addition, histological changes were observed in the kidneys (vacuolation and necrosis in proximal renal tubules) and thymus (lymphocyte apoptosis) in males and females at ≥300 mg/kg, and adrenal gland (medullary cell vacuolation), lungs (bronchial smooth muscle cell vacuolation), and stomach (ulcer) in males and females at ≥1000 mg/kg.

3.(iii).A.(2).2) Fourteen-day oral toxicity study in rats (Attached document 4.2.3.2.2, 4.2.3.2.3)

Eltrombopag olamine (3, 10, 40 mg/kg as eltrombopag) was orally administered to male and female SD rats (n = 10/sex) for 14 days. Findings included reduced body weight gain, decreased food consumption, and increased testis weight in males at 40 mg/kg, and centrilobular hepatocyte vacuolation in males and females at 40 mg/kg. Based on the above, the no observed adverse effect level (NOAEL) was determined to be 10 mg/kg.

Eltrombopag olamine (20, 40 mg/kg as eltrombopag) was orally administered to female SD rats (n = 10) for 14 days. Findings included changes in clinical chemistry parameter values (increased total bilirubin) and centrilobular hepatocyte vacuolation at ≥20 mg/kg, and increased liver weight and discolored and fragile liver at 40 mg/kg. All of these findings disappeared after a 4-week recovery period.

3.(iii).A.(2).3) Twenty-eight-week oral toxicity study in rats (Attached document 4.2.3.2.5)

Eltrombopag olamine (3, 10, 30, 60 mg/kg as eltrombopag) was orally administered to male and female SD rats (n = 12/sex) for 28 weeks. Males and females in the 60 mg/kg group died or were sacrificed moribund due to the treatment. Findings included increased urine protein and protein/creatinine ratio in males at ≥30 mg/kg, changes in general conditions (e.g., decreased spontaneous motor activity, irregular respiration, emaciation, pallor), decreased food consumption, cataract, erythrocyte parameter changes (e.g., decreased erythrocyte count, increased reticulocyte count) in males and females at 60 mg/kg, reduced body weight gain in males at 60 mg/kg, and increased liver weight in females at 60 mg/kg. Histopathological findings included hepatic lesions (hepatocyte vacuolation, hypertrophy, degeneration, necrosis), lens degeneration, vacuolation and necrosis of adrenal gland cortex zona fasciculata cells in females at ≥30 mg/kg and in males and females at 60 mg/kg, and endosteal hyperplasia in the femur or tibia in males at 60 mg/kg. Changes in urinalysis parameters observed in males at ≥30 mg/kg were determined not to be toxicological findings because no relevant histological changes were

observed, and pathological findings in hepatocytes in females at 30 mg/kg were also determined not to be toxicological findings because these findings occurred infrequently in slight severity and no change was observed in liver weight. Based on the above, the NOAEL was determined to be 30 mg/kg in both males and females.

3.(iii).A.(2).4) Fourteen-day oral toxicity study in dogs (Attached document 4.2.3.2.7)
Eltrombopag olamine (3, 10, 30 mg/kg as eltrombopag) was orally administered to male and female beagle dogs (n = 3/sex) for 14 days. Increased serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and decreased reticulocyte count were observed in males and females at 30 mg/kg. The NOAEL in this study was determined to be 10 mg/kg in both males and females.

3.(iii).A.(2).5) Fifty-two-week oral toxicity study in dogs (Attached document 4.2.3.2.9)
Eltrombopag olamine (3, 10, 30 mg/kg as eltrombopag) was orally administered to male and female beagle dogs (n = 4/sex) for 52 weeks. In males at ≥10 mg/kg and females at 30 mg/kg, increased bone alkaline phosphatase (ALP) accompanied by increased total ALP was observed. The mechanism of the increased ALP (total ALP, bone ALP) was unknown, but it was determined not to be a toxicological finding because neither related histological changes nor changes in clinical chemistry parameters suggesting effects on the hepatobiliary system and bones were observed. Based on the above, the NOAEL was determined to be 30 mg/kg in both males and females.

3.(iii).A.(3) Genotoxicity
Genotoxicity studies conducted include *in vitro* studies of bacterial reverse mutation assay (Attached document 4.2.3.3.1.1) and mouse lymphoma TK assay (Attached document 4.2.3.3.1.2 to 4.2.3.3.1.4) and *in vivo* studies of bone marrow micronucleus test in rats (Attached document 4.2.3.3.2.1) and unscheduled DNA synthesis assay in rat hepatocytes (Attached document 4.2.3.3.2.2). In the mouse lymphoma TK assay, all of eltrombopag olamine, eltrombopag and 2-aminoethanol, a counterion of eltrombopag, were positive, but all of the other assays provided negative results including *in vivo* genotoxicity studies. Accordingly, eltrombopag was determined to have no genotoxic risk in humans.

3.(iii).A.(4) Carcinogenicity
3.(iii).A.(4).1) Studies in mice (Attached document 4.2.3.4.1.5)
Eltrombopag olamine (25, 75, 150, 300 mg/kg as eltrombopag) was orally administered to male and female CD-1 mice (n = 60/sex) for 2 years. In males and females at ≥150 mg/kg, worsened general conditions and a high death rate related to eltrombopag were observed, those in the 300 mg/kg group were withdrawn from the treatment at Week 3 and sacrificed, and the dose of eltrombopag was decreased to 115 mg/kg at Week 21 and thereafter in females in the 150 mg/kg group, and both males and females in the 150 mg/kg group were withdrawn from the treatment at Week 43 and sacrificed at Week 64. Since those above mentioned dose groups were prematurely withdrawn from the treatment, they have not been evaluated for the carcinogenicity. No eltrombopag-related neoplastic lesions were observed in the 25 and 75 mg/kg groups, and thus eltrombopag was determined to have no carcinogenicity in mice. Non-neoplastic lesions observed included renal findings (e.g., renal tubule degeneration, necrosis, regenerative changes) and cataract.

3.(iii).A.(4).2) Studies in rats (Attached document 4.2.3.4.1.6)
Eltrombopag olamine (10, 20, 40 mg/kg as eltrombopag) was orally administered to male and female SD rats (n = 60/sex) for 2 years. No eltrombopag-related neoplastic lesions were observed, and thus eltrombopag was determined to have no carcinogenicity in rats. Non-neoplastic lesions observed included decreased hemoglobin (Hb) and hematocrit (Ht), cataract associated with anterior and posterior capsule changes, and hepatic findings (basophilic and eosinophilic

degenerated cell foci) in males in the 40 mg/kg, group and lens degeneration and chronic progressive nephropathy in males and females in the 40 mg/kg group.

3.(iii).A.(5) Reproductive and developmental toxicity

3.(iii).A.(5).1) Fertility study in male rats (Attached document 4.2.3.5.1.1)

Eltrombopag olamine (10, 20, 40 mg/kg as eltrombopag) was orally administered to male SD rats (n = 25) from 14 days before mating start and then throughout the gestation period of the mated females (treatment period was 42-46 days). Reduced body weight gain, decreased food consumption, and increased testis weight were observed in parent animals in the 40 mg/kg group, but eltrombopag did not affect reproductive function, embryo-fetal survival rate or fetal body weight. Increased testis weight was determined to have no toxicological significance, because neither effects on the reproductive function nor related histological changes were observed. Based on the above, the NOAEL for general toxicity and fertility in paternal rats was determined to be 20 and 40 mg/kg, respectively.

3.(iii).A.(5).2) Study of fertility and early embryonic development to implantation in female rats (Attached document 4.2.3.5.1.2)

Eltrombopag olamine (10, 20, 60 mg/kg as eltrombopag) was orally administered to female SD rats (n = 25) from 15 days before mating to Gestation day 6. Reduced body weight gain and food consumption, and increased rates of pre-implantation and post-implantation loss as well as decreased fetal body weight were observed in the 60 mg/kg group. Based on the above, the NOAEL for general toxicity, fertility and early embryonic development in maternal rats was determined to be all 20 mg/kg.

3.(iii).A.(5).3) Embryo-fetal development study in rats (Attached document 4.2.3.5.2.1)

Eltrombopag olamine (10, 20, 60 mg/kg as eltrombopag) was orally administered to pregnant SD rats (n = 22) from Gestation day 6 to Gestation day 17. Reduced body weight gain and food consumption in parent animals, decreased fetal body weight, and increased frequency of cervical ribs were observed in parent animals in the 60 mg/kg group. Based on the above, the NOAEL in maternal rats and for embryo-fetal development was determined to be both 20 mg/kg.

3.(iii).A.(5).4) Embryo-fetal development study in rabbits (Attached document4.2.3.5.2.3)

Eltrombopag olamine (30, 80, 150 mg/kg as eltrombopag) was orally administered to pregnant NZW rabbits (n = 22) from Gestation day 7 to Gestation day 19. Two rabbits in the 150 mg/kg group died. In the surviving animals in the 150 mg/kg group, body weight loss and reduced body weight gain were observed in parent animals. Based on the above, the NOAEL in maternal rabbits and for embryo-fetal development was determined to be 80 and 150 mg/kg, respectively.

3.(iii).A.(5).5) Study of prenatal and postnatal development and maternal function in rats (Attached document 4.2.3.5.3.1)

Eltrombopag olamine (10, 20, 60 mg/kg as eltrombopag) was orally administered to pregnant SD rats (n = 23-24) from Gestation day 6 to Postpartum day 20. Some animals in the 60 mg/kg group died or sacrificed moribund during the late pregnancy or immediately after delivery, and eltrombopag was discontinued before or after delivery. Cannibalism was observed in animals that delivered offspring before discontinuation.

Abnormal general conditions (e.g., decreased spontaneous motor activity, watery stool, ptosis), reduced body weight gain, decreased food consumption, and body weight loss were observed in the 60 mg/kg group. Based on the above, the NOAEL for maternal animals and offspring was determined to be both 20 mg/kg. Unchanged eltrombopag was detected in the plasma of F_1 offspring during the lactation period and eltrombopag was determined to be transferred into milk.

3.(iii).A.(5).6) Study in rats at 4 days of age (Attached document 4.2.3.5.4.2)
Eltrombopag olamine (1, 5, 15 mg/kg as eltrombopag) was orally administered to male and female SD rats (4 days of age, n = 10/sex) for 28 days. Findings included discolored skin and fur and increased red cell distribution width (RDW) in males and females in the 15 mg/kg group, tendency toward reduced body weight gain and decreased erythrocyte parameters (e.g., erythrocyte count, Hb) in males in the 15 mg/kg group, and increased reticulocyte count in females in the 15 mg/kg group. However, these findings were determined to have no toxicological significance because they were mild and small changes and showed apparent regenerative reactions. Based on the above, the NOAEL in rats at 4 days of age was determined to be 15 mg/kg.

3.(iii).A.(5).7) Study in rats at 32 days of age (Attached document 4.2.3.5.4.3)
Eltrombopag olamine (5, 15, 40 mg/kg as eltrombopag) was orally administered to male and female SD rats (32 days of age, n = 10/sex) for 32 days. Findings included decreased erythrocyte parameters (erythrocyte count, Hb, Ht) and increased RDW in males and females in the 40 mg/kg group and increased reticulocyte count in females in the 40 mg/kg group, but these findings were all mild and they were determined to have no toxicological significance. Although a hyaline droplet in the renal tubule was observed in males in the ≥15 mg/kg groups and increased urine protein in males in the 40 mg/kg group, hyaline droplet was determined to have no toxicological significance, because it is a spontaneous finding in males (Durham SK et al. *Handbook of Toxicologic Pathology.* 2002;Vol 1:437-46); it was immunohistochemically found to contain $\alpha_{2\mu}$-globulin specific to male rats; the urinalysis parameter values remained unchanged except for mild urine protein; and no histological lesions were observed in the kidneys. Based on the above, the NOAEL in rats at 32 days of age was determined to be 40 mg/kg.

3.(iii).A.(6) Other toxicity studies
3.(iii).A.(6).1) Immunotoxicity study (Attached document 4.2.3.7.2.1)
Eltrombopag olamine (10, 20, 40 mg/kg as eltrombopag) was orally administered to male and female SD rats (n = 10/sex) for 4 weeks to evaluate the effects on the primary antibody response to keyhole limpet hemocyanin (KLH), a T-cell dependent antigen. However, a decreasing tendency of anti-KLH IgM antibody was observed but no effect on anti-KLH IgG antibody was observed in males in the 40 mg/kg group, and no effect on anti-KLH IgM or IgG antibody was observed in females in the 40 mg/kg group. Therefore, eltrombopag was determined to have no immunotoxicity.

3.(iii).A.(6).2) Studies for cataract
Cataract developed in a dose- and time-dependent manners in rats in the 28-week oral toxicity study and mice and rats in the carcinogenicity studies. In female mice highly susceptible to cataract, studies were conducted to examine the time to onset, progression, week age-dependency, and photo-involvement of cataract. These studies were conducted under non-GLP conditions.

(a) Time to onset and progression of cataract in mice (Attached document 4.2.3.7.3.1, 4.2.3.7.3.2, Reference data)
Eltrombopag olamine (150 mg/kg as eltrombopag) was orally administered to female CD-1 mice (6 weeks of age, n = 40) for 12 weeks. Ophthalmological examinations were performed at the baseline and during the treatment period, and histological examination was performed on the eyes after the last dose. The ophthalmological examinations showed that cataract developed at Weeks 6 to 7, and the severity intensified even after the withdrawal. The histological examination showed degeneration, necrosis, small and large vacuolation of lens fibers, cell migration in the equator, enlarged cell nucleus, and nuclear defect, Morgan body (eosinophilic body), perinuclear vacuolation, cell sequence derangement, and karyorrhexis.

Eltrombopag olamine (150 mg/kg as eltrombopag) was orally administered to female CD-1 mice (26 weeks of age, n = 15) for 12 weeks. Ophthalmological examinations were performed at the

baseline and during the treatment period, and histological examination was performed on the eyes after the last dose. The ophthalmological examinations showed no eltrombopag-related abnormal findings in the anterior and posterior eye segment in any animal, but the histological examination on the eyes after the last dose showed slight eltrombopag-related degeneration of lens fibers.

The above findings suggested that susceptibility to cataract might depend on the weeks of age.

(b) Effects of environment light on cataract in mice (Attached document 4.2.3.7.3.3, Reference data)
Eltrombopag olamine (150 mg/kg as eltrombopag) was orally administered to female CD-1 mice (6 weeks of age, n = 40) under ambient or red light conditions for 12 weeks. Ophthalmological examinations were performed at the baseline and during the treatment period, and histological examination was performed on the eyes after the last dose. The histological examination showed that no large differences in the incidence of histological changes in the lens between ambient light and red light groups were found, but the incidence of severe changes (e.g., lens fiber liquefaction) was higher in the ambient light group than those in the red light group. The severity of these histological changes was related to the time of onset of cataract (slit-lamp biomicroscopy) and opacitas (macroscopic observation); the earlier onset tended to be severer. The above findings suggested that ambient light might be involved in the onset of eltrombopag-related cataract.

3.(iii).A.(6).3) Toxicity of impurities
The upper specification limit (≤[redacted]%) for impurity gsk003 in the drug substance exceeded the qualification threshold (0.15%). However, the estimated exposures to gsk003 at the NOAEL in the repeat-dose toxicity studies for ≥14 days and the negative dose in the genotoxicity study in rats and dogs, as well as at the negative dose in the carcinogenicity studies in mice were ≥30 times that in humans at the maximum recommended clinical dose.

Based on the above, gsk003 was determined to raise no safety issues at up to the upper specification limit (≤[redacted]%).

3.(iii).A.(6).4) Photosafety
Eltrombopag has an absorption spectrum in the ultraviolet-visible region (absorption maximum at 413 nm) and is distributed to the skin and eyes, even though the concentration is low. Therefore, *in vitro* and *in vivo* phototoxicity, and *in vitro* photogenotoxicity studies were conducted. Only the *in vivo* phototoxicity study in SKH1-hr hairless mice was conducted under non-GLP conditions.

(a) *In vitro* phototoxicity study (Attached document 4.2.3.7.7.1, Reference data)
Balb/c 3T3 fibroblast cells were added with eltrombopag olamine (0.1721, 0.5439, 1.721, 5.439, 17.21, 54.39, 172.1, 543.9 μg/mL as eltrombopag) and were irradiated with UV-A (5 J/cm^2). By measuring the absorption of neutral red taken into the cells, 50% inhibitory concentration (IC_{50}) of neutral red uptake and a photo irritation factor (PIF) (PIF = IC_{50} [-UV] / IC_{50} [+UV]) were calculated. The IC_{50} of eltrombopag before and after irradiation was 9.808 and 0.543 μg/mL, respectively, and PIF was 18.06, indicating positive phototoxicity.

(b) *In vivo* phototoxicity studies (Attached document 4.2.3.7.7.2 to 4.2.3.7.7.4, Reference data)
Eltrombopag olamine (25, 75, 150 mg/kg as eltrombopag) was orally administered to male and female SKH1-hr hairless mice (n = 6/sex) for 14 days and irradiated with UV for approximately 30 minutes after the last dose to evaluate phototoxicity. In all groups, no skin reactions attributable to UV irradiation were observed, indicating no phototoxicity.

Eltrombopag olamine (100, 150 mg/kg as eltrombopag) was orally administered to female

pigmented (B6C3F1) and albino (CD-1) mice (n = 75/group) for 12 weeks and irradiated with UV irradiation approximately 2 hours after administration 5 days a week to evaluate phototoxicity. Neither pigmented nor albino mice showed any sign of eltrombopag-related phototoxicity. The results suggested that pigmented mice might be more susceptible to cataract than albino mice, but not that UV might be involved in the onset of cataract.

Eltrombopag olamine (40 mg/kg as eltrombopag) was orally administered to male pigmented (Long Evans) and albino (SD) rats (n = 8/group) for 14 days, and irradiated with UV for approximately 30 minutes after the final dose to evaluate phototoxicity. Neither pigmented nor albino rats showed any abnormality in the eyes irrespective of UV irradiation.

(c) *In vitro* photogenotoxicity studies (Attached document 4.2.3.7.7.5, 4.2.3.7.7.6, Reference data)

CHO cells were added with eltrombopag olamine (3.65, 7.3, 14.6, 29.2, 58.4 μg/mL as eltrombopag) to evaluate the structural and numerical effects on the chromosomes with and without UV irradiation. Abnormal structure was observed in the cells treated with eltrombopag at 29.2 μg/mL (cytotoxicity threshold concentration) due to UV irradiation at 700 mJ/cm^2. On the other hand, in the cells irradiated with UV at 350 mJ/cm^2, cells with abnormal chromosomes did not increase even at 58.4 μg/mL (cytotoxicity threshold concentration). Also in the cells without UV irradiation, cells with abnormal chromosomes did not increase.

CHO cells were added with eltrombopag olamine (7.5, 10, 12.5, 15, 17.5, 20, 22.5, 25, 27.5, 30, 32.5, 35, 37.5, 40, 42.5, 45 μg/mL as eltrombopag) to evaluate the structural and numerical effects on the chromosomes with and without UV irradiation (700 mJ/cm^2). In the cells with UV irradiation, structural abnormality increased at 15 and 20 μg/mL (cytotoxicity threshold concentration). On the other hand, in the cells without UV irradiation, cells with abnormal chromosomes did not increase.

3.(iii).A.(6).5) Nephrotoxicity

Repeat-dose toxicity studies in female mice were conducted to investigate renal tubular toxicity detected in mice. All studies were conducted under non-GLP conditions.

(a) Four-week oral dose study in mice (Attached document 4.2.3.7.7.7, Reference data)

Eltrombopag olamine (150, 250 mg/kg as eltrombopag) was orally administered to female CD-1 mice (n = 12) for 4 weeks. Animals in the 250 mg/kg group were found moribund or died. The treatment was discontinued on Day 11 followed by necropsy on all animals.

Histological changes in the kidneys included renal tubule degeneration or dilatation in the outer medullary and corticomedullary junction in the ≥150 mg/kg groups, and 1 animal per group was associated with epithelial regenerative changes and hyperplasia. In the 150 mg/kg group, interstitial inflammatory cell infiltration and renal tubule basophilic changes (regenerative change) associated with spontaneous chronic nephropathy were frequently observed.

(b) Twenty-eight-week oral dose study in mice (Attached document 4.2.3.7.7.8, Reference data)

Eltrombopag olamine (150 mg/kg as eltrombopag) was orally administered to female CD-1 mice (n = 40) for 28 weeks. Some animals were sacrificed moribund or died. Some of dead animals showed renal tubule degeneration and necrosis, but this finding was considered to be a secondary change attributable to circulatory disturbance in moribund conditions, because no such change was observed in surviving animals. Although high urine protein/creatinine ratio was observed, no eltrombopag-related histological changes in the kidneys were shown in necropsy 193 days after the first dose.

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

3.(iii).B.1) Toxicity attributable to the on target of eltrombopag

Given that the appropriate animal species in which the on target effect of eltrombopag can be evaluated is only chimpanzee, PMDA asked the applicant to explain whether or not toxicological findings that are expected to be attributable to the TPO-R activation of eltrombopag and adverse events in clinical studies related to these findings were observed.

The applicant explained as follows:

In humans, TPO-R is mainly expressed in platelets, megakaryocytes, and a part of CD34 positive bone marrow hematopoietic progenitor cells (Li J et al. *Br J Haematol.* 1999;106:345-56), and thus effects of the excessive pharmacological action of TPO-R agonist may include thromboembolic events resulting from increased platelets and megakaryocytes and their activated function, effects on the bone marrow (e.g., fibril formation, abnormal cellular ratio), and malignant tumor. Adverse events in clinical studies related to these expected toxicological findings included platelet count increased (9% in Japanese Study TRA108109) and thromboembolic adverse events (4.3% in Japanese Study TRA108109; 3.3% in combined analysis of Foreign Studies TRA100773A, TRA100773B, TRA102537, TRA108057, and TRA105325), but not an increased risk for malignant tumors. Precautions for increased platelet count, thromboembolism, and myelofibrosis, which are potentially related to the on target effect of eltrombopag, are provided in the proposed package insert.

PMDA considers as follows:

Although precautions for adverse events potentially related to the on-target effects of eltrombopag are provided in the proposed package insert, the on-target effects of eltrombopag have not fully been evaluated because chimpanzees could not be used in the toxicity studies, and a study has reported that TPO-R is expressed in human brain (Columbyova L et al. *Cancer Res.* 1995;55:3509-12), therefore, toxicity attributable to the on-target effects of eltrombopag are not sufficiently understood. Thus, it is inappropriate to provide precautions only for the events directly attributable to the prolonged drug efficacy. Accordingly, it is necessary to describe precautions in the proposed package insert that toxicity attributable to the on-target effects of eltrombopag have not been evaluated in toxicity studies. In addition, the safety of eltrombopag should be continuously evaluated by incorporating post-marketing information and the latest knowledge about TPO-R function, etc., taking into account that the number of subjects in clinical studies was limited.

3.(iii).B.2) Cataract observed in rodents

Considering that cataract was observed in rodents and progressed even after withdrawal in repeat-dose toxicity studies and carcinogenicity studies, PMDA asked the applicant to explain the pathogenic mechanism of cataract caused by eltrombopag and treatment for cataract in clinical practice.

The applicant explained as follows:

Clinical studies have not shown any relationship between eltrombopag and the progression of cataract, and thus an increased risk of cataract caused by eltrombopag has not been suggested in humans. However, in a study where ^{14}C-labeled eltrombopag was orally administered to mice, the radioactivity was detected in the eyes, suggesting that eltrombopag could be distributed to the eyes but the specific mechanism of action or causal factors of cataract remain unknown. In addition, it is difficult to take measures to prevent the development of cataracts in clinical practice, though cataract was observed in rodents. Considering these findings, the following caution statement has been included in the "Important Precautions" section of the proposed package insert: "it is desirable to routinely conduct ophthalmological examinations for cataract." The standard treatment for cataract as provided for cataract related to existing risk factors or corticosteroids would be recommended when such an event occurs in a patient receiving

eltrombopag.

PMDA considers as follows:
Cataract attributable to eltrombopag has not been observed in humans but the concerned finding was remarkable in mice, and the pathogenic mechanism of cataract remains unclear. Therefore, the relevance to humans cannot be ruled out. The concerned finding should be described in the package insert to provide caution, and the relevant information should be provided to healthcare professionals and patients. In addition, it should be carefully monitored also in the post-marketing surveillance.

3.(iii).B.3) Photogenotoxicity
Regarding the positive result with UV irradiation at 700 mJ/cm^2 in an *in vitro* photogenotoxicity study, the applicant discussed that "the concerned photogenotoxicity would not have clinical significance because it was observed under a practically improbable condition of light intensity." Based on the above, PMDA asked the applicant to explain the safety margin of 700 mJ/cm^2, taking the general light intensity exposed in daily life into account.

In response to the PMDA's inquiry, the applicant investigated the light exposure in daily life and explained that the UV-A irradiation (700 mJ/cm^2) used in the *in vitro* photochromosome aberration assay fell within the normal range of ambient light exposure expected in general outdoor activities of humans.

Considering that the light intensity within a range of light exposure in general outdoor activities of humans resulted in positive reactions in photogenotoxicity studies, PMDA asked the applicant to explain the potential for inducing photogenotoxicity in patients receiving eltrombopag; the necessity of photocarcinogenicity studies or other *in vivo* non-clinical studies for evaluation of photocarcinogenicity; and the necessity of providing cautions for photogenotoxicity and photocarcinogenicity in the proposed package insert.

The applicant explained as follows:
Although the positive reaction was observed with UV-A irradiation at 700 mJ/cm^2 in the *in vitro* photochromosome aberration assay of eltrombopag, neither skin phototoxicity nor photosensitizing effect was observed in the *in vivo* phototoxicity studies in mice and humans; therefore, the concerned result in the *in vitro* photogenotoxicity study was not considered to raise concerns about phototoxicity and photocarcinogenicity of eltrombopag in clinical use.asayoko101
Thus, the applicant considered it unnecessary to conduct photocarcinogenicity studies or other *in vivo* non-clinical studies for evaluation of photocarcinogenicity or provide cautions for photogenotoxicity and photocarcinogenicity inproposed the package insert, either.

PMDA considers as follows:
It is unnecessary to conduct additional non-clinical studies for re-evaluation of the observed photogenotoxicity, because neither skin phototoxicity nor photosensitizing effect was observed in the *in vivo* phototoxicity studies. Still, the applicant's explanation cannot eliminate the concern about skin carcinogenesis associated with light exposure. Thus, potential pathogenic risks for skin cancer involved in light exposure should be described in proposed the package insert, if neither photocarcinogenicity nor photogenotoxicity study is conducted.

3.(iii).B.4) Effects on the bone and adrenal gland
Considering that findings in the bone and adrenal gland were observed in the 28-week repeat-oral dose toxicity study in rats, PMDA asked the applicant to explain the safety in humans.

The applicant explained as follows:
Both findings in the bone and adrenal gland in rats were observed at the lethal dose. The applicant

considered that the risk in clinical use is low because such changes did not occur in rats in the 40 mg/kg (equivalent to 3.4-4.5 times the clinical exposure) group in the carcinogenicity study, in which the treatment period was longer than that in the above repeat-dose toxicity study; these changes did not occur in dogs; and the relevant findings were not observed in clinical studies.

PMDA accepted the applicant's response.

PMDA considers as follows:
The submitted toxicity data at least have covered standard evaluation on the off-target effects, although the data have not sufficiently ensured the safety of eltrombopag due to unavailability of studies in chimpanzees as a suitable animal species for toxicity evaluation of eltrombopag. Since eltrombopag has safety concerns about cataract and photogenotoxicity, it is necessary to provide the information in the package insert about the above concerns based on the toxicity data. The concerns about cataract will be further discussed in the "4.(iii).B.4) Safety."

4. Clinical data

In all of the following studies, eltrombopag olamine was used, but the doses are expressed on an eltrombopag basis (eltrombopag olamine is hereinafter referred to as "eltrombopag").

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

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

4.(i).A.(1) Bioequivalence

The formulation for both 12.5 mg tablets and 25 mg tablets to be marketed in Japan is identical to that used in the Japanese phase II/III study (Japanese Study TRA108109). [redacted]. The formulation for the 25 mg tablets used in foreign phase III studies is identical to that for the 25 mg tablets to be marketed in Japan.

4.(i).A.(2) Food effect (Foreign Study SB-497115/005, Attached document 5.3.1.1.1; Studied period, [redacted] to [redacted] 20[redacted])

Following a single oral dose of eltrombopag 50 mg (25 mg tablet × 2, the formulation that is identical to the to-be-marketed formulation) to 16 foreign healthy adult male subjects in an open-label, randomized, three-period crossover manner (treatment periods separated by a ≥5-day washout period), the effects of food on the plasma eltrombopag concentrations were investigated. In the study, the FDA's standardized high fat diet (high-fat diet with the total energy of 682-1000 cal containing 52 g of carbohydrate, 34 g of protein, 40 g of fat, and 427 mg of calcium) was used.

After the administration of eltrombopag in the fasting and postprandial states, median t_{max} was 3.5 and 4.0 hours, respectively; C_{max} was 5.55 ± 1.84 (mean ± standard deviation [SD]) and 1.93 ± 0.56 μg/mL, respectively; $AUC_{0-\infty}$ was 67.61 ± 18.90 and 27.42 ± 7.56 μg·h/mL, respectively; and $t_{1/2}$ was 16.12 ± 2.18 and 15.28 ± 2.43 hours, respectively. The pharmacokinetics of eltrombopag was affected by food; the C_{max} and $AUC_{0-\infty}$ were decreased by 65% and 59%, respectively, due to the consumption of the FDA standardized high-fat diet.

4.(i).A.(3) Effects of food and antacids (Foreign Study TRA104631, Attached document5.3.1.1.2; Studied period, August to October 2005)

Following a single oral dose of eltrombopag 75 mg (75 mg tablet × 1) to 26 foreign healthy adult subjects in an open-label, randomized, five-period crossover manner (treatment periods separated

by a 7- to 14-day washout period), the effects of food and cation-containing antacids on the plasma eltrombopag concentrations were investigated. Table 1 shows pharmacokinetic parameters in the subjects receiving a single dose of eltrombopag 75 mg under different regimens.

Table 1. Pharmacokinetic parameters in the subjects receiving a single dose of eltrombopag 75 mg according to different regimens (Adapted from application data)

Regimen	n	C_{max} (μg/mL)	$AUC_{0-\infty}$ (μg·h/mL)	t_{max} (h)	$t_{1/2}$ (h)
A: Administration in the fasted state	24	6.73 ± 2.72	84.69 ± 36.85	4.00 (2.00-6.00)	17.02 ± 2.71
B: Administration after low-calcium/low-fat diet	24	5.80 ± 2.19	76.80 ± 30.29	4.00 (2.07-6.00)	17.22 ± 2.55
C: Administration in combination with a cation-containing antacid (in the fasted state)	25	2.51 ± 1.84	30.66 ± 23.44	4.00 (1.00-8.00)	15.30 ± 3.16
D: Administration after low-calcium/high-fat diet	25	6.75 ± 2.55	86.41 ± 33.65[1]	4.00 (2.00-6.00)	17.37 ± 3.04[1]
E: Administration at 1 hour before low-calcium/high-fat diet	25	5.81 ± 2.77	74.27 ± 31.35	3.00 (2.00-5.00)	17.71 ± 2.97

Parameters except for t_{max}: Mean ± SD, t_{max}: Median (range), 1: n = 24

The ratio of C_{max} of eltrombopag after low-calcium (40 to <50 mg) and low-fat (5%) diet to that in the fasted state (B/A) was 0.874 (90% confidence interval [CI], 0.699-1.094), and the ratio of C_{max} of eltrombopag after low-calcium and high-fat (50%) diet to that in the fasted state (D/A) was 1.010 (0.808-1.262). The B/A ratio and D/A ratio for $AUC_{0-\infty}$ were 0.928 (0.763-1.127) and 1.025 (0.843-1.247), respectively. The ratio of C_{max} of eltrombopag 1 hour before low-calcium and high-fat diet to that after low-calcium and high-fat diet (E/D) was 0.846 (0.679-1.053), and the E/D ratio for $AUC_{0-\infty}$ was 0.852 (0.703-1.034). The ratios of C_{max} and $AUC_{0-\infty}$ of eltrombopag in combination with a cation-containing antacid (GAVISCON EXTRA STRENGTH™ containing 1524 mg of aluminum hydroxide and 1425 mg of magnesium carbonate) to those in the fasted state (C/A) were 0.302 (0.241-0.377) and 0.295 (0.243-0.358), respectively; the cation-containing antacid decreased these parameters by approximately 70%.

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

4.(i).B.1) Necessity of including timing of dosing in relation to meals in the dosage regimen

The pharmacokinetics of eltrombopag has been shown to be affected by meals and antacids, and the fasted administration has been specified in the "DOSAGE AND ADMINISTRATION" section in the US labeling. On the other hand, the proposed dosage and administration in Japan did not include any requirement with regard to meals. In addition, although the "Precautions for Dosage and Administration" section in the proposed package insert included a statement that "concomitant use of antacids, dairy products, and products containing multivalent cations (e.g., iron, calcium, aluminum, magnesium, selenium, zinc) may decrease the blood eltrombopag concentration and such products should not be taken within 4 hours before and after administration of eltrombopag;" however, it was subsequently stated that "eltrombopag may be administered just after a meal if the calcium content in the meal is low (<50 mg)."

PMDA asked the applicant to specify that eltrombopag should be administered before a meal or between meals as specified in the clinical studies and the dosage regimen approved in the US, taking into account that changes in plasma eltrombopag concentrations due to a meal taken before dosing may affect the efficacy and safety of eltrombopag depending on the amount of multivalent cations contained in the meal; and it would be difficult for patients to determine the amount of multivalent cations contained in the meal for the acceptability on their own even though cautions about the amount of multivalent cations contained in meals were provided.

The applicant explained as follows:
Considering that the efficacy and safety of eltrombopag may be affected by multivalent cations contained in meals; and it would be difficult for subjects to determine the amount of multivalent cations contained per meal for acceptability, it will be specified that eltrombopag is administered in the fasted state by avoiding the administration within 2 hours before and after a meal (total 4 hours), as with the dosage regimen employed in Japanese and foreign clinical studies. To minimize effects of food on the pharmacokinetics of eltrombopag wherever possible, the applicant will provide instructions about intake of food products (dairy products) and other drug products (including supplements) in which the high content of multivalent cations would be obvious even for subjects. It will be instructed that, as with antacid, such products should not be taken within 4 hours before and after administration of eltrombopag (total 8 hours). The rationale for the above instruction was shown below.

The results of a clinical pharmacology study (Foreign Study TRA104631) investigating effects of food and antacids could be explained by chelation between eltrombopag and multivalent cations. Accordingly, eltrombopag has to be administered separately from meals or products containing multivalent cations including calcium. Pharmacokinetic data in subjects who received eltrombopag separately from a meal or a drug containing high-multivalent cation are not available. However, based on the report (Nix DE et al. *Clin Pharmacol Ther.* 1989;46:700-5) that pharmacokinetics of ciprofloxacin, plasma ciprofloxacin concentrations are considerably affected by concomitant use with antacids (concomitant use decreased the AUC by 85%), would not be affected by antacids when administering separately with 6 hours in-between, Japanese and foreign clinical studies were conducted by specifying the timing of dosing as "antacids and calcium supplements containing a high amount of multivalent cations should not be taken within 6 hours before and after administration of eltrombopag." In the US, the application was submitted including the statement that "eltrombopag and any product containing high amount of multivalent cations should be administered separately with 6 hours in-between" in the dosage regimen. However, in the US, literature search for fluoroquinolone antibacterial agents known to involve particular substances in their chelation was conducted after the filing of the application, and in consideration of the search results and compliance with a regimen of eltrombopag, the relevant statement was specified as "eltrombopag should not be administered within 4 hours before and after a meal." In addition, a statement was also included that multivalent cation-containing food products (not limited to dairy products) should not be taken within 4 hours before and after administration of eltrombopag (total 8 hours). The dosage and administration including the above statements were approved. Concerning the timing of dosing in relation to meals, the Japanese and foreign clinical studies were conducted with the requirement "eltrombopag should be administered in the fasted state (meals prohibited within 2 hours before and after administration)." However, the US labeling has specified that eltrombopag can be administered until 1 hour before a meal, because Foreign Study TRA104631 showed that the pharmacokinetics would not be considerably affected by low-calcium diet started 1 hour after administration.

Based on the above, the applicant considers that the statement that "eltrombopag may be administered just after meals if calcium content in meals is low (<50 mg)" will be deleted, and another statement that "eltrombopag should be administered in the fasted state by avoiding the administration within 2 hours before and after a meal" would be added on the "Precautions for Dosage and Administration" section.

PMDA considers as follows:
Concerning the timing of dosing in relation to meals, the Japanese and foreign clinical studies were conducted with the requirement "eltrombopag should be administered in the fasted state (meals prohibited within 2 hours before and after administration)," and the dosage regimen approved in the US has instructed that eltrombopag should be administered 1 hour before or 2 hours after a meal. Taking the above into account, the applicant's explanation that "eltrombopag

should be administered in the fasted state by avoiding the administration within 2 hours before and after a meal." should be included in the "Dosage and Administration" section but not in the "Precautions for Dosage and Administration" section. Concerning the interval between eltrombopag and multivalent-cation containing drug, there are no data justifying the requirement that such drugs should not be taken within 4 hours before and after administration of eltrombopag (total 8 hours), but at present, the timing of dosing in relation to meals may have to be specified based on the dosage regimen approved in the US. The requirement for meals in the dosage and administration will be finalized, taking account of comments raised in the Expert Discussion.

4.(i).B.2) Appropriateness of using and evaluating data from foreign studies for effects of food

Foreign clinical studies have shown that pharmacokinetics of eltrombopag is affected by meals, but in Japan, effects of meals have not been studied, and thus effects of meals in standard Japanese meals and those of concomitant multivalent cation-containing antacids in Japanese population remain unknown.

PMDA has concluded that the timing of dosing of eltrombopag in relation to meals and administration of antacids may be specified based on foreign clinical study data. On the other hand, the relationship between the timing of dosing of eltrombopag in relation to the intake of meals or antacids and the blood eltrombopag concentration has not been investigated in detail. PMDA considers that the precautionary statement for the dosage and administration may have to be specified based on the existing data. If the specified interval is longer than the duration essentially required to maintain the therapeutic effect of eltrombopag, the concerned precautionary statement might adversely affect the compliance with administration of eltrombopag. PMDA thus considers it also useful to investigate the appropriate timing of dosing of eltrombopag in relation to meals in detail by conducting a study in the Japanese population.

Necessity of investigation of effects of food intake and of concomitant use of multivalent cation-containing antacids (including dosing interval) on pharmacokinetics of eltrombopag in the post-marketing clinical study will be finalized, taking account of comments raised in the Expert Discussion.

4.(ii) Summary of clinical pharmacology studies

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

4.(ii).A.(1) Studies using human biomaterials

4.(ii).A.(1).1) Plasma protein binding rate (Attached document 4.2.2.3.7, 5.3.2.1.1)

Human plasma was incubated with eltrombopag at 2, 10, 50, and 100 μg/mL at 37°C for 18 hours, and the plasma protein binding rate was ≥99.9%. The binding rate of eltrombopag to human serum albumin was ≥99.95%. Eltrombopag did not bind to α_1-acid glycoprotein at 15 μM (physiological concentration), but the binding rate at 150 μM (equivalent to α_1-acid glycoprotein concentration increased under pathological conditions) was approximately 77% to 90%.

4.(ii).A.(1).2) Metabolism by drug-metabolizing enzymes

(a) Metabolites in human biomaterials (Attached document 5.3.2.2.1 to 5.3.2.2.4)

Human hepatocytes were incubated with ^{14}C-labeled (pyrazole ring) eltrombopag at 10 or 50 μM at 37°C for up to 24 hours. As a result, eltrombopag was mainly metabolized to its cysteine conjugates (Metabolite G) and glucuronide conjugates (Metabolite K). For others, glutathione conjugates (Metabolite F) and oxidant (Metabolite N, predicted to be its carbonyl form) of eltrombopag were also detected in trace amount. Following incubation with ^{14}C-labeled eltrombopag (benzoic acid) at 12.5 μM, a mono-oxygenated eltrombopag (Metabolite J), Metabolite G, Metabolite K, and a carboxylated eltrombopag in which a methyl was oxidized to a carboxylic acid (Metabolite O) of eltrombopag were detected.

Human feces were incubated with ^{14}C-labeled eltrombopag (benzoic acid) at approximately 113 μM at 37°C under anaerobic conditions for 24 hours, and as a result, hydrazine linkage cleavage of eltrombopag M21, and N-acetylated eltrombopag M18 and M23 (hydrazine linkage cleavage estimated from the molecular weight) were detected.

Human kidney microsome and S9 fraction were incubated with ^{14}C-labeled eltrombopag (pyrazole ring) at 20 μM at 37°C under aerobic or anaerobic conditions for 1 hour, and as a result, unchanged eltrombopag was mainly detected.

(b) Identification of CYP isoenzymes involved in metabolism of eltrombopag (Attached document 5.3.2.2.5)
Human liver microsome was incubated with ^{14}C-labeled eltrombopag (pyrazole ring) at 5 and 50 μM (final concentrations) at 37°C for up to 60 minutes. Metabolite J and unidentified Metabolite AY were generated by incubation at 5 μM, and unidentified Metabolite AX at 50 μM. Formation of Metabolite J was inhibited by furafylline, a CYP1A2 inhibitor, by 100% (at 5 μM) and by 70% (at 50 μM) on average, respectively. In addition, its formation was inhibited by quercetin, a CYP2C8 inhibitor, by 57% (at 5 μM) and by 10% (at 50 μM) on average. Furthermore, in the CYP1A2 expression system, its monoxide (M6), Metabolite J, Metabolite AX, Metabolite AY, and Metabolite AZ were formed, and in the CYP2C8 expression system, M6, Metabolite J, Metabolite AX, and Metabolite AY were formed. In the CYP2C9, CYP2C19, CYP2D6, and CYP3A4 systems, only Metabolite AY was formed. The unidentified Metabolite AY was formed without any NADPH production system, suggesting that the Metabolite AY would be formed by a non-enzymatic reaction.

(c) Identification of isozymes of the glucuronidation enzyme involved in the metabolism (Attached document 5.3.2.2.6)
Human liver microsome was incubated with ^{14}C-labeled eltrombopag (pyrazole ring) at 10 μM (final concentration) at 37°C for up to 60 minutes, and as a result, the glucuronide conjugates, Metabolite K, was formed. Of the human UDP-glucuronosyltransferase (UGT) expression systems, UGT1A1 and UGT1A3 systems generated the concerned Metabolite K, but the UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B4, UGT2B7, UGT2B15, and UGT2B17 systems did not.

4.(ii).A.(1).3) Effects on drug-metabolizing enzymes
(a) Inhibitory effects on CYPs (Attached document 5.3.2.2.7, 5.3.2.2.8)
Human CYP expression systems were incubated with eltrombopag at up to 100 μM at 37°C for 10 minutes, and as a result, the IC_{50} against the activity of CYP1A2 (7-ethoxyresorufin O-dealkylation), CYP2C9 (7-methoxy-4-trifluoromethylcoumarin-3-acetic acid O-dealkylation), CYP2C19 (3-butyryl-7-methoxycoumarin O-dealkylation or 7-ethoxy 4-trifluoromethylcoumarin O-dealkylation), CYP2D6 (4-methylaminomethyl-7-methoxycoumarin O-dealkylation) and CYP3A4 (diethoxyfluorescein O-dealkylation and 7-{3-(4-phenylpiperazin-1-ylmethyl)benzyl}resorufin O-dealkylation) was 3.5, 9.3, 32, 27, 19, and 68 μM, respectively.

In the liver microsome, eltrombopag did not inhibit the activity of CYP1A2, CYP2A6, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, or CYP4A9/11 at up to 100 μM, but inhibited that of CYP2C8 (Paclitaxel 6α-hydroxylation) and CYP2C9 (Diclofenac 4'-hydroxylation) with the IC_{50} being 24.8 and 20.2 μM, respectively.

(b) Inhibitory effects on UGTs (Attached document 5.3.2.2.9)
Human UGT expression systems were incubated with eltrombopag at 0.25, 0.825, 2.5, 8.25, 25, 82.5, and 250 μM (final concentration) at 37°C for 10 minutes, and as a result, eltrombopag inhibited the activity of UGT1A9, UGT1A3, UGT1A1, UGT2B15, UGT1A6, UGT2B7, and UGT1A4 with the IC_{50} being 3.0, 11, 13, 20, 21, 21, and 33 μM, respectively.

(c) Inducibility to CYPs (Attached document5.3.2.2.10)
Primary human hepatocytes were incubated with eltrombopag at 0.3, 3, and 30 μM (final concentration) at 37°C for 48 hours to investigate induced mRNA amounts and enzyme activities of CYP1A2, CYP2B6, and CYP3A4.

Following addition with omeprazole, phenobarbital, and rifampicin, which are inducers of CYP1A2, CYP2B6, and CYP3A4, respectively, in the primary cultured hepatocytes, the induced mRNA amounts and enzyme activities were 810 and 19 times, 17 and 3.4 times, and 110 and 11 times, respectively, greater than those induced by the control (0.1% DMSO). On the other hand, following addition with eltrombopag, the induced mRNA amounts and enzyme activities of CYP1A2, CYP2B6, and CYP3A4 were 0.09 to 2.0 times and 0.12 to 0.61 times, 0.45 to 1.3 times and 0.30 to 1.6 times, and 0.08 to 1.8 times and 0.29 to 1.4 times, respectively, greater than those induced by the control (0.1% DMSO).

4.(ii).A.(1).4) Transport by transporters
(a) Transport by P-glycoprotein (Attached document5.3.2.3.1)
MDCKII-MDR1 cells in which human P-glycoprotein (Pgp) was expressed were used to investigate Pgp-mediated transport of ^{14}C-labeled eltrombopag (approximately 3 μM). The permeability of amprenavir, a substrate of Pgp, of the basolateral membrane surface (B) and apical membrane surface (A) (B→A/A→B ratio) was 28, while in the presence of GF120918A (2 μM), a Pgp inhibitor, the ratio was 1.3. On the other hand, the B→A/A→B ratio of eltrombopag was 1.0, and the ratio was 1.7 in the presence of GF120918A. The passive membrane permeability coefficient of eltrombopag was estimated to be 65.0 ± 15.0 nm/s (mean ± SD). The above data indicated that eltrombopag is not a substrate of Pgp and can passively pass through the cell membrane at a moderate rate (50-250 nm/s).

(b) Transport by breast cancer resistance protein (Attached document5.3.2.3.2)
MDCKII-BCRP cells in which human breast cancer resistance protein (BCRP) was expressed were used to investigate BCRP-mediated transport of ^{14}C-labeled eltrombopag (3 μM). The B→A/A→B ratio of cimetidine, a substrate of BCRP, was 10, while the ratio was 1.2 in the presence of GF120918A (2 μM). The B→A/A→B ratio of eltrombopag was 49, while the ratio was 6.2 in the presence of GF120918A. The above data indicated that eltrombopag is a substrate of BCRP.

(c) Transport by OATP1B1 (Attached document5.3.2.3.3, 5.3.2.3.4)
CHO-OATP1B1 cells in which human OATP1B1 was expressed were used to investigate OATP1B1-mediated transport of ^{14}C-labeled eltrombopag (pyrazole ring) (0.6 μM) or ^{14}C-labeled eltrombopag (benzoic acid) (3, 30, 100 μM).

The uptake rate of ^{14}C-labeled eltrombopag in CHO-OATP1B1 cells in the presence and absence of rifamycin, an OATP inhibitor, at 10 μM was 17.4 ± 1.70 pmol/min/mg protein (mean ± SD) and 14.2 ± 1.15 pmol/min/mg protein, respectively. The uptake rate of ^{14}C-labeled eltrombopag (benzoic acid) in CHO-OATP1B1 cells was not clearly changed by varying eltrombopag concentrations (3-100 μM), incubated temperature (0°C, 37°C) and type of inhibitors (rifamycin at 10 μM, ciclosporin A at 3 μM). The above data indicated that eltrombopag is not a substrate of OATP1B1.

4.(ii).A.(1).5) Effects on transporters
(a) Inhibitory effects on Pgp (Attached document5.3.2.3.5)
MDCKII-MDR1 cells in which human Pgp was expressed were used to investigate effects of eltrombopag (0.1, 1, 3, 10, 30, 50, 75, 100 μM) on transport of ^{3}H-labeled digoxin (30 nM).

GF120918A (2 μM), a Pgp inhibitor, decreased the transport rate of digoxin to 19.5% on average. On the other hand, the transport rate of digoxin in the presence of eltrombopag was between 86.4% and 135% of that of digoxin alone on average, indicating that eltrombopag dose not inhibit Pgp-mediated transport of digoxin.

(b) Inhibitory effects on BCRP (Attached document5.3.2.3.6)
MDCKII-BCRP cells in which human BCRP was expressed were used to investigate effects of eltrombopag (0.3, 0.5, 1, 3, 5, and 10 μM) on transport of cimetidine (100 nM).

GF120918A (2 μM), a BCRP inhibitor, decreased the transport rate of cimetidine to 11% on average. In the presence of eltrombopag at ≤1 μM, the transport rate of cimetidine was 102% to 111% of that with cimetidine alone on average, while in the presence of eltrombopag at 3, 5, and 10 μM, the rate was decreased to 43%, 27%, and 22%, respectively, on average. Eltrombopag inhibited BCRP-mediated transport of cimetidine ($IC_{50,}$ 2.7 μM).

(c) Inhibitory effects on OATP1B1 (Attached document5.3.2.3.7)
CHO-OATP1B1 cells in which human OATP1B1was expressed were used to investigate effects of eltrombopag (0.1, 1, 3, 10, 30, 100 μM) on transport of ^{3}H-labeled estradiol 17β-D-glucuronide (EG) (0.025 μM).

Rifamycin (10 μM), an OATP1B1 inhibitor, decreased the transport rate to 4.9% of that with EG alone on average. Eltrombopag at 0.1, 1, 3, 10, 30, and 100 μM inhibited the transport rate of EG to 104%, 83.8%, 48.4%, 6.7%, 3.7%, and 1.1%, respectively, of that of EG alone on average in a concentration-dependent manner. Eltrombopag inhibited human OATP1B1-mediated transport of EG (IC_{50}, 2.71 μM).

4.(ii).A.(2) Investigations in healthy adult subjects
4.(ii).A.(2).1) Single-dose study in Japanese healthy adult subjects (Japanese Study TRA104603, Attached document5.3.3.1.1; Studied period, June 2005 to March 2006)
Single oral doses of eltrombopag 30, 50, 75, or 100 mg were administered to 16 fasting Japanese healthy adult male subjects (n = 4 subjects/group) in a four-period crossover manner (periods separated by a 12-day washout period). Table 2 shows the resultant pharmacokinetic parameters of plasma eltrombopag concentrations.

Table 2. Pharmacokinetic parameters in Japanese healthy adult subjectsreceiving a single oral dose of eltrombopag (Adapted from application data)

	C_{max} (μg/mL)	t_{max} (h)	$AUC_{0-\infty}$ (μg·h/mL)	$t_{1/2}$ (h)
30 mg (n = 12)	4.00 ± 0.86	3.0 (2.0-5.0)	64.5 ± 14.6	23.1 ± 2.8
50 mg (n = 12)	7.26 ± 1.49	3.5 (2.0-5.0)	130.8 ± 22.3	27.5 ± 5.8
75 mg (n = 12)	10.1 ± 2.15	3.5 (1.5-4.0)	182.7 ± 56.8	27.9 ± 4.4
100 mg (n = 11)	13.1 ± 3.46	4.0 (2.0-5.0)	244.2 ± 53.6	28.1 ± 6.5

Parameters except for t_{max}, Mean ± SD; t_{max}, Median (range)

4.(ii).A.(2).2) Multiple -dose study in Japanese healthy adults (Japanese Study TRA105580, Attached document5.3.3.1.2; Studied period, June to September 2006)
A single oral dose of eltrombopag at 25, 50, or 75 mg was administered to fasting Japanese healthy adult male subjects followed by a 5-day washout period, and then the multiple oral doses were administered once daily for 10 days. Table 3 shows the resultant pharmacokinetic parameters of plasma eltrombopag concentrations following the single dose and on Day 10 of the multiple dosing period.

Table 3. Pharmacokinetic parameters in Japanese healthy adult subjects receiving single and multiple oral doses of eltrombopag (Adapted from application data)

Dose (mg)	Single/ Multiple	n	C_{max} (μg/mL)	t_{max} (h)	$AUC_{0-\tau}$ (μg·h/mL)	$AUC_{0-\infty}$ (μg·h/mL)	$t_{1/2}$ (h)	CL/F (L/h)
25	Single	10	3.56 ± 1.13	3.0 (2.0-5.0)	33.2 ± 10.1	55.4 ± 23.2	29.6 ± 5.0	0.534 ± 0.256
	Multiple Day 10	10	4.83 ± 1.17	3.0 (1.5-5.0)	58.9 ± 18.4	-	39.7 ± 3.2	0.478 ± 0.196
50	Single	10	6.44 ± 2.14	3.0 (1.5-5.0)	63.9 ± 17.6	106.6 ± 32.4	31.0 ± 5.9	0.525 ± 0.218
	Multiple Day 10	9	10.60 ± 2.38	4.0 (2.0-5.0)	133.8 ± 33.6	-	51.3 ± 12.2	0.396 ± 0.102
75	Single	10	8.39 ± 2.84	3.0 (2.0-6.0)	80.7 ± 20.7	134.9 ± 37.4	32.4 ± 7.6	0.604 ± 0.201
	Multiple Day 10	10	12.78 ± 2.84	4.0 (2.0-5.0)	164.2 ± 35.5	-	47.8 ± 11.5	0.476 ± 0.102

Parameters except for $t_{max,}$: Mean ± SD; t_{max}, Median (range)

4.(ii).A.(2).3) Single- and multiple- dose study in foreign healthy adults (Foreign Study SB-497115/002, Attached document5.3.3.1.3; Studied period, ■ 20■ to ■ 20■)

A single oral dose of eltrombopag at 5, 10, 20, 30, 50, or 75 mg were administered to foreign healthy adult male subjects followed by a 7-day washout period, and then the multiple oral doses were administered once daily for 10 days. Table 4 shows the resultant pharmacokinetic parameters of plasma eltrombopag concentrations following the single dose and on Day 10 of the multiple dosing period.

Table 4. Pharmacokinetic parameters in foreign healthy adult receiving single and multiple oral doses of eltrombopag (Adapted from application data)

Dose (mg)	Single/ Multiple	C_{max} (μg/mL)	t_{max} (h)	$AUC_{0-\tau}$ (μg·h/mL)[a]	$AUC_{0-\infty}$ (μg·h/mL)[a]	$t_{1/2}$ (h)[a]
5	Single	0.33 ± 0.08	2.50 (2.0-4.0)	3.11 ± 0.93	3.86 ± 1.34	10.79 ± 3.86
	Multiple Day 10	0.34 ± 0.08	4.00 (2.0-6.0)	3.58 ± 1.07	-	8.74 ± 1.48
10	Single	0.66 ± 0.21	3.00 (2.0-6.0)	6.33 ± 1.87	9.15 ± 3.24	16.60 ± 4.46
	Multiple Day 10	0.74 ± 0.24	3.00 (2.0-6.0)	8.10 ± 2.74	-	13.46 ± 6.44
20	Single	1.31 ± 0.36	3.00 (2.0-6.0)	12.71 ± 3.91	17.59 ± 7.26	15.00 ± 3.18
	Multiple Day 10	1.64 ± 0.58	4.00 (2.0-6.0)	17.82 ± 6.58	-	12.98 ± 3.32
30	Single	2.78 ± 0.86	2.50 (1.5-4.0)	22.11 ± 5.88	30.45 ± 8.54	15.76 ± 1.68
	Multiple Day 10	3.07 ± 0.76	3.00 (2.0-4.0)	30.13 ± 8.44	-	12.43 ± 1.92
50	Single	5.21 ± 1.77	3.00 (2.0-4.0)	43.09 ± 13.73	61.68 ± 21.27	18.20 ± 3.01
	Multiple Day 10	5.96 ± 1.72	4.00 (2.0-6.0)	59.44 ± 16.84	-	12.98 ± 1.52
75	Single	6.25 ± 1.87	4.00 (2.1-6.0)	52.39 ± 14.52	76.00 ± 28.16	16.85 ± 5.93
	Multiple Day 10	7.34 ± 1.12	5.00 (2.0-10.0)	80.87 ± 18.54	-	15.76 ± 7.67

Parameters except for t_{max}, Mean ± SD, $t_{max,}$ Median (range); n = 9 (30 mg and 75 mg following the single oral dose and on Day 10 of the multiple oral dosing period, n = 8)

a. Single dose, blood sampling until 48 hours after administration; multiple dose (on Day 10), blood sampling until 24 hours after administration (Day 10).

4.(ii).A.(2).4) Mass balance study in foreign healthy adult subjects (Study TRA102861, Attached document5.3.3.1.5, 5.3.3.1.6; Studied period, September to October 2005, Reference data)

Following a single oral dose of ^{14}C-labeled eltrombopag (pyrazole ring) solution (75 mg, 100 μCi) to 6 foreign healthy adult male subjects, the C_{max} of unchanged eltrombopag and radioactivity in plasma were 10.85 (geometric mean) μg/mL and 10.02 μg eq/g, respectively, the $AUC_{0-\infty}$ was 144.74 μg·h/mL and 240.49 μg eq·h/g, respectively, $t_{1/2}$ was 32.34 and 49.32 hours, respectively, and median t_{max} was both 2.5 hours. The $AUC_{0\text{-last}}$ of unchanged eltrombopag accounted for approximately 64% of that of the plasma radioactivity. Glucuronide conjugates and oxidant of eltrombopag, metabolites of eltrombopag, were detected, but both accounted for <10% of the total plasma radioactivity.

The mean total radioactivity recovered until 168 hours post-dose was 89.6% (range, 83.8%-93.2%) of the dose, and 30.7% (23.4%-45.4%) and 58.9% (40.9%-69.8%) of the administered radioactivity were recovered in urine and feces, respectively. The major urine metabolite was a glucuronide conjugates of phenylpyrazole formed by hydrazine linkage cleavage of eltrombopag and accounted for approximately 20% of the dose. No unchanged eltrombopag was detected in the urine. In the feces, approximately 20% of the dose was recovered as unchanged eltrombopag, and a total of approximately 21% was recovered as the metabolites including the glutathione conjugates, glutamylcysteine conjugates, and cysteine conjugates.

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

4.(ii).A.(3).1) Pharmacokinetics in Japanese patients with chronic ITP (Japanese Study TRA108109, Attached document5.3.3.2.1; Studied period, [redacted] 20[redacted] to [redacted] 20[redacted])

Table 5 shows pharmacokinetic parameters of eltrombopag at steady state in previously treated Japanese patients with chronic ITP in Study TRA108109. Of 21 patients in whom plasma concentrations were measured, 1 with plasma eltrombopag concentrations below the quantitation limit at all the sampling points and 3 in whom the plasma eltrombopag concentration did not reach a steady state at all due to the dose change on the day of blood sampling for pharmacokinetic analysis were excluded from the pharmacokinetic analysis set.

Table 5. Pharmacokinetic parameters in Japanese patients with chronic ITP receiving single and multiple oral doses of eltrombopag (Adapted from application data)

Dose (mg)	n	C_{max} (μg/mL)	t_{max} (h)	$AUC_{0-\tau}$ (μg·h/mL)	$t_{1/2}$[b] (h)
12.5	8	2.99 ± 1.25	3.19 (2.00-4.17)	41.64 ± 24.36[a]	19.5 ± 7.16[a]
25	5	6.78 ± 2.62	4.00 (2.00-4.00)	92.53 ± 41.12	27.0 ± 7.66
50	4	11.88 ± 3.93	2.97 (1.92-4.17)	171.6 ± 75.24	18.2 ± 4.94

Parameters except for t_{max}, Mean ± SD; t_{max}, Median (range)
a. n = 7; b. Reference values for point calculation until 24 hours
Data from patients who received eltrombopag at the same dose for the last 6 days or longer (including the day of blood collection)

2) Population pharmacokinetic analysis (Attached document5.3.3.5.1, Reference data)

Population pharmacokinetic (pop-PK) analysis was performed using the data from Foreign Studies SB-497115/002 and TRA102860 in foreign healthy adult subjects, Japanese Study TRA105580 in Japanese healthy adult subjects, and the Foreign Study TRA100773 in foreign patients with ITP. Pop-PK analysis initially included 201 subjects, but in 1 subject in the Foreign Study TRA102860, plasma eltrombopag concentrations were below the lower limit of

quantitation at all time points, and in 1 patient in the Foreign Study TRA100773A, the concentrations were unmeasurable. Therefore, the above 2 subjects were excluded from the data set for Pop-PK analysis. Finally, the pop-PK analysis was performed on plasma concentration data consisting of 4093 points in 199 subjects.

The characteristics of the subjects analyzed were as follows: age, 30 (18-85) years (median [minimum-maximum]); body weight, 73 (43-122) kg; body mass index, 24 (18.1-45.8); sex, 128 male subjects and 71 female subjects; race, 30 Japanese subjects, 19 non-Japanese Asian subjects, 125 Caucasian subjects, 10 African American subjects, and 15 other subjects; health condition, 111 healthy adult subjects and 88 patients with ITP; dosage form, 55 subjects received capsules, and 144 subjects received tablets; creatinine clearance (CL_{cr}), 108 ± 25.8 (mean ± SD) mL/min; ALT, 25.4 ± 19.8 IU/L; AST, 23.9 ± 14.7 IU/L; albumin, 4.50 ± 0.510 g/dL; total bilirubin, 0.764 ± 0.369 mg/dL; concomitant use with corticosteroids in 24 subjects, concomitant use without corticosteroids in 175 subjects; and dose level, 9 subjects at eltrombopag 5 mg, 9 subjects at 10 mg, 9 subjects at 20 mg, 10 subjects at 25 mg, 37 subjects at 30 mg, 54 subjects at 50 mg, 45 subjects at 75 mg, 10 subjects at 100 mg, 9 subjects at 150 mg, and 7 subjects at 200 mg. Pharmacokinetic analysis was performed using a 2-compartment model, consisting of the first-order absorption, lag time of absorption, and study period variation, in which the above factors were set as covariates, to investigate effects of individual covariates on the absorption rate constant (Ka), apparent total body clearance (CL/F), apparent distribution volume of central compartment (Vc/F), exchange rate constant (Q/F) between compartments, and distribution volume in peripheral compartment (Vp/F). As a result, covariates significantly affecting CL/F included body weight, dose, health condition (healthy subjects or patients), race, sex, and concomitant use of corticosteroids; ones significantly affecting Vc/F were body weight and dose (<20 mg or ≥20 mg); and covariate significantly affecting Q/F and Vp/F was body weight.

Estimated parameters in typical Caucasian male patients with ITP who weighed 70 kg and did not concomitantly receive corticosteroids were 0.668 L/h (95% CI, 0.561-0.775 L/h) for CL/F, 8.76 L (8.14-9.38 L) for Vc/F, 11.3 L (10.1-12.5 L) for Vp/F, and 0.399 L/h (0.361-0.437 L/h) for Q/F. In patients with chronic ITP who orally received eltrombopag 50 mg once daily, geometric mean parameter values after reaching a steady state were estimated to be 99 μg·h/mL (88-111 μg·h/mL) for $AUC_{0-\tau}$ and 7.53 μg/mL (6.83-8.31 μg/mL) for C_{max}.

The mean CL/F of eltrombopag was lower by 33% (26%-41%) in Asian subjects than that in the other races, lower by 26% (7%-45%) in patients concomitantly treated with corticosteroids than that in patients without corticosteroids, and lower by 19% (7%-31%) in female subjects than that in male subjects. On the other hand, the CL/F in healthy subjects was higher by 17% (0%-34%) than that in patients with chronic ITP. The geometric mean $AUC_{0-\tau}$ in ITP patients was higher by 87% in Asian subjects than in the other races and higher by 50% in female subjects than in male subjects. Of the pharmacokinetic parameters in subjects who received eltrombopag <20 mg, mean CL/F and Vc/F were estimated to be higher by 68% (46%-90%) and 55% (37%-73%), respectively, than those in subjects who received eltrombopag ≥20 mg. However, doses of <20 mg were given as capsules, and which of low dose or dosage form (capsules) affected pharmacokinetics of eltrombopag remained unknown.

In addition, age and mildly decreased renal function did not affect the pharmacokinetics of eltrombopag.

4.(ii).A.(3).3) Population pharmacokinetic/pharmacodynamic analyses (Attached document5.3.3.5.2, 5.3.3.5.3, Reference data)

Using the data set for pop-PK analysis in the section 4.(ii).A.(3).2), population pharmacokinetic/pharmacodynamic analyses (pop-PK/PD analyses) were performed to investigate the relationship between plasma eltrombopag concentrations and platelet count. The

platelet count data were obtained from 111 healthy adult subjects (1728 time points) and 88 ITP patients (627 time points) of 199 subjects included in the above pop-PK analysis. The analysis data set additionally included the platelet count data obtained at 590 time points from a total of 67 subjects in Studies TRA100773A and TRA100773B (29 subjects and 38 subjects, respectively) where the placebo was administered to obtain the baseline data.

The final model was established as 7-compartment indirect reaction model consisting of 3 PK compartments and 4 PD compartments. Among body weight, sex, race, age, baseline platelet count, concomitant use with corticosteroids, and previous treatment for ITP, which were analyzed as the covariates, sex and age were identified as significant covariates.

Using the final model, the percentage of subjects who had a particular platelet count after 2 weeks of eltrombopag treatment in Asian (non-Japanese) and non-Asian ITP patients (Foreign Study TRA100773) was predicted. At the doses up to 50 mg/day, the percentages of Asians with a platelet count of 50,000 to 200,000, >200,000, and >400,000/μL were higher than those in non-Asian patients; 14% of Asian patients in the 50 mg/day group were estimated to have a platelet count >400,000/μL after 2 weeks of treatment with eltrombopag, while that of non-Asian patients in the 50 mg/day group was estimated to be 5%. Of Japanese patients with chronic ITP with the starting dose of 12.5 mg, 28% was estimated to have platelet count of 50,000 to 400,000/μL and 1% to have that of >400,000/μL after 2 weeks of treatment with eltrombopag. At the starting doses of 25 mg/day and 50 mg/day, 47% and 61% of the patients, respectively, were estimated to have a platelet count of ≥50,000/μL after 2 weeks of treatment with eltrombopag.

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

4.(ii).A.(4).1) Pharmacokinetics in subjects with hepatic impairment (Foreign Study TRA103452, Attached document5.3.3.3.1; Studied period, April 2006 to March 2007, Reference data)

Eltrombopag was administered at a single oral dose of 50 mg to foreign healthy adult subjects as well as patients with mild (Child-Pugh score, 5-6), moderate (Child-Pugh score, 7-9), and severe (Child-Pugh score, ≥10) hepatic impairment. As a result, C_{max} of eltrombopag was 5.89 ± 2.40 (mean ± SD), 5.11 ± 2.15, 4.41 ± 2.27, and 3.36 ± 1.83 μg/mL, $AUC_{0-\infty}$ was 75.54 ± 45.62, 98.49 ± 29.49, 145.46 ± 78.37, and 143.98 ± 82.76 μg·h/mL, and $t_{1/2}$ was 22.70 ± 8.33, 40.44 ± 18.43, 46.43 ± 13.62, and 45.95 ± 6.22 hours, respectively.

4.(ii).A.(4).2) Pharmacokinetics in subjects with renal impairment (Foreign Study TRA104412, Attached document5.3.3.3.2; Studied period, September 2006 to January 2008, Reference data)

Eltrombopag was administered at a single oral dose of 50 mg to foreign healthy adult subjects as well as patients with mild (CL_{cr}, 50-80 mL/min), moderate (CL_{cr}, 30-49 mL/min), and severe (CL_{cr}, <30 mL/min) renal impairment. As a result, C_{max} of eltrombopag was 6.46 ± 2.05 (mean ± SD), 4.63 ± 1.92, 5.89 ± 3.69, and 4.18 ± 3.04 μg/mL, $AUC_{0-\infty}$ was 68.40 ± 24.49, 49.68 ± 26.20, 48.72 ± 33.44, and 46.17 ± 46.78 μg·h/mL, and $t_{1/2}$ was 26.15 ± 4.80, 21.05 ± 8.87, 17.00 ± 7.24, and 18.10 ± 12.73 hours, respectively. $AUC_{0-\infty}$ (geometric mean) in subjects with mild, moderate, and severe renal impairment was lower by 32%, 36%, and 60%, respectively, than that in healthy adult subjects, and C_{max} (geometric mean) was lower by 30%, 19%, and 54%, respectively, than that in healthy adult subjects. However, inter-subject variability was large, and the exposure in healthy adult subjects overlapped with that in subjects with renal impairment. No significant differences were found between the exposure in healthy adult subjects and that in subjects with renal impairment, except subjects with severe renal impairment.

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

4.(ii).A.(5).1) Effects on CYPs (Foreign Study SB-497115/002, Attached document5.3.3.4.1; Studied period, [redacted] 20[redacted] to [redacted] 20[redacted])

A total of 24 foreign healthy adult subjects received midazolam 5 mg (CYP3A4 probe substrate) on Day 1, caffeine 100 mg (CYP1A2 probe substrate), omeprazole 20 mg (CYP2C19 probe substrate), and flurbiprofen 50 mg (CYP2C9 probe substrate) on Day 2, and then received eltrombopag at multiple oral dose of 75 mg once daily from Day 3 to Day 7. They concomitantly received eltrombopag 75 mg and midazolam 5 mg on Day 8, and eltrombopag 75 mg, caffeine 100 mg, omeprazole 20 mg, and flurbiprofen 50 mg on Day 9.

The least squares mean $AUC_{0-\infty}$ of midazolam on Days 1 and 8 was 83.51 and 86.84 ng·h/mL, respectively, and the ratio of the least squares geometric mean following concomitant use of eltrombopag with midazolam to that following administration of midazolam alone was 1.04 (90% CI, 0.96-1.13), and neither inhibition nor induction was found in metabolism of CYP3A4 probe substrate. Comparisons between Days 2 and 9 were made on the plasma paraxanthine/caffeine concentration ratio at 8 hours after administration, urine total 4-hydroxyflurbiprofen/(urine 4-hydroxyflurbiprofen + flurbiprofen) concentration ratio and urine free 4-hydroxyflurbiprofen/(urine 4-hydroxyflurbiprofen + flurbiprofen) concentration ratio until 12 hours after administration, and plasma omeprazole/5-hydroxyomeprazole concentration ratios at 2 and 3 hours after administration. As a result, neither inhibition nor induction was observed in metabolism of probe substrates of CYP1A2, 2C9 or 2C19.

4.(ii).A.(5).2) Drug interaction with rosuvastatin (Foreign Study TRA105120, Attached document5.3.3.4.2; Studied period, May to October 2006, Reference data)
Since rosuvastatin has been known to involve OATP1B1 transporter in its hepatic uptake process (Kitamura S et al. *Drug Metab Dispos.* 2008;36:2014-23, McTaggart F et al. *Am J Cardiol.* 2001;87(suppl):28B-32B, Nezasa K et al. *Xenobiotica.* 2003;33:379-88, Trauner M et al. *Physiol Rev.* 2003;83:633-71) and to be a substrate of BCRP (Hirano M et al. *Mol Pharmacol.* 2005;68:800-7, Huang L et al. *Drug Metab Dispos.* 2006;34:738-42, Zhang W et al. *Clin Chim Acta.* 2006;373:99-103), drug interaction between eltrombopag and rosuvastatin was studied.

A total of 39 foreign healthy adult subjects (21 Asian subjects, 18 non-Asian subjects) received rosuvastatin 10 mg, then eltrombopag 75 mg once daily on Days 6 to 9, and eltrombopag 75 mg and rosuvastatin 10 mg on Day 10. As shown in Table 6, C_{max} and $AUC_{0-\infty}$ of plasma rosuvastatin following concomitant use of eltrombopag with rosuvastatin were 2.03 and 1.55 times higher than those following administration of rosuvastatin alone.

Table 6. Pharmacokinetic parameters of plasma rosuvastatin by regimen (Adapted from the submitted data)

Pharmacokinetic parameter of plasma rosuvastatin	Rosuvastatin + eltrombopag (Regimen C)	Rosuvastatin (Regimen A)	Rosuvastatin + eltrombopag vs. rosuvastatin
$AUC_{0-\infty}$ (ng·h/mL)	96.0 (50)	61.9 (72)	1.55 (1.42-1.69)
C_{max} (ng/mL)	12.1 (53)	5.97 (81)	2.03 (1.82-2.26)

Pharmacokinetic parameters are expressed as a geometric mean (CVb%), while comparisons between regimens are made based on the least squares geometric mean (90% CI).
Regimen A, Single dose of rosuvastatin10 mg alone
Regimen C, Eltrombopag 75 mg once daily for 5 days + single dose of rosuvastatin 10 mg concomitantly given on Day 5 of eltrombopag dosing

$AUC_{0-\infty}$ of plasma rosuvastatin following administration of rosuvastatin alone in Asian subjects was 2.09 times higher than that in non-Asian subjects, and $AUC_{0-\infty}$ of plasma rosuvastatin following concomitant use of rosuvastatin with eltrombopag in Asian subjects was 1.46 times higher than that in non-Asian subjects. C_{max} of plasma rosuvastatin in Asian subjects was also

higher than that in non-Asian subjects. Table 7 shows the comparison of pharmacokinetic parameters of plasma rosuvastatin between Asian and non-Asian subjects.

Table 7. Pharmacokinetic parameters of plasma rosuvastatin by ethnic (Adapted from application data)

Plasma rosuvastatin	Rosuvastatin (Regimen A)			Rosuvastatin + eltrombopag (Regimen C)		
	Asian (n = 21)	Non-Asian (n = 18)	Comparison between Asian and non-Asian	Asian (n = 21)	Non-Asian (n = 18)	Comparison between Asian and non-Asian
$AUC_{0-\infty}$ (ng·h/mL)	87.0 (58)	41.6 (58)	2.09 (1.60-2.72)	114 (47)	78.2 (45)	1.46 (1.12-1.91)
C_{max} (ng/mL)	8.93 (63)	3.74 (59)	2.39 (1.81-3.16)	14.4 (51)	9.91 (47)	1.45 (1.10-1.92)

Pharmacokinetic parameters are expressed as a geometric mean (CVb%), while comparisons between regimens are made based on the least squares geometric mean (90% CI).
Regimen A, Single dose of rosuvastatin10 mg alone
Regimen C, Eltrombopag 75 mg once daily for 5 days + single dose of rosuvastatin 10 mg concomitantly given on Day 5 of eltrombopag dosing

On the other hand, geometric mean C_{max} of eltrombopag in Asian and non-Asian subjects following concomitant use of rosuvastatin with eltrombopag was 8.14 and 7.83 μg/mL, respectively; and $AUC_{0-\infty}$ was 105 and 99.7 μg·h/mL, respectively.

4.(ii).A.(6) Pharmacodynamic studies

4.(ii).A.(6).1) Effects of eltrombopag on platelet count

In Japanese Studies TRA104603 and TRA105580 in Japanese healthy adult, single doses of eltrombopag at 30 to 100 mg and 25 to 75 mg, respectively, did not significantly increase the platelet count.

In Japanese Study TRA105580, Japanese healthy adults received multiple oral doses of eltrombopag 25, 50, and 75 mg once daily for 10 days. The platelet count started increasing on Day 3 and reached the peak 4 to 6 days after the last dose (14-16 days after the initiation of multiple dose administration) as shown in the figure below. The count returned to the reference value 16 days after the last dose (26 days after the initiation of multiple dose administration) in all subjects except for 1 subject in the 25 mg group. In this subject in the 25 mg group, the platelet count returned to the reference value 64 days after the last dose without any treatment. The maximum platelet count in subjects who received eltrombopag at multiple oral doses of 25, 50, and 75 mg once daily for 10 days was 1.5, 1.7, and 1.9 times, respectively, greater than the baseline value on average, and the platelet count tended to increase with the dose (Figure 1). At any dose, eltrombopag did not affect ADP-induced platelet aggregation.

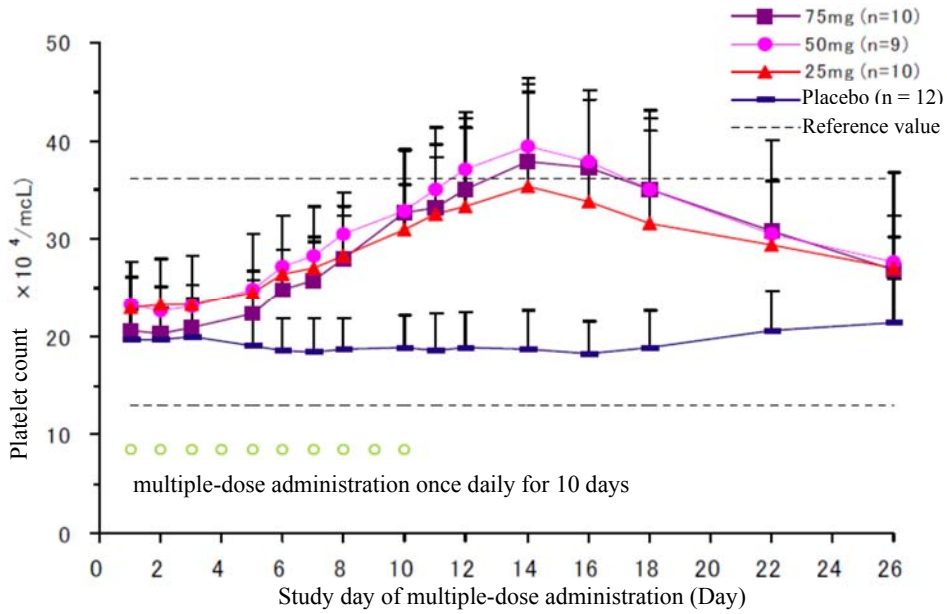


Figure 1. Mean platelet count over time in Japanese healthy adult subjects who received multiple oral doses of eltrombopag (bar, SD) (Adapted from application data)

In Foreign Study SB-497115/002 in foreign healthy adults, a single dose of eltrombopag did not significantly increase the platelet count. In Foreign Study SB-497115/002 at multiple oral dose of eltrombopag 5 to 75 mg once daily for 10 days, the platelet count started increasing on Day 8, reached the peak approximately 6 days after the last dose (16 days after the initiation of multiple dose administration), and returned to the baseline values 12 days after the last dose (22 days after the initiation of multiple dose administration). At the doses of ≥30 mg, the platelet count increased concentration-dependently.

4.(ii).A.(6).2) Effects of eltrombopag on QTc (Foreign Study TRA102860, Attached document5.3.4.1.1; Studied period, March 2006 to August 2007)
To investigate effects of eltrombopag on QTc, a double-blind, placebo- and positive-controlled (moxifloxacin), crossover study (periods separated by a ≥14-day washout period) was conducted in foreign healthy adults. Eltrombopag 50, 150 mg, or placebo of eltrombopag were orally administered once daily for 5 days, and on Day 5, a single oral dose of moxifloxacin 400 mg or placebo of moxifloxacin was administered.

C_{max} on Day 5 of multiple doses of eltrombopag 50 and 150 mg for 5 days was 6.40 and 19.0 μg/mL with $AUC_{0-\tau}$ being 65.4 and 204 μg·h/mL, respectively. On the other hand, C_{max} of moxifloxacin was 2.05 μg/mL with AUC_{0-last} being 22.6 μg·h/mL. These parameters were expressed as the geometric mean values.

The upper limit of 90% CI for the mean difference in change from baseline in the mean Fridericia-corrected QT interval (QTcF) between eltrombopag and placebo (ddQTcF) was below 10 msec at all the sampling points; QTc interval was not prolonged. On the other hand, the lower limit of 90% CI for moxifloxacin was above 5 msec at ≥1 time point.

4.(ii).A.(6).3) Phototoxicity study (Foreign Study TRA106914, Attached document5.3.4.1.2; Studied period, March to September 2008, Reference data)
Foreign healthy adult subjects (n = 12 subjects/group) orally received eltrombopag 75 mg or

placebo of eltrombopag once daily as well as ciprofloxacin 500 mg (positive control) twice daily for 6 days to investigate photosensitivity.

Before and after administration of the investigational drug, ultraviolet irradiation (UV-A, 315-400 nm; UV-B, 290-315 nm) was applied, and the minimal erythemal dose (MED) 24 hours after irradiation was determined to calculate the delayed phototoxic index (delayed PI = MED before dosing/MED after administration). Ultraviolet irradiation at 335 ± 30 nm and 365 ± 30 nm resulted in comparable delayed PI between the eltrombopag and placebo groups, but the difference in delayed PI between the eltrombopag and ciprofloxacin groups (eltrombopag – ciprofloxacin) decreased at all wavelengths after treatment, while that between the ciprofloxacin and placebo groups (ciprofloxacin – placebo) increased at all wavelengths after treatment.

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

4.(ii).B.1) Difference in pharmacokinetics and pharmacodynamics between Japanese and foreign subjects

The applicant explained the differences in pharmacokinetics as follows:
In Japanese and foreign healthy adult subjects who received single oral dose of eltrombopag 50 mg, C_{max} distribution ranges largely overlapped, and $AUC_{0-\infty}$ in Japanese subjects tended to be higher than that in foreign subjects (mainly non-Asian subjects). In addition, distribution ranges of the $t_{1/2}$ following a single oral dose of 50 mg (when measured until 120 hours after administration) overlapped, but the geometric mean was 21.3 to 25.8 hours in foreign subjects and 30.5 hours in Japanese subjects; $t_{1/2}$ tended to be slightly longer in Japanese subjects than in foreign subjects. C_{max} and $AUC_{0-\tau}$ in Japanese healthy adult subjects who received multiple doses of eltrombopag 50 mg once daily for 10 days were 1.6 and 2 times, respectively, higher than those in foreign healthy adult subjects who received multiple oral doses once daily for 5 days. In Study TRA108109, $AUC_{0-\tau}$ at steady state in Japanese ITP patients at a dose of 50 mg was 1.85 times that in non-Asian subjects mainly consisting of Caucasian calculated by pop-PK analysis in foreign subjects.

As described above, the $AUC_{0-\tau}$ in Japanese healthy adult subjects was twice that in foreign healthy adult subjects, and even in comparison between ITP patients, similar differences were found.

The applicant explained the differences in pharmacodynamics of eltrombopag between Japanese and foreign subjects as follows:
In the Japanese Study TRA105580 and the Foreign Study SB-497115/002, Japanese and foreign (mainly Caucasian) healthy adult subjects received a single oral dose of eltrombopag 25 to 75 mg followed by multiple oral doses for 10 days. The rate of change in platelet count from the baseline to after 10-day multiple oral doses increased dose-dependently, indicating no difference between Japanese and foreign subjects, but the increase in platelet count at the same dose was higher in Japanese subjects than in foreign subjects (the maximum change after 10-day multiple doses of 50 mg once daily; 164,700 ± 54,580/μL in Japanese subjects, 143,300 ± 51,600/μL in foreign subjects). The difference in this pharmacodynamic response between Japanese and foreign subjects may have been affected by ethnic differences in exposure of eltrombopag.

PMDA considers as follows:
The results of the comparison of AUC at multiple doses between Japanese and foreign healthy adult subjects were affected by the difference in treatment period; however, the exposure in Japanese ITP patients was approximately twice higher than that in foreign (non-Asian) ITP patients. Therefore, pharmacokinetics of eltrombopag in Japanese subjects can be different from that in foreign subjects. On the other hand, the following findings are similar between Japanese and foreign subjects: the rate of change and change in platelet count from the baseline increased

with the increasing eltrombopag dose; the platelet count increased during treatment period and then decreased after the discontinuation of treatment (platelet counts over time with muliple-dose administration). However, inter-individual variability in plasma eltrombopag concentration and platelet count were found to be large in both Japanese and foreign subjects. It is necessary to monitor the efficacy and safety of eltrombopag in each patient appropriately during the treatment.

4.(ii).B.2) Appropriateness of setting the dosage and administration different from those in other countries

The applicant explained the difference in pharmacokinetics of eltrombopag between Japanese and foreign subjects as follows:

In Japanese and foreign healthy adult subjects who received a single oral dose of eltrombopag 50 mg, C_{max} distribution ranges largely overlapped, and $AUC_{0-\infty}$ in Japanese subjects tended to be higher than that in foreign (mainly non-Asian) subjects. In addition, distribution ranges of $t_{1/2}$ following a single oral dose of 50 mg (when measured until 120 hours after administration) overlapped, but the geometric mean of $t_{1/2}$ was 21.3 to 25.8 hours in foreign subjects and 30.5 hours in Japanese subjects, which tended to be slightly longer in Japanese subjects than that in foreign subjects. C_{max} and $AUC_{0-\tau}$ in Japanese healthy adult subjects who received multiple doses of eltrombopag 50 mg once daily for 10 days were 1.6 and 2 times, respectively, higher than those in foreign subjects who received multiple oral doses once daily for 5 days. In Study TRA108109, $AUC_{0-\tau}$ at steady state in Japanese ITP patients at a dose of 50 mg was 1.85 times that in non-Asian subjects mainly consisting of Caucasian calculated by pop-PK analysis in foreign subjects.

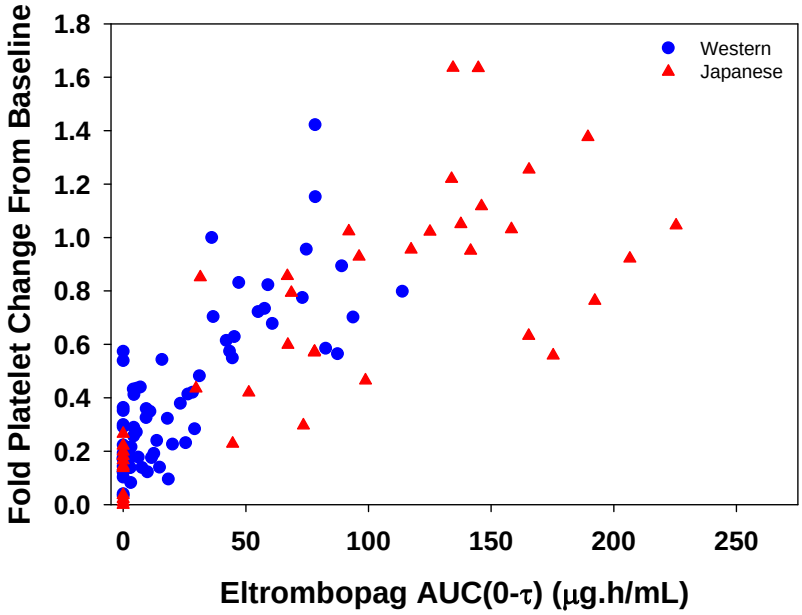
PMDA asked the applicant about the reason why the dosage and administration approved in the US have specified that "the starting dose of eltrombopag is 25 mg once daily" in East Asian patients.

The applicant explained as follows:

In comparison of the data in Asian subjects (data from Japanese Studies TRA104603 and TRA105580, pop-PK analysis) and those in non-Asian subjects (mainly Caucasian), both of which were submitted to FDA, the AUC of eltrombopag in Asian subjects was approximately higher by 70% to 80% than that in non-Asian subjects, suggesting that Asians may be more quickly to achieve the platelet count of 200,000/μL, which would require the dose reduction. Since pharmacokinetics data from Asian subjects mostly consisted of those from East-Asian subjects, the starting dose in East-Asian subjects (25 mg) was selected at a half of the starting dose in Non-Asian subjects (50 mg). Data of the pop-PK/PD analysis also showed that at the same dose level, the percentage of patients with high platelet count was higher in Asian subjects than that in non-Asian subjects [see "4.(ii).A.(3).3) Population pharmacokinetic/pharmacodynamic analyses]. In addition, pooled analysis including Foreign Studies TRA100773A, TRA100773B, TRA102537, TRA105325, and TRA108057 showed that the percentage of the subjects with hepatobiliary disorders accounted for 12% of East-Asian subjects and 2% of Caucasian subjects; the percentage was higher in East-Asians than in Caucasians.

PMDA asked the applicant to clarify at which time point plasma samples used for evaluating the correlation between $AUC_{0-\tau}$ and the change rate of platelet count were collected and then to explain the relationship between AUC of eltrombopag and increased platelet count, because the applicant explained that although the platelet counts over time following multiple oral doses of eltrombopag in Japanese healthy adult subjects did not show an increase in platelet count with the dose [see "4.(ii).A.(6).1) Effects of eltrombopag on platelet count"], the change rate of platelet count tended to increase with increasing $AUC_{0-\tau}$ (Figure 2) in the Japanese Study TRA105580 and the Foreign Study SB-497115/002 where Japanese and foreign (mainly Caucasian) healthy adult subjects received a single oral dose of eltrombopag 25 to 75 mg followed by multiple oral doses for 10 days.

The applicant explained as follows:



Western, Placebo or eltrombopag 5 to 75 mg was administered for 10 days (Foreign Study SB-497115/002).
Japanese, Placebo or eltrombopag 25 to 75 mg was administered for 10 days (Japanese Study TRA105580).

Figure 2. Relationship between $AUC_{0-\tau}$ and the change rate of platelet count in Japanese and foreign healthy adult subjects (Adapted from application data)

The correlation between $AUC_{0-\tau}$ and the change rate of platelet count shown in Figure 2 was evaluated based on the maximum change rate of platelet count from the baseline in each subject during multiple dosing and AUC at steady state in each subject (Day 10 of multiple dosing). The platelet counts over time following multiple oral dose of eltrombopag in Japanese healthy adult subjects was based on the mean of measured platelet count and presented by dose, the fact that the mean baseline value at a dose of 75 mg was lower than those at doses of 25 and 50 mg was not taken into consideration. Furthermore, the platelet count reached the peak on Day 14 or 16 in most subjects following multiple doses of eltrombopag for 10 days, but some presented the peak on Day 12 at the earliest and on Day 22 at the latest. Therefore, differences in platelet counts over time among dose groups were slightly small.

The exposure to eltrombopag almost linearly increased with the dose but showed inter-individual variability, resulting in considerably overlapped AUC distributions among dose groups. However, concerning the relationship between the individual AUC and the maximum change rate of platelet count, the applicant considered that the change rate of platelet count tended to increase with increasing $AUC_{0-\tau}$ of eltrombopag.

PMDA considers as follows:
From the viewpoints of pharmacokinetics and pharmacodynamics, it would be appropriate that the starting dose of eltrombopag in Japanese subjects was lower than that approved in the US, because AUC in Japanese subjects was approximately twice higher than that in foreign subjects (mainly Caucasian), the change rate of platelet count from the baseline tended to increase with increasing AUC of eltrombopag following multiple doses, and also the starting dose in East-Asian subjects in the US was a half that in non-Asian subjects. PMDA will address the appropriateness of the dosage and administration for eltrombopag in "4.(iii).B.7). Dosage and administration."

4.(ii).B.3) Pharmacokinetics in special populations

4.(ii).B.3).(a) Necessity of dose-adjustment in patients with hepatic impairment

PMDA asked the applicant the reason for selecting the starting dose of 25 mg for patients with moderate to severe hepatic impairment, a half of the standard starting dose of 50 mg, in the dosage and administration approved in the US.

The applicant explained as follows:

Data from Foreign Study TRA103452 where eltrombopag 50 mg was administered as a single oral dose to foreign patients with hepatic impairment showed that the geometric mean $AUC_{0-\infty}$ of eltrombopag in patients with moderate and severe hepatic impairment were higher by 93% and 80% than that in healthy adult subjects. Based on the above data, FDA presented the view that the dosing should be started at 25 mg for patients with moderate and severe hepatic impairment because the exposure in such patients could be higher than that in ordinary patients. Even if the starting dose of 25 mg is selected for patients with moderate and severe hepatic impairment, the dose may be increased appropriately based on the platelet count. The applicant therefore considered that the starting dose of 25 mg for ITP patients with moderate and severe hepatic impairment would be justified.

PMDA considers as follows:

Patients with hepatic impairment show the higher AUC of eltrombopag than that in patients with normal hepatic function and the treatment should be started carefully. However, the usual starting dose in Japan is set at 12.5 mg, which is one-fourth of that approved in the US, and then the dose will be adjusted based on the platelet count, it is unnecessary to set an even lower starting dose for patients with moderate to severe hepatic impairment.

PMDA asked the applicant to revise the description for patients with hepatic impairment in the "Careful Administration" section and the information on the pharmacokinetics in patients with hepatic impairment in the "Pharmacokinetics" section in the proposed package insert so that more specific values including variability could be provided, because the possibility that AUC of eltrombopag could be increased with increasing severity of the hepatic impairment was not described but large variability in AUC values was only included. The applicant took actions accordingly.

4.(ii).B.3).(b) Pharmacokinetics in patients with renal impairment

PMDA asked the applicant the reason for lower AUC of eltrombopag in patients with renal impairment than that in patients with normal renal function.

The applicant explained as follows:

In Foreign Study TRA104412, $AUC_{0-\infty}$ of eltrombopag in patients with mild, moderate, and severe renal impairment was lower than that in healthy adult subjects, but pharmacokinetics of eltrombopag was unlikely to be changed due to decreased renal function based on distributions of individual $AUC_{0-\infty}$ of eltrombopag in Foreign Study TRA104412 and the data from a foreign mass balance study (Foreign Study TRA102861). In terms of individual $AUC_{0-\infty}$ in subjects with moderate and severe renal impairment, some showed low $AUC_{0-\infty}$, but another portion showed high $AUC_{0-\infty}$ as well, indicating larger inter-individual variability than that in healthy adult subjects. Although the percentage of subjects with renal impairment showing slightly low exposure was greater than that showing slightly high exposure, the cause remained unknown.

PMDA considers as follows:

It is difficult to determine whether or not the decreased renal function changed the pharmacokinetics of eltrombopag based on the data from Foreign Study TRA104412, but it should be noted that some subjects with renal impairment showed AUC higher than the maximum

AUC in patients with normal renal function. The proposed package insert specifies that "patients with renal impairment" are included in the "Careful Administration" section, and caution has been provided that the safety should be carefully monitored in addition to the platelet counts over time, therefore, PMDA has determined that the applicant's action is appropriate.

4.(ii).B.4) Drug interaction

4.(ii).B.4).(a) Transporter-mediated drug interaction

PMDA asked the applicant to explain the appropriateness of using the data from a drug interaction study of rosuvastatin and eltrombopag in foreign subjects, considering some differences in pharmacokinetics of rosuvastatin and eltrombopag between Japanese and foreign subjects.

The applicant explained as follows:

A drug interaction study of eltrombopag and rosuvastatin (Foreign Study TRA105120) was conducted at 2 institutions in the US and Singapore in 39 subjects including 21 Asian subjects, and a stratified analysis by race (Asian and non-Asian) was also performed. In the pharmacokinetics of rosuvastatin (Crestor tablets) in Japanese subjects, $AUC_{0-\infty}$ following a single dose of rosuvastatin alone and AUC_{0-24} following multiple doses of rosuvastatin alone were found comparable to or slightly higher than $AUC_{0-\infty}$ of rosuvastatin following a single dose of rosuvastatin alone in Asian subjects in Foreign Study TRA105120. Following administration of eltrombopag alone to Japanese and non-Japanese Asian ITP patients, $AUC_{0-\tau}$ was 1.85 and 1.87 times, respectively, higher than that in non-Asian (mainly Caucasian) ITP patients, showing similar exposures. Based on the above, the pharmacokinetic data of rosuvastatin and eltrombopag are not be largely different between Japanese and non-Japanese Asian subjects. On the other hand, in the overall population in Foreign Study TRA105120, C_{max} and $AUC_{0-\infty}$ of rosuvastatin in combination with eltrombopag increased 2.03 and 1.55 times, respectively. Stratified analysis showed that C_{max} and $AUC_{0-\infty}$ of rosuvastatin in combination with eltrombopag in Asian subjects increased 1.61 and 1.32 times, and the effect of the concomitant use of rosuvastatin with eltrombopag in Asian subjects was smaller than that in non-Asian subjects. Accordingly, drug interaction between eltrombopag and rosuvastatin in Japanese subjects can be inferred from the data in Asian subjects (n = 21) from Foreign Study TRA105120. However, data showing the increased exposure to rosuvastatin due to the concomitant use will be provided in the "Pharmacokinetics" section in the proposed package insert, including not only the data of slightly increased exposure in Asian subjects (n = 21) but also those of substantially increased exposure in all subjects including non-Asian subjects (n = 39), and rosuvastatin will be listed as a drug requiring precautions for concomitant use to provide cautions.

PMDA has determined that it is appropriate to provide cautions based on the data from a study on the drug interaction with rosuvastatin, albeit foreign study data, and has accepted the applicant's explanation.

Concerning transporter-mediated drug interactions, the applicant explained in the submitted data that eltrombopag may affect pharmacokinetics of drugs transported by BCRP and OATP1B1, and the concerned possibility is described in the "Precautions" section in the proposed package insert. However, PMDA considers it more desirable to describe the concerned information in the "Pharmacokinetics" section in the proposed package insert, because *in vitro* study data mainly indicated that eltrombopag serves as an OATP1B1 inhibitor as well as BCRP substrate and inhibitor; and drugs other than rosuvastatin cannot be listed specifically as substrates and inhibitors of OATP1B1 and BCRP have not been fully known in clinical practice.

4.(ii).B.4).(b) Drug interactions between eltrombopag and drugs that may be coadministered for treatment of ITP

PMDA asked the applicant to explain the reason for necessity to investigate interaction of eltrombopag with drugs that may be coadministered for treatment of ITP.

The applicant explained as follows:
ITP-therapeutic drugs frequently coadministered with eltrombopag in clinical studies in Japanese and foreign patients included corticosteroids, danazol, and immunoglobulin. The primary concomitant ITP-therapeutic drug is considered to be corticosteroids, the first-line drug.

Only prednisolone was used in Japanese Study TRA108109 as a corticosteroid. Prednisolone is known to be mainly metabolized by CYP3A4 (according to the package insert of Predonine tablets 5 mg). On the other hand, eltrombopag undergoes oxidative metabolism involving CYP1A2 and CYP2C8 and then glucuronidation as a secondary metabolic pathway [see "4.(ii).A.(1) Studies with human biological samples"]. Multiple oral doses of eltrombopag 75 mg were administered to foreign healthy adult subjects to investigate CYP inhibitory or inductive potential, and as a result, eltrombopag did not inhibit or induce metabolism of a probe substrate of CYP1A2, CYP2C9, CYP2C19, or CYP3A4 [see "4.(ii).A.(5) Drug interactions"]. Accordingly, eltrombopag is unlikely to affect blood corticosteroid concentrations.

Concerning effects of corticosteroids on pharmacokinetics of eltrombopag, "concomitant use with or without corticosteroids" was selected as a covariate in the relationship between the dose and plasma concentration in a final model of pop-PK analysis based on the data from Foreign Studies TRA100773A and TRA100773B. Post-Hoc-estimated C_{max} and $AUC_{0-\tau}$ of eltrombopag at steady state in subjects receiving eltrombopag 50 mg in combination with corticosteroids were higher by 18% and 32%, respectively, than those in subjects receiving eltrombopag without corticosteroids. However, the 95% CI of the geometric mean AUC was 95 to 153 μg·h/mL in subjects receiving eltrombopag in combination with corticosteroids and 80 to 105 μg·h/mL in those receiving eltrombopag without corticosteroids. Since both intervals overlapped with each other, it was unlikely that corticosteroids largely affect blood eltrombopag concentrations.

Pharmacodynamic interaction potential between eltrombopag and corticosteroids was investigated based on the data from Japanese Study TRA108109 in 23 subjects consisting of 18 subjects receiving eltrombopag with corticosteroids and 5 subjects receiving eltrombopag without corticosteroids. The platelet counts over time and maximum change were not largely different between the subjects receiving eltrombopag with and without corticosteroids for 6 weeks after the start of treatment with eltrombopag during which the dose change of corticosteroids was not allowed by the protocol. Considering large inter-individual variability, the investigation did not suggest any difference in increase of platelet count after the start of treatment with eltrombopag between subjects receiving eltrombopag with and without corticosteroids.

Although no drugs that affect blood danazol concentrations have been found, danazol is considered to inhibit CYP3A4, because danazol increased blood concentrations of simvastatin, atorvastatin calcium hydrate, carbamazepine, tacrolimus hydrate, and ciclosporin, which are known to be mainly metabolized by CYP3A4, when these drugs are concomitantly used (package insert of Bonzol tablets 100 mg).

Based on the above, the drug interactions of eltrombopag with corticosteroids and danazol are considered unlikely to occur. In addition, immunogenicity of eltrombopag has not been detected and drug interaction between eltrombopag and immunoglobulin is considered unlikely to occur when immunoglobulin is concomitantly used.

PMDA considers as follows:
Based on the results of pop-PK analysis using foreign clinical study data, it cannot be ruled out that concomitant corticosteroids may affect blood eltrombopag concentrations. However, given that Japanese clinical study data have not shown marked effects of concomitant corticosteroids on platelet count, and taking into account the applicant' discussion about the interactions with

other ITP-therapeutic drugs, it is acceptable that the drug interaction studies with other concomitant ITP-therapeutic drugs including corticosteroids are not be conducted. It is necessary to collect information via post-marketing surveillance and to take actions as required.

4.(iii) Summary of clinical efficacy and safety

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

As the evaluation data, a total of 9 clinical studies (2 Japanese phase I studies, 1 Japanese phase II/III study, 1 Japanese phase III study, 4 foreign phase I studies, 1 foreign phase III study) were submitted. As the reference data, a total of 11 foreign clinical studies were submitted [for the pharmacokinetics, see "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and "4.(ii) Summary of clinical pharmacology studies"]. The major clinical study data are shown below.

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

4.(iii).A.(1).1) Japanese single dose study (Japanese Study TRA104603, Attached document5.3.3.1.1; Studied period, June 2005 to March 2006)

A double-blind, dose-escalation, four-treatment, four-period crossover study (with treatment periods separated by a 12-day washout period) was conducted in 16 Japanese healthy adult male subjects to evaluate the safety, tolerability, and pharmacokinetics of eltrombopag. Subjects received a single oral dose of eltrombopag at escalating doses of 30, 50, 75, and 100 mg, or placebo in the fasted state (fasted from 12 hours pre-dose to 4 hours post-dose) in each period. One subject discontinued the study due to adverse events.

The incidence of adverse events was 8.33% (1 of 12 subjects) in the 30 mg-dosing period, 8.33% (1 of 12 subjects) in the 50 mg-dosing period, 16.67% (2 of 12 subjects) in the 75 mg-dosing period, and 12.5% (2 of 16 subjects) in the placebo-dosing period. They included pyrexia (1 subject in the 30 mg-dosing period), total bile acids increased (1 subject in the 50 mg-dosing period, 1 subject in the 75 mg-dosing period), bilirubin total increased (1 subject in the 75 mg-dosing period), ALT increased, and acute pharyngitis (1 subject each in the placebo-dosing period). No clinically significant abnormalities in vital signs or electrocardiogram (ECG) were observed.

4.(iii).A.(1).2) Japanese single and multiple dose study (Japanese Study TRA105580, Attached document5.3.3.1.2; Studied period, June to September 2006)

A single-blind, parallel-group study was conducted in 42 Japanese healthy adult male subjects to evaluate the safety, tolerability, and pharmacokinetics of single and multiple oral doses of eltrombopag. Subjects received a single oral dose of eltrombopag (25, 50, or 75 mg), or placebo in the fasted state (fasted from 10 hours before dosing to 4 hours after administration), followed by a 5-day washout period, and then received the same investigational drug once daily in the fasted state for 10 days. Of 42 subjects (12 subjects in the placebo group, 10 subjects in the 25 mg group, 10 subjects in the 50 mg group, 10 subjects in the 75 mg group) receiving the investigational drug, 1 subject in the 50 mg group discontinued the study due to personal reasons (withdrawn 72 hours after administration of a single dose).

The incidence of adverse events was 10% (1 of 10 subjects) in the 25 mg group, 30% (3 of 10 subjects) in the 50 mg group, and 20% (2 of 10 subjects) in the 75 mg group. They included amylase increased (1 subject in the 25 mg group), creatine kinase increased (1 subject in the 50 mg, 1 subject in the 75 mg groups), urticaria and white blood cell count decreased (1 subject each in the 50 mg group), and eosinophil percentage increased (1 subject in the 75 mg group). No clinically significant abnormalities in vital signs or ECG were observed.

4.(iii).A.(1).3) Foreign single dose study (Foreign Study SB-497115/005, Attached document5.3.1.1.1; Studied period, [redacted] to [redacted] 20[redacted])
An open-label, three-period crossover study (with treatment periods separated by a ≥5-day washout period) was conducted in 18 foreign healthy adult subjects in the UK to evaluate relative bioavailability of eltrombopag 25 mg capsules or 25 mg tablets as well as the pharmacokinetics of eltrombopag 25 mg tablets in the fasted and fed states. In each period, subjects were assigned to any of 3 regimens to receive a single oral dose of eltrombopag 50 mg (Regimen A, two 25 mg capsules administered in the fasted state; Regimen B, two 25 mg tablets administered in the fasted state; Regimen C, two 25 mg tablets administered after a meal). Of subjects assigned to Regimen A in Period 1, 2 subjects discontinued the study due to abnormal findings in Holter ECG during Period 1. Accordingly, 18 subjects received the investigational drug under Regimen A, but 16 subjects each received it under Regimen B and Regimen C.

The incidence of adverse events was 11.1% (2 of 18 subjects) under Regimen A, 31.3% (5 of 16 subjects) under Regimen B, and 18.8% (3 of 16 subjects) under Regimen C. The most commonly reported adverse event was upper abdominal pain (1 subject under Regimen B, 1 subject under Regimen C). Except for electrocardiogram abnormal findings under Regimen A in 2 subjects, no clinically significant abnormalities in laboratory values, vital signs, or ECG were observed.

4.(iii).A.(1).4) Foreign single dose study (Foreign Study TRA104631, Attached document5.3.1.1.2, 5.3.3.4.3; Studied period, August to October 2005)
An open-label, five-period crossover study (with treatment periods separated by a 7- to 14-day washout period) was conducted in 26 foreign healthy adult subjects in the US to evaluate effects of food and antacids on the pharmacokinetics of eltrombopag. In each period, subjects were assigned to any of 5 regimens to receive a single oral dose of eltrombopag 75 mg (Regimen A, administration in the fasted state; Regimen B, administration after low-fat diet [low-calcium without dairy products]; Regimen C, coadministration with cation-containing antacids in the fasted state; Regimen D, administration after high-fat diet [low-calcium without dairy products]; Regimen E, administration 1 hour before high-fat diet [low-calcium without dairy products]). A total of 3 subjects discontinued the study due to a request from the subject, protocol deviation, and creatine kinase increased for each.

The incidence of adverse events was 38% (9 of 24 subjects) under Regimen A, 25% (6 of 24 subjects) under Regimen B, 32% (8 of 25 subjects) under Regimen C, 24% (6 of 25 subjects) under Regimen D, and 31% (8 of 26 subjects) under Regimen E. Adverse events reported by ≥2 subjects in any regimens included headache (7 subjects under Regimen A, 3 subjects under Regimen B, 3 subjects under Regimen C, 3 subjects under Regimen D, 4 subjects under Regimen E), nausea (0 subjects, 1 subject, 2 subjects, 1 subject, 0 subjects), and dizziness (0 subjects, 0 subjects, 2 subjects, 1 subject, 0 subjects). No clinically significant abnormalities were observed in laboratory values, vital signs, or ECG.

4.(iii).A.(1).5) Foreign single and multiple dose study (Foreign Study SB-497115/002, Attached document5.3.3.1.3, 5.3.3.4.1; Studied period, [redacted] 20[redacted] to [redacted] 20[redacted])
A single-blind, parallel-group, dose-escalation study (Part 1) and an open-label study (Part 2) were conducted in the UK to evaluate the safety, tolerability, and pharmacokinetics of single and multiple oral doses of eltrombopag. In Part 1, 73 foreign healthy adult subjects orally received a single dose of eltrombopag at 5, 10, 20, 30, 50, or 75 mg, or placebo, followed by a 7 day washout period, and then orally received the same investigational drug once daily for 10 days. In Part 2, 24 foreign healthy adult subjects orally received a single dose of midazolam 5 mg on Days 1 and 8, single doses of caffeine 100 mg, omeprazole 20 mg, and flurbiprofen 50 mg on Days 2 and 9, and multiple doses of eltrombopag 75 mg once daily for 7 days from Day 3 to Day 9. In Part 1, 73 subjects received the investigational drug (18 subjects in the placebo group, 9 subjects in the 5 mg group, 9 subjects in the 10 mg group, 9 subjects in the 20 mg group, 9 subjects in the 30 mg

group, 10 subjects in the 50 mg group, 9 subjects in the 75 mg group), and in Part 2, 24 subjects in the 75 mg group received the investigational drug. Four subjects in Part 1 discontinued the study.

The incidence of adverse events in Part 1 was 55.6% (10 of 18 subjects) in the placebo group, 44.4% (4 of 9 subjects) in the 5 mg group, 77.8% (7 of 9 subjects) in the 10 mg group, 88.9% (8 of 9 subjects) in the 20 mg group, 77.8% (7 of 9 subjects) in the 30 mg group, 40.0% (4 of 10 subjects) in the 50 mg group, and 77.8% (7 of 9 subjects) in the 75 mg group, while that in Part 2 was 45.8% (11 of 24 subjects) in the 75 mg group. The most commonly reported adverse event in Part 1 and Part 2 was both headache (Part 1, 2 subjects in the placebo group, 2 subjects in the 5 mg group, 3 subjects in the 10 mg group, 3 subjects in the 20 mg group, 1 subject in the 30 mg group, 1 subject in the 50 mg group, 2 subjects in the 75 mg group; Part 2, 4 subjects in the 75 mg group). No clinically significant abnormalities in laboratory values, vital signs, or ECG were observed.

4.(iii).A.(1).6) Foreign multiple dose study (Foreign Study TRA102860, Attached document5.3.3.1.4, 5.3.4.1.1: Studied period; Part 1, March to August 2006; Part 2, March to August 2007)

A double-blind, parallel-group, dose-escalation study (Part 1) and a double-blind, four-period crossover study (Part 2, with treatment periods separated by a ≥14-day washout period) were conducted in the US to evaluate the safety, pharmacokinetics, and effects on myocardial repolarization of multiple oral doses of eltrombopag. In Part 1, 33 foreign healthy adult subjects orally received eltrombopag 100, 150, or 200 mg, or placebo once daily for 5 days. In Part 2, 87 foreign healthy adult subjects orally received eltrombopag 50 or 150 mg, or placebo once daily in a crossover manner for 5 days, during which on Day 5, subjects who had orally received eltrombopag 50 or 150 mg for 5 days received a single oral dose of placebo, and subjects who had orally received placebo for 5 days received a single oral dose of moxifloxacin 400 mg or placebo on Day 5. In Part 1 of this study, 33 subjects received the investigational drug, which included 6 subjects in the placebo group, 10 subjects in the 100 mg group, 9 subjects in the 150 mg group, and 8 subjects in the 200 mg. In Part 1 and Part 2, 4 subjects and 39 subjects, respectively, discontinued the study due to adverse events (2 subjects in Part 1, 6 subjects in Part 2).

The incidence of adverse events in Part 1 was 50% (3 of 6 subjects) in the placebo group, 70% (7 of 10 subjects) in the 100 mg group, 89% (8 of 9 subjects) in the 150 mg group, and 75% (6 of 8 subjects) in the 200 mg group, and that in Part 2 was 58% (37 of 64 subjects) in the placebo-dosing period, 66% (41 of 62 subjects) in the 50 mg-dosing period, 58% (45 of 77 subjects) in the 150 mg-dosing period, and 52% (33 of 63 subjects) in the moxifloxacin-dosing period. Adverse events reported by ≥3 subjects in any group in Part 1 included vessel puncture site haemorrhage (3 subjects in the placebo group, 1 subject in the 100 mg group, 1 subject in the 150 mg group, and0 subjects in the 200 mg group; the numbers of subjects experiencing each event are described in the same order for treatment groups), headache (2, 1, 2 , 4), dermatitis contact (0, 1, 4, 1), and vessel puncture site haematoma (0, 0, 3, 0). Adverse events reported by ≥3 subjects in any dosing-period in Part 2 included ecchymosis (8 subjects in the placebo-dosing period, 10 subjects in the 50 mg-dosing period, 9 subjects in the 150 mg-dosing period, 5 subjects in the moxifloxacin-dosing period), headache (7, 7, 10, 8), application site dermatitis (6, 9, 11, 9), contusion (6, 2, 4, 1), vessel puncture site haemorrhage (4, 4, 4, 4), excoriation (3, 4, 1, 2), blood creatine phosphokinase increased (3, 1, 4, 4), diarrhea (1, 2, 4, 0), nausea (1, 2, 3, 4), haematuria (1, 0, 3, 0), atrioventricular block second degree (0, 4, 1, 2), dermatitis (0, 3, 0, 0), dizziness (0, 2, 1, 5), abdominal pain (0, 1, 4, 1).

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

4.(iii).A.(2).1) Foreign phase II study (Foreign Study TRA100773A, Attached document5.3.5.1.3; Studied period, February 2005 to August 2006, Reference data)

A double-blind, parallel-group comparative study was conducted at a total of 44 institutions in 14 countries including the US to evaluate the efficacy, safety, and pharmacokinetics of eltrombopag in adult patients with chronic ITP (target sample size, 68 patients/group; 272 patients in total). In this study, patients were stratified by the use of ITP-therapeutic drugs at baseline, splenectomy status, and platelet count at baseline (≤15,000/μL or >15,000/μL) and assigned to each dose group accordingly.

Eltrombopag 30, 50, or 75 mg, or placebo was to be orally administered once daily (medication takenbefore breakfast or by avoiding 2 hours before and after administration) for 6 weeks, and administration of the investigational drug was to be discontinued when the platelet count was found at >200,000/μL.

The main inclusion criteria were patients who did not respond to treatment for ITP or experienced recurrence within 3 months after the last treatment session, and had a platelet count of <30,000/μL on Day 1 of the study (or within 24 hours before the first dose).

In this study, 2 interim analyses were planned to determine whether to terminate the study early based on the superiority of eltrombopag to placebo or the lack of the efficacy of eltrombopag. The first interim analysis performed on data from 104 subjects available as of September 2, 2005 showed the superiority of eltrombopag 50 and 75 mg to the placebo in terms of the primary endpoint (both $P < 0.001$, logistic regression analysis using stratification factors at the assignment as mediators, one-sided significance level of 0.0113 based on Pocock Alpha Spending Function, closed testing procedure), and thus the early termination of this study was determined. Hereinafter, results from the final analysis performed on the data from a total of 118 subjects, which were obtained until database lock after determination of early termination of this study are described.

Of 118 randomized subjects (29 subjects in the placebo group, 30 subjects in the 30 mg group, 30 subjects in the 50 mg group, 29 subjects in the 75 mg group), 117 subjects (29, 30, 30, 28) received the investigational drug, and all of the subjects were included in the safety analysis population. Of these, 109 subjects (27, 29, 27, 26) with a baseline platelet count of <30,000/μL were included in the primary efficacy analysis population. A total of 43 subjects (7, 7, 13, 16) discontinued the study mainly due to a platelet count of >200,000/μL (28 subjects in total; 1, 4, 11, 12), adverse events (6 subjects in total; 3, 0, 2, 1), insufficient response (3 subjects in total; 0, 2, 0, 1), other reasons (3 subjects in total; 1, 1, 0, 1), request from the subjects (2 subjects in total; 2, 0, 0, 0), and protocol violation (1 subject in total; 0, 0, 0, 1).

At baseline, 32% of the subjects (38 of 117 subjects) received ITP-therapeutic drugs concomitantly; 47% (55 of 117 subjects) were splenectomized; and 48% (56 of 117 subjects) had a platelet count of ≤15,000/μL.

The primary efficacy endpoint was set as the percentage of subjects who achieved a platelet count of ≥50,000/μL on Week 6 after treatment (response rate). As a result, the response rate was 11.1% (3 of 27 subjects) in the placebo group, 27.6% (8 of 29 subjects) in the 30 mg group, 70.4% (19 of 27 subjects) in the 50 mg group, and 80.8% (21 of 26 subjects) in the 75 mg group. Logistic regression analysis was performed using stratification factors at the assignment as mediators to compare the response rate between eltrombopag and placebo. As a result, significant differences were found between the eltrombopag 75 mg and the placebo group and between the eltrombopag 50 mg and the placebo group, but not between the eltrombopag 30 mg and the placebo group ($P < 0.001$, $P < 0.001$, $P = 0.070$, respectively; one-sided significance level of 0.0113, closed testing procedure).

Concerning the incidence and severity of bleeding, the secondary endpoints, the percentage of the subjects who had "any bleeding (WHO Grade 1-4)" at baseline was 55.6% (15 of 27 subjects) in the placebo group, 65.5% (19 of 29 subjects) in the 30 mg group, 63.0% (17 of 27 subjects) in the 50 mg group, and 72.0% (18 of 25 subjects) in the 75 mg group, while that on Weeks 1 to 6 after treatment was 50.0% to 59.3% in the placebo group, 35.7% to 42.9% in the 30 mg group, 11.8% to 48.1% in the 50 mg group, and 25.0% to 61.5% in the 75 mg group.

For the safety, the incidence of adverse events during the treatment period was 59% (17 of 29 subjects) in the placebo group, 47% (14 of 30 subjects) in the 30 mg group, 47% (14 of 30 subjects) in the 50 mg group, and 61% (17 of 28 subjects) in the 75 mg group. Adverse events occurring in ≥5% of subjects in any group are as shown in Table 8.

Table 8. Adverse events occurring in ≥5% of subjects in any group (Adapted from application data)

	Placebo group N = 29	Eltrombopag 30 mg group N = 30	Eltrombopag 50 mg group N = 30	Eltrombopag 75 mg group N = 28
Number of subjects with adverse event	17 (59)	14 (47)	14 (47)	17 (61)
Headache	6 (21)	4 (13)	3 (10)	6 (21)
Fatigue	5 (17)	0	1 (3)	2 (7)
Constipation	2 (7)	1 (3)	0	2 (7)
Rash	1 (3)	1 (3)	0	2 (7)
AST increased	0	1 (3)	0	2 (7)
Anaemia	2 (7)	1 (3)	1 (3)	1 (4)
Oedema peripheral	2 (7)	0	1 (3)	1 (4)
Diarrhoea	2 (7)	0	0	1 (4)
Dysgeusia	2 (7)	0	0	1 (4)
Epistaxis	0	4 (13)	0	0
Pain in extremity	1 (3)	2 (7)	0	0
Arthralgia	3 (10)	1 (3)	0	0
Abdominal distension	2 (7)	1 (3)	0	0
Haemorrhoids	2 (7)	0	0	0

n (%)

Serious adverse events during the treatment period were found in 2 subjects in the placebo group (hepatitis toxic, varicose vein ruptured) and 2 subjects in the eltrombopag 50 mg group (herpes zoster, embolism/hepatitis/renal failure/pulmonary embolism). One death was reported in the eltrombopag 50 mg group, in whom hepatitis, renal failure, embolism, pulmonary embolism, and cardiopulmonary failure were observed. Anatomicopathological findings in this subject indicated that respiratory disorder which is possibly lead to cardiac failure, direct death cause, was associated with a history of pneumonectomy for lung cancer and acute exacerbation of chronic obstructive pulmonary disease (COPD), and the pulmonary embolism was considered to be the secondary change of COPD and thus causally unrelated to eltrombopag.

Neither hematological nor clinical chemistry findings showed any clear significant problematic trend due to eltrombopag.

As described above, the efficacy and safety of eltrombopag were comparable between 50 mg and 75 mg, and the number of subjects with a platelet count of >200,000/μL in these dose groups was small. In the subsequent foreign clinical studies in patients with chronic ITP, the starting dose of eltrombopag was thus set at 50 mg.

4.(iii).A.(2).2) Foreign phase II study (Foreign Study TRA108057/REPEAT, Attached document5.3.5.2.1; Studied period, March 2007 to June 2008, Reference data)
An open-label, noncontrolled study in adult patients with chronic ITP was conducted at a total of 25 institutions in 9 countries including the US to evaluate the efficacy and safety of 3 treatment cycles of eltrombopag 50 mg, each of which consisted of the once-daily multiple oral dose (treatment period) and off-therapy (rest period) (target sample size, 50 patients).

The main inclusion criteria were adult patients with chronic ITP who had a platelet count of ≥20,000/μL and ≤50,000/μL and had a history of at least 1 therapy for ITP.

A total of 66 subjects were enrolled in this study and received eltrombopag, and all of them were included in the safety analysis population. The subjects who received eltrombopag and responded to eltrombopag in Cycle 1 were included in the primary efficacy analysis population. A total of 18 subjects were withdrawn from the treatment mainly due to non-response to eltrombopag in Cycle 1 (9 subjects), elevated platelet count >50,000/μL that was prolonged until the start of the subsequent treatment cycle after the rest period (2 subjects), insufficient response (2 subjects), request from the subject (2 subjects), moving (1 subject), adverse event (1 subject), and discretion of the attending physician (1 subject).

The durations of the treatment and rest periods were determined based on the individual platelet count. In this study, the treatment period was up to 6 weeks, and when the platelet count exceeded 200,000/μL or the treatment period reached 6 weeks, the treatment was interrupted for a rest period. In addition, the rest period was up to 4 weeks, and when the platelet count decreased to <20,000/μL or the rest period reached 4 weeks with the platelet count <50,000/μL, the subsequent treatment cycle was started.

For the efficacy, a responder was defined as "a subject with platelet count ≥50,000/μL and ≥2 times the baseline platelet count," and in the cases where the study treatment was early discontinued due to the platelet count >200,000/μL, the platelet count at the study discontinuation was used for evaluation. The primary endpoint was the percentage of the subjects responded to eltrombopag in Cycle 2 or 3 with respect to responders in Cycle 1 (consistent response [persistence of effectiveness]). In both Cycles 2 and 3, the study treatment was started at the same dose as that in the end of the previous cycle, and then the dose was increased to 75 mg when the platelet count was <50,000/μL on Week 3 and thereafter.

For the consistent response (persistence of effectiveness), of 65 subjects included in the evaluation in Cycle 1, 52 subjects (80%) were assessed as responders, and of these 52 responders in Cycle 1, 45 subjects (87%) responded to the study treatment in Cycle 2 or 3 (95% CI, 74%-94%). Of 52 responders in Cycle 1, 48 subjects (92%) were included in the evaluations of both Cycles 2 and 3, and of these 48 subjects, 34 (71%) were assessed as responders in all of 3 cycles (95% CI, 56%-83%). The platelet counts over time in each cycle are shown in Figure 3.

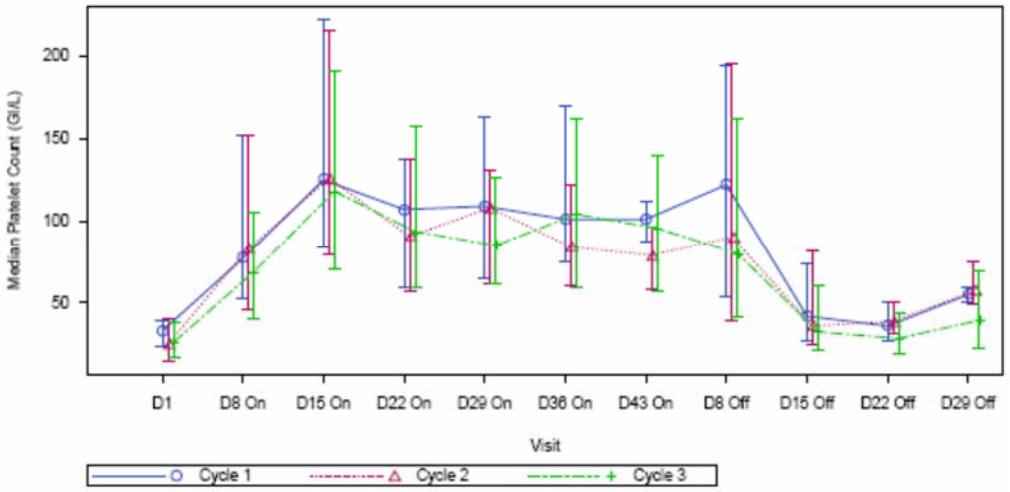


Figure 3. Median platelet counts over time (ITT population)
(Adapted from application data)

For the inhibitory effect on bleeding, the percentages of the subjects with "any bleeding (WHO Grade 1-4)" and those with "clinically significant bleeding (WHO Grade 2-4)" decreased from those at baseline in all of the treatment cycles. During the rest period, the percentages of the subjects with "any bleeding (WHO Grade 1-4)" and those with "clinically significant bleeding (WHO Grade 2-4)" tended to increase following the discontinuation of eltrombopag treatment in all of the treatment cycles. No WHO Grade 3 or 4 bleeding events occurred during the study period.

For the safety, the incidence of adverse events was 68% (45 of 66 subjects) during the treatment period and 63% (41 of 65 subjects) during the rest period. Adverse events reported by ≥5 subjects during either treatment or rest period included headache (14 subjects during the treatment period, 5 subjects during the rest period), diarrhoea (7, 4), fatigue (6, 6), nasopharyngitis (6, 6), and back pain (3, 5). Serious adverse events in this study were pneumonia during the treatment period reported by 1 subject and ear haemorrhage/epistaxis/mouth haemorrhage, pancreatic cancer, and abdominal pain upper during the rest period reported by 1 subject each, but all of them were associated as causally unrelated to the investigational drug. Death occurred in 1 subject with pancreatic cancer. No clinically significant abnormalities in hematological or clinical chemistry findings were observed.

From the baseline (Day 1 of each cycle) to the rest period, the platelet count decreased to <20,000/μL or to <10,000/μL in 44% of the subjects (29 of 66 subjects). During the rest period, the platelet count decreased to <20,000/μL and decreased from the baseline by ≥10,000/μL in 32% of the subjects (21 of 66 subjects), and it decreased to <10,000/μL at least once and from the baseline platelet count by ≥10,000/μL in 12% (8 of 66 subjects).

Neither particular adverse events with increased incidence or severity, nor increased anti-platelet antibody titer occurred throughout the repeated treatment cycles.

4.(iii).A.(3) Phase II/III studies

4.(iii).A.(3).1) Japanese phase II/III study (Japanese Study TRA108109, Attached document5.3.5.1.1, 5.3.3.2.1; Studied period, September 2007 to December 2008)

A clinical study consisting of the double-blind and open-label periods was conducted in adult patients with chronic ITP at 7 institutions in Japan to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of eltrombopag. During the double-blind period,

eltrombopag 12.5, 25 mg, or placebo was orally administered once daily in the fasted state (meals prohibited within 2 hours before and after administration) for 7 weeks. During the open-label period, eltrombopag 12.5, 25, or 50 mg was orally administered once daily in the fasted state for 19 weeks to patients who received eltrombopag during the double-blind period, and eltrombopag 12.5, 25, or 50 mg was orally administered once daily in the fasted state for 26 weeks to patients who received placebo during the double-blind period (target sample size for the double-blind period, 12 patients in the eltrombopag groups, 8 patients in the placebo group; target sample size for the open-label period, up to 20 patients).

The main inclusion criteria were adult patients with chronic ITP who were diagnosed ITP ≥6 months before the inclusion, had a platelet count <30,000/μL, and did not respond to the treatment.

All of the 23 patients who were enrolled in the double-blind period and received the investigational drug (15 patients in the eltrombopag groups, 8 patients in the placebo group) were included in the safety and efficacy analysis populations. During the double-blind period, 1 patient in the eltrombopag group discontinued the study due to adverse events, and the remaining 22 patients entered the study in the open-label period. Except for 2 patients withdrawn from the study due to insufficient response during the open-label period, the remaining 20 patients completed the study.

The median age of the subjects enrolled in this study was 58.0 years in the eltrombopag groups and 60.5 years in the placebo group, and the female subjects accounted for 53% (8 of 15 subjects) in the eltrombopag groups and 88% (7 of 8 subjects) in the placebo group. At baseline, the percentage of the subjects concomitantly receiving ITP-therapeutic drugs was 80% (12 of 15 subjects) in the eltrombopag groups and 88% (7 of 8 subjects) in the placebo group. The percentage of the "splenectomized" subjects was 73% (11 of 15 subjects) in the eltrombopag groups and 63% (5 of 8 subjects) in the placebo group. The percentage of the subjects with baseline platelet count >15,000/μL was 80% (12 of 15 subjects) in the eltrombopag groups and 25% (2 of 8 subjects) in the placebo group. The most frequently used previous ITP-therapeutic drug (ITP-therapeutic drugs discontinued before the start of study treatment) was corticosteroids in both eltrombopag and placebo groups, and 33% (5 of 15 subjects) in the eltrombopag groups and 25% (2 of 8 subjects) in the placebo group had used corticosteroids.

This study consisted of the double-blind and open-label periods. During the double-blind period, eltrombopag 12.5 mg or placebo was administered for 3 weeks, and then the dose was adjusted in accordance with the "criteria for dose adjustment (double-blind period)" as shown in Table 9 to continue the treatment with the investigational drug at the adjusted doses (eltrombopag or placebo) for 4 weeks. During the open-label period, the dose of eltrombopag was further adjusted in accordance with the "criteria for dose adjustment (open-label period for the eltrombopag groups)" as shown in Table 10 to continue the treatment with eltrombopag at the adjusted doses for 19 weeks, or it was further adjusted in accordance with the "criteria for dose adjustment (open-label period for the placebo group)" as shown in Table 11 to continue the treatment with placebo at the adjusted doses for 26 weeks.

Table 9. Criteria for dose adjustment (double-blind period) (Adapted from the submitted data)

Treatment group	Week 0	Week 3	
		Criteria (platelet count)	Daily dose after adjustment
Eltrombopag	Eltrombopag 12.5 mg tablet (starting drug, 1 tablet)	<100,000/μL	Increased to 25 mg
		≥100,000 and ≤400,000/μL	Maintain 12.5 mg
		>400,000/μL	Treatment discontinued
Placebo	Eltrombopag 12.5 mg placebo tablet (starting drug, 1 tablet)	<100,000/μL	Placebo tablet × 2
		≥100,000 and ≤400,000/μL	Placebo tablet × 1
		>400,000/μL	Treatment discontinued

Table 10. Criteria for dose adjustment (open-label period) (for the subjects receiving eltrombopag during the double-blind period) (Adapted from application data)

Week 7 (and thereafter)*		Daily dose after adjustment
Criteria (platelet count)	Daily dose	
<50,000/μL	12.5 mg	Increased to 25 mg
	25 mg	Increased to 50 mg
	50 mg	Maintained at 50 mg
≥50,000 and ≤200,000/μL	12.5 mg	Maintained at 12.5 mg
	25 mg	Maintained at 25 mg
	50 mg	Maintained at 50 mg
>200,000 and ≤400,000/μL	12.5 mg	Interrupt until the platelet count is decreased to ≤150,000/μL Then resume at 12.5 mg
	25 mg	Reduced to 12.5 mg
	50 mg	Reduced to 25 mg
>400,000/μL Treatment interrupt for at least 7 days and until the platelet count is decreased to ≤150,000/μL	12.5 mg	After the rest period, resumed at 12.5 mg
	25 mg	After the rest period, resumed at the reduced dose of 12.5 mg
	50 mg	After the rest period, resumed at the reduced dose of 25 mg

*At Week 7 and thereafter, the platelet count was measured every 4 weeks (every 2 weeks where necessary) unless any dose of eltrombopag or the other ITP-therapeutic drug was changed within 4 weeks or every week if the dose was changed, and then every 4 weeks (every 2 weeks where necessary) if the dose was not changed during the 4-week period after the previous dose change in order to adjust the dose.

Table 11. Criteria for dose adjustment (open-label period) (for the subjects receiving placebo during the double-blind period) (Adapted from application data)

Week 7		Week 10		Week 13 (and thereafter)*		
Criteria (platelet count)	Daily dose after adjustment	Criteria (platelet count)	Daily dose after adjustment	Criteria (platelet count)	Daily dose	Daily dose after adjustment
<50,000/μL	12.5 mg	<50,000/μL	25 mg	<50,000/μL	12.5 mg	Increased to 25 mg
					25 mg	Increased to 50 mg
					50 mg	Maintain 50 mg
≥50,000/μL	Treatment discontinued	≥50,000 and ≤400,000/μL	12.5 mg	≥50,000 and ≤200,000/μL	12.5 mg	Maintained at 12.5 mg
					25 mg	Maintained at 25 mg
					50 mg	Maintained at 50 mg
				>200,000 and ≤400,000/μL	12.5 mg	Treatment interrupted until the platelet count is decreased to ≤150,000/μL Then resumed at 12.5 mg
					25 mg	Reduced to 12.5 mg
					50 mg	Reduced to 25 mg
		>400,000/μL	Treatment discontinued	>400,000/μL Treatment interrupted for at least 7 days and until the platelet count is decreased to ≤150,000/μL	12.5 mg	After the rest period, resumed at 12.5 mg
					25 mg	After the rest period, resumed at the reduced dose of 12.5 mg
					50 mg	After the rest period, resumed at the reduced dose of 25 mg

*On Week 13 and thereafter, the platelet count was measured every 4 weeks (every 2 weeks where necessary) unless any dose of eltrombopag or the other ITP-therapeutic drug was changed within 4 weeks or every week if the dose was changed, and then every 4 weeks (every 2 weeks where necessary) if the dose was not changed during the 4-week period after the previous dose change in order to adjust the dose.

The short-term and long-term efficacy was evaluated, and the median of the mean daily dose was 18.8 and 32.0 mg, respectively. As the objective of the long-term evaluation exercise was to evaluate the efficacy and safety of long-term treatment with eltrombopag, the data at Week 0 from the subjects who were assigned to the eltrombopag group in the double-blind period and those at Week 7 from the subjects who were assigned to the placebo group were specified as the baseline data.

The short-term evaluation for the efficacy showed that the percentage of the subjects with platelet count increased to ≥50,000/μL and ≤400,000/μL on Day 43 (response rate), the primary endpoint, was 60.0% (9 of 15 subjects) (95% CI, 32.29%-83.66%) in the eltrombopag group and 0% (0 of 8 subjects) (95% CI, 0.00%-36.94%) in the placebo group. The change of response rate, platelet count, and bleeding episodes were selected as the secondary endpoints. The response rate in the eltrombopag group was 26.7% on Day 15 during the treatment period at a dose of 12.5 mg and then increased to 33.3% on Day 22. After dose adjustment, it remained as high as 60.0% to 66.7% from Day 29 to Day 43. On the other hand, in the placebo group, no responders were observed throughout the 6-week treatment period. The median platelet count in the eltrombopag groups reached around 30,000/μL between Day 8 and Day 15 at a dose of 12.5 mg, and between Day 29 and Day 43 after dose adjustment, it remained above 50,000/μL. On the other hand, the median platelet count in the placebo group did not exceed 30,000/μL throughout the 6-week treatment period. Throughout the 6-week treatment period, the percentage of the subjects with "bleeding episodes" was 7% to 29% in the eltrombopag group, which was decreased from the baseline (33%) and remained lower than that in the placebo group (38%-75%).

In the long-term evaluation for the efficacy, the primary endpoint was defined as the case where responses as expected were observed at ≥75% of 6 evaluation time points at Week 6 and thereafter (Weeks 6, 10, 14, 18, 22, and 26). The percentage of the subjects achieving the primary endpoint (responders) was 43.5% (10 of 23 subjects) (95% CI, 23.19%-65.51%). The secondary endpoints included change of the response rate, platelet count, bleeding episodes, reduced dose or discontinuation of concomitant ITP-therapeutic drugs, percentage of subjects receiving rescue treatment (new ITP-therapeutic drugs, increased dose of concomitant ITP-therapeutic drugs from the baseline, platelet transfusion or splenectomy). The response rate was increased, to 17.4% on Day 15 and 21.7% on Day 22 during the 12.5 mg treatment period, and remained between 47.8% and 69.6% from Day 29 to Week 26. The response rate at Week 1 after the completion of treatment was 39.1% and decreased to around the baseline (4.3%) at Week 2 after the completion of treatment. The platelet counts over time during treatment with eltrombopag in the long-term evaluation are shown in Figure 4.

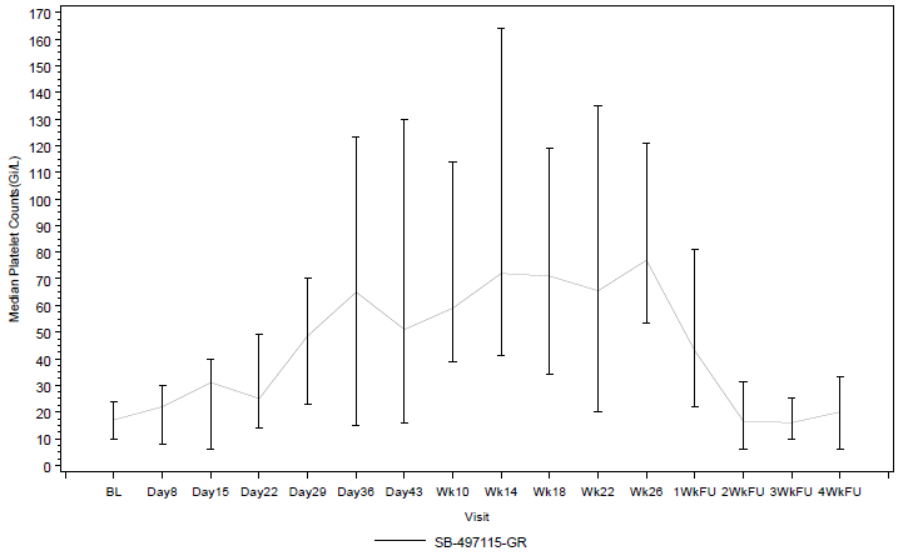


Figure 4. Platelet counts over time (long-term evaluation, Observed data) (Adapted from the submitted data)

The percentage of the subjects with "bleeding episodes" remained lower than the baseline (48%) throughout the 26-week treatment period. After the completion of treatment, the percentage of the subjects with "bleeding episodes" increased. The percentage was 18% at Week 1 after the completion of treatment and remained between 57% and 65% from Week 2 to Week 4 after the completion of treatment. The percentage of the subjects in whom dose-reduction or discontinuation of concomitant ITP-therapeutic drugs at baseline was performed during the 26-week treatment period was 36.8% (7 of 19 subjects), and the relevant drugs were all corticosteroids. None of the subjects discontinued the concomitant ITP-therapeutic drugs. Two subjects (9%) received rescue treatment during the 26-week treatment period due to the platelet count decreased after dose reduction of eltrombopag or concomitant ITP-therapeutic drugs (corticosteroids).

For the safety, the incidence of adverse events during the 6-week treatment period (short-term evaluation) was 73% (11 of 15 subjects) in the eltrombopag group and 25% (2 of 8 subjects) in the placebo group. They included nasopharyngitis (4 subjects in the eltrombopag group), ALT increased (3 subjects in the eltrombopag group), headache (1 subject in the eltrombopag group, 1 subject in the placebo group), gastroenteritis, pharyngitis, AST increased, blood ALP increased, blood creatine phosphokinase decreased, transient ischaemic attack, palpitations, nausea, fatigue,

hypermagnesaemia, hypophosphataemia, back pain, musculoskeletal pain, cystitis-like symptom, dysmenorrhoea (1 subject each in the eltrombopag group), and cataract (1 subject in the placebo group). All of them were mild or moderate in severity.

The incidence of adverse events during the 26-week eltrombopag treatment period and follow-up period (long-term evaluation) was 96% (22 of 23 subjects). They included nasopharyngitis (10 subjects), ALT increased (4 subjects), nausea, AST increased, headache, conjunctival haemorrhage (3 subjects each), cystitis, gastroenteritis, herpes simplex, rhinitis, platelet count increased, back pain, myalgia, fatigue, limb injury, oropharyngeal pain, haemorrhagic diathesis, and hypokalaemia (2 subjects each). Except for thrombocytopenia which occurred in 1 subject during the follow-up period and was severe, all of the adverse events were mild or moderate.

No deaths occurred. Serious adverse events were reported by 6 subjects in the eltrombopag group, including transient ischaemic attack in 1 subject during the 6-week treatment period as well as haemorrhagic diathesis in 2 subjects, thrombocytopenia, prostate cancer, and renal impairment in 1 subject each after the above treatment period. Except for transient ischaemic attack, all events were assessed as unrelated to the investigational drug. Except for transient ischaemic attack and adverse events that occurred during the follow-up period, there were no adverse events leading to investigational drug discontinuation. Of serious adverse events, all events resolved except for prostate cancer.

4.(iii).A.(4) Phase III study

4.(iii).A.(4).1) Japanese phase III study (Japanese Study TRA111433, Attached document5.3.5.2.3; Studied period, [redacted] 20[redacted] to ongoing; Date of data cut-off, [redacted] [redacted] 20[redacted])

An open-label, uncontrolled study was conducted at 6 institutions in Japan to evaluate the safety and efficacy of long-term treatment with eltrombopag in subjects who was enrolled in Japanese Study TRA108109 (target sample size, 22 subjects).

The starting dose was the final dose in the Japanese Study TRA108109 (12.5 mg for 6 subjects, 25 mg for 3 subjects, 50 mg for 10 subjects), and the dose was to be adjusted in accordance with the criteria for dose adjustment in Table 12.

Table 12. Criteria for dose adjustment (Adapted from the submitted data)

Criteria (platelet count)	Daily dose	Daily dose after adjustment
<50,000/μL	12.5 mg	Increased to 25 mg
	25 mg	Increased to 37.5 mg
	37.5 mg	Increased to 50 mg
	50 mg	Maintained at 50 mg
≥50,000 and ≤200,000/μL	12.5 mg	Maintained at 12.5 mg
	25 mg	Maintained at 25 mg
	37.5 mg	Maintained at 37.5 mg
	50 mg	Maintained at 50 mg
>200,000 and ≤400,000/μL	12.5 mg	Reduced to 12.5 mg given every other day
	25 mg	Reduced to 12.5 mg
	37.5 mg	Reduced to 25 mg
	50 mg	Reduced to 37.5 mg
>400,000/μL Treatment interrupt for at least 7 days and until the platelet count is decreased to ≤150,000/μL	12.5 mg	After the rest period, resumed at the dose of 12.5 mg given every other day
	25 mg	After the rest period, resumed at the reduced dose of 12.5 mg
	37.5 mg	After the rest period, resumed at the reduced dose of 25 mg
	50 mg	After the rest period, resumed at the reduced dose of 37.5 mg

Dose was adjusted by measuring the platelet count every week (at Week 4 and thereafter, every 4 weeks or every 2 weeks as required if the dosage and administration of eltrombopag or other ITP-therapeutic drugs remained unchanged for 4 weeks).

Of 20 subjects who completed the preceding study, 19 entered this study. All of the 19 subjects received eltrombopag in this study and were included in the safety and efficacy analyses. As of the data cut-off time point ([redacted], 20[redacted]), the median treatment period of eltrombopag in this study was 335.0 days (range, 260-464 days). However, 1 subject was withdrawn from the study treatment on Day 336 due to insufficient response.

For the efficacy, the percentage of the subjects with platelet count ≥50,000/μL and ≤400,000/μL increased from 5.3% (1 of 19 subjects) at the baseline to 21% (4 of 19 subjects) at Week 1, and remained between 50% and 80% from Week 2 to Week 52 (Table 13).

Table 13. Subjects with platelet count ≥50,000 μL and ≤400,000 μL after administration of the investigational drug (FAS: Full Analysis Set) (Adapted from the submitted data)

Evaluation time point	N	n (%)	Evaluation time point	N	n (%)
Baseline	19	1 (5.3)			
Week 1	19	4 (21.1)	Week 32	16	11 (68.8)
Week 2	19	12 (63.2)	Week 36	18	12 (66.7)
Week 3	19	15 (78.9)	Week 40	15	6 (40.0)
Week 4	19	14 (73.7)	Week 44	13	6 (46.2)
Week 8	19	14 (73.7)	Week 48	9	8 (88.9)
Week 12	16	11 (68.8)	Week 52	8	5 (62.5)
Week 16	17	13 (76.5)	Week 56	5	2 (40.0)
Week 20	15	11 (73.3)	Week 60	3	1 (33.3)
Week 24	17	14 (82.4)	Week 64	1	1 (100)
Week 28	16	13 (81.3)	Final dose/discontinuation	19	12 (63.2)

N: FAS at each evaluation time point
n: Number of subjects with platelet count ≥50,000/μL and ≤400,000/μL

To control the platelet count, 3 subjects received the investigational drug at the dose of 12.5 mg every other day. Even in the subjects receiving eltrombopag at the dose of <12.5 mg/day or at alternate administration of different doses in response to the platelet count, the platelet count was almost maintained in a range from ≥50,000/μL to ≤400,000/μL after the dose adjustment.

The percentage of the subjects with bleeding episodes was 63% (12 of 19 subjects) at baseline and decreased after the start of treatment with the investigational drug. Of 15 subjects who concomitantly used ITP-therapeutic drugs at baseline, 10 (67%) decreased the dose at baseline of concomitant ITP-therapeutic drugs or discontinued them during treatment with the investigational drug. Of these, 9 subjects maintained to decrease or discontinue the dose for ≥24 weeks without any rescue treatment (new combination of ITP-therapeutic drugs, increased dose of concomitant ITP-therapeutic drugs from the baseline, platelet transfusion and splenectomy).

The incidence of adverse events was 100% (19 of 19 subjects), and the adverse events reported by ≥2 subjects included nasopharyngitis (9 subjects), bronchitis and headache (3 subjects each), cataract, diarrhoea, eczema, AST increased, compression fracture, myalgia, insomnia, and hypertension (2 subjects each). Of the adverse events "related to the investigational drug," the events reported by ≥2 subjects were only cataract. All of the adverse events were mild or moderate in severity, and no severe events were observed. No deaths occurred. Serious adverse events included cataract, Mallory-Weiss syndrome, menorrhagia, and osteonecrosis in 1 subject each. All of these serious adverse events were moderate and, except for cataract, assessed as "unrelated to the investigational drug." Except for osteonecrosis, all of them resolved during the study treatment.

4.(iii).A.(4).2) Foreign phase III study (Foreign Study TRA102537/RAISE, Attached document5.3.5.1.2; Studied period, November 2006 to July 2008)

A double-blind, parallel-group study was conducted in adult patients with chronic ITP at a total of 75 institutions in 23 countries including the US to evaluate the efficacy, safety, and tolerability of eltrombopag (target sample size; 126 subjects in the eltrombopag group, 63 subjects in the placebo group, 189 subjects in total). Eltrombopag 50 mg or placebo was orally administered once daily for 6 months (meals prohibited within 2 hours before and after administration). In this study, subjects were stratified by use of ITP-therapeutic drugs at the baseline, splenectomy status, and platelet count at baseline (≤15,000/μL or >15,000/μL) and then randomized to the eltrombopag or placebo group at the ratio of 2:1.

The main inclusion criteria were patients with chronic ITP who had the platelet count <30,000/μL at baseline and a history of ≥1 type of ITP therapy.

A total of 197 subjects enrolled in this study (135 subjects in the eltrombopag group, 62 subjects in the placebo group) were included in the intention-to-treat (ITT) population, of whom, 196 subjects who received the investigational drug at least once (135 in the eltrombopag group, 61 in the placebo group) were included in the safety analysis population. A total of 30 subjects (23 in the eltrombopag group, 7 in the placebo group) were withdrawn from the study treatment mainly due to the occurrence of adverse events in 17 subjects (13, 4), request from the subjects in 6 subjects (4, 2), lost to follow-up in 3 subjects (3, 0), insufficient response, noncompliance with visit schedule in 1 subject each (1, 0), and other reasons in 2 subjects (1, 1).

The percentage of the subjects who concomitantly received ITP-therapeutic drugs at the baseline was 47% (63 of 135 subjects) in the eltrombopag group and 50% (31 of 62 subjects) in the placebo group; that of the splenectomized subjects was 37% (50 of 135 subjects) and 34% (21 of 62 subjects), respectively; and that of the subjects with baseline platelet count ≤15,000/μL was 50% (67 of 135 subjects) and 48% (30 of 62 subjects), respectively.

The starting dose of eltrombopag was 50 mg once daily (meals prohibited within 2 hours before and after administration), and then at Week 3 and thereafter, the dose was adjusted to 25, 50, or 75 mg according to the platelet count in each subject. In a case where the platelet count was <50,000/μL, the dose was increased (up to eltrombopag 75 mg or corresponding placebo); in a case where it was 50,000 to 200,000/μL, the dose was maintained; in a case where it was 200,000 to 400,000/μL, the dose was reduced; and in a case where it exceeded 400,000/μL, treatment was discontinued until it decreased to ≤150,000/μL. At Week 6 and thereafter during the study period, the dose reduction and withdrawal of the concomitant ITP-therapeutic drugs as well as emergency treatment were allowed.

For the efficacy, the number of the subjects with “the platelet count ≥50,000 and ≤400,000/μL” (number of responders) and the percentage (response rate) in the ITT population were changed over time as shown in Table 14. During the study period, 21% in the eltrombopag group and 72% in the placebo group were never assessed as responders (platelet count ≥50,000 and ≤400,000/μL).

Table 14. Response rate over time (primary data set, ITT population) (Adapted from the submitted data)

	Eltrombopag group (N = 135)		Placebo group (N = 62)	
	Number of subjects evaluated	Number of responders (response rate)	Number of subjects evaluated	Number of responders (response rate)
Baseline[a]	135	1[b] (1)	61	1[b] (2)
Day 8	134	50 (37)	60	4 (7)
Day 15	133	61 (46)	60	5 (8)
Day 22	133	68 (51)	59	5 (8)
Day 29	131	64 (49)	60	6 (10)
Day 36	134	75 (56)	60	5 (8)
Day 43	134	73 (54)	59	8 (14)
Week 10	108	56 (52)	47	8 (17)
Week 14	114	52 (46)	50	9 (18)
Week 18	112	52 (46)	48	8 (17)
Week 22	113	55 (49)	47	9 (19)
Week 26	132	68 (52)	58	10 (17)
Week 1 of the follow-up period	110	46 (42)	54	8 (15)
Week 2 of the follow-up period	118	26 (22)	55	10 (18)
Week 4 of the follow-up period	119	24 (20)	58	8 (14)

a. Baseline value in 1 subject in the placebo group is missing.
b. At baseline, subjects with platelet count ≥50,000/μL were found in 1 subject each in the eltrombopag and placebo groups.

The odds of the platelet count increasing effect (≥50,000 and ≤400,000/μL) during the 6-month treatment period in the ITT population, which was specified as the primary endpoint, was significantly higher in the eltrombopag group than that in the placebo group ($P < 0.001$, repeated measurement model on binary data [adjusted by stratification factors at assignment], two-sided significance level of 1%). The odds ratio of the eltrombopag group to the placebo group was 8.2 (99% CI, 3.59-18.73).

The percentage of the subjects who received rescue treatment (new ITP therapeutic drugs, increased dose of concomitant ITP-therapeutic drugs from the baseline, platelet transfusion or splenectomy) during the treatment period, which was specified as the secondary endpoint, was 18% (24 of 135 subjects) in the eltrombopag group and 40% (25 of 62 subjects) in the placebo group. The percentage of the subjects in whom responses as expected were determined in ≥75% of the treatment period of 6 months was 38% (51 of 135 subjects) in the eltrombopag group and 7% (4 of 62 subjects) in the placebo group.

In terms of the incidence of bleeding, the percentages of the subjects with “any bleeding (WHO Grade 1-4)” and those with “clinically significant bleeding (WHO Grade 2-4)” are as shown in Figures 5 and 6.

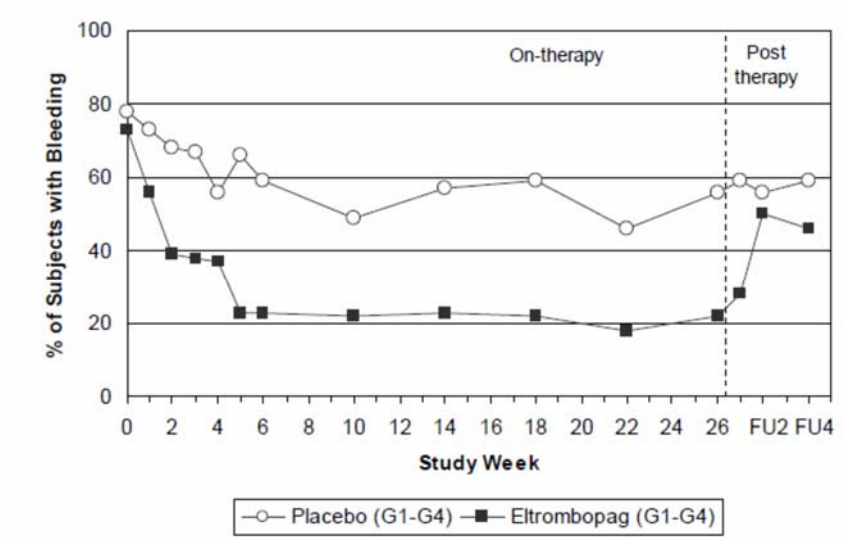


Figure 5. Percentage of the subjects with "any bleeding (WHO Grade 1-4)" over time (ITT population) (Adapted from the submitted data)

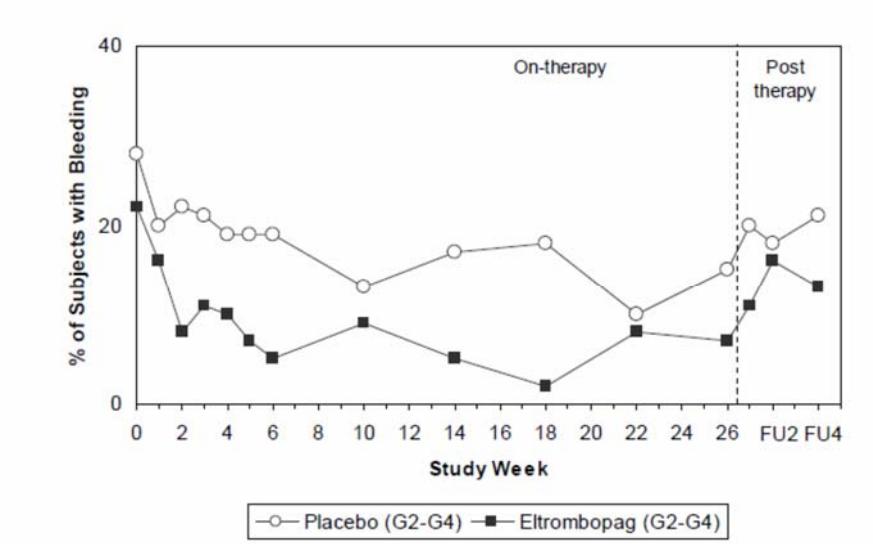


Figure 6. Percentage of the subjects with "clinically significant bleeding (WHO Grade 2-4)" over time (ITT population) (Adapted from the submitted data)

The percentage of the subjects who received ITP-therapeutic drugs at baseline was 47% (63 of 135 subjects) in the eltrombopag group and 50% (31 of 62 subjects) in the placebo group, but that of the subjects who the dose of the concomitant ITP-therapeutic drugs reduced or discontinued them was 59% (37 of 63 subjects) in the eltrombopag group and 32% (10 of 31 subjects) in the placebo group. Of the subjects who had the dose of the baseline concomitant ITP-therapeutic drugs reduced or discontinued them, 84% (31 of 37 subjects) in the eltrombopag group and 60% (6 of 10 subjects) in the placebo group needed no rescue treatment.

For the safety, the incidence of adverse events that occurred during the treatment period was 87% (118 of 135 subjects) in the eltrombopag group and 92% (56 of 61 subjects) in the placebo group. Adverse events occurring in ≥5% in either group are shown in Table 15.

Table 15. Adverse events occurring in ≥5% in either group (Adapted from the submitted data)

	Placebo group N = 61	Eltrombopag group N = 135
Number of subjects with any adverse event	56 (92)	118 (87)
Headache	20 (33)	41 (30)
Diarrhoea	6 (10)	17 (13)
Nausea	4 (7)	16 (12)
Nasopharyngitis	8 (13)	14 (10)
Upper respiratory tract infection	7 (11)	14 (10)
Fatigue	8 (13)	13 (10)
Pain in extremity	6 (10)	9 (7)
ALT increased	4 (7)	10 (7)
Vomiting	1 (2)	10 (7)
Urinary tract infection	4 (7)	9 (7)
Arthralgia	3 (5)	9 (7)
Oropharyngeal pain	3 (5)	9 (7)
Myalgia	2 (3)	8 (6)
Pharyngitis	1 (2)	8 (6)
AST increased	2 (3)	7 (5)
Epistaxis	6 (10)	7 (5)
Back pain	3 (5)	7 (5)
Influenza	3 (5)	7 (5)
Cough	4 (7)	6 (4)
Abdominal pain upper	5 (8)	6 (4)
Constipation	5 (8)	6 (4)
Dizziness	6 (10)	5 (4)
Pruritus	5 (8)	4 (3)
Cataract	4 (7)	4 (3)
Hypertension	3 (5)	4 (3)
Oedema peripheral	6 (10)	2 (1)
Dyspepsia	4 (7)	2 (1)
Ecchymosis	4 (7)	2 (1)
Insomnia	4 (7)	2 (1)
Anxiety	3 (5)	2 (1)
Conjunctival haemorrhage	3 (5)	2 (1)
Contusion	3 (5)	2 (1)
Neck pain	3 (5)	2 (1)
Non-cardiac chest pain	3 (5)	2 (1)
Abdominal distension	3 (5)	1 (<1)
Conjunctivitis	4 (7)	1 (<1)
Fall	3 (5)	1 (<1)
Swelling face	3 (5)	1 (<1)
Cellulitis	4 (7)	0
Eye swelling	3 (5)	0

n (%)

In the placebo group, 1 subject died of brain stem haemorrhage. In this subject, the platelet count was 2000/μL at baseline and 1000/μL at the occurrence of the serious adverse event. The concerned event was assessed as unrelated to the investigational drug.

Serious adverse events were reported by 15 (11%) subjects in the eltrombopag group and 11 (18%) subjects in the placebo group during the treatment period. They included headache (3 subjects in the eltrombopag group, 0 subjects in the placebo group), cataract (1, 2), ALT increased (1, 1), aortic aneurysm, rectosigmoid cancer, pulmonary embolism, pulmonary infarction, thrombophlebitis superficial, spinal compression fracture, loss of consciousness, duodenal ulcer haemorrhage, haemorrhagic anaemia, deep vein thrombosis, AST increased,

hypokalaemia, urinary tract infection, transaminases increased (1, 0), heart rate increased, menorrhagia, gastrointestinal haemorrhage, respiratory tract haemorrhage, retinal haemorrhage, haemorrhage urinary tract, orchitis, brain stem haemorrhage, urogenital haemorrhage, hand fracture, cataract subcapsular, renal function test abnormal, hyperkalaemia, and cellulitis (0, 1).

During the follow-up period, serious adverse events were reported by 6 subjects. They included peritoneal haemorrhage/acute myeloid leukaemia, and bronchitis in 1 subject each in the placebo group and chest pain, cerebral haemorrhage, pulmonary embolism/intra-abdominal haemorrhage, and cataract in 1 subject each in the eltrombopag group. Serious adverse events assessed as related to the investigational drug were only cataract.

4.(iii).A.(4).3) Foreign phase III study (Foreign Study TRA100773B, Attached document5.3.5.1.4; Studied period, February 2006 to January 2007, Reference data)
A double-blind, parallel-group study was conducted in adult patients with chronic ITP at a total of 63 institutions in 23 countries including the US to evaluate the efficacy, safety, and pharmacokinetics of eltrombopag (target sample size; 66 subjects in the eltrombopag group, 33 subjects in the placebo group, 99 subjects in total). In this study, subjects were stratified by use of ITP-therapeutic drugs at baseline, splenectomy status, and platelet count at baseline (≤15,000/μL or >15,000/μL) and then randomized to the eltrombopag or placebo group at the ratio of 2:1.

Eltrombopag 50 mg or placebo was to be administered once daily (meals prohibited within 2 hours before and after administration) for 6 weeks, the investigational drug should be discontinued when the platelet count exceeded 200,000/μL, and the dose might be increased to eltrombopag 75 mg or corresponding placebo on Day 22 and thereafter when the platelet count was <50,000/μL.

The inclusion criteria were the same as in Foreign Study TRA100773A.

All of the 114 randomized subjects (76 subjects in the eltrombopag group, 38 subjects in the placebo group) received the investigational drug and thus were included in the safety analysis population. Of these subjects, 112 with baseline platelet count <30,000/μL (74, 38) were included in the primary efficacy analysis population. In addition, 32 subjects (24, 8) discontinued the study mainly due to the platelet count >200,000/μL in 19 subjects (18, 1) and adverse events in 5 subjects (3, 2).

Of the 114 subjects, 43% (49) received eltrombopag concomitantly with other ITP-therapeutic drugs, 39% (45) were splenectomized, and 48% (55) had a platelet count of ≤15,000/μL at baseline. All of the subjects had previously received at least 1 type of IPT therapy including splenectomy.

For the efficacy, the percentage of subjects who achieved the platelet count ≥50,000/μL at Week 6 of the study treatment (response rate), the primary endpoint, was 58.9% (43 of 73 subjects) in the eltrombopag 50 mg group and 16.2% (6 of 37 subjects) in the placebo group. The response rate was compared between the eltrombopag and placebo groups based on the logistic regression model using stratification factors at the assignment as moderators. As a result, a significant difference was found between the groups ($P < 0.001$). The percentage of the subjects with “any bleeding (WHO Grade 1-4)” at Week 6 was 39% (20 of 51 subjects) in the eltrombopag 50 mg group, which was lower than 60% (18 of 30 subjects) in the placebo group.

For the safety, the incidence of adverse events during the treatment period was 59% (45 of 76 subjects) in the eltrombopag group and 37% (14 of 38 subjects) in the placebo group. Adverse events in ≥5% in either group included headache (6, 4), nausea (6, 0), nasopharyngitis (5, 3),

diarrhoea (4, 1), vomiting (4, 0), and gingival bleeding (0, 3).

Serious adverse events were reported by 2 subjects in the eltrombopag group and by 2 subjects in the placebo group during the treatment period. They included gastrointestinal haemorrhage, cerebral haemorrhage (1, 0), gastrointestinal haemorrhage/cerebral haemorrhage, and haematuria/face injury (0, 1). The serious adverse events in 2 subjects in the eltrombopag group were both assessed as unrelated to the investigational drug. In this study, no deaths occurred.

4.(iii).A.(4).4) Foreign phase III study (Foreign Study TRA105325/EXTEND, Attached document5.3.5.2.2; Studied period, [redacted] 20[redacted] to ongoing; Date of data cut-off, [redacted] 20[redacted][cut-off date for serious adverse events, February 18, 2008], Reference data)
An open-label, uncontrolled study was conducted in adult patients with chronic ITP, who were enrolled in Foreign Studies TRA102537, TRA100773A, TRA100773B, and TRA108057, at a total of 74 institutions in 22 countries including the US to evaluate the safety of long-term treatment with eltrombopag (target sample size, approximately 200 subjects).

The starting dose of eltrombopag was 50 mg, and then the dose was adjusted to 25, 50, or 75 mg according to the platelet count in each subject. In a case where the platelet count was <50,000/μL, the dose was increased, in a case where it was 50,000 to 200,000/μL, the dose was maintained, in a case where it was 200,000 to 400,000/μL, the dose was reduced, and in a case where it exceeded 400,000/μL, treatment was discontinued until it decreased to ≤150,000/μL. The dose was allowed to be reduced to <25 mg/day.

As of the date of data cut-off ([redacted], 20[redacted]), 207 subjects were enrolled in this study and received eltrombopag, and all of them were included in the safety and efficacy analyses. The median treatment period of eltrombopag was 91.5 days (range, 2-523 days). A total of 35 subjects discontinued the study mainly due to insufficient response (13 subjects), request from the subjects (9), adverse events (8), noncompliance (2), protocol violation (1), and other reasons (2).

For the efficacy, the percentage of the subjects who maintained a platelet count of ≥50,000/μL and ≥2 times the baseline for a certain period was 51% (92 of 179 subjects) for ≥4 weeks, 35% (44 of 125 subjects) for ≥10 weeks, 24% (18 of 75 subjects) for ≥25 weeks, and 7% (2 of 27 subjects) for ≥52 weeks. Of the subjects assessed as responders to eltrombopag in the preceding study, subjects in whom the platelet count increased to ≥50,000/μL and ≥2 times the baseline in this study accounted for 81% (17 of 21 subjects) of the subjects previously participating in Foreign Study TRA102537, 96% (47 of 49 subjects) of those previously participating Foreign Studies TRA100773A and TRA100773B, and 85% (22 of 26 subjects) of those previously participating in Foreign Study TRA108057. Of 69 subjects who concomitantly received ITP-therapeutic drugs at baseline, 33 subjects discontinued these concomitant drugs or decreased the dose of these drugs reduced, and of these, 23 subjects completely discontinued these concomitant drugs or maintained the reduced dose of these concomitant drugs for ≥4 weeks and received no rescue treatment until the date of data cut-off. Furthermore, of 23 subjects, 15 subjects maintained the withdrawal status or reduced dose of ITP-therapeutic drugs for ≥24 weeks.

For the safety, the incidence of adverse events during the treatment period was 72% (150 of 207 subjects), and adverse events with an incidence of ≥10% included headache (15%), upper respiratory tract infection (13%), and diarrhoea (10%). The incidence of adverse events assessed as related to the investigational drug was 25% (51 of 207 subjects), and major events included headache in 10 (5%) subjects and nausea in 8 (4%). For others, 9 subjects experienced some hepatobiliary adverse events, which were hyperbilirubinaemia (including blood bilirubin increased) in 5 (2%) subjects, ALT increased in 5 (2%), AST increased in 4 (2%), and blood ALP increased in 1 (<1%).

Until the date of data cut-off for serious adverse events in this study (February 18, 2008), 3 subjects died. One subject died during the treatment period, but the cause was traffic accident in which the subject was involved as a passenger. The other 2 subjects died after Day 31 of the follow-up period. Either death was assessed as unrelated to the investigational drug by the investigator. After the data cut-off, deaths of 2 subjects were reported. Of these, 1 subject suddenly died, and the other one died of intraventricular haemorrhage, both after Day 31 of the follow-up period.

4.(iii).A.(5) Other study

4.(iii).A.(5).1) Foreign clinical study (Foreign Study TRA108132/LENS, Attached document 5.3.5.4.1; Studied period, [redacted] 20[redacted] to ongoing; Date of data cut-off, February 26, 2008, Reference data)

This study included the subjects who received the investigational drug (eltrombopag or placebo) in the phase II or phase III studies of eltrombopag (for any target indication). A long-term observation study was conducted in 14 countries including the US to follow up the safety on the eyes (incidence of cataract, changes over time in the lens) in subjects who received the investigational drug in the Foreign Studies TRA100773A and TRA100773B in patients with chronic ITP, Foreign Study SB-49115/003 in cancer patients, and Foreign Study TPL102537 in patients with thrombocytopenia associated with hepatitis C. As of the date of data cut-off (February 26, 2008), 55 subjects were enrolled in this study and 54 of them who had ophthalmological examination data after the study treatment in the preceding study were included in the analysis for cataract. The median age was 54 years, and 67% (36 of 54 subjects) were female subjects. Of 54 subjects in the analysis, 47 (87%) had at least one risk factor, and of these, 18 had multiple factors. A total of 39 subjects received eltrombopag in the preceding study, and the cumulative dose and treatment period of eltrombopag were 600 to 6825 mg and 9 to 122 days, respectively. Of 54 subjects, 17 had chronic ITP.

During this study, cataract was newly reported by 4 of 54 subjects (3 patients with chronic ITP, 1 patient with hepatitis C). It was reported that cataract developed in 2 subjects as well as developed and progressed in 2 subjects. All these subjects had received eltrombopag in the preceding studies. Of these 4 subjects, 3 (2 patients with chronic ITP, 1 patient with hepatitis C) were assessed as clinically significant ophthalmic adverse events by the Clinical Events Committee (CEC).

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

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

PMDA asked the applicant to explain the current status of treatment for chronic ITP, for which eltrombopag may be indicated, and predicted discrimination from the existing therapeutic drugs.

The applicant explained as follows:

ITP is divided into the acute form that resolves spontaneously within 6 months and the chronic form that lasts for ≥6 months. As a part of treatment for ITP, emergency treatment of high-dose intravenous immunoglobulin, platelet transfusion, or steroid pulse therapy may be indicated for serious bleeding episodes (intra-cerebral, intrathoracic and intra-abdominal haemorrhage) in patients with highly haemorrhagic acute ITP and chronic ITP. For the other forms of chronic ITP, the following treatment protocol has been proposed: patients with *H. pylori*-positive ITP should preferentially undergo eradication therapy; and *H. pylori*-negative ITP patients or ITP patients not responding to eradication should receive corticosteroids or splenectomy if the platelet count is ≤20,000 μL or if serious bleeding episodes are found irrespective of the platelet count (Ikeda, et al., *The Rare and Intractable Diseases Research Project subsidied by the Health and Labour Sciences Research Grants, FY 2004 General and Partial Research Report, "Investigative Research for Coagulation Disorders." [Yasuo Ikeda, principal researcher],* 2005;13-26). The concerned treatment protocol has given the priority to corticosteroids rather than splenectomy.

Corticosteroids therapy can increase the platelet count in over two thirds of the patients, however, only ≤20% of the patients can discontinue corticosteroids or keep the dose low. Splenectomy may be indicated for patients who hardly control the platelet count or bleeding tendency at the maintenance dose of corticosteroids and for patients who experience severe adverse reactions to corticosteroids. In addition, for patients who cannot maintain the platelet count at a less haemorrhagic level with corticosteroids and splenectomy, the secondary treatments such as immunosuppressive agents (cyclophosphamide, azathioprine), danazol, and high-dose dexamethasone are given, but no established therapies are available.

Japanese Study TRA108109 included patients who were diagnosed with ITP ≥6 months before the baseline, and who had a history of ≥1 type of ITP therapy and a baseline platelet count of <30,000μL. Data from this study demonstrated that increased platelet count, improvement of bleeding episodes, and reduced doses of concomitant ITP-therapeutic drugs were found after administration of eltrombopag. Therefore, eltrombopag should be indicated for patients with chronic ITP who have not sufficiently responded to corticosteroids or splenectomy. Since eltrombopag increases the platelet count in both splenectomized and non-splenectomized patients, it can serve as an important therapeutic option for intractable splenectomized ITP patients. Furthermore, eltrombopag may be indicated for patients in whom conventional treatment options are limited, such as patients who have background ineligible for corticosteroid therapy, those who can hardly tolerate corticosteroids, and those who should avoid splenectomy due to a predicted post-splenectomy risk.

PMDA considers as follows:
Regarding clinical positioning of eltrombopag, the applicant claims that eltrombopag is indicated for "patients with chronic ITP who have not sufficiently responded to other treatments" and the applicant's claim is appropriate because Japanese Study TRA108109 has demonstrated the efficacy and safety of eltrombopag in patients who had previously received at least 1 type of ITP therapy and who had a platelet count of <30,000/μL at baseline. Regarding previous ITP therapies, the applicant claims that corticosteroids and splenectomy can be accepted as "conventional treatment" and the applicant's claim is appropriate because Japanese Study TRA108109 has demonstrated the efficacy and safety in patients with a history of treatment with corticosteroids or splenectomy.

In addition, eltrombopag may be indicated for patients ineligible for corticosteroid therapy due to adverse drug reactions or intolerant of splenectomy. Taking the seriousness of the target disease into account, PMDA acknowledges that it is inevitable to use eltrombopag in patients who cannot undergo corticosteroid therapy or splenectomy and whose platelet count or bleeding episodes are hardly controlled, although the use of eltrombopag in such patients is not actively recommended because of poor evidence.

4.(iii).B.2) Use of foreign clinical study data
PMDA asked the applicant to explain the appropriateness of use of the foreign clinical study data for demonstrating the efficacy and safety of eltrombopag in Japanese ITP patients.

The applicant responded as follows:
Regarding diagnosis of ITP, in Japan, the Study Group for Idiopathic Organ Dysfunction that is an intractable disease specified by the Ministry of Health, Labour and Welfare issued the diagnostic criteria for ITP in 1990, and in the US, the American Society of Hematology (ASH) published "A Practice Guideline Developed by Explicit Methods for The American Society of Haematology (ASHGL)" as a guideline for diagnosis and management of ITP in 1996. Currently, the diagnosis is made in a similar manner in and outside of Japan, although the previous diagnostic criteria in Japan were different from those in foreign countries in terms of the following: the

Japanese diagnostic criteria require bone marrow test and platelet-related IgG test, while ASHGL does not require such tests, however, in the new diagnostic criteria proposed by the Ministry of Health, Labour and Welfare (MHLW), the Research on Rare and Intractable Diseases project, the Study Group for Coagulation Disorders (MHLW Study Group), the criteria do not require bone marrow test or platelet-related IgG test as found in foreign countries (Kuwana M et al. *J Thromb Haemost.* 2006;4:1936-43) and basically intend to exclude other diseases associated with a decreased platelet count.

The treatment for chronic ITP is basically intended to improve bleeding episodes and to prevent serious bleeding but not to normalize the platelet count, and thus therapeutic strategy would be determined in consideration of the platelet count and frequency of bleeding episodes and balance between the drug effects and adverse drug reactions. In Japan, the MHLW Study Group published the "Guideline for management of adult ITP" ("Japanese GL [JGL]") in 2004, and in the US, ASH published the ASHGL in 1996. These guidelines presented similar primary therapeutic strategies for chronic ITP, which are based on the platelet count and bleeding episodes. However, the Japanese guideline recommends to perform *H. pylori* eradication therapy in *H. pylori*-positive patients after definitive diagnosis of ITP, but in the US and Europe, the eradication therapy is not generally performed in *H. pylori*-positive patients. Except for the *H. pylori* eradication therapy, therapeutic practices are not largely different between Japan and foreign countries. Differences in pharmacokinetic and pharmacodynamic data between Japanese and foreign subjects are as described above [see "4.(ii).B.1) Difference in pharmacokinetics and pharmacodynamics between Japanese and foreign subjects"].

As described above, the diagnosis and treatment procedures for ITP, which can be considered as extrinsic ethnic factors, are not largely different between Japan and foreign countries, and the relationship between AUC and platelet count increase is similar in Japanese and Caucasian subjects, although the pharmacokinetics, which can be considered as an intrinsic ethnic factor, is found different between Japanese and Caucasian subjects [see "4(ii).B.1) Difference in pharmacokinetics and pharmacodynamics between Japanese and foreign subjects"]. In the Japanese Study TRA108109, the dose was selected based on differences in pharmacokinetics between Japanese and Caucasian subjects using the dose in Foreign Study TRA102537 as reference. As a result, the platelet counts over time and adverse events (classes and incidence) were similar in Japanese Study TRA108109 and Foreign Study TRA102537. Therefore, the applicant considers it appropriate to use the foreign clinical study data.

PMDA considers as follows:
The data from Foreign Study TRA102537 as reference are acceptable, in addition to those from Japanese Study TRA108109, which were conducted in a very limited number of patients, to explain the efficacy and safety of eltrombopag in Japanese patients, because except for the priority of eradication therapy for *H. pylori*-positive patients, therapeutic strategy for chronic ITP in foreign patients is similar to that in Japanese patients in terms of therapeutic goals and treatment procedures such as use of corticosteroids and splenectomy, and the characteristics of patients enrolled in Japanese Study TRA108109 and Foreign Study TRA102537 were similar except for a history of eradication therapy in *H. pylori*-positive patients; and the dose of eltrombopag will be adjusted by monitoring the platelet count, although it was different between Japanese Study TRA108109 and Foreign Study TRA102537 due to the differences in pharmacokinetics between Japanese subjects and Caucasian subjects.

4.(iii).B.3) Efficacy
4.(iii).B.3).(a) Appropriateness of the primary endpoint
The applicant explained the appropriateness of the primary endpoint in the Japanese and foreign clinical studies as follows:
In Japanese Study TRA108109 and Foreign Study TRA102537, the primary endpoint was set

using an increase in the platelet count for the efficacy analysis, and patients in whom the platelet count increased from <30,000/μL at baseline to ≥50,000/ μL were defined as responders. The applicant considers it appropriate to evaluate clinical usefulness of eltrombopag based on such primary endpoint, because the mortality risk in intractable ITP patients with a platelet count of <30,000/μL have been reported to be as high as 4.2 times that in the general population (Portielje JEA et al. *Blood.* 2001;97:2549-54), and both JGL and ASHGL recommend that patients with a platelet count of >50,000/μL be followed up without treatment.

PMDA considers as follows:
Both JGL and ASHGL recommend that chronic ITP patients be treated so as to achieve a platelet count of ≥50,000/μL, and thus the setting of the primary endpoint in Japanese Study TRA108109 and Foreign Study TRA102537 is considered reasonable to some extent and the efficacy of eltrombopag can be evaluated based on the concerned primary endpoint. In addition, the efficacy of eltrombopag should be evaluated based on not only data on the primary endpoint but also those on the reduction of bleeding episodes in association with the increase in platelet count induced by eltrombopag. Eltrombopag is expected to be used for an extended period as it is not a curative treatment for ITP, it is necessary to investigate whether or not the efficacy of eltrombopag can be maintained based on the data from the long-term evaluation in Japanese Study TRA108109 and from extension studies (Japanese Study TRA111433, Foreign Study TRA105325).

4.(iii).B.3).(b) Efficacy of eltrombopag
For review on the efficacy of eltrombopag, PMDA considered the following points important, and thus implemented the investigations.

i) Platelet count increasing effect
In the short-term evaluation for the efficacy in Japanese Study TRA108109, the response rate on Day 43 of the eltrombopag treatment was 60.0% (9 of 15 subjects) (95% CI, 32.29%-83.66%) in the eltrombopag group, which was higher than 0% (0 of 8 subjects) (95% CI, 0.00%-36.94%) in the placebo group. In addition, in the long-term evaluation for the efficacy, the percentage of the subjects in whom responses as expected were observed at ≥75% of 6 evaluation time points between Week 6 and Week 26 was 43.5% (10 of 23 subjects) (95% CI, 23.19%-65.51%). Based on the above, Japanese Study TRA108109 has demonstrated that eltrombopag can increase platelet count for a period up to 26 weeks in Japanese patients with chronic ITP, although the number of the patients included in the study was limited. In addition, the efficacy of eltrombopag demonstrated by Japanese Study TRA108109 can be supported by the data from Foreign Study TRA102537 in which the odds ratio of the platelet count increasing effect of eltrombopag during the 6-month treatment period (primary endpoint) with respect to that of the placebo was significantly as high as 8.2 (99% CI, 3.59-18.73).

ii) Inhibitory effects of eltrombopag against bleeding episodes
The applicant explained the reduction by eltrombopag of bleeding episodes in patients with chronic ITP as follows:
In Japanese Study TRA108109, the percentage of the subjects with “bleeding episodes” throughout the 26-week treatment period was lower than that at the baseline. In Foreign Study TRA102537, risks of “any bleeding (WHO Grade 1-4)” and “clinically significant bleeding (WHO Grade 2-4)” in the eltrombopag group were significantly lower than those in the placebo group, and the percentage of the subjects requiring additional hemostatic treatment following invasive procedures was 29% (4 of 14 subjects) in the eltrombopag group and 50% (2 of 4 subjects) in the placebo group.

PMDA considers that eltrombopag is expected to reduce bleeding episodes in patients with chronic ITP based on data from Japanese Study TRA108109 and Foreign Study TRA102537.

iii) Efficacy of >26-week long term treatment with eltrombopag

The applicant explained the maintenance of the platelet count increasing effect of eltrombopag administered for an extended period >26 weeks as follows:

Japanese Study TRA111433, a long-term treatment extension study, includes the subjects who had completed Japanese Study TRA108109. All of 19 subjects transferred from Japanese Study TRA108109 have received eltrombopag for >6 months, and of 18 subjects in whom treatment period reached Week 36, 12 subjects (66.7%) were assessed as responders (≥50,000/μL, ≤400,000/μL). Only 1 subject discontinued eltrombopag due to insufficient response (Day 336) (as of data cut-off date, [redacted], 20[redacted]). In addition, in Foreign Study TRA105325, an extension study of Foreign Study TRA102537, the median platelet count almost remained >50,000/μL between Weeks 2 and 55.

PMDA considers as follows:

Although the data from Japanese Study TRA111433 and Foreign Study TRA105325 suggest the efficacy of eltrombopag during the >26-week long-term treatment, given that eltrombopag may be administered in clinical practice for a further extended period, the efficacy of eltrombopag during the treatment period exceeding 26 weeks has not been fully confirmed at present. Therefore, it is necessary to collect information about the long-term efficacy of eltrombopag continuously after market launch and to make the information available in clinical practice as appropriate.

iv) Effects of patient background factors on the efficacy of eltrombopag

PMDA asked the applicant to present the results of efficacy analysis for the subjects participating in Japanese Study TRA108109 and Foreign Study TRA102537 stratified into sub-populations according to patient characteristics (baseline platelet count, concomitant ITP-therapeutic drugs, splenectomy status), and then to explain the relationship of the patient characteristics with the efficacy of eltrombopag.

The applicant explained as follows.

The response rate of eltrombopag by patient characteristic at each evaluation time point between Weeks 6 and 26 of the treatment period in Japanese Study 108109 are as shown below. When stratified according to the baseline platelet count, the response rate in 10 subjects with a baseline platelet count of ≤15,000/μL was 22.2% to 50.0%, and that in 13 subjects with a baseline platelet count of >15,000/μL was 66.7% to 92.3%. When stratified according to concomitant ITP-therapeutic drugs at baseline, the response rate in 19 subjects with concomitant ITP-therapeutic drugs at baseline was 38.9% to 63.2%, and that in 4 subjects without concomitant ITP-therapeutic drugs was 50.0% to 100.0%. When stratified according to splenectomy status at baseline, the response rate in 16 splenectomized subjects was 50.0% to 68.8%, and that in 7 non-splenectomized subjects was 33.3% to 71.4%.

The interactions between the platelet count increasing effect (% responders) and patient characteristics (baseline platelet count [>15,000/μL or ≤15,000/μL], concomitant ITP-therapeutic drugs, splenectomy status) were evaluated using repeated measurement model with generalized estimating equation based on binary data (responder) in foreign study TRA102537. As a result, no interactions involving any patient characteristics were found. The platelet counts over time by patient characteristic in Foreign Study TRA102537 are as shown below. The median platelet count was higher in subjects receiving eltrombopag than in those receiving placebo irrespective of the baseline platelet count (>15,000/μL or ≤15,000/μL), concomitant ITP-therapeutic drugs, or splenectomy. In the eltrombopag group, the increase in platelet count in subjects with a baseline platelet count of ≤15,000/μL was smaller than that in those with a baseline platelet count >15,000/μL, but the median platelet count in subjects with a baseline platelet count of ≤15,000/μL remained between 40,000 and 50,000/μL throughout the 26-week treatment period. In the

splenectomized subjects, the increase in platelet count was slow compared with non-splenectomized subjects.

PMDA considers as follows:
The increase in platelet count after administration of eltrombopag in the sub-population with a baseline platelet count of ≤15,000/μL tended to be smaller than that in the sub-population with a baseline platelet count of >15,000/μL in Japanese and foreign clinical studies. However, taking into account that the efficacy in the eltrombopag group was superior to that in the placebo group in any sub-population stratified by a patient characteristic in Foreign Study TRA102537, the efficacy of eltrombopag can be expected irrespective of the above patient characteristic.

PMDA asked the applicant to stratify the subjects into sub-populations according to the baseline platelet count (cut-off value) and to discuss the efficacy of eltrombopag by sub-population because treatment guidelines used in Japan and foreign countries indicate that chronic ITP patients with a platelet count of ≤20,000/μL need treatment even though they do not experience bleeding episodes, and those with a platelet count of ≤10,000/μL have a risk of serious bleeding.

The applicant presented the response rate in sub-populations stratified according to the baseline platelet count in the table below.

Table 16. Response rate after administration of eltrombopag by baseline platelet count, long-term evaluation (Japanese Study TRA108109) (Adapted from the submitted data)

Evaluation time point	≤10,000/μL	>10,000/μL	≤20,000/μL	>20,000/μL
Day 8	0/6 (0)	1/17 (5.9)	1/14 (7.1)	0/9 (0)
Day 15	0/6 (0)	4/17 (23.5)	3/14 (21.4)	1/9 (11.1)
Day 22	0/6 (0)	5/17 (29.4)	3/14 (21.4)	2/9 (22.2)
Day 29	1/6 (16.7)	10/17 (58.8)	6/14 (42.9)	5/9 (55.6)
Day 36	1/6 (16.7)	12/17 (70.6)	5/14 (35.7)	8/9 (88.9)
Day 43	1/6 (16.7)	11/17 (64.7)	6/14 (42.9)	6/9 (66.7)
Week 10	3/6 (50.0)	9/15 (60.0)	6/12 (50.0)	6/9 (66.7)
Week 14	2/6 (33.3)	12/17 (70.6)	7/14 (50.0)	7/9 (77.8)
Week 18	2/6 (33.3)	9/16 (56.3)	5/13 (38.5)	6/9 (66.7)
Week 22	1/6 (16.7)	10/15 (66.7)	6/13 (46.2)	5/8 (62.5)
Week 26	1/6 (16.7)	15/17 (88.2)	7/14 (50.0)	9/9 (100.0)

n/N (%)

Table 17. Response rate in the eltrombopag group by baseline platelet count (Foreign Study TRA102537) (Adapted from the submitted data)

Evaluation time point	≤10,000/μL	>10,000/μL	≤20,000/μL	>20,000/μL
Day 8	9/50 (18)	41/84 (49)	25/90 (28)	25/44 (57)
Day 15	12/50 (24)	49/83 (59)	32/90 (36)	29/43 (67)
Day 22	13/50 (26)	55/83 (66)	38/90 (42)	30/43 (70)
Day 29	13/49 (27)	51/82 (62)	35/88 (40)	29/43 (67)
Day 36	17/51 (33)	58/83 (70)	44/91 (48)	31/43 (72)
Day 43	18/51 (35)	55/83 (66)	41/90 (46)	32/44 (73)
Week 10	13/44 (30)	43/64 (67)	30/74 (41)	26/34 (76)
Week 14	16/46 (35)	36/68 (53)	30/79 (38)	22/35 (63)
Week 18	16/45 (36)	36/67 (54)	30/76 (39)	22/36 (61)
Week 22	16/45 (36)	39/68 (57)	34/79 (43)	21/34 (62)
Week 26	21/51 (41)	47/81 (58)	40/89 (45)	28/43 (65)

n/N (%)

PMDA considers as follows:
The subjects of Japanese Study TRA108109 and Foreign Study TRA102537 were stratified by the baseline platelet count of 20,000/μL as the cut-off value to compare the response rate in the same sub-population between these studies. As a result, no large differences were found, but the response rate in the sub-population with a platelet count of >20,000/μL tended to be higher than that in the sub-population with a platelet count of ≤20,000/μL. This trend was also observed when the cut-off value was set at 10,000/μL. The response rate until Day 43 in the sub-population with a baseline platelet count of ≤10,000/μL was lower in the sub-population of Japanese Study TRA108109 than in that of Foreign Study TRA102537, although very few subjects were included in the relevant sub-population. The concerned difference may be attributable to the difference in the starting dose between these studies, but the result suggested that the initial response to eltrombopag in Japanese patients with a baseline platelet count of ≤10,000/μL could be slightly weaker than that in patients in Foreign Study TRA102537. On the other hand, the consistent efficacy was observed after Day 43 irrespective of the baseline platelet count. Therefore, PMDA concluded that a certain effect can be expected in any Japanese sub-population.

PMDA asked the applicant to explain the percentage of *H. pylori*-positive subjects in Japanese Study TRA108109 and a relationship between a treatment history for infection with *H. pylori* and the efficacy of eltrombopag, because Japanese patients with chronic ITP are frequently *H. pylori*-positive, and the treatment guideline recommends performing eradication therapy in *H. pylori*-positive patients.

The applicant responded as follows:
Japanese Study TRA108109 included 13 *H. pylori*-positive patients, 6 *H. pylori*-negative patients, and 4 patients whose *H. pylori* status was unknown. The response rate in 12 patients who were positive for *H. pylori* and who had a history of eradication therapy was between 66.7% and 91.7% from Week 4 to Week 26, and 1 subject who was positive for *H. pylori* but did not undergo eradication therapy and received eltrombopag showed a response on Day 15 and thereafter. Accordingly, the efficacy of eltrombopag would almost remain unchanged irrespective of a past history of the *H. pylori* eradication therapy or *H. pylori* carrier status.

PMDA considers that approximately a half of the subjects participating in Japanese Study TRA108109 had a history of the *H. pylori* eradication therapy, and this reflects the current status of the patients with chronic ITP in Japan. According to the applicant's explanation, the efficacy of eltrombopag would remain unchanged irrespective of a past history of the *H. pylori* eradication therapy or *H. pylori* carrier states, although the efficacy of eltrombopag was evaluated in very few subjects. PMDA accepted the explanation.

Based on the above, PMDA has concluded that the study data have demonstrated the efficacy of eltrombopag in patients with chronic ITP.

4.(iii).B.4) Safety
4.(iii).B.4).(a) Risk of thromboembolism
PMDA asked the applicant to compare patient characteristics between the subjects with thrombosis or thromboembolism-related events and subjects without such events in Japanese and foreign clinical studies and then to investigate if the excessive increase in platelet count after administration of eltrombopag may have acted as a risk factor for such events.

The applicant responded as follows:
Of 23 subjects in Japanese Study TRA108109, 1 subject experienced a thromboembolic adverse event. This subject experienced a mild transient ischaemic attack on Day 9 of eltrombopag

12.5 mg/day and eltrombopag was withdrawn on the following day. The platelet count before and after the event was 76,000 and 120,000/μL, respectively, and the subject received corticosteroids and danazol before the start of the eltrombopag treatment. Of 446 subjects in foreign clinical studies including 3 for whom adverse events were reported after preparation of the submitted data, 17 experienced thromboembolic events. The platelet count obtained around the onset of the concerned adverse events in 17 subjects was 14,000/μL to 407,000/μL. Of 17 subjects, 10 (59%) presented a platelet count below the lower limit of the reference range (<150,000/μL), and 5 presented a platelet count of <50,000/μL.

In 5 (29%) of 17 subjects, a platelet count obtained around the onset of thromboembolic event was within the reference range (≥150,000/μL and <400,000/μL), and >400,000/μL in 1 (6%) of 17. In the remaining 1 subject, the platelet count around the onset of thromboembolic event was unknown, but the platelet count 11 days before the onset was 2000/μL, and intravenous immunoglobulin was given 4 days before the onset.

For the relationship between the maximum platelet count and the onset of the thromboembolic events, a total of 446 subjects in foreign clinical studies were stratified according to the maximum platelet count, and then 80, 193, and 171 subjects were assigned to the groups with a maximum platelet count of >400,000/μL, within the reference range, and below the lower limit of reference range, respectively. As a result, such events occurred in 6 (8%) of 80 subjects with a maximum platelet count of >400,000/μL, in 6 (3%) of 193 subjects with that within the reference range, and in 5 (3%) of 171 subjects with that below the lower limit of reference range. In addition, of 17 subjects with the thromboembolic events, 14 (82%) experienced these events when the platelet count was lower than the maximum during the treatment period.

In addition, characteristics of the patients and risk factors for thromboembolism were analyzed in 14 (3.3%) of 422 subjects experienced or were suspected to experience thromboembolic adverse events in foreign clinical studies as of the data cut-off date (August 1, 2008) for submission. As a result, of these 14 subjects, 6 subjects was given corticosteroids, a risk factor for thromboembolic adverse events, and 4 subjects who experienced venous events during hospitalization did not receive anticoagulant agents as preventive medication. Intravenous immunoglobulin, another risk factor for such events, was administered to 3 subjects 5 to 8 days before the onset of thromboembolic adverse events. Although the investigators conducted additional examination for risk factors of thromboembolism in a few subjects, 1 subject with thromboembolic adverse events in Foreign Study TRA102537 was found lupus anticoagulant positive. In 1 subject with a history of myocardial infarction at the initial enrollment who completed Foreign Study TRA100773A and then entered Foreign Study TRA105325, transient ischaemic attack (Grade 1) and myocardial infarction (Grade 4) occurred on Days 59 and 513, respectively, after the start of the treatment.

As described above, all of the subjects with thromboembolic adverse events were found to have risk factors related to such events, but the relationship between thromboembolic adverse events and risk factors remained to be clarified.

In the phase III placebo-controlled double-blind study (ELEVATE Study) in patients with chronic liver disease (CLD), thrombosis/thromboembolism-related events occurred in 7 subjects (8 events) in the eltrombopag group, consequently, this study was discontinued. Based on the above, PMDA asked the applicant to explain the relationship of platelet count and other patient characteristics with the thrombosis/thromboembolism-related events reported in the ELEVATE Study.

The applicant responded as follows:
The subjects in this study underwent surgical invasive procedures after receiving eltrombopag 75

mg or placebo once daily for 14 days. The concerned adverse events were reported by 6 of 7 subjects within 3 weeks after the last dose of eltrombopag and around the maximum platelet count after surgery, suggesting that the occurrence may be related to the rapid increase in platelet count. CLD is highly associated with a risk of portal vein thrombosis, and 7 of 8 thromboembolic events in the ELEVATE Study occurred in the portal system. The trend of thromboembolic events in this study was different from that in clinical studies conducted in ITP patients.

As described above, clearly different pathology of CLD from that of chronic ITP is inferred to have mainly contributed to different trends of thrombotic /thromboembolic events.

PMDA considers as follows:
Most of patients with chronic ITP who experienced thromboembolic adverse events had risk factors related to thromboembolism including hospitalization and history of use of corticosteroids and intravenous immunoglobulin and 1 subject was found to be lupus anticoagulant positive. Furthermore, no specific trend was observed in the relationship between thromboembolic adverse events and platelet count in patients with chronic ITP, which is different from that in CLD patients. Thus, effects of eltrombopag on thromboembolic adverse events in patients with chronic ITP remain unknown. However, the above information should be made available in clinical practice. Furthermore, it is necessary to collect the information on thromboembolic adverse events via post-marketing surveillance and take actions such as providing cautions where necessary.

4.(iii).B.4).(b) Rebound effects after withdrawal
In Japanese Study TRA108109, the percentage of the subjects with bleeding episodes remained higher after the last dose of eltrombopag than at baseline. PMDA asked the applicant to explain whether or not the result is attributable to decreased platelet count that occurred as a rebound effect after the withdrawal of eltrombopag.

The applicant responded as follows:
The frequency of bleeding episodes at baseline was determined by the measurement only at 1 time point and it is difficult to determine whether the increased frequency of bleeding episodes for 4 weeks after the last dose is a rebound effect or not by comparison with the data at 1 baseline time point. Japanese Study TRA108109 had a pre-treatment observation period of 3 to 4 weeks from the screening to the start of the treatment, and the comparison of the frequencies during almost the same duration was possible. The percentage of the subjects with bleeding episodes at one of the pre-treatment visits was 70% (16 of 23 subjects), which was comparable to that at any of the post-treatment visits of 74% (17 of 23 subjects). Of 17 subjects with bleeding episodes after the last dose, 4 did not have bleeding episodes at any pre-treatment visit, and 2 of 4 presented transiently decreased platelet count after the last dose. In foreign clinical studies, the percentage of the subjects with any bleeding episode after the last dose was not higher than that at baseline. Based on the above, the increased frequency of bleeding episodes after the last dose in Japanese Study TRA108109 was not considered as a rebound effect caused by withdrawal of eltrombopag.

In addition, the applicant defined a transient decrease in platelet count as the case where "the platelet count decreased to <10,000/μL and by ≥10,000/μL from the baseline" to investigate haemorrhagic adverse events and rescue treatment during the follow-up period of 4 weeks in the subjects in whom a transient decrease in platelet count occurred within 4 weeks after suspension or withdrawal of the investigational drug. The applicant explained the results as follows:
In Japanese Study TRA108109, 3 subjects (13%) had transiently platelet count decreased, but none of them experienced clinically significant bleeding episodes or haemorrhagic adverse events. In Foreign Study TRA102537, the percentage of the subjects who had a transient decrease in platelet count within 4 weeks after suspension or completion of the study treatment was 7% in both eltrombopag and placebo groups (9 subjects in the eltrombopag group, 4 subjects in the placebo group), and 1 of these subjects in the eltrombopag group experienced a haemorrhagic

adverse event. Pooled analysis of Foreign Studies TRA100773A and TRA100773B showed that 11 (10%) subjects in the eltrombopag 50 mg group and 6 (9%) in the placebo group had a transient decrease in platelet count, and 2 of these subjects in the eltrombopag 50 mg group experienced haemorrhagic adverse events when the platelet count reached the minimum and received rescue treatment. Of 8 subjects (12%) who had a transient platelet count during the follow-up period (rest period) of 4 weeks in Foreign Study TRA108057, none experienced haemorrhagic adverse events during the same period, but 4 subjects received rescue treatment after the end of the study treatment (high-dose intravenous immunoglobulin in 3 subjects, prednisolone and danazol in 1 subject). In Foreign Study TRA105325, 5 subjects had a transient decrease in platelet count after suspension or completion of the study treatment, and the other 4 subjects had platelet count decreased to <20,000/μL and by ≥10,000/μL from the baseline. These 9 subjects did not experience haemorrhagic adverse events, but 3 of these subjects received rescue treatment (high-dose intravenous immunoglobulin, platelet transfusion), and all of them showed infection signs when a transient decrease in platelet count was noted. A transient decrease in platelet count occurred in several subjects following the completion or suspension of the eltrombopag treatment, but such events occurred even in the placebo group at a similar frequency, and no clinically significant haemorrhagic adverse events were associated.

However, the platelet count decreased to around the baseline 2 weeks after the last dose of eltrombopag in both Japanese and foreign clinical studies. The following caution statement about bleeding episodes after the completion of treatment will be included in the "Precautions" section in the proposed package insert: "In many patients, the platelet count may return to the baseline within 2 weeks after the withdrawal of eltrombopag, increasing a risk of bleeding and then potentially causing bleeding (see 'Serious adverse drug reactions'). The platelet count should be monitored every week for the first 4 weeks after the withdrawal of eltrombopag."

PMDA considers as follows:
As the applicant explained that a transient decrease in platelet count occurred after the withdrawal of eltrombopag, the possibility of a rebound effect cannot be ruled out. On the other hand, in almost all the subjects, the platelet count decreased to the baseline level within 2 weeks after the withdrawal of eltrombopag. It is necessary to pay attention to the bleeding risk after the withdrawal (completion) of the eltrombopag treatment irrespective of the status of a rebound effect, and thus it is appropriate to provide cautions against bleeding after the withdrawal of treatment in the proposed package insert. The experience with the treatment of eltrombopag in Japanese ITP patients is very limited and it is necessary to collect the information on the platelet count and haemorrhagic adverse events as well as rescue treatment after the withdrawal of treatment via post-marketing surveillance. The appropriateness of the cautions for haemorrhagic adverse events after the withdrawal as well as the necessity of collection of post-marketing information will be finalized, taking account of comments raised in the Expert Discussion.

4.(iii).B.4).(c) Abnormal hepatobiliary laboratory values
Based on cautions against a hepatotoxic risk provided by the "WARNING" section in the US labeling, PMDA asked the applicant to explain the appropriateness of the contents of the cautions provided in the proposed package insert in Japan, including monitoring conditions for hepatic impairment (parameters, frequency) and the withdrawal criteria for eltrombopag.

The applicant responded as follows:
Since the platelet count is frequently measured due to the necessity of eltrombopag, the protocols of the clinical studies in patients with chronic ITP specified that biochemical tests including hepatic function tests should be performed in parallel with the platelet count measurement to collect the safety data at the maximum and included the withdrawal criteria based on the hepatic function parameter values to ensure the safety in the subjects. However, in clinical practice, it is not practically feasible to perform the tests at the same frequency as that in clinical studies; and

most of the events were reversible and mild, and no clinically significant signs suggesting hepatic impairment were observed. The applicant thus considers it unnecessary to perform the tests routinely at a high frequency. For this reason, the US labeling for eltrombopag recommends performing liver function tests (e.g., AST [GOT], ALT [GPT], bilirubin) before the start of the treatment, every 2 weeks during dose adjustment, and every month after the dose determination, and specifies the withdrawal criteria in response to elevated ALT as "if ALT levels increase to ≥3 times upper limit of normal (ULN) and are; (a) progressive, (b) persistent for ≥4 weeks, (c) accompanied by increased direct bilirubin, and (d) accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation." In the US, approximately 1 year has passed since the launch, but the above provision related to the liver function test in the US labeling has not raised any issues. The applicant thus considers it appropriate to include the precautions for hepatic impairment in the proposed package insert in Japan prepared in accordance with the US labeling.

PMDA considers as follows:
Data from Japanese and foreign clinical studies do not seem to suggest that eltrombopag increase the incidence of hepatic impairment, but in a foreign clinical study, serious hepatic impairment was found after eltrombopag treatment. It is necessary to pay attention to hepatobiliary laboratory value abnormalities following the eltrombopag treatment. Precautions for monitoring of liver function tests and hepatic impairment included in the proposed package insert are almost comparable to the withdrawal criteria set in the Japanese clinical studies. Since no serious hepatic impairment occurred in these studies, these precautions are almost appropriate. The final decision on the precautions will be made, taking account of comments raised in the Expert Discussion. In addition, it is necessary to collect the information on the safety and the incidence and outcome of hepatic disorder in patients with hepatic impairment separately in post-marketing surveillance.

4.(iii).B.4).(d) Cataract
The applicant explained the risk for cataract in humans based on the finding of cataract observed following the administration of eltrombopag in the toxicity studies in rodents [see 3.(iii).B.2) Cataract observed in rodents] as follows:
In Japanese Study TRA108109, none of the subjects receiving eltrombopag experienced cataract following administration of eltrombopag. In Foreign Study TRA102537, 12 of 135 subjects in the eltrombopag group and 13 of 61 subjects in the placebo group were found to have cataract at baseline, and 4 subjects in the eltrombopag group and 3 subjects in the placebo group experienced progression of cataract. Cataract developed in 7 subjects in the eltrombopag group and 3 subjects in the placebo group. In Foreign Studies TRA100773A and TRA100773B, development or progression of cataract was reported by 5 of 106 subjects in the eltrombopag 50 mg group, 1 of 28 subjects in the eltrombopag 75 mg group, and 2 of 67 subjects in the placebo group. In all affected subjects, the relationship with long-term use of corticosteroids was suspected. In Foreign Study TRA108057, 4 of 66 subjects were found to have cataract before the eltrombopag treatment, but progression of cataract was not observed during the study period. Cataract developed in 3 subjects. In Foreign Study TRA105325, of 205 subjects who underwent ≥1 session of ophthalmological examination, 9 experienced development or progression of cataract. However, all subjects had a risk factor of cataract including a long-term use of corticosteroids, and consequently, external ophthalmologists' assessment concluded that no ocular toxicity signs related to eltrombopag were observed.

PMDA considers as follows:
Aggravation and development of cataract associated with eltrombopag were observed in non-clinical toxicity studies, and the currently available information cannot clarify the effects of long-term treatment with eltrombopag on aggravation and development of cataract. Therefore, the applicant's proposal that a precaution for periodic ophthalmological examinations for cataract during the eltrombopag treatment will be included in the proposed package insert is appropriate.

Since patients with chronic ITP have a risk factor of cataract including long-term use of corticosteroids, it is necessary to collect the information on effects of concomitant use of eltrombopag with corticosteroids on development of cataract. Such information should be collected via post-marketing surveillance and actions should be taken as appropriate.

4.(iii).B.4).(e) Increased bone marrow reticulin fiber

The applicant explained a risk of increased bone marrow reticulin fiber due to eltrombopag as follows:

ITP patients have increased reticulin fiber in the bone marrow (Mufti G et al. *J Support Oncol.* 2007;5(suppl 2):80-1), and chronic stimulation of megakaryocyte by TPO-R agonist may lead to increased reticulin and collagen fibrosis in the bone marrow, resulting in clinical findings similar to those of myelofibrosis. In Japanese Study TRA108109 as well as Foreign Studies TRA102537, TRA108057, and TRA105325, peripheral blood smear preparations were examined for reticulin or collagen fibrosis in the bone marrow when the differential white blood count profile indicated the presence of immature or atypical cells. In Japanese Study TRA108109, peripheral blood smear preparations from 14 subjects (8 in the eltrombopag group, 6 in the placebo group) were examined, but no clinically significant cells including dacryocytes and nucleated erythrocytes, which are observed in myelofibrosis, were observed. In 3 foreign studies, 97 examination sessions with peripheral blood smear preparations from 52 subjects were performed, and as a result, clinically significant immature or atypical cells (nucleated erythrocytes, 2 subjects; blast cells, 4 subjects) were observed in 6 subjects (1 session for each subject), but no recurrence due to extended treatment occurred. In Foreign Study TRA105325, 46 subjects were subjected to bone marrow biopsy 12 months after the treatment, but cell density data did not indicate any abnormalities. Bone marrow aspiration was performed at the same time in 19 of 46 subjects undergoing bone marrow biopsy, and no subjects presented karyotype abnormality or myeloblasts at >3%. As described above, there were no clinically significant morphological changes in the bone marrow, or signs or symptoms suggesting myelofibrosis and bone marrow dysfunction caused by the eltrombopag treatment.

PMDA considers as follows:

In Japanese and foreign clinical studies, there were no findings suggesting that eltrombopag increased reticulin and collagen fibers or developed myelofibrosis at 12 months of the eltrombopag treatment, but the information available for the relationship of eltrombopag with bone marrow fibrosis are extremely limited, and following the eltrombopag treatment, transient abnormalities have been observed in the differential white blood count profile. It is appropriate to include cautions against myelofibrosis and the following statement in the proposed package insert: peripheral blood smear preparations should be examined as appropriate; and when any abnormality was found, the treatment with eltrombopag should be discontinued, and the bone marrow should be examined.

4.(iii).B.4).(f) Effects on development of hematologic malignancy

Taking into account that eltrombopag enhanced the growth of 2 types of leukemia cell strains (N2C-TPO and HEL92.1.7 cells) highly expressing TPO-R and megakaryocyte markers *in vitro*, PMDA asked the applicant to explain whether or not leukemia should be suspected in patients with decreased response to eltrombopag.

The applicant explained as follows:

Haematological malignancies including leukemia occurred in 1 subject receiving eltrombopag in Foreign Study TRA105325, according to the data from Japanese and foreign clinical studies in patients with chronic ITP. This subject received eltrombopag for 122 days in the preceding Foreign Study TRA108057, and then was enrolled in extension Foreign Study TRA105325. The subject was diagnosed with diffuse large B-cell lymphoma on Day 64 of the eltrombopag treatment in the extension study. The investigator assessed this event as not related to eltrombopag.

Accordingly, the applicant considered that eltrombopag would not increase a risk of haematological malignancies. However, it cannot be ruled out that the TPO-R agonist enhances progression of haematological malignancies including myelodysplastic syndrome, and thus the applicant plans to include the following description in the "Important Precautions" section in the proposed package insert: "thrombopoietin receptor agonists may progress existing haematological malignancies such as myelodysplastic syndrome. However, in clinical studies conducted in patients with idiopathic thrombocytopenic purpura, no differences were found in the incidence of haematological malignancies between the eltrombopag and placebo groups."

PMDA considers as follows:
Only limited ITP patients received eltrombopag and a risk of haematological malignancies in patients with chronic ITP caused by eltrombopag cannot be ruled out. As of now, it is appropriate to provide a caution that existing haematological malignancies including myelodysplastic syndrome may be progressed. In addition, it is necessary to collect the information on development of haematological malignancies in patients receiving eltrombopag via post-marketing surveillance and provide the information as appropriate. In addition, it is necessary to provide an appropriate caution that for a patient deemed a non-responder to eltrombopag, the long-term treatment should not be unnecessarily carried out, and the possibility of other diseases should be considered because ITP and myelodysplastic syndrome cannot be differentiated in some patients when a platelet count decreased.

4.(iii).B.5) Safety of eltrombopag in special populations
4.(iii).B.5).(a) Use in pregnant women
In consideration that eltrombopag may be used to control the platelet count in patients with chronic ITP during their pregnancy and delivery, PMDA asked the applicant to explain the appropriateness of administering eltrombopag to pregnant women or to women who may possibly be pregnant.

The applicant responded as follows:
Since non-clinical study data of eltrombopag did not show direct effects of eltrombopag on embryos or fetuses, the applicant considers it unnecessary to provide precautions for pregnant women or women who may possibly be pregnant. Currently available reports on exposure to eltrombopag in pregnant women have only included a report on 1 ITP patient who received eltrombopag 25 mg/day during pregnancy in the US (unknown duration of treatment). Her neonate delivered prematurely experienced respiratory distress syndrome, jaundice, and ITP (unknown outcome) but no teratogenicity was found. Information on effects of eltrombopag administered during pregnancy on mother and offspring are limited, and the safety in pregnant women has not been established. On the other hand, approximately 1 year has passed since the launch in the US, but there is no information indicating a risk of its use in pregnant women. The applicant thus considers it appropriate to administer eltrombopag to pregnant women or women who may possibly be pregnant when the therapeutic benefit outweighs the risks.

PMDA considers as follows:
In non-clinical toxicity studies of eltrombopag, fetal deaths occurred at the maternally toxic dose, and the concerned information is provided in the US labeling. In addition, placental transfer of eltrombopag has not been investigated. Based on the above, the applicant should provide not only a general caution statement to pregnant women and women who may possibly be pregnant but also currently available relevant non-clinical toxicity data so that such women will be thoroughly informed of the cautions.

4.(iii).B.6) Indication
Based on results that the efficacy and safety of eltrombopag in patients with acute ITP remain unknown because clinical studies included in this application were conducted in patients with

chronic ITP, PMDA asked the applicant to explain the justification for selecting "idiopathic thrombocytopenic purpura (ITP)" as the proposed indication of eltrombopag

The applicant explained as follows:
Since the use of eltrombopag should be considered when other treatment options are confirmed to be not sufficiently effective and eltrombopag has not been used in patients with acute ITP, the proposed indication of eltrombopag is changed to "chronic idiopathic thrombocytopenic purpura."

The "Precautions for Indications" section in the proposed package insert of eltrombopag states that "(1) Eltrombopag should be used when other treatment options are not sufficiently effective or have limitations due to tolerability." PMDA asked the applicant to explain their views on the criteria for deciding "when other treatment options are not sufficiently effective" and whether or not the relevant information should be provided via the proposed package insert.

The applicant explained as follows:
Patients with a platelet count of ≤30,000/μL or those with a platelet count from 30,000 to 50,000/μL, who are accompanied by bleeding episodes, are treated with corticosteroids, while patients in whom the platelet count cannot be kept at ≥30,000/μL even with corticosteroids at the maintenance dose (5-10 mg/day) or patients who experience remarkable adverse reactions to corticosteroids undergo splenectomy. Furthermore, for patients with intractable ITP in whom corticosteroids and splenectomy are not sufficiently effective (non-responders or patients with a platelet count of ≤30,000/μL), immunosuppressive agents including cyclophosphamide and azathioprine, danazol, and high-dose of dexamethasone are used as the secondary treatment. As described above, treatment may be generally judged to be not sufficiently effective if the platelet count is not kept at ≥30,000/μL, but whether or not treatment is sufficiently effective will be comprehensively judged based on the platelet count and clinical symptoms. For instance, even if the platelet count is ≤30,000/μL, only careful follow-up (without treatment) may be selected for the patients without bleeding episodes or with the decreased bleeding tendency maintained; and on the other hand, even if the platelet count is from 30,000 to 50,000/μL, other treatment options may be considered for the patients with bleeding episodes. Accordingly, the applicant considers it difficult to specify in the proposed package insert the criteria to decide whether or not other treatment options are sufficiently effective. However, the "Precautions for Indications" section in the proposed package insert will include an additional statement "Eltrombopag should be used when a haemorrhage risk is assessed to be high based on the platelet count and clinical symptoms," as therapeutic strategy for chronic ITP is determined in consideration of comprehensive balance including not only the platelet count but also clinical symptoms.

PMDA considers as follows:
In consideration of clinical study design and results, the applicant's view is acceptable to change the indication to "chronic idiopathic thrombocytopenic purpura," as with the indication in foreign countries. At present, it is appropriate to provide the caution statements that "Eltrombopag should be used when other treatment options are not sufficiently effective or have limitations due to tolerability" and that "Eltrombopag should be used when a haemorrhage risk is assessed to be high based on the platelet count and clinical symptoms" in the "Precautions for Indications" section in the proposed package insert. However, the appropriateness of the caution statements provided in the proposed package insert will be finalized, taking account of comments raised in the Expert Discussion.

4.(iii).B.7) Dosage and administration
4.(iii).B.7).(a) Appropriateness of proposed dosage and administration
PMDA asked the applicant to explain the appropriateness of the proposed dosage and administration of eltrombopag in Japan which is different from that approved in the US.

The applicant responded as follows:
In the US, regulatory submissions for short-term and long-term uses of eltrombopag were separately planned. Foreign Studies TRA100773A and TRA100773B (6-week treatment for both) were conducted to evaluate the short-term use. In Foreign Study TRA100773A, the efficacy and safety of eltrombopag at the doses of 30, 50, and 75 mg were evaluated, and the results showed that eltrombopag increased the platelet count in a short term and 50 mg of eltrombopag was well tolerated. Therefore, the starting dose was set at 50 mg in Foreign Study TRA100773B because eltrombopag at 50 mg increased the platelet count fast and was tolerant. Also in Foreign Study TRA102537 (26-week treatment) which was conducted to evaluate the long-term use, the starting dose of 50 mg was also selected based on the results from Foreign Studies TRA100773A and TRA100773B, and the dose was allowed to be adjusted to 75 or 25 mg according to the platelet count. On the other hand, results of phase I studies in foreign (mainly Caucasian) and Japanese healthy adult subjects showed that AUC in Japanese subjects was twice that in Caucasian subjects at the same dose, indicating differences in the pharmacokinetics between Japanese and foreign subjects, and the development plan of eltrombopag in Japan initially intended the long-term use. Therefore, the starting dose was set at 12.5 mg in Japanese Study TRA108109. Although the low starting dose may take more time to increase the platelet count to an appropriate level than the medium starting dose, gradual dose-escalation from the low starting dose can avoid an excessive increase of the platelet count. Therefore, the applicant considers that the proposed dosage and administration in Japan would specify a more careful titration method compared with that approved in the US. Although the dose increment in the proposed dosage and administration in Japan is set at 12.5 mg/day, which is a half of that in the US, the applicant considers it appropriate, based on the data from the pharmacokinetic studies in Japan and foreign countries. The ongoing Japanese Study TRA111433 demonstrated that the dose adjustment in increments of 12.5 mg is useful in maintaining the platelet count at 50,000 to 400,000/μL.

For the maximum daily dose of eltrombopag, a foreign phase I multiple dose study (10-day treatment) demonstrated acceptable tolerability at the doses up to 75 mg. In a clinical study in ITP patients in the US, the maximum dose was set at 75 mg/day based on the data from Foreign Studies TRA100773A and TRA100773B. In addition, subsequent Foreign Studies TRA102537 and TRA105325 demonstrated the efficacy and safety of eltrombopag at the doses of 25 to 75 mg/day administered for an extended period, resulting in the approval of the maximum dose of 75 mg/day.

In Japan, phase I studies demonstrated acceptable tolerability at the doses up to 100 mg administered as a single dose and up to 75 mg administered as multiple doses (10-day treatment). Given the fact that $AUC_{0-\tau}$ in Japanese healthy adult subjects was approximately 2 times that in Caucasian subjects as described above, $AUC_{0-\tau}$ at a dose of 50 mg/day in Japanese subjects might be higher than that at a dose of 75 mg/day in Caucasian subjects. However, a maximum dose of 50 mg/day was selected because acceptable tolerability in Japanese healthy adult subjects was demonstrated at doses up to 100 mg administered as a single dose and up to 75 mg/day administered as multiple doses. The applicant considers it appropriate to set the maximum dose at 50 mg/day for the proposed dosage and administration in Japan, taking into account that Japanese Study TRA108109 demonstrated the safety and efficacy at doses of 12.5 to 50 mg/day in Japanese patients with chronic ITP.

PMDA considers as follows:
It is appropriate to set the starting dose of eltrombopag at 12.5 mg/day for the following reasons: (i) the results of Japanese Study TRA108109 where the starting dose was set at 12.5 mg showed that the long-term efficacy and safety of eltrombopag in patients with chronic ITP who had been previously treated were not particularly different from those in Foreign Study TRA102537; (ii)

in Japanese Study TRA108109 where one dose adjustment was made to ensure the efficacy, the median of the mean daily dose in a short-term administration was 18.8 mg/day, which was <25 mg/day; and (iii) 2 of 23 subjects in this Japanese study were withdrawn from the study treatment at a dose of 12.5 mg/day due to excessively high platelet count >200,000/μL. In addition, the median of the mean daily dose of eltrombopag in the short-term evaluation in Japanese Study TRA108109 was 18.8 mg, and the mean daily dose in the long-term evaluation (after Day 43) remained between 29.0 and 38.1 mg. Therefore, the dose adjustment in 12.5 mg increments is also generally appropriate.

The maximum dose was set at 50 mg/day throughout the 26-week treatment period in Japanese Study TRA108109. Relationship between the dose of eltrombopag and platelet count was investigated for each subject. Of 18 subjects who had the dose increased to 50 mg at least once due to a platelet count of <50,000/μL during the treatment period, 16 subjects responded to the increased dose of 50 mg (presenting the increased platelet count) without particular safety issues. For this reason, the daily maximum dose is allowed be set at 50 mg.

In addition, in Japanese Study TRA108109, only 6 Japanese patients had a platelet count of ≤10,000/μL at baseline, but they poorly responded to eltrombopag initially, compared with the same patient sub-population in Foreign Study TRA102537 [see "4.(iii).B.3).(b).iv) Effects of patient background factors on the efficacy of eltrombopag]. Although the subjects were limited, it cannot be ruled out that the poor response might have been caused by the low starting dose of eltrombopag in Japanese Study TRA108109, which was 12.5 mg, one fourth of that in Foreign Study TRA102537. On the other hand, even in the concerned patient sub-population, the data demonstrated that dose adjustment according to the platelet count led to a certain level of the response rate without any safety issues. Based on the currently available information, it is acceptable to set the starting dose at 12.5 mg. However, since ITP patients with a platelet count of ≤10,000/μL may experience serious bleeding, the platelet count should be increased immediately. Therefore, it is necessary to collect information on the safety and efficacy of eltrombopag in ITP patients with a platelet count of ≤10,000/μL in post-marketing surveillance.

4.(iii).B.7).(b) Discontinuation criteria for non-responders to eltrombopag

Considering that some patients did not respond to eltrombopag, PMDA asked the applicant to explain the measures for preventing injudiciously continued administration of eltrombopag in non-responder patients.

The applicant responded as follows:

The effect of eltrombopag generally appears within 1 to 2 weeks. If the platelet count does not increase following the 4-week treatment of eltrombopag at 50 mg, the maximum dose in Japan, and a clinically significant bleeding tendency does not resolve, the withdrawal of eltrombopag should be considered. To prevent injudiciously continued administration of eltrombopag in non-responder patients with chronic ITP, the following caution statement will be included in the "Precautions for Dosage and Administration" section in the proposed package insert: "discontinuation of eltrombopag should be considered for the patient in whom the platelet count does not increase following the 4-week treatment with eltrombopag at the daily dose of 50 mg, and clinically significant bleeding tendency does not resolve."

PMDA considers as follows:

It is appropriate to determine whether or not the treatment should be continued based on the platelet count following the 4-week treatment of eltrombopag 50 mg, because (1) in the subjects in whom the dose was increased to 50 mg at least once due to a platelet count of <50,000/μL during the 26-week treatment period in Japanese Study TRA108109, the platelet count increased following the dose increase to 50 mg [see "4.(iii).B.7).(a) Appropriateness of proposed dosage

and administration"]; and because in healthy adult subjects, the platelet-increasing effect of eltrombopag appeared 8 days after the start of the multiple-dose administration and reached the peak 6 days after the last dose (16 days after the start of the multiple-dose administration) in most subjects [see "4.(ii).A.(6).1) Effects of eltrombopag on platelet count], suggesting that the 4-weeks treatment period would be long enough to observe response to the increased dose. Since the correlation between the platelet count and bleeding tendency varies from individual to individual, PMDA considers that the usefulness of eltrombopag is expected when bleeding episodes improve even if the increase in platelet count is mild, and that the applicant's proposal is acceptable.

4.(iii).B.7).(c) Measures to prevent rapid increase in platelet count due to treatment with eltrombopag

PMDA asked the applicant to present measures to prevent a rapid increase in the platelet count due to treatment with eltrombopag, considering changes in blood platelet over time and the patterns of occurrence of adverse events in subjects receiving eltrombopag.

The applicant responded as follows:

In Japanese Study TRA108109 and Foreign Study TRA102537, the dose was adjusted according to the platelet count to prevent a rapid increase in the platelet count. In Japanese Study TRA108109, 3 of 23 subjects suspended the eltrombopag treatment due to an increase in platelet count to >400,000/μL. In these subjects, the time to achieve the platelet count >400,000/μL was 92, 142, and 162 days after the start of treatment or all 15 days after the dose adjustment (dose increase from 25 to 50 mg). In addition, the duration of the platelet count remaining at >400,000/μL was 10, 8, and 8 days. On the other hand, in Foreign Studies TRA100773A, TRA100773B, TRA108057, and TRA102537, the median time to achieve the platelet count >400,000/μL was 15 or 16 days after the start of treatment. In Foreign Study TRA105325, the median time (range) to achieve the platelet count >400,000/μL was 46 days (8-558 days) after the start of treatment, but when data from subjects who received rescue drugs before achieving the platelet count >400,000/μL were excluded, it was 22 days (8-558 days). The above data showed that the time to achieve the platelet count >400,000/μL would be 2 to 3 weeks after the start of treatment or dose adjustment.

Adverse reactions caused by rapid increase in the platelet count may be thromboembolic events. In Japanese Study TRA108109, 1 of 23 subjects experienced transient ischaemic attack. The concerned subject started the eltrombopag treatment at a dose of 12.5 mg, and transient ischaemic attack was suspected on Day 9. The event resolved 3 days after the onset. In the concerned subject, the platelet count was changed as follows: 19,000/μL (baseline) →76,000/μL (8 days after the start of treatment) →154,000/μL (5 days after withdrawal) →25,000/μL (19 days after withdrawal) →18,000/μL (26 days after withdrawal). On the other hand, investigation of the relationship between the platelet count and thromboembolic events in Foreign Studies TRA100773A, TRA100773B, TRA108057, TRA102537, and TRA10325 showed no specific trend between platelet count and thromboembolic adverse events. [see 4.(iii).B.4).(a) Risk of thromboembolism].

Approximately 1 year has passed since the market launch without any issues in the US, and therefore, the "Precautions for Dosage and Administration" in the package insert to be used in Japan will include the following dose adjustment criteria which is the same as specified in the dosage and administration approved in the US:

- The platelet count should be measured every week for at least the first 2 to 3 weeks after the start of treatment or dose adjustment of eltrombopag. The same dose should be maintained for at least 2 weeks to check the effect of the dose administered.
- The dose reduction of eltrombopag is recommended when the platelet count ranges from

200,000 to 400,000/μL.
- Eltrombopag should be interrupted when the platelet count exceeds 400,000/μL. Eltrombopag should be resumed at a dose reduced from the previous one when the platelet count decreased to 150,000/μL.

PMDA considers as follows:
The dose adjustment procedures mentioned above are appropriate since the adjustment procedures are almost comparable to the criteria for dose adjustment in Japanese Study TRA108109 except for the dose, although it remains unknown whether thromboembolic events can be avoided by monitoring the platelet count carefully and adjusting the dose in accordance with the above criteria. However, the criteria used in Japanese Study TRA108109 specified a reduction of the dose to the next lower dose for the patient with a platelet count of 200,000 to 400,000/μL, and therefore, more careful actions are necessary for the above procedure.

PMDA asked the applicant to explain the appropriateness of the upper limit of platelet count at 400,000/μL in Japan, considering that in Europe, eltrombopag has been approved for the use in patients with chronic ITP under the dosage and administration by which the dose is adjusted to control the platelet count up to 250,000/μL based on the data from Foreign ELEVATE Study in patients with chronic hepatic diseases accompanied by thrombocytopenia.

The applicant responded as follows:
No clinical studies setting the upper limit of platelet count at 250,000/μL have been conducted in patients with chronic ITP, and in Japanese and foreign clinical studies in patients with chronic ITP setting the upper limit of platelet count at 400,000/μL, no specific trend was observed between platelet count increased and thromboembolic events due to the eltrombopag treatment. Therefore, even if the upper limit of the platelet count was set at 400,000/μL, thromboembolism, which occurred in Foreign ELEVATE Study, would be unlikely to occur in patients with chronic ITP. The applicant thus considers it appropriate to set the upper limit of platelet count at 400,000/μL. However, pathology of chronic ITP are different from that of chronic hepatic diseases, but Foreign ELEVATE Study suggested that the thromboembolic events might be related to platelet count increased. The following caution statement will be included in the proposed package insert: the platelet count exceeding the normal range may increase the risk of thromboembolism, and the dose should be adjusted at the lowest dose level therapeutically required.

PMDA accepts the applicant's claim that a relationship between the platelet count and thromboembolic adverse events in patients with chronic ITP remains to be clarified at present, but considers it necessary to present findings in Foreign ELEVATE Study as the relevant information appropriately.

4.(iii).B.7).(d) Dose for resumption of treatment
PMDA asked the applicant to consider whether or not cautions to conform to the following protocols should be provided more specifically: the protocols of Japanese Study TRA108109 and Foreign Study TRA102537 specified that after withdrawal, eltrombopag should be resumed at a dose reduced by 1 level from the dose at withdrawal.

The applicant explained as follows:
The applicant investigated the relationship between the doses before and after withdrawal and platelet counts over time in subjects who were included in Japanese Study TRA108109 and Foreign Study TRA102537 and who resumed treatment with eltrombopag after withdrawal. As a result, of 3 subjects who resumed treatment at the reduced dose after withdrawal in Japanese Study TRA108109, 1 treated with eltrombopag at a dose of 25 mg (reduced from 50 mg) presented a rapid decrease in platelet count, but 2 treated with eltrombopag at a dose of 12.5 mg (reduced

from 25 mg) had the platelet count appropriately maintained. In Foreign Study TRA102537, of 8 subjects who resumed treatment at the withdrawal dose without dose decrease (25 mg/day, 6 subjects; 50 mg/day, 1 subject; 75 mg/day, 1 subject), 7 (88%) met the withdrawal criteria again. As shown above, when the treatment is resumed after withdrawal, the platelet count can be maintained appropriately at a dose reduced by 1 level from the dose at withdrawal.

In Japan, dose-adjustment in increments of 12.5 mg is feasible, but the feasible increment in foreign countries is different. PMDA considers it desirable to describe the dose-decrease method at resumption of eltrombopag after withdrawal more specifically but the details will be reviewed, taking account of comments raised in the Expert Discussion.

4.(iii).B.7).(e) Regimen for the case where the dose-adjustment in increments of <12.5 mg/day is necessary

The applicant explained the dose adjustment in patients who are considered to be overdosed with eltrombopag 12.5 mg once-daily regimen as follows:

Since the dose adjustment deviated from the protocol was not allowed in Japanese Study TRA108109, no subjects fell into modification of the dosing interval, and 4 of 23 subjects had eltrombopag interrupted at a dose of 12.5 mg/day in accordance with the protocol. In 2 of the 4 subjects, the dose was initially reduced from 25 to 12.5 mg due to a platelet count of >200,000/μL, but the platelet count remained at >200,000/μL during the first 1 week after dose reduction, resulting in discontinuation of eltrombopag. In the remaining 2 subjects, the platelet count exceeded 200,000/μL during the treatment with eltrombopag at a dose of 12.5 mg, resulting in discontinuation of eltrombopag. As described above, the platelet count remained high under the eltrombopag 12.5 mg once-daily regimen in some subjects. The platelet count appropriate for patients will be controlled by modifying the dosing interval to reduce the daily dose of eltrombopag.

PMDA asked the applicant to explain the efficacy and safety of eltrombopag at the modified dosing interval in patients who actually required a dose reduction to <12.5 mg/day.

The applicant presented the interim analysis report of Japanese Study TRA111433 (submitted in [redacted], 20[redacted]), which allowed eltrombopag to be administered at different doses alternatively or at modified dosing intervals to the subjects requiring the dose adjustment to <12.5 mg/day and explained as follows:

Of 19 subjects in Japanese Study TRA111433, 9 had to receive eltrombopag at a dose <12.5 mg/day or at different doses alternatively to adjust the dose, in order to control the platelet count within a range from ≥50,000/μL to ≤400,000/μL. A total of 19 dose adjustments were made. 3 subjects received eltrombopag at the dose <12.5 mg/day by modifying the dosing interval, 8 subjects received it at different doses alternatively (some used both regimens). With these regimens allowed, the treatment period (after regimen modification) was 7 to 239 days. The regimen with doses of 12.5 and 25 mg administered alternatively was most frequently adopted, which was required by 4 of 19 subjects. In subjects under regimens with 12.5 mg at a modified dosing interval (<12.5 mg/day) or ones with different doses administered alternatively, the platelet count after regimen modification was almost maintained within a range from ≥50,000/μL to ≤400,000/μL without any particular safety issues.

PMDA considers as follows:

Only 3 patients received eltrombopag at a dose of 12.5 mg every alternate day, and at present, it cannot be concluded that the alternate-day regimen is superior to repeating of withdrawal and resumption of treatment with eltrombopag from the viewpoints of the efficacy and safety. Therefore, it is inappropriate to recommend the regimen with a modified dosing interval in the "Precautions for Dosage and Administration" section by stating that "the dosing interval may be modified for patients requiring a dose adjustment to <12.5 mg/day." Concerning whether

withdrawal and resumption of the treatment should be repeated, or regimens allowing continuous treatment but lacking in evidence of the efficacy and safety should be presented for patients in whom eltrombopag may be overdosed at 12.5 mg/day, a final decision will be made, taking account of comments raised in the Expert Discussion.

4.(iii).B.8) Others

4.(iii).B.8).(a) Function of platelet increased by eltrombopag

The applicant explained the function of platelets increased by eltrombopag as follows:
Pharmacodynamic analysis in Japanese Study TRA105580 and Foreign Studies SB-497115/002 and TRA102860 in Japanese and foreign healthy adult subjects did not show any effects of eltrombopag on platelet aggregation in any study. A platelet function test in Foreign Study TRA100773A conducted in patients with chronic ITP showed that the platelet aggregation was changed from abnormal to normal during the eltrombopag treatment period in 10 of 23 subjects, but no opposite change (from normal to abnormal) was observed. In Foreign Study TRA109678, platelet function was evaluated *in vitro* using platelet samples collected from the subjects at baseline and during the eltrombopag treatment period. The results suggested that eltrombopag would be unlikely to induce platelet activation or platelet hyperfunction in the body. In addition, there are no findings showing that platelets produced by eltrombopag in patients with chronic ITP are different from those in healthy adult subjects in terms of the morphology and function.

PMDA considers that the function of platelets increased by eltrombopag has no specific problem.

4.(iii).B.8).(b) Effects of eltrombopag on anti-platelet antibody

The applicant explained effects of eltrombopag on anti-platelet antibody as follows:
In all of Foreign Studies TRA102537, TRA108057, and TRA105325, of 3 types of anti-platelet antibodies (anti-GPIIb/IIIa, anti-GPIb/IX, and anti-GPIa/IIa antibodies), at least 1 was detected in a part of the subjects, but the level of anti-platelet antibodies did not show any consistent change during the study period. Accordingly, anti-platelet antibody is most unlikely to develop or increase in association with the platelet-increasing effect of eltrombopag.

PMDA accepted the applicant's explanation.

4.(iii).B.9) Post-marketing surveillance

PMDA asked the applicant to plan post-marketing surveillances to evaluate the long-term safety (including haematological malignancies and rebound effects due to withdrawal of eltrombopag) and efficacy of eltrombopag, since very few Japanese subjects were included in Japanese clinical studies, and the information on the safety of long-term treatment with eltrombopag was not sufficient.

The applicant explained the post-marketing surveillance as follows:
A drug use-results survey in all of the patients with chronic ITP who received eltrombopag and provided the consent to the participation in the survey is currently planned, aiming to evaluate the safety and efficacy of long-term treatment with eltrombopag (1 year from start of the treatment, up to 2 years) in clinical practice. In this survey, thromboembolism is set as the priority investigation item, and the platelet count will be measured during the 1-month follow-up period after the withdrawal of eltrombopag to ascertain whether or not a rebound effect occurs. The investigation items will include a history of previous treatment for ITP, use status of eltrombopag (dose, treatment period, actual dose changes [increase or decrease]), and concomitant ITP-therapeutic drugs. Furthermore, information on platelet count decreased after the withdrawal or suspension of the treatment, hepatobiliary-related events, haemorrhagic adverse events, cataract, increased bone marrow reticulin, haematological malignancies, and renal-function-related events will be collected from use-results surveys, spontaneous reports, presentations at academic meetings, literatures, and databases in foreign countries.

PMDA considers as follows:
The applicant's proposed investigation items are almost appropriate, but the currently available experience with eltrombopag treatment in Japanese ITP patients is very limited. Therefore, all ITP patients treated with eltrombopag should be included in the surveillance (all-case surveillance). In addition, it is important to examine whether or not the patients ineligible for treatment with eltrombopag can be predicted by setting the characteristics of patients as investigation items. The conduct of all-case surveillance and the appropriateness of the surveillance plan 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

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

A document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, there were no particular problems. Thus, PMDA has concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

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

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data (5.3.5.1.1, 5.3.3.2.1) submitted in the new drug application. As a result, defective contract documents for partial consignment of practical works and protocol deviations (non-compliance with renal function test schedule) were found at some clinical trial sites. The inspection revealed that the sponsor did not immediately inform the investigators and heads of the clinical trial sites of the information about unknown serious adverse events, for which a causal relationship could not be ruled out, when the information became available to the sponsor. PMDA has concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

IV. Overall Evaluation

Based on the submitted data, PMDA has concluded that the efficacy of eltrombopag for chronic idiopathic thrombocytopenic purpura (ITP) has been demonstrated, and the safety of eltrombopag is acceptable in view of its observed benefits. Eeltrombopag is a TPO-R agonist activating a part of the TPO signal transduction pathway through interaction with TPO-R and can be useful in patients with chronic ITP resistant or intolerable to the conventional treatment. The appropriateness of the dosage and administration and cautions as well as post-marketing information to be investigated should be further reviewed. All the patients treated with eltrombopag should be included in the post-marketing surveillance.

PMDA considers that the product may be approved if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

Review Report (2)

August 17, 2010

I. Product Submitted for Registration

[Brand name]	Revolade Tablets 12.5 mg and 25 mg
[Nonproprietary name]	Eltrombopag Olamine
[Applicant]	GlaxoSmithKline K.K.
[Date of application]	September 30, 2009

II. Content of the Review

The outline of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described 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 Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1. Dosage and Administration and Precautions for Dosage and Administration

(1) Requirement for meals and concomitant use with multivalent-cation containing drugs

The following conclusions by PMDA were discussed:

- The "Dosage and Administration" section should include a statement that eltrombopag should be administered on an empty stomach (>2 hours before or after a meal), although the time window of dosing might be narrowed, because the plasma eltrombopag concentration has been shown to decrease greatly following fed administration compared with fasted administration, and the efficacy and safety of eltrombopag were demonstrated in Japanese and foreign clinical studies where eltrombopag was to be administered >2 hours before or after a meal.
- It is inevitable to provide a caution that "dosing interval between eltrombopag and multivalent-cation containing drugs should be ≥4 hours" as done in the US, because concomitant use with multivalent-cation containing drugs has been clearly shown to decrease the plasma eltrombopag concentration, but the length of dosing interval to prevent the such concomitant use of the drugs from affecting the pharmacokinetics of eltrombopag remains unknown.

The following comments were raised from the expert advisors:

- The above statement should be included in the "Dosage and Administration" section if the requirement with regard to meals is appropriate for information provision, although it might be undesirable if the narrowed dosing window leads to poor compliance.
- Administration at bedtime may meet the requirement and maintain the compliance.
- Data have demonstrated that the pharmacokinetics of eltrombopag is affected by meals and it is important to specify the requirement even though instructions for the drug use may be complicated.
- For patients who cannot comply with the dosage and administration including requirements for meals, eligibility for eltrombopag treatment should be considered.
- Information on the reason why the dosing timing has been specified with regard to meals should be provided by the package insert.

Concerning dosing intervals with multivalent-cation containing drugs, cautions may be provided based on the foreign data as done in foreign countries and it would be unnecessary to conduct post-marketing clinical studies for the pharmacokinetics of concomitant use of eltrombopag with

multivalent-cation containing drugs in Japanese patients. The expert advisors agreed that information on the relationships of such drugs with the dosing time of eltrombopag and meal time should be collected via post-marketing surveillance.

Based on the above, PMDA has concluded that the "Dosage and Administration" section has to include a statement that eltrombopag should be administered on an empty stomach (>2 hours before or after a meal), and thus the appropriate statement for "Dosage and Administration" of eltrombopag is "The usual initial adult dosage of eltrombopag is 12.5 mg once daily administered orally on an empty stomach (>2 hours before or after a meal). The dose may be adjusted according to the patient's platelet count and condition. The maximum daily dose is 50 mg."

(2) Dose adjustment procedure

Concerning the dose adjustment method of eltrombopag according to the platelet count, the following comments were raised from the expert advisors:

The proposed package insert specified that the dose should be increased at a platelet count of ≤50,000/μL, decreased at a platelet count of 200,000 to 400,000/μL, and withdrawn at a platelet count of ≥400,000/μL. The above instructions may be in accordance with the dose adjustment criteria in clinical studies where the platelet count-increasing effect of eltrombopag was to be evaluated, but if such instructions are followed in clinical practice where eltrombopag would be used to alleviate the bleeding tendency, an undesirable overdose may be caused. The acceptable platelet count in patients with chronic ITP may be around 30,000/μL if active bleeding is absent or may be around 50,000/μL (for outpatients, around 100,000/μL) if active bleeding is considered. The dose reduction or withdrawal should be therefore suggested if the platelet count exceeds 50,000/μL.

Furthermore, the following comments were raised from the expert advisors:

- Eeltrombopag should be used at a therapeutically minimum dose, and thus the dose reduction should be considered as appropriate even at a platelet count of approximately 50,000/μL to 200,000/μL although appropriate platelet counts vary from individual to individual.
- The dose must be decreased at a platelet count of 200,000 to 400,000/μL.

In consideration of the above, PMDA asked the applicant to revise the dose adjustment procedure in accordance with the conclusion of the Expert Discussion, for instance, including an additional cautionary statement in the "Precautions for Dosage and Administration" section to the effect that dose reduction may be considered as appropriate even at a platelet count of 50,000 to 200,000/μL. The statement was not clearly noted in the proposed package insert.

The applicant responded that the cautionary statements will be revised in accordance with the direction of PMDA, and PMDA accepted this response.

(3) Appropriateness of dose adjustment to <12.5 mg once daily

For patients in whom the dose of eltrombopag 12.5 mg once daily is assessed to be excessive, the applicant proposed a prolonged dosing interval in the proposed package insert. In response to this proposal, PMDA has concluded that this proposal cannot be recommended in the package insert as an option of the dosage and administration, because the efficacy and safety of the alternate-day regimen is unknown and it cannot be determined that continuation of the alternate-day regimen is superior (or not inferior) to repeating of withdrawal and resumption of the treatment. The above conclusion of PMDA was discussed.

The following comments were raised from the expert advisors:

- Since eltrombopag is used while the platelet count is being monitored, alternate-day treatment at 12.5 mg may not cause any significant issues despite a lack of evidence and may

be better compared with withdrawal and resumption of the treatment in maintaining the platelet count at a certain level. However, since the patient characteristics may vary and the evidence for dose adjustment to <12.5 mg/day is limited, and it is difficult to present recommended regimens more specifically at present.

- It is practical to determine the dosage and administration individually by attempting different approaches for each patient, and thus the modified dose adjustment to <12.5 mg/day can be used at the discretion of the attending physician.
- From viewpoints of both efficacy and safety, setting the rest period seems acceptable for the patients in whom dose adjustment to <12.5 mg/day is necessary, but it is difficult to describe the specific regimen at the dose of <12.5 mg/day in the package insert based on the currently available information, and thus a change to the other treatment should be considered for patients in whom the dose of 12.5 mg/day is excessive.

In the end, PMDA's conclusion was supported by the expert advisors.

In consideration of the above, PMDA asked the applicant to delete the description for dose adjustment to <12.5 mg once daily from the "Precautions for Dosage and Administration" section in the proposed package insert.

The applicant responded that the concerned description will be deleted, and PMDA accepted this response.

(4) Platelet counts over time after withdrawal of the treatment

The following conclusion of PMDA was supported by the expert advisors: It is appropriate to provide in the proposed package insert a caution against bleeding after withdrawal, because a transient decrease in platelet count occurred after the withdrawal of the eltrombopag treatment, thereby failing to rule out rebound effects, and because the platelet count decreased to the baseline level within 2 weeks after the withdrawal of the eltrombopag treatment in almost all subjects, indicating that cautions against disappearance of the drug effect and haemorrhage risk after the withdrawal (termination) of the eltrombopag treatment should be provided, and the relevant information should be collected via post-marketing surveillance.

2. Indications

In consideration of the designs of and results from the clinical studies, PMDA has concluded that eltrombopag is indicated for "chronic idiopathic thrombocytopenic purpura," and the "Precautions for Indications" section should include the cautionary statements that "Eltrombopag should be used when other treatment options are not sufficiently effective or have limitations due to tolerability." and "Eltrombopag should be used when a haemorrhage risk is assessed to be high based on the platelet count and clinical symptoms."

For the above conclusions, the expert advisors commented that eltrombopag would not cure "chronic idiopathic thrombocytopenic purpura" but provide symptomatic treatment, that is, it alleviates the bleeding tendency by increasing the platelet count, and thus, the indication should be set as "alleviation of the bleeding tendency due to chronic idiopathic thrombocytopenic purpura." Discussion, however, involved a view that the bleeding tendency would not be an absolute condition required for the indication. The above conclusions of PMDA were finally supported by the expert advisors.

3. Monitoring of liver function test

Issues about the monitoring of liver function tests specified in "Important Precautions" section in the proposed package insert, including the frequency, criteria for treatment withdrawal in patients

with abnormal values, and appropriateness or sufficiency of precautionary statements about hepatic impairment, were discussed considering that the foreign labeling and results from Japanese and foreign clinical studies do not suggest that increased frequency of hepatic impairment associated with eltrombopag. Concerning PMDA's conclusion that attention should be paid to abnormal hepatobiliary laboratory values associated with eltrombopag, the following comments were raised from the expert advisors:

- At present, the monitoring method for hepatic impairment described in the proposed package insert is appropriate.
- An appropriate precautionary statement would be "liver function test should be performed as appropriate, since hepatic impairment may occur" at present, because the criteria for treatment withdrawal in patients with hepatic impairment in the proposed package insert, which was defined in accordance with the US labeling, is unlikely to be supported by scientific evidence.
- Precautionary statements should specify that liver function test be performed at the same timing as the test for the platelet count after the start of treatment, and that after the platelet count is stabilized without any abnormal findings in terms of the hepatic functions, liver function test be performed every month.
- It would be necessary to identify the high-incidence period of hepatic impairment, and when the high-incident period and stable dose period overlap, liver function test should be performed every 2 weeks even during the stable dose period.

In addition, the following comments were raised from the expert advisors:

- The test after confirmation of hepatic impairment or withdrawal criteria should be specified, taking account of characteristics of individual patients.
- The withdrawal criteria described in the "Adverse Reactions" section in the proposed package insert is more appropriate in consideration of the patient safety.

Finally, the expert advisors reached an agreement with inclusion of the following statement in the "Important Precautions" section: "Hepatic impairment may occur following treatment with eltrombopag. Liver function test (AST [GOT], ALT [GPT], bilirubin) should be performed at baseline, every 2 weeks during the dose adjustment period, and every month during the stable dose period (see the "Clinically Significant Adverse Reactions" section)."

In consideration of the above, PMDA asked the applicant to revise the description related to hepatic impairment in the "Important Precautions" section.

The applicant responded that the description will be revised in accordance with the direction of PMDA, and PMDA accepted this response.

4. Post-marketing surveillance

PMDA's conclusion on post-marketing requirements is as follows:

The applicant's plans for post-marketing requirements, described below, are largely appropriate. The drug use-results survey will be conducted to evaluate the safety and efficacy of long-term treatment with eltrombopag (1 year from the start of treatment, up to 2 years) in routine clinical practice by setting thromboembolism (priority investigation item), platelet counts over time after the withdrawal of eltrombopag, history of previous treatment of ITP, actual use of eltrombopag, and concomitant ITP therapeutic drugs as the investigation items, and by collecting the information on hepatobiliary-related events, haemorrhagic adverse events, and adverse events related to cataract and renal functions. In addition, the literature search will be performed to collect information on the occurrence of increased bone marrow reticulin and haematologic malignancy, whose frequency is unknown or likely to be low, through spontaneous adverse reaction reports, presentations at academic meetings, literature, and databases in foreign countries.

However, all the ITP patients treated with eltrombopag should be included in the surveillance (all-case surveillance) and it would be also necessary to set the investigation items so as to investigate a relationship between platelet count and bleeding and identify the characteristics of patients who are ineligible for treatment with eltrombopag.

The above conclusions of PMDA were supported by the expert advisors.

In addition, the following comments were raised from the expert advisors:

- Information useful for evaluation of eligibility of patients should be collected.
- The safety information should be collected without fail from patients in whom chronic ITP was ruled out eventually.
- A flexible surveillance plan should be prepared so that patients receiving eltrombopag for >2 years can be included in the surveillance, where necessary, in response to the information collected in the post-marketing surveillance and future findings such as information from foreign countries.

In consideration of the above, PMDA asked the applicant to submit an outline of the post-marketing surveillance plan in which the above information could be appropriately collected.

The applicant revised the outline of the post-marketing surveillance plan and responded as follows:
Drug use-results surveys will include all of the patients treated with eltrombopag. The investigation items will be reviewed, aiming to ensure investigations requested by PMDA. The plan will include a rule so that the follow-up period can be extended where necessary.

PMDA accepted the applicant's response since the submitted outline of the plan is almost appropriate, although the details of the protocol will have to be further examined.

III. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the indication and dosage and administration as shown below, with the following condition. The re-examination period of the product should be 10 years, and both drug substance and drug product are classified as a powerful drug, and the product is not classified as a biological product or a specified biological product.

[Indication]	Chronic idiopathic thrombocytopenic purpura
[Dosage and administration]	The usual initial adult dosage of eltrombopag is 12.5 mg once daily administered orally on an empty stomach (>2 hours before or after a meal). The dose may be adjusted according to the patient's platelet count and condition. The maximum daily dose is 50 mg.
[Conditions for approval]	Since the product has been studied in only a limited number of patients in Japan, the applicant is required to conduct a drug use-results survey involving all patients treated with the product after market launch until data from a certain number of patients have been accumulated in order to understand the characteristics of patients treated. At the same time, the data about the safety and efficacy of the product should be collected without delay and

necessary measures should be taken to ensure that the product is properly used.