Report on the Deliberation Results

August 10, 2017

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

Brand Name	Revolade Tablets 12.5 mg, Revolade Tablets 25 mg
Nonproprietary Name	Eltrombopag Olamine (JAN*)
Applicant	Novartis Pharma K.K.
Date of Application	November 30, 2016

Results of Deliberation

In its meeting held on August 1, 2017, the First Committee on New Drugs concluded that the application for partial change for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 10 years.

Condition of Approval

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

July 20, 2017
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Revolade Tablets 12.5 mg, Revolade Tablets 25 mg
Nonproprietary Name	Eltrombopag Olamine
Applicant	Novartis Pharma K.K.
Date of Application	November 30, 2016
Dosage Form/Strength	Each tablet contains eltrombopag olamine equivalent to 12.5 mg or 25 mg of eltrombopag
Application Classification	Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage
Items Warranting Special Mention	Orphan drug (Drug Designation No. 391 [*28 yaku*]; PSEHB/PED Notification No. 1124-6, issued by the Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated November 24, 2016)
Reviewing Office	Office of New Drug I

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of aplastic anemia, and that the products has acceptable safety in view of its benefits (see Attachment).

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

Indications

1. Chronic idiopathic thrombocytopenic purpura
2. Aplastic anemia

(Underline denotes additions.)

Dosage and Administration

1. Chronic idiopathic thrombocytopenic purpura

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 based on the patient's platelet count and condition. The maximum daily dose is 50 mg.

2. Aplastic anemia

Patients naïve to anti-thymocyte globulin

In combination with anti-thymocyte globulin, the usual adult dosage of eltrombopag is 75 mg once daily administered orally on an empty stomach (>2 hours before or after a meal). The dose may be reduced based on the patient's condition.

Patients with an insufficient response to existing treatment

The usual initial adult dosage of eltrombopag is 25 mg once daily administered orally on an empty stomach (>2 hours before or after a meal). The dose may be adjusted based on the patient's condition. The maximum daily dose is 100 mg.

(Underline denotes additions.)

Condition of Approval

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

June 16, 2017

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency.

Product Submitted for Approval

Brand Name	Revolade Tablets 12.5 mg, Revolade Tablets 25 mg
Nonproprietary Name	Eltrombopag Olamine
Applicant	Novartis Pharma K.K.
Date of Application	November 30, 2016
Dosage Form/Strength	Each tablet contains eltrombopag olamine equivalent to 12.5 mg or 25 mg of eltrombopag

Proposed Indications

1. Chronic idiopathic thrombocytopenic purpura
2. Aplastic anemia

(Underline denotes additions.)

Proposed Dosage and Administration

1. Chronic idiopathic thrombocytopenic purpura

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 based on the patient's platelet count and condition. The maximum daily dose is 50 mg.

2. Aplastic anemia

Patients who had an insufficient response to or were unsuitable for existing treatment

The usual initial adult dosage of eltrombopag is 25 mg once daily administered orally on an empty stomach (>2 hours before or after a meal). The dose may be adjusted based on the patient's platelet count. The maximum daily dose is 100 mg.

In combination with anti-thymocyte globulin

The usual adult dosage of eltrombopag is 75 mg once daily administered orally on an empty stomach (>2 hours before or after a meal). The dose may be reduced based on the patient's platelet count.

(Underline denotes additions.)

Table of Contents

List of Abbreviations

AA	Aplastic anemia
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AML	Acute myeloid leukemia
AST	Aspartate aminotransferase
ATG	Anti-thymocyte globulin
ATG/CsA	Anti-thymocyte globulin/ciclosporin
$AUC_{0\text{-inf}}$	Area under concentration-time curve up to infinity
$AUC_{0\text{-}\tau}$	Area under concentration-time curve during dose interval
CTD	Common technical document
C_{max}	Maximum concentration
CR	Complete response
CsA	Ciclosporin
FAS	Full Analysis Set
GCP	Good Clinical Practice
HLA	Human leukocyte antigen
ITP	Idiopathic thrombocytopenic purpura
MCV	Mean corpuscular volume
MDS	Myelodysplastic syndrome
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
NR	No response
OATP1B1	Organic anion transporting polypeptide 1B1
PMDA	Pharmaceuticals and Medical Devices Agency
PNH	Paroxysmal nocturnal hemoglobinuria
PR	Partial response
QTcF	QT interval corrected for heart rate according to Fridericia's formula
Reference Guide for Treatment of Aplastic Anemia 2016	Reference Guide for the Treatment of Aplastic Anemia 2016 (edited by the Research and Study Team on Idiopathic Hematopoietic Disorders; Research Project on Policy of Measures for Intractable/Rare Diseases; funded by Health and Labour Sciences Research Grant)
Study E1201	A Japanese phase II/III study (CTD 5.3.5.2-1, Study No. CETB115E1201)
Study E1202	A Japanese phase II/III study (CTD 5.3.5.2-2, Study No. CETB115E1202)
t_{max}	Time to reach maximum concentration
TPO	Thrombopoietin

UGT1A1	UDP (uridine diphosphate)-glucuronosyltransferase 1A1
ULN	Upper limit normal
γ-GTP	γ-glutamyltransferase

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Aplastic anemia (AA) is a bone marrow failure syndrome characterized by peripheral pancytopenia and bone marrow hypoplasia. Affected patients commonly present with anemia symptoms, such as shortness of breath on exertion, palpitations, and dizziness, and bleeding symptoms such as subcutaneous bleeding spots, gingival bleeding, and epistaxis.

Therapeutic choice for AA depends on age, severity, availability of a donor, responsiveness to immunosuppressive therapy, etc. Bone marrow transplantation is the first-line therapy for patients with slightly severe or greater AA aged <40 years who have a human leukocyte antigen (HLA)-identical sibling donor. However, bone marrow transplantation is not indicated for patients aged ≥40 years or have no matched donor (Reference Guide for Treatment of Aplastic Anemia 2016). Currently, a combination of human anti-thymocyte globulin (ATG) and ciclosporin (CsA) (ATG/CsA) is the standard treatment for patients with slightly severe or greater AA who are ineligible for transplantation, but more effective treatment is needed in clinical practice. Blood transfusion is the mainstream treatment for patients with AA who are non-responders to or ineligible for ATG/CsA. However, transfusion is associated with risks of infections, refractoriness to platelet transfusion, etc., and, therefore, other treatment options are awaited.

Eltrombopag olamine (hereinafter referred to as eltrombopag) is a thrombopoietin (TPO) receptor agonist. Eltrombopag interacts with TPO receptors expressed in megakaryocytes and bone marrow progenitor cells, thereby enhancing the proliferation and differentiation of these cells (*Stem Cell Res.* 2012;9:7-86). Eltrombopag was approved for the indication of "chronic idiopathic thrombocytopenic purpura" in October 2010 in Japan. TPO receptors are expressed in hematopoietic stem cells and other precursor cells of other lineages, as well as platelets and megakaryocytes (*Blood.* 1996;87:2162-2170). The National Institute of Health (NIH) therefore conducted a clinical trial (Study NIH 09-H-0154) in patients with severe AA refractory to ATG/CsA and reported that eltrombopag stimulates hematopoiesis (*N Engl J Med.* 2012;367:11-19).

The applicant has recently filed a partial change application for the marketing approval of eltrombopag, claiming the efficacy and safety of eltrombopag based on the results of 2 Japanese phase II/III clinical studies in patients with AA with an insufficient response to existing treatment and ATG-therapy-naïve patients with AA (Studies CETB115E1201 and CETB115E1202). Eltrombopag was approved for the indication of severe AA refractory to immunosuppressive therapy in August 2014 in the US and in September 2015 in Europe. As of June 2017, eltrombopag has been approved in ≥30 countries. Eltrombopag was also designated as an orphan drug with a proposed indication of treatment of aplastic anemia on November 24, 2016 (Drug Designation No. 391 [*28 yaku*]).

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

The application was submitted for the approval of a new indication and a new dosage, and thus no quality-related data were submitted.

3. Nonclinical Pharmacology and Outline of the Review Conducted by PMDA

The application was filed for the approval of a new indication and a new dosage, and no new study data were submitted in light of eltrombopag's specificity shown only to human or chimpanzee TPO receptors[1)] and no chimpanzee AA model reported or established, etc. TPO receptors are expressed in bone marrow hematopoietic stem cells and precursor cells (*Blood.* 1996;87:2162-2170), and the stimulating effect of TPO on hematopoiesis has been suggested (*Blood.* 1994;84:4045-4052; *Blood.* 2002;100:786-790; and other articles). These findings suggest that eltrombopag promotes proliferation and differentiation of bone marrow hematopoietic stem cells and precursor cells, which are mediated by TPO receptors, and in turn increases multilineage blood cell counts.

4. Nonclinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The application was filed for the approval of a new indication and a new dosage, and no new nonclinical pharmacokinetic study data were submitted because the nonclinical pharmacokinetics were evaluated at the initial approval.[1)]

5. Toxicity and Outline of the Review Conducted by PMDA

The application was filed for the approval of a new indication and a new dosage, and no nonclinical toxicity data were submitted.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Biopharmaceutic Studies and Associated Analytical Methods

The Japanese phase II/III studies (Study CETB115E1201 [Study E1201] and Study CETB115E1202 [Study E1202]) used the tablet formulation identical to that for commercial-use. The foreign phase I study (Study RAD201583) used the commercially-available tablets. Plasma concentrations of unchanged eltrombopag were measured with liquid chromatography-tandem mass spectrometry with a lower limit of quantification of 100 ng/mL.

6.2 Clinical Pharmacology

6.2.1 Japanese phase II/III study in patients with AA with an insufficient response to existing treatment (CTD 5.3.5.2-1, Study CETB115E1201 [July 2014 to [redacted] 20[redacted], to be conducted until the day of approval])

The study is outlined in Section 7.1.1.

The pharmacokinetics of eltrombopag was investigated in Japanese patients with moderate or more severe AA, aged ≥18 and <80 years, with a platelet count <30,000/μL, who were refractory to ATG therapy, who had relapsed after ATG therapy, or who were ineligible for ATG therapy (target sample size, 20).

---

1) Review Report for Revolade Tablets 12.5 mg and 25 mg (August 17, 2010)

Eltrombopag therapy was started at a dose of 25 mg once daily administered orally on an empty stomach (>2 hours before or after a meal). The dose was increased by 25 mg every 2 weeks based on the patient's platelet count, up to a maximum daily dose of 100 mg.

All 21 patients enrolled in this study received eltrombopag and were included in the pharmacokinetics analysis set.

In 5 patients, pharmacokinetic parameters of eltrombopag (25 mg once daily) on Day 14 were evaluated. C_{max} was 6.4 ± 4.2 μg/mL, AUC_{last} 123.0 ± 92.9 μg·h/mL, and median t_{max} 2.0 hours.

The trough plasma concentrations of eltrombopag on Day 15 following administration of 25, 50, 75, or 100 mg once daily are shown in Table 1.

Table 1. Trough plasma concentrations of eltrombopag in patients with AA with an insufficient response to existing treatment

Eltrombopag dose	Number of patients	Plasma eltrombopag concentrations (μg/mL)
25 mg[a)]	21	3.7 ± 2.4
50 mg[b)]	20	8.5 ± 6.4
75 mg[b)]	20	15.2 ± 12.0
100 mg[b)]	19	19.3 ± 15.0

Mean ± standard deviation
a) Trough level on Day 15 after the start of treatment
b) Trough level on Day 15 after dose adjustment

6.2.2 Japanese phase II/III study in ATG therapy-naïve patients with AA (CTD 5.3.5.2-2, Study CETB115E1202 [May 2015 to [redacted] 20[redacted], to be conducted until the day of approval])

The study is outlined in Section 7.1.2.

The pharmacokinetics of eltrombopag was investigated in Japanese patients with moderate or more severe AA, aged ≥18 and ≤70 years, who were previously untreated with ATG therapy (target sample size, 10).

Eltrombopag therapy was started at a dose of 75 mg once daily administered orally on an empty stomach (>2 hours before or after a meal). The dose was decreased by 25 mg every 2 weeks based on the patient's platelet count.

Of 11 patients enrolled in this study, 10 received eltrombopag and were included in the pharmacokinetics analysis set.

In the 10 patients, plasma eltrombopag concentration was measured on Day 15 at 4 hours post-dose of 75 mg once daily. The mean plasma eltrombopag concentration was 28.4 ± 9.0 μg/mL.

The trough plasma concentrations of eltrombopag on Day 15 following administration of 25, 50, or 75 mg once daily are shown in Table 2.

Table 2. Trough plasma concentrations of eltrombopag in patients naïve to ATG therapy

Eltrombopag dose	Number of patients	Plasma eltrombopag concentrations (μg/mL)
25 mg[a)]	1	6.1
50 mg[a)]	2	20.8 ± 7.9
75 mg[b)]	10	21.8 ± 7.4

Mean ± standard deviation.
a) Trough level on Day 15 after dose adjustment
b) Trough level on Day 15 after the start of treatment.

6.2.3 Foreign phase I study (study of drug-drug interaction with CsA) (CTD 5.3.3.4-1, Study RAD201583 [November 2014 to December 2014])

A randomized, open-label, 3-treatment, 3-period, crossover study was conducted in non-Japanese healthy men and women aged ≥18 and ≤64 years (target sample size, 39) at 1 study site in the US to evaluate the effect of CsA on the pharmacokinetics of eltrombopag and the safety of the combination of eltrombopag and CsA.

A single oral dose of eltrombopag 50 mg (without CsA), a single oral dose of eltrombopag 50 mg combined with CsA 200 mg, or a single oral dose of eltrombopag 50 mg combined with CsA 600 mg was administered in the Periods 1, 2, or 3. The treatment periods were separated by a washout period of 3 to 10 days.

All 39 randomized patients received eltrombopag and were included in the pharmacokinetics analysis set and safety analysis set. Pharmacokinetics parameters of eltrombopag are shown in Table 3.

Table 3. Pharmacokinetic parameters of eltrombopag with or without concomitant CsA

	C_{max} (μg/mL)	Ratio [90% CI][c)]	$AUC_{0\text{-}inf}$ (μg·h/mL)	Ratio [90% CI][d)]
Without CsA	5.7 (23.6)	—	72.6 (31.7)[a)]	—
With CsA 200 mg	4.1 (47.0)	74.6 [65.2, 85.3]	55.9 (50.4)[a)]	81.7 [72.5, 92.1]
With CsA 600 mg	3.6 (56.0)[a)]	60.8 [53.1, 69.6]	58.1 (56.5)[b)]	76.5 [67.6, 86.5]

n = 39, geometric mean (% geometric coefficient of variation).
a) n = 37, b) n = 33.
c) Ratio of the least-squares geometric mean calculated from a mixed linear model: (C_{max} with CsA)/(C_{max} without CsA).
d) Ratio of the least-squares geometric mean calculated from a mixed linear model: ($AUC_{0\text{-}inf}$ with CsA)/($AUC_{0\text{-}inf}$ without CsA).

The safety analysis revealed that adverse events occurred in 15.4% (6 of 39) of subjects receiving eltrombopag alone, 30.8% (12 of 39) of subjects receiving eltrombopag 50 mg + CsA 200 mg, and 69.2% (27 of 39) of subjects receiving eltrombopag 50 mg + CsA 600 mg. Adverse drug reactions occurred in 2.6% (1 of 39) of subjects receiving eltrombopag alone, 20.5% (8 of 39) of subjects receiving eltrombopag 50 mg + CsA 200 mg, and 69.2% (27 of 39) of subjects receiving eltrombopag 50 mg + CsA 600 mg. Adverse events occurring at an incidence of ≥5.0% in any group are shown in Table 4. All the adverse events were assessed as adverse drug reactions, except for headache in 2 subjects receiving eltrombopag alone and upper respiratory tract infection in 2 subjects receiving eltrombopag 50 mg + CsA 200 mg. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

Table 4. Adverse events occurring in ≥2 subjects in any group

	Without CsA (n = 39)	With CsA 200 mg (n = 39)	With CsA 600 mg (n = 39)
All	15.4 (6)	30.8 (12)	69.2 (27)
Feeling hot	0 (0)	7.7 (3)	61.5 (24)
Headache	7.7 (3)	10.3 (4)	25.6 (10)
Nausea	0 (0)	5.1 (2)	12.8 (5)
Vomiting	0 (0)	0 (0)	5.1 (2)
Dizziness	0 (0)	0 (0)	5.1 (2)
Upper respiratory tract infection	0 (0)	5.1 (2)	0 (0)

MedDRA/J ver.17.1. Incidence % (number of subjects affected).

6.R Outline of the review conducted by PMDA

The applicant's explanation about the effects of CsA on the pharmacokinetics of eltrombopag:

In the study evaluating a drug–drug interaction with CsA in non-Japanese healthy adults (Study RAD201583), C_{max} and $AUC_{0\text{-}inf}$ of eltrombopag 50 mg decreased by approximately 25% and 18%, respectively, in combination with CsA 200 mg and by approximately 39% and 24%, respectively, in combination with CsA 600 mg. The current package insert of eltrombopag, in its "Precautions for concomitant use" section, thus calls attention to decreases in C_{max} and AUC of eltrombopag in combination use with CsA. Meanwhile, trough levels of eltrombopag in Japanese patients with AA with an insufficient response to existing treatment in Study E1201 were analyzed based on a concomitant use or non-use of CsA. The mean trough level (minimum, maximum) of eltrombopag 50 mg was 6.6 μg/mL (0.7, 24.2) in 12 patients receiving eltrombopag alone and 11.4 μg/mL (4.0, 18.5) in 8 patients receiving eltrombopag + CsA. The trough levels of eltrombopag in patients receiving eltrombopag + CsA[2)] fell within the range of trough levels in patients receiving eltrombopag alone, but the mean trough level was approximately 73% higher than that in patients receiving eltrombopag alone. The reason remains unclear for the higher mean trough level in patients receiving eltrombopag + CsA than in patients receiving eltrombopag alone by such percentage in Study E1201, unlike the drug–drug interaction study (Study RAD201583). Nevertheless, the trough levels of eltrombopag in patients receiving eltrombopag + CsA fell within the trough levels in patients receiving eltrombopag alone. The incidences of adverse events and adverse drug reactions show no marked differences between patients receiving eltrombopag with and without CsA. These facts suggest that changes in plasma eltrombopag concentrations associated with the concomitant CsA in patients with AA have no clinically significant effects. Thus, at present, the high plasma concentration (mean trough) of eltrombopag following treatment with eltrombopag + CsA in Study E1201 needs not be mentioned via the package insert.

PMDA's view:

The trough levels of eltrombopag in patients receiving eltrombopag + CsA fell within that in patients receiving eltrombopag alone, while no marked differences in incidences of adverse events and adverse drug reactions were seen between the 2 patient populations. Furthermore, eltrombopag dose is adjusted based on the patient's condition. Accordingly, the combination of eltrombopag and CsA is unlikely to pose a significant concern at present. However, the fact that the treatment with eltrombopag + CsA caused higher

2) In patients receiving eltrombopag + CsA, CsA was prescribed at a dose of 25 to 250 mg (twice daily).

plasma concentration (mean trough level) of eltrombopag in Study E1201 should be mentioned in the package insert. Moreover, because of the limited number of patients enrolled in Study E1201, safety and efficacy data of eltrombopag combined with CsA should be continuously collected in its post-marketing surveillance, etc.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted data from 2 Japanese phase II/III studies (Study CETB115E1201 [Study E1202] and Study CETB115E1202 [Study E1202]) as evaluation data for efficacy and safety. In the 2 studies, AA severity was determined according to the severity classification defined in the Reference Guide for Treatment of Aplastic Anemia 2016 (Table 5). ATG refers to anti-human thymocyte globulin derived from rabbits, unless otherwise specified.

Table 5. AA severity classification

Mild	**Other than shown below**
Moderate	**≥2 of the following criteria are met: reticulocytes <60,000/μL; neutrophils <1,000/μL; or platelets <50,000/μL**
Slightly severe	**2 of the following criteria are met and regular red blood cell transfusion is required: reticulocytes <60,000/μL; neutrophils <1,000/μL; or platelets <50,000/μL**
Severe	**≥2 of the following criteria are met: reticulocytes <20,000/μL; neutrophils <500/μL; or platelets <20,000/μL**
Most severe	**Neutrophils <200/μL, and ≥1 of the following criteria is (are) met: reticulocytes <20,000/μL; or platelets <20,000/μL**

7.1 Phase II/III studies

7.1.1 Phase II/III study (CTD 5.3.5.2-1, Study CETB115E1201 [July 2014 to [redacted] 20[redacted], to be conducted until the day of approval])

A multicenter, open-label, uncontrolled study was conducted in patients with moderate or more severe AA who had an insufficient response to or were unsuitable for existing treatment at 12 study sites in Japan (Table 6) (target sample size, 20) to evaluate the efficacy and safety of eltrombopag.

Table 6. Main inclusion and exclusion criteria

Main inclusion criteria	**• ≥18 and <80 years of age • Moderate (Table 5) or more severe AA and platelets <30,000/μL • Patients who were refractory to ATG therapy, who had relapsed after ATG therapy, or who were ineligible for ATG**
Main exclusion criteria	**• Patients for whom an HLA-identical sibling donor was available (however, the following patients could be enrolled: patients who had relapsed after hematopoietic stem cell transplantation, who were ineligible for hematopoietic stem cell transplantation, or who did not want to receive hematopoietic stem cell transplantation) • Patients who received ATG therapy within the past 12 months • Patients with congenital AA (e.g., Fanconi anemia, dyskeratosis congenita) • Patients with a PNH granulocyte clone size of ≥50% as determined by flow cytometry • Patients with chromosomal abnormalities**

Eltrombopag therapy was started at a dose of 25 mg once daily administered orally on an empty stomach (>2 hours before or after a meal). Dose increase was allowed by 25 mg every 2 weeks based on platelet count, up to a daily dose of 100 mg (until Week 26 in Table 7). Treatment was continued for patients who had a hematological response (Table 8) or showed a tendency toward improved blood cell counts at Month 3 (Week 13). Patients who had a hematological response at Month 6 (Week 26) entered in the extension phase

and continued to receive eltrombopag at adjusted doses until discontinuation criteria met (the extension phase in Table 7).

Table 7. Criteria for eltrombopag dose adjustment

Until Week 26	
Platelet count	**Eltrombopag dose**
After 2 weeks of therapy: <50,000/μL or no decrease in platelet transfusion volume	**Increase the daily dose by 25 mg every 2 weeks to a maximum of 100 mg/day.**
After 2 weeks of therapy: ≥50,000/μL and ≤100,000/μL	**No change**
>100,000/μL without platelet transfusion	**Reduce the daily dose by 25 mg every 2 weeks until a platelet count of ≥50,000/μL and ≤100,000/μL is achieved and maintained.**
>200,000/μL without platelet transfusion	**Suspend until a platelet count of <50,000/μL. Once achieved, reinitiate at a dose reduced by 25 mg (for patients taking 25 mg/day before suspension, reinitiate at 25 mg/day).**
Extension phase	
Criteria for each blood cell lineage	**Eltrombopag dose**
The following parameter levels are maintained for ≥8 weeks: Platelets: >50,000/μL without platelet transfusion Hemoglobin: >10 g/dL without blood transfusion Neutrophils: >1,000/μL	**Reduction by 50% (minimum 12.5 mg/day). (from) (to) 100 mg → 50 mg 75 mg → 37.5 mg 50 mg → 25 mg 25 mg → 12.5 mg**
The above levels are maintained for further 8 weeks after the 50%-dose reduction.	**Suspend.**
Any of the parameter levels decreases to the following levels after the 50%-dose reduction. Platelets: <30,000/μL Hemoglobin: <9 g/dL Neutrophils: <500/μL	**Dose increase allowed: (after 50% reduction) (to) 50 mg → 75 mg 37.5 mg → 50 or 62.5 mg 25 mg → 37.5 mg 12.5 → 25 mg The dose can be increased up to 100 mg/day based on the patient's condition but should be increased by 12.5 mg as a rule (or by 25 mg at the discretion of the investigator).**
Any of the parameter levels decreases as above after suspension.	**Therapy may be reinitiated at the dose before suspension.**

All 21 patients enrolled in this study received eltrombopag and were included in the full analysis set (FAS) and the safety analysis set. The FAS was the primary efficacy analysis set. Eltrombopag was discontinued in 5 patients by Week 26 (meeting discontinuation criteria in 2 patients, discretion of the investigator, lack of efficacy, and protocol deviation in 1 patient each). A total of 16 patients completed the evaluation at Week 26. Among them, 10 patients had a hematological response and were enrolled in the extension phase. Of the 10 patients, 2 patients discontinued eltrombopag by Week 52 (lack of efficacy and consent withdrawal in 1 patient each), and 8 patients remained in eltrombopag therapy after Week 52.

The primary endpoint was "the hematological response rate at Week 26 (the percentage of patients meeting the criteria for efficacy evaluation in Table 8)." The response rate (95% confidence interval [CI]) was 47.6% (25.7, 70.2) (10 of 21 patients), and the lower limit of the 95% confidence interval was above the prespecified threshold of 15% for efficacy evaluation.

The hematological responses were, namely, (multiple answers allowed) "erythrocyte (hemoglobin) response" in 10 patients, "platelet response" in 4 patients, and "neutrophil response" in 3 patients. "Response in the 3

blood cell lineages" was observed in 1 patient, "response in 2 blood cell lineages" in 5 patients, and "response in 1 blood cell lineage" in 4 patients.

Table 8. Criteria for efficacy evaluation

Hematological response was confirmed by any of the following criteria met.	
Platelets	Increase by ≥20,000/μL from baseline or requiring no platelet transfusion for 8 weeks
Hemoglobin	Patients with hemoglobin <9 g/dL and receiving no red blood cell transfusion at baseline Increase by ≥1.5 g/dL Patients receiving red blood cell transfusion at baseline Decrease by ≥4 units (1 unit = blood 200 mL) in the volume of red blood cell transfusion at Week 8 of treatment compared with –8 weeks pre-dose
Neutrophils	Increase by ≥500/μL from baseline or increase by ≥100% in patients with baseline neutrophils <500/μL

The safety analysis revealed, by Week 52, adverse events and adverse drug reactions observed in 100% (21 of 21) and 57.1% (12 of 21) of patients, respectively. Adverse events occurring in ≥2 patients are shown in Table 9. Adverse drug reactions observed in ≥2 patients were blood alkaline phosphatase increased, blood bilirubin increased, hepatic function abnormal, hyperbilirubinaemia, and rash with an incidence of 9.5% (2 of 21 patients) each.

Table 9. Adverse events occurring in ≥2 patients (by Week 52)

Adverse events	Incidence (n)	Adverse events	Incidence (n)
All adverse events	100 (21)	Diarrhoea	9.5 (2)
Nasopharyngitis	38.1 (8)	Dyspepsia	9.5 (2)
Hepatic function abnormal	14.3 (3)	Enterocolitis	9.5 (2)
Urticaria	14.3 (3)	Gastroenteritis	9.5 (2)
Abdominal pain upper	9.5 (2)	Hyperbilirubinaemia	9.5 (2)
Back pain	9.5 (2)	Hypersensitivity	9.5 (2)
Blood alkaline phosphatase increased	9.5 (2)	Purpura	9.5 (2)
Blood creatinine increased	9.5 (2)	Pyrexia	9.5 (2)
Blood bilirubin increased	9.5 (2)	Rash	9.5 (2)
Decreased appetite	9.5 (2)		

MedDRA/J ver.18.1. Incidence % (number of patients affected).

No deaths occurred. Serious adverse events were observed in 19.0% (4 patients; retinal detachment, enterocolitis, pain, and decreased appetite in 1 patient each), but all events were assessed as unrelated to eltrombopag. An adverse event led to treatment discontinuation in 4.8% (1 patient; hepatic function abnormal), and a causal relationship with eltrombopag was not ruled out for the event. However, the event resolved after discontinuation of eltrombopag.

7.1.2 Phase II/III study (CTD 5.3.5.2-2, Study CETB115E1202 [May 2015 to [redacted] 20[redacted], to be conducted until the day of approval])

A multicenter, open-label, uncontrolled study was conducted in treatment-naïve patients with moderate or more severe AA (Table 10) at 11 study sites in Japan (target sample size, 10) to evaluate the efficacy and safety of the combination of eltrombopag with ATG/CsA.

Table 10. Main inclusion and exclusion criteria

Main inclusion criteria	• **≥18 and ≤70 years of age** • **Moderate (Table 5) or more severe AA** • **Requiring ATG/CsA therapy**
Main exclusion criteria	• **Patients with congenital AA (e.g., Fanconi anemia, dyskeratosis congenita)** • **Patients for whom an HLA-identical sibling donor was available or who previously underwent hematopoietic stem cell transplantation (However, patients could be included if they were ineligible for hematopoietic stem cell transplantation or did not want to receive hematopoietic stem cell transplantation.)** • **Patients who had previously received rabbit or equine ATG therapy, antilymphocyte globulin-based treatment, or high-dose corticosteroids for treatment of AA** • **Patients receiving CsA within 6 months after the start of ATG therapy** • **Patients with a PNH granulocyte clone size of ≥50% as determined by flow cytometry** • **Patients with chromosomal abnormalities**

The day ATG/CsA therapy[3)] was started was defined as Day 1. On Day 15, eltrombopag therapy began at a dose of 75 mg once daily administered orally on an empty stomach (>2 hours before or after a meal). Eltrombopag was administered for 26 weeks (Week 26 in Table 11) while the dose was decreased by 25 mg/day every 2 weeks based on the patient's platelet count (the minimum dose, 12.5 mg/day). Patients who had no response (NR) at Week 26 could enter the extension phase if judged by the investigators to require eltrombopag therapy. In the extension phase, the patients continued to receive eltrombopag at adjusted doses (the extension phase in Table 11).

[3)] Drugs were administered according to their approved dosage regimens.
ATG (Thymoglobuline): administered intravenously by drip infusion for 5 days at a dose determined by the investigator.
CsA: From Day 1, orally administered at a daily dose of 6 mg/kg divided into 2 doses, in combination with ATG. The dose was adjusted to achieve the target blood trough CsA level of 150 to 250 ng/mL. CsA was administered until at least Week 26 (suspension allowed) and could be continued after Week 26 when the investigator judged it necessary.

Table 11. Criteria for eltrombopag dose adjustment

Until Week 26	
Platelet count	**Eltrombopag dose**
>200,000/μL	**Decrease by 25 mg every 2 weeks to lowest dose that maintains platelet count ≥50,000/μL and ≤200,000/μL (minimum, 12.5 mg/day) (if the platelet count is maintainwed within the range even at 12.5 mg/day, discontinue eltrombopag).**
>400,000/μL	**Suspend until platelet count decreases to <200,000/μL. Once achieved, reinitiate at a dose reduced by 25 mg (for patients taking 25 mg/day before suspension, reinitiate at 25 mg/day).**
Extension phase	
Platelet count	**Eltrombopag dose**
<50,000/μL or no decrease in platelet transfusion volume	**Increase by 25 mg every 2 weeks (maximum, 75 mg/day)**
≥50,000/μL and ≤100,000/μL	**No change**
>100,000/μL	**Decrease by 25 mg every 2 weeks to lowest dose that maintains platelet count ≥50,000/μL and ≤100,000/μL.** **Continue with the current dose without reduction when** **・CR achieved by Week 26,** **・CR expected in the extension phase, or** **・CR achieved in the extension phase.**
>200,000/μL	**Suspend until platelet count decreases to <50,000/μL. Once achieved, reinitiate at a dose reduced by 25 mg (for patients taking 25 mg/day before suspension, reinitiate at 12.5 mg/day).**
Criteria for each blood cell lineage	**Eltrombopag dose**
The following parameter levels are maintained for ≥8 weeks: **Platelets: >50,000/μL** **Hemoglobin: >10 g/dL** **Neutrophils: >1,000/μL**	**Reduce by 50% (minimum, 12.5 mg/day).**
The above levels are maintained for another 8 weeks after 50% dose reduction.	**Suspend.**
Any of the parameter levels decrease to the following levels after 50% dose reduction **Platelets: <30,000/μL** **Hemoglobin: <9 g/dL** **Neutrophils: <500/μL**	**Increase by 12.5 mg every 2 weeks (maximum, 75 mg/day).**
Any of the parameter levels decrease to the above after suspension	**Therapy may be reinitiated at the dose before suspension.**

Table 12. Criteria for efficacy evaluation

	Severe or most severe at baseline	**Moderate or slightly severe at baseline**
NR (no response)	**Worsening or remaining severe or most severe**	**Worsening or failing to meet CR or PR criteria**
PR (partial response)	**Independent from transfusion (platelet or red blood cells) and not meeting the criteria for severe AA**	**Any of the following is met:** **• Platelet or red blood cell transfusion dependent at baseline has become transfusion-independent.** **• Blood cell value of 2 times baseline or normal in ≥1 blood cell lineage** **• Hemoglobin level higher by >3 g/dL than baseline level of <6 g/dL** **• Neutrophil count higher by > 500/μL than baseline count of <500/μL** **• Platelet count higher by >20,000/μL than baseline count of <20,000/μL**
CR (complete response)	**Meeting all the following:** **• Hemoglobin level ≥12 g/dL (women) or ≥13 g/dL (men)** **• Neutrophil count ≥1,500/μL** **• Platelet count ≥150,000/μL**	

Of 11 patients enrolled in this study, 10 received eltrombopag and were included in the FAS and the safety analysis set. The FAS was the primary efficacy analysis set. Eltrombopag was discontinued by Week 26 in 1 patient, who met a discontinuation criterion (changes in QTcF from baseline of >60 milliseconds). A total of

9 patients entered the extension phase, and 3 of the 9 discontinued eltrombopag by Week 52 due to "lack of efficacy."

The primary endpoint was "the response rate at Week 26 (the percentage of patients meeting the criteria for CR or PR in Table 12)," and the response rate (95% CI) was 70.0% (34.8, 93.3) (7 of 10 patients). All patients had PR, and none achieved CR.

The safety analysis revealed adverse events occurring by Week 52 in 100% (10 of 10) of patients and adverse drug reactions in 50.0% (5 of 10) of patients. Adverse events occurring in ≥2 patients are shown in Table 13. Adverse drug reactions occurring in ≥2 patients were myalgia in 30.0% (3 of 10) of patients, blood bilirubin increased in 20.0% (2 of 10) of patients, and nausea in 20.0% (2 of 10) of patients.

Table 13. Adverse events occurring in ≥2 patients (by Week 52)

Events	Incidence (n)	Events	Incidence (n)
All adverse events	100 (10)	Hypertension	30.0 (3)
Nausea	60.0 (6)	Myalgia	30.0 (3)
Headache	50.0 (5)	Stomatitis	30.0 (3)
Constipation	40.0 (4)	Back pain	20.0 (2)
Oedema	40.0 (4)	Bone pain	20.0 (2)
Pyrexia	40.0 (4)	Chronic gastritis	20.0 (2)
Renal impairment	40.0 (4)	Dry eye	20.0 (2)
Vomiting	40.0 (4)	Dyspepsia	20.0 (2)
ALT increased	30.0 (3)	Insomnia	20.0 (2)
Blood bilirubin increased	30.0 (3)	Rash	20.0 (2)
Hyperglycaemia	30.0 (3)	Upper respiratory tract infection	20.0 (2)

MedDRA/J ver.19.1. Incidence % (number of patients affected).

No deaths occurred. Serious adverse events were observed in 20.0% (2 of 10) of patients (febrile neutropenia in 1 patient and nephrolithiasis in 1 patient). Both events were assessed as unrelated to eltrombopag. An adverse event led to treatment discontinuation in 10.0% (1 of 10) of patients (electrocardiogram QT prolonged). A causal relationship between the event and eltrombopag was ruled out, and the outcome was reported as improved.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

Based on the review in the Sections 7.R.1.1 to 7.R.1.3, PMDA considers that eltrombopag is expected to have efficacy in patients with AA with an insufficient response to existing treatment and ATG-therapy-naïve patients with AA. However, because of the limited number of patients in Studies E1201 and E1202, efficacy data of eltrombopag should be continuously collected in its post-marketing surveillance, etc.

PMDA will make a final conclusion on the efficacy of eltrombopag taking into account the comments from the Expert Discussion.

7.R.1.1 Justification for the open-label, uncontrolled study design

The applicant's explanation about the reason for conducting Studies E1201 and E1202 as open-label, uncontrolled studies:

AA is one of Diseases Subject to Specific Disease. The total numbers of patients with AA in Japan is estimated to be 14,009 (as of 2013) based on the number of holders of the Recipient Certificate Issued for Specific Disease Medical Treatment or the Certificate of Registered Patient for Specific Disease (Overview/Divisional Research Report for fiscal 2014: Research and Study on Idiopathic Hematopoietic Disorders, funded by Health Labour Sciences Research Grant from the Ministry of Health, Labour and Welfare for Research Project on Policy of Measures for Intractable Diseases).

In the US, eltrombopag was approved in August 2014, and in Europe in September 2015, for the indication of "severe aplastic anemia refractory to immunosuppressive therapy" based on data from an open-label, uncontrolled study, NIH09-H-0154 (Study 154)[4)] conducted by the NIH in patients with AA refractory to ATG/CsA therapy (*N Engl J Med.* 2012;367:11-19). An open-label, uncontrolled study, NIH12-H-0150 (Study 150),[5)] is currently conducted by the NIH to evaluate the additive effect of eltrombopag to ATG/CsA therapy in ATG-therapy-naïve patients with AA. An additional application is to be submitted in the US and Europe to seek approval for the indication of AA in ATG-therapy-naïve patients, with favorable interim results yielded from the study.

In Japan, Study E1201 was planned in Japanese patients with moderate or more severe AA, who were refractory to immunosuppressive therapy including ATG therapy, who had relapsed, or who were ineligible for such immunosuppressive therapy, by reference to Study 154. Moreover, Study E1202 was designed to enroll Japanese patients with moderate or more severe AA naïve to ATG therapy who were eligible to ATG/CsA therapy, by reference to Study 150. Because of the limited number of Japanese patients with AA eligible for the studies, both studies were conducted in open label and uncontrolled manners, as with the foreign studies.

PMDA's view:
In light of the limited number of Japanese patients with AA eligible for eltrombopag therapy, it would be inevitable to design Studies E1201 and E1202 as open-label, uncontrolled studies, as with the foreign studies (Studies 154 and 150).

7.R.1.2 Efficacy of eltrombopag in patients with AA with an insufficient response to existing treatment

7.R.1.2.1 Patient population and primary endpoint

The applicant's explanation about the target patient population and the primary endpoint of Study E1201:

---

4) A single-center, open-label, uncontrolled study in patients with severe AA aged ≥12 years insufficiently responding to ATG/CsA therapy, with platelet count of ≤30,000/μL, to evaluate the efficacy and safety of eltrombopag. Eltrombopag was started at 50 mg (25 mg in East Asian patients) once daily orally administered, with a maximum dose of 150 mg (75 mg in East Asians). As with Study E1201, the dose was adjusted as appropriate based on platelet count.

5) A single-center, open-label, uncontrolled study in ATG therapy-naïve patients with severe AA aged ≥2 years to evaluate the efficacy and safety of eltrombopag. Patients were eligible for the study if they had bone marrow cell density of <30% (excluding lymphocytes) and met at least 2 of the following: neutrophil count of <500/μL; platelet count of <20,000/μL, or reticulocyte count of <60,000/μL. Eltrombopag was started at 150 mg administered orally once daily. As with Study E1202, the dose was reduced as appropriate based on platelet count.

Study E1201 was conducted in patients with moderate or more severe AA (Table 5) who were refractory to ATG/CsA therapy, who had relapsed after ATG/CsA therapy, or who were ineligible for ATG/CsA therapy (Table 6), by reference to the patient population in Study 154. The criterion of platelet count was <30,000/μL, which indicates bleeding risk and may require blood transfusion.

As with Study 154, the primary endpoint of Study E1201 was the percentage of patients achieving "hematological response" (Table 8) that refers to improvement in any of the 3 blood cell lineages or reduced blood transfusion volume. Response to therapy in patients with AA is determined on the basis of hematological improvement such as that in platelet count, hemoglobin level, and neutrophil count and the need for blood transfusion. The criteria for response to therapy in Study 154 were defined with reference to international criteria for response to immunosuppressive therapy (*Br J Haematol.* 2009;147:43-70). "Improvement in any of the 3 blood cell lineages" is assessed based on laboratory data of platelet count, hemoglobin level, and neutrophil count and thus allows objective evaluation. Furthermore, improvement even in 1 lineage yields clinical benefits (e.g., reduction of blood transfusion volume, reduced risk of bleeding, relief of anemia symptoms, and reduced risk of infections). Therefore, "improvement in any of the 3 blood cell lineages" is considered clinically meaningful. The reduction of blood transfusion volume is clinically meaningful in light of refractoriness to platelet transfusion, risk of transfusion-associated infections, and post-transfusion iron overload, etc. resulting from frequent transfusion. Study E1201 would demonstrate the efficacy of eltrombopag by hematological response rates, i.e., the common primary endpoint, if they were comparable between the 2 studies. While the primary endpoint was evaluated at Week 12 or 16 in Study 154, it was assessed at Week 26 in Study E1201 according to the opinion of the US Food and Drug Administration (FDA) that hematological response should be checked at Month 6 of treatment at the earliest from a clinical point of view because of a risk of relapse or chronicity of AA, and because the determination of response to immunosuppressive therapy (ATG) also requires 6 months (see Review Report for Thymoglobuline for Intravenous Infusion 25 mg, May 15, 2008).

The rationale for the efficacy criteria: The hypothesized hematological response rate in Study E1201 was 35% based on that of 32.6% (14 of 43 patients) at Month 6 of eltrombopag therapy in Study 154. The efficacy criteria of eltrombopag was the lower limit of 95% confidence interval of >15%, based on the efficacy rate of 17.9% (5 of 28 patients)[6] in a Japanese clinical study of ATG[7] (see Review Report for Thymoglobuline for Intravenous Infusion 25 mg, May 15, 2008) and a reported efficacy rate of around 20% following resumed ATG therapy in patients unresponsive to ATG (*Investigative Research Team on Idiopathic Hematopoietic Disorder, Health Labour Sciences Research Grant for the Research Project Overcoming Intractable Diseases.* 2011:3-32), as well as advice from medical experts. From a viewpoint of

6) A sum of the efficacy rates of 13.3% (2 of 15 patients) in the ATG 2.5 mg/kg group and 23.1% (3 of 13 patients) in the ATG 3.75 mg/kg group.

7) Percentage of patients responsive or more responsive to treatment (very responsive, a change in severity from severe to mild, or a change in severity from severe to moderate or from moderate to mild and an increase in hemoglobin level by ≥2 g/dL in the absence of blood transfusion; responsive, no change in severity from severe or moderate with an increase in hemoglobin level by ≥2 g/dL in the absence of blood transfusion; slightly responsive, defined as a change in severity from severe to moderate or from moderate to mild without an increase in hemoglobin level by ≥2 g/dL in the absence of blood transfusion; unresponsive, any condition other than very responsive, responsive, or slightly responsive).

feasibility, the sample size of Study E1201 would be approximately 20 patients because of the limited number of eligible patients in Japan. However, even the sample size of 20 would suffice to achieve the lower limit of 95% confidence interval of >15% if the hematological response rate was 35%.
The "hematological response rate at Week 26" (95% CI), the primary endpoint of Study E1201, was 47.6% (25.7, 70.2) (10 of 21 patients), and the lower limit of the 95% confidence interval exceeded the prespecified threshold of efficacy evaluation, 15%. Accordingly, the efficacy of eltrombopag has been demonstrated in patients with AA with an insufficient response to existing therapy.

PMDA's view:
The applicant determined the target patient population and the primary endpoint for Study E1201 by reference to Study 154, which is acceptable. In Study E1201, the hematological response rate at Week 26 of eltrombopag therapy was 47.6% (25.7, 70.2) (10 of 21 patients), and the lower limit of the 95% confidence interval exceeded the prespecified threshold for efficacy evaluation of 15%. The result suggests eltrombopag's efficacy in patients with AA insufficiently responding to existing treatment.

7.R.1.2.2 Secondary endpoints

The time course of efficacy of eltrombopag is shown in Table 14. Of 10 hematological responders at Week 26, none experienced relapse by Week 52. The hematological response rate (95% CI) at the final evaluation was 57.1% (34.0, 78.2) (12 of 21 patients), and more patients had "tri-lineage response" at Week 52 than Week 26. Patients who continued to receive eltrombopag therapy showed no tendency toward significant decline in efficacy.

Table 14. Efficacy by time (Study E1201)

	Week 13	Week 26	Week 52	Final evaluation
Hematological response rate (n) [95% CI]	61.9% (13/21) [38.4, 81.9]	47.6% (10/21) [25.7, 70.2]	42.9% (9/21) [21.8, 66.0]	57.1% (12/21) [34.0, 78.2]
Types of response				
Uni-lineage response				
Platelet	0% (0)	0% (0)	0% (0)	0% (0)
Red blood cell	28.6% (6)	19.0% (4)	14.3% (3)	19.0% (4)
Neutrophil	23.8% (5)	0% (0)	0% (0)	0% (0)
Bi-lineage response				
Platelet/red blood cell	0% (0)	14.3% (3)	9.5% (2)	9.5% (2)
Platelet/neutrophil	0% (0)	0% (0)	0% (0)	4.8% (1)
Red blood cell /neutrophil	4.8% (1)	9.5% (2)	0% (0)	4.8% (1)
Tri-lineage response	4.8% (1)	4.8% (1)	19.0% (4)	19.0% (4)
Details of response[a)]				
Platelet count	4.8% (1)	14.3% (3)	23.8% (5)	23.8% (5)
Platelet transfusion	0% (0)	9.5% (2)	9.5% (2)	14.3% (3)
Hemoglobin level	4.8% (1)	4.8% (1)	4.8% (1)	4.8% (1)
Red blood cell transfusion	33.3% (7)	42.9% (9)	38.1% (8)	47.6% (10)
Neutrophil count	33.3% (7)	14.3% (3)	19.0% (4)	28.6% (6)

a) One patient meeting ≥2 criteria was counted in each criterion. Because there was a patient who met 2 criteria for platelet, the sum of the numbers of patients with hematological response in platelet does not agree with the total number of these patients.

By Week 26, a total of 85.7% (18 of 21) of patients met the criteria for hematological response, and the median time to response [95% CI] estimated by the Kaplan–Meier method was 1.84 months [1.12, 2.10].

Baseline platelet transfusion dependence (receiving ≥1 platelet transfusion within 4 weeks before the start of eltrombopag therapy) was seen in 6 patients. Of these, 4 patients became transfusion-independent after the start of eltrombopag therapy. All 15 patients with baseline transfusion independence remained independent at the data cutoff (Week 52).

Baseline red blood cell transfusion dependence (receiving ≥1 red blood cell transfusion within 8 weeks before the start of eltrombopag therapy) was seen in 19 patients. Of these, 9 patients became transfusion-independent after the start of eltrombopag therapy. Two patients with baseline transfusion independence remained independent at the data cutoff (Week 52).

PMDA confirmed that no tendency toward inconsistency between the secondary endpoint data and the primary endpoint data in Study E1201.

7.R.1.2.3 Efficacy by patient characteristics

The "hematological response rate at Week 26," as the primary endpoint, is shown by patient characteristics in Table 15. The hematological response rates tended to vary with patient characteristics, but precise examination was precluded by extremely limited number of patients in each subgroup.

Table 15. Hematological response rates by patient characteristics at Week 26 (Study E1201)

Sex	**Men**	**44.4% (4/9)**	**Severity**	**Not severe**	**53.3% (8/15)**
	Women	**50.0% (6/12)**		**Severe**	**33.3% (2/6)**
Age	**<65 years**	**37.5% (6/16)**	**Prior ATG therapy**	**With**	**25.0% (3/12)**
	≥65 years	**80.0% (4/5)**		**Without**	**77.8% (7/9)**
Platelet count at baseline	**<15,000/μL**	**43.8% (7/16)**	**Concomitant use of AA drugs**	**With**	**60.0% (9/15)**
	≥15,000/μL	**60.0% (3/5)**		**With CsA**	**75.0% (6/8)**
				Without	**16.7% (1/6)**

PMDA considers that data on efficacy by patient characteristics should be continuously collected via post-marketing surveillance, etc. to investigate factors affecting the efficacy of eltrombopag.

7.R.1.3 Efficacy of eltrombopag in ATG-therapy-naïve patients with AA

7.R.1.3.1 Patient population and primary endpoint

The applicant's explanation about the target patient population and the primary endpoint of Study E1202:
Study E1202 was conducted in patients with moderate or more severe AA (Table 5) who required ATG/CsA therapy (Table 10). The target patient population was selected by reference to Study 150, which was intended to evaluate the additive effect of eltrombopag to ATG/CsA therapy in ATG-therapy-naïve patients with AA.

The primary endpoint was the response rate (the percentage of patients meeting the criteria for CR or PR) based on the international criteria for response to immunosuppressive therapy (*Br J Haematol.* 2009;147:43-70) and was evaluated at Week 26, as with Study E1201. A literature search was conducted for efficacy criteria concerning ATG/CsA therapy in ATG-therapy-naïve patients with severe AA. It revealed that response rates at Month 6 of treatment were 34% to 45%, not exceeding 50% (*Blood.* 2012;119:5391-5396; *Ann Hematol.* 2013;92:817-824; and other articles) and there was no published

prospective study of ATG/CsA therapy in ATG-therapy-naïve patients with non-severe AA. In light of these results and comments from experts, the expected efficacy rate of eltrombopag used with ATG/CsA should be set at 60%, and the response rate of ≥60% would explain additive effect of eltrombopag to ATG/CsA therapy.

The "response rate at Week 26" (95% CI), the primary endpoint of Study E1202, was 70.0% (34.8, 93.3) (7 of 10 patients), which exceeded the expected efficacy rate of 60%. The results suggest promising efficacy of eltrombopag in ATG-therapy-naïve patients with AA.

PMDA's view:
The applicant's explanation about the target patient population and the primary endpoint of Study E1202 is reasonable. The data from a Japanese clinical study on ATG yielded the efficacy rate of 17.9% (5 of 28 patients) (see Review Report for Thymoglobuline for Intravenous Infusion 25 mg, May 15, 2008). Based on this result and published literature, eltrombopag is expected to have efficacy in ATG-therapy-naïve patients with AA when used with ATG/CsA.

7.R.1.3.2 Secondary endpoints

The time course of efficacy of eltrombopag is shown in Table 16. Of 7 patients who responded at Week 26, 1 patient experienced relapse of platelet count decrease during suspension of eltrombopag as per the dose adjustment criteria (Table 11). Eltrombopag therapy resumed but failed, resulting in treatment discontinuation. The response rate at the final evaluation was 60.0% (6 of 10 patients). Patients who continued to receive eltrombopag therapy showed no tendency toward declined efficacy.

Table 16. Efficacy by time (Study E1202)

		Week 14	Week 26	Week 52	Final evaluation
Response rate (n) [95% CI]		20.0% (2/10) [2.5, 55.6]	70.0% (7/10) [34.8, 93.3]	60.0% (6/10) [26.2, 87.8]	60.0% (6/10) [26.2, 87.8]
Categories					
CR rate (n)		0% (0)	0% (0)	0% (0)	0% (0)
PR rate (n)		20.0% (2)	70.0% (7)	60.0% (6)	60.0% (6)
Items relevant to criteria of PR					
Severe	Independent from platelet and red blood cell transfusions and not meeting the criteria for severe AA	0% (0)	40.0% (4)	30.0% (3)	30.0% (3)
Not severe	At baseline, platelet or red blood cell transfusion-dependent At evaluation, transfusion-independent	20.0% (2)	20.0% (2)	20.0% (2)	20.0% (2)
Not severe	At baseline, transfusion-independent At evaluation, blood cell value increased to 2 times baseline or normal in ≥1 blood cell lineage (and remaining free from platelet or red blood cell transfusion)	0% (0)	10.0% (1)	10.0% (1)	10.0% (1)

The median time to response (min, max) in 7 patients achieving response by Week 26 was 3.75 months (2.5, 4.8).

A total of 8 patients were platelet transfusion-dependent at baseline. Of these, 4 were transfusion-independent at the data cutoff (Week 52). Two patients with baseline platelet transfusion independence remained independent of transfusion at the data cutoff (Week 52).

A total of 6 patients were red blood cell transfusion-dependent at baseline. Of these, 3 were transfusion-independent at the data cutoff (Week 52). Of 4 patients with baseline red blood cell transfusion independence, 3 remained independent of transfusion at the data cutoff (Week 52).

PMDA confirmed that there were no problematic tendencies in the results of secondary endpoints of Study E1202.

7.R.1.3.3 Efficacy by patient characteristics

Results of the response rate at Week 26, the primary endpoint, are shown by patient characteristics in Table 17. Although investigation is limited by the small number of patients, there were no tendencies of patient characteristic factors raising concerns in efficacy. There was only 1 patient aged ≥65 years, precluding adequate evaluation.

Table 17. Response rate at Week 26 (Study E1202)

Sex		Age		Severity		PNH-type cells	
Male	Female	<65 years	≥65 years	Not severe	Severe	Negative	Positive
66.7% (2/3)	71.4% (5/7)	77.8% (7/9)	0.0% (0/1)	100.0% (3/3)	57.1% (4/7)	75.0% (3/4)	66.7% (4/6)

PMDA considers that efficacy data by patient characteristics should be continuously collected via post-marketing surveillance, etc. because of very limited number of patients evaluated.

7.R.2 Safety

PMDA, based on the reviews in Sections 7.R.2.1 to 7.R.2.4, considers that the safety of eltrombopag is acceptable in patients with AA with an insufficient response to existing treatment and ATG-therapy-naïve patients with AA. PMDA will make a final decision on the safety of eltrombopag, taking into account the comments from the Expert Discussion.

7.R.2.1 Safety of eltrombopag in patients with AA with an insufficient response to existing treatment

Table 9 shows the occurrence of adverse events by Week 52 in Study E1201. Relatively frequent adverse events were nasopharyngitis observed in 38.1% (8 of 21) of patients, urticaria in 14.3% (3 of 21) of patients, and hepatic function abnormal in 14.3% (3 of 21) of patients. The majority of the events were mild or moderate in severity. No deaths or serious adverse drug reactions occurred. An adverse drug reaction of hepatic function abnormal led to treatment discontinuation in 1 patient but resolved after discontinuation of eltrombopag.

Table 18 shows the occurrence of adverse events in Study E1201 by time of administration. There was no tendency toward increased adverse events with prolonged treatment.

Table 18. Occurrence of adverse events by time (Study E1201)

	To Day 30 (n = 21)	Days 31–90 (n = 21)	Days 91–180 (n = 20)	Days 181–270 (n = 18)	Days 271–360 (n = 9)	Total (n = 21)
Adverse event	61.9 (13)	85.7 (18)	60.0 (12)	50.0 (9)	55.6 (5)	100 (21)
Serious adverse event	4.8 (1)	4.8 (1)	0 (0)	5.6 (1)	11.1 (1)	19.0 (4)
Adverse event leading to treatment discontinuation	4.8 (1)	0 (0)	0 (0)	0 (0)	0 (0)	4.8 (1)
Nasopharyngitis	4.8 (1)	19.0 (4)	0 (0)	16.7 (3)	0 (0)	38.1 (8)
Hepatic function abnormal	4.8 (1)	0 (0)	0 (0)	5.6 (1)	11.1 (1)	14.3 (3)
Urticaria	9.5 (2)	4.8 (1)	0 (0)	0 (0)	0 (0)	14.3 (3)

MedDRA/J ver.18.1. Incidence % (number of patients affected). The adverse events listed in this table are those with a total incidence of ≥10%.

The applicant's explanation about the safety of eltrombopag in patients with AA in comparison with data from clinical studies conducted in patients with chronic idiopathic thrombocytopenic purpura (ITP), which is the approved indication:

Table 19 shows the occurrence of adverse events in Study E1201 and Japanese clinical studies in patients with ITP (pooled data from Studies TRA108109 and TRA111433). The incidences of urticaria and hepatic function abnormal were relatively higher in Study E1201 than in studies in patients with ITP. The safety profile of eltrombopag does not differ markedly between patients with AA with an insufficient response to existing treatment and patients with ITP because urticaria and hepatic function abnormal in Study E1201 were mild or moderate in severity in most of affected patients and, in terms of hepatic function abnormal, liver function test abnormal was frequently observed in studies in patients with ITP.

Table 19. Adverse event occurring in ≥2 patients in either of the study with patients with AA (Study E1201) or the patients with ITP (Studies TRA108109 and TRA111433)

	AA Study E1201 (n = 21)	ITP Studies TRA108109 and TRA111433 (n = 23)		AA Study E1201 (n = 21)	ITP Studies TRA108109 and TRA111433 (n = 23)
Nasopharyngitis	38.1 (8)	73.9 (17)	Oropharyngeal pain	4.8 (1)	8.7 (2)
Urticaria	14.3 (3)	4.3 (1)	Influenza	4.8 (1)	8.7 (2)
Hepatic function abnormal	14.3 (3)	0 (0)	Hypertension	4.8 (1)	13.0 (3)
Diarrhoea	9.5 (2)	17.4 (4)	Hypokalaemia	0 (0)	21.7 (5)
Abdominal pain upper	9.5 (2)	4.3 (1)	Myalgia	0 (0)	17.4 (4)
Enterocolitis	9.5 (2)	0 (0)	Insomnia	0 (0)	17.4 (4)
Dyspepsia	9.5 (2)	0 (0)	Cataract	0 (0)	13.0 (3)
Decreased appetite	9.5 (2)	0 (0)	Conjunctival haemorrhage	0 (0)	13.0 (3)
Blood alkaline phosphatase increased	9.5 (2)	4.3 (1)	Bronchitis	0 (0)	13.0 (3)
Blood bilirubin increased	9.5 (2)	4.3 (1)	Cystitis	0 (0)	13.0 (3)
Blood creatinine increased	9.5 (2)	0 (0)	Rhinitis	0 (0)	13.0 (3)
Pyrexia	9.5 (2)	8.7 (2)	Compression fracture	0 (0)	13.0 (3)
Back pain	9.5 (2)	8.7 (2)	Eczema	0 (0)	13.0 (3)
Gastroenteritis	9.5 (2)	8.7 (2)	Anaemia	0 (0)	8.7 (2)
Rash	9.5 (2)	0 (0)	Haemorrhagic diathesis	0 (0)	8.7 (2)
Purpura	9.5 (2)	0 (0)	Conjunctivitis allergic	0 (0)	8.7 (2)
Hyperbilirubinaemia	9.5 (2)	0 (0)	Platelet count increased	0 (0)	8.7 (2)
Hypersensitivity	9.5 (2)	0 (0)	Fatigue	0 (0)	8.7 (2)
Iron deficiency anaemia	4.8 (1)	13.0 (3)	Chest pain	0 (0)	8.7 (2)
Nausea	4.8 (1)	13.0 (3)	Tenosynovitis	0 (0)	8.7 (2)
Vomiting	4.8 (1)	8.7 (2)	Hypoaesthesia	0 (0)	8.7 (2)
Haemorrhoids	4.8 (1)	8.7 (2)	Rhinitis allergic	0 (0)	8.7 (2)
AST increased	4.8 (1)	21.7 (5)	Herpes simplex	0 (0)	8.7 (2)
ALT increased	4.8 (1)	17.4 (4)	Pharyngitis	0 (0)	8.7 (2)
Arthralgia	4.8 (1)	8.7 (2)	Limb injury	0 (0)	8.7 (2)
Headache	4.8 (1)	17.4 (4)	Dry skin	0 (0)	8.7 (2)

MedDRA/J ver.18.1 (Study E1201) and ver.19.1 (Studies TRA108109 and TRA111433). Incidence % (number of patients affected).

PMDA's view:

Study E1201 revealed no tendencies of particular clinical concern in the occurrence of adverse events, no tendency toward increasing the incidence of adverse events in association with long-term treatment, or no clinically significant difference in the safety profile of eltrombopag as compared with patients with ITP, the approved indication. Accordingly, in the treatment of patients with AA with an insufficient response to existing treatment, acceptable safety of eltrombopag can be assured by adherence to the safety measures taken for patients with ITP.

Meanwhile, safety data of eltrombopag in patients with AA with an insufficient response to existing treatment should be continuously collected via post-marketing surveillance, etc. because of very limited number of patients enrolled in Study E1201.

7.R.2.2 Safety of eltrombopag in ATG-therapy-naïve patients with AA

The occurrence of adverse events (by Week 52) in ATG-therapy-naïve patients with AA in Study E1202 is shown in Table 13. Relatively frequent adverse events were nausea observed in 60.0% (6 of 10) of patients,

headache in 50.0% (5 of 10) patients, constipation in 40.0% (4 of 10) of patients, oedema in 40.0% (4 of 10) of patients, pyrexia in 40.0% (4 of 10) of patients, renal impairment in 40.0% (4 of 10) of patients, and vomiting in 40.0% (4 of 10) of patients. All the events were mild or moderate in severity. Adverse drug reactions occurring in ≥2 patients were myalgia in 30.0% (3 of 10) of patients, blood bilirubin increased in 20.0% (2 of 10) of patients, and nausea in 20.0% (2 of 10) of patients, and they were all mild or moderate in severity. No deaths, serious adverse drug reactions, or adverse drug reactions leading to treatment discontinuation were observed.

Table 20 shows the occurrence of adverse events in Study E1202 by time of administration. There was no tendency toward increased incidences of adverse events in association with prolonged treatment.

Table 20. Occurrence of adverse events by time (Study E1202)

	To Day 30 (n = 10)	Days 31–90 (n = 10)	Days 91–180 (n = 10)	Days 181–270 (n = 9)	Days 271–360 (n = 8)	Total (n = 10)
Adverse event	100 (10)	60.0 (6)	60.0 (6)	44.4 (4)	62.5 (5)	100 (10)
Serious adverse event	0 (0)	0 (0)	0 (0)	0 (0)	25.0 (2)	20.0 (2)
Adverse event leading to treatment discontinuation	0 (0)	0 (0)	10.0 (1)	0 (0)	0 (0)	10.0 (1)
Nausea	30.0 (3)	30.0 (3)	0 (0)	0 (0)	0 (0)	60.0 (6)
Headache	20.0 (2)	10.0 (1)	0 (0)	11.1 (1)	12.5 (1)	50.0 (5)
Constipation	30.0 (3)	0 (0)	0 (0)	11.1 (1)	0 (0)	40.0 (4)
Oedema	40.0 (4)	0 (0)	0 (0)	0 (0)	0 (0)	40.0 (4)
Pyrexia	40.0 (4)	0 (0)	0 (0)	0 (0)	0 (0)	40.0 (4)
Renal impairment	20.0 (2)	10.0 (1)	0 (0)	0 (0)	12.5 (1)	40.0 (4)
Vomiting	10.0 (1)	10.0 (1)	0 (0)	11.1 (1)	12.5 (1)	40.0 (4)

MedDRA/J ver.19.1. Incidence % (number of patients affected). The listed adverse events occurred at a total incidence of ≥40%.

PMDA's view:

Although the extremely limited number of enrolled patients should be noted, there were no tendencies raising clinically significant concerns in the occurrence of adverse events, or there was no tendency toward increased incidences of adverse events with prolonged treatment. The safety of eltrombopag in treatment-naïve patients with AA should be continuously investigated via post-marketing surveillance, etc.

7.R.2.3 Adverse events of interest

Sections 7.R.2.3.1 to 7.R.2.3.7 discuss hepatobiliary events, thromboembolic events, chromosome abnormality and hematological malignancy, kidney-related events, bleeding events, eye-related events (particularly cataract), and thrombocytopenia after completion of treatment, which are the adverse events of clinical interest identified by the applicant, as well as myelofibrosis listed in the "Clinically Significant Adverse Reactions" section of the package insert.

PMDA's view:

Currently, the reviews in Sections 7.R.2.3.1 to 7.R.2.3.7 identify no particular clinical concerns about hepatobiliary events, thromboembolic events, chromosome abnormality and hematological malignancy, kidney-related events, bleeding events, eye-related events (particularly cataract), thrombocytopenia after completion of treatment, and myelofibrosis. However, because of the limited number of patients enrolled in

the Japanese clinical studies, data related these events should be continuously collected via post-marketing surveillance, etc. for further investigation.

7.R.2.3.1 Hepatobiliary events

The applicant's explanation:

Eltrombopag is metabolized in the liver and therefore is known to increase hepatic enzymes. Moreover, eltrombopag is an inhibitor of UGT1A1, which is responsible for glucuronidation of bilirubin, and of OATP1B1, which is a hepatic transporter of bilirubin. These facts suggest that eltrombopag increases indirect bilirubin levels (*Chem Biol Interact.* 2004;150:179-187; *J Biol Chem.* 2001;276:9626-9630).

Table 21 shows the occurrence of hepatobiliary events (by Week 52) in Studies E1201 and E1202. Most of the events were mild or moderate in severity and resolved during treatment or after dose reduction or treatment suspension.

Table 21. Occurrence of hepatobiliary events in Studies E1201 and E1202 (by Week 52)

	Study E1201 Refractory AA (n = 21)		Study E1202 Untreated AA (n = 10)
Total	**47.6 (10)**	**Total**	**70.0 (7)**
Hepatic function abnormal	**14.3 (3)**	**ALT increased**	**30.0 (3)**
Hyperbilirubinaemia	**9.5 (2)**	**Blood bilirubin increased**	**30.0 (3)**
Blood alkaline phosphatase increased	**9.5 (2)**	**Blood alkaline phosphatase increased**	**10.0 (1)**
Blood bilirubin increased	**9.5 (2)**	**γ -GTP increase**	**10.0 (1)**
Liver disorder	**4.8 (1)**	**Hepatic function abnormal**	**10.0 (1)**
ALT increased	**4.8 (1)**	**Liver injury**	**10.0 (1)**
AST increased	**4.8 (1)**		

MedDRA /J ver.18.1 for Study E1201. MedDRA/J ver.19.1 for Study E1202. Incidence % (number of patients affected).

In Study E1201, severe hepatic function abnormal was reported in 1 patient,[8)] but the hepatic function recovered to baseline after discontinuation of eltrombopag.

PMDA's view:

Most of the hepatobiliary events observed in Studies E1201 and E1202 (by Week 52) were mild or moderate in severity and resolved during treatment or after dose reduction or treatment suspension. Severe hepatic function disorder was reported in 1 patient, and the outcome of the event was "resolved." Healthcare professionals should pay attention to hepatic function during treatment with eltrombopag, and hepatic function disorder-related data should be collected via post-marketing surveillance, etc. for further investigation.

8) ALT was as high as 81 IU/L at baseline. After the start of treatment with eltrombopag, ALT and AST increased to >5 times and >3 times the upper limit of normal (ULN), respectively. ALT and AST levels gradually improved after discontinuation of eltrombopag and recovered to the baseline levels 57 days after discontinuation of eltrombopag.

7.R.2.3.2 Hematological malignancy and chromosome abnormality

The applicant's explanation:

TOP receptor agonists may aggravate existing hematopoietic malignancy such as myelodysplastic syndrome (MDS). AA, in some cases, is known to transition to MDS or acute myeloid leukemia (AML) during a follow-up period (Reference Guide for Treatment of Aplastic Anemia 2016). Therefore, hematological malignancy and chromosome abnormality were examined.

In either Studies E1201 or E1202, no transition to hematological malignancy including MDS occurred. Moreover, there was no clear tendency toward increasing blasts in bone marrow or peripheral blood during treatment period. Chromosome abnormalities were detected in 3 patients[9)] in Study E1201. However, chromosome 7 abnormality, which is a risk factor for transition to MDS and AML with a poor prognosis, was not detected. Trisomy 8 was identified in 1 patient and reported as an adverse event after treatment discontinuation, but it returned to a normal karyotype by the final evaluation. No chromosome abnormality was reported as an adverse event in Study E1202.

Some chromosome abnormalities are potential poor prognostic factors, which is a clinical concern. Chromosome abnormality was thus investigated in foreign studies as well. In Study 154, 3 patients had a diagnosis of MDS after treatment with eltrombopag. Chromosome abnormalities were detected in 8 patients after treatment with eltrombopag, and 5 of the 8 patients had chromosome 7 abnormalities.[10)] Of the 3 patients with a diagnosis of MDS,[11)] 2 had monosomy 7. In the 8 patients with chromosome abnormalities, the median time (min, max) to detection of abnormalities was 3.1 months (3, 14), and the median time (min, max) to detection of chromosome 7 abnormalities was 2.7 months (3, 9). In the foreign study, Study 133,[12)] 1 patient[13)] had a diagnosis of AML after treatment with eltrombopag. Chromosome abnormalities were detected in the 4 patients after treatment with eltrombopag, and 1 of the 4 patients had chromosome 7 deletion and discontinued eltrombopag therapy. In Study 150, 1 patient had a diagnosis of MDS after treatment with eltrombopag. Chromosome abnormalities were detected in 4 patients after treatment with eltrombopag, and 1 of the 4 patients had monosomy 7 and had a diagnosis of MDS.[14)]

PMDA's view:

---

9) Trisomy 8 was detected in 1 patient. Due to no improvement in blood cells, and eltrombopag therapy was discontinued according to the study protocol. In another patient, the partial deletion of Y chromosome was detected, and morphological dysplasia was found through the central evaluation by a microscopist, which led to the discontinuation of eltrombopag. In the other patient, an abnormal karyotype 46XY, inv(10)(p13q24) was detected at Week 13 of treatment. Eltrombopag was continued, and similar abnormalities were no longer detected.

10) Monosomy in 4 patients, and partial deletion in 1 patient

11) Of 2 patients with monosomy 7, 1 patient died of MDS/AML 6 months after the last dose of eltrombopag, and another underwent bone marrow transplantation. In the remaining 1 patient with a diagnosis of MDS, deletion of chromosome 13 was detected along with ringed sideroblasts of <5%, and the patient underwent bone marrow transplantation.

12) An open-label, uncontrolled study to evaluate the efficacy and safety of 6-month treatment with eltrombopag in patients with refractory severe AA aged ≥2 years and weighing ≥12 kg.

13) The patient received eltrombopag for approximately 3 months, but evaluation was not performed at Month 3. Transition to leukemia was reported. At a month after the last dose of eltrombopag, the patient died of sepsis following induction chemotherapy.

14) Monosomy 7 was found at Month 3 of treatment, and eltrombopag was discontinued. The patient had a diagnosis of MDS 1 month later. At approximately 2 years after the last dose of eltromabopag, the patient died of relapsed AML following bone marrow transplantation.

Although there was no transition to MDS or AML occurring in Studies E1201 and 1202 (by Week 52), Studies 154, 133, and 150 revealed transition to MDS or AML as well as chromosome 7 abnormalities with poor prognosis. In response, these findings should be communicated appropriately via the package insert, etc.

7.R.2.3.3 Kidney-related events

The applicant's explanation:

Renal tubular toxicity was observed in repeated-dose toxicity studies in mice and rats (see Review Report for Revolade Tablets 12.5 and 25 mg, dated August 17, 2010), which was characterized by degeneration, necrosis, or regenerative changes. Kidney-related events were therefore investigated in Studies E1201 and E1202 as detailed below.

In Study E1201 (by Week 52), renal function-related adverse events occurred in 3 patients (blood creatinine increased in 2 and renal disorder in 1). All events were mild in severity, and eltrombopag therapy was continued without dose adjustment.

In Study E1202 (by Week 52), renal function-related adverse events occurred in 5 patients (renal impairment in 3, renal impairment and dysuria and renal disorder in 1 patient each). All events were mild or moderate in severity, and eltrombopag therapy was continued without dose adjustment.

PMDA's view:

The kidney-related adverse events observed in Studies E1201 and E1202 were mild or moderate in severity, and are thus of no significant concerns at present.

7.R.2.3.4 Thromboembolic events

The applicant's explanation:

A platelet count beyond the normal range can increase the risk of thromboembolism. Thromboembolism was reported in patients treated with eltrombopag and even with a platelet count within or below the normal range. Therefore, thromboembolic events were investigated in Studies E1201 and E1202.

No thromboembolic events occurred in Studies E1201 and E1202 (by Week 52).

7.R.2.3.5 Events related to eye (especially cataract)

The applicant's explanation:

Cataract was observed in toxicity studies in mice and rats (see Review Report for Revolade Tablets 12.5 and 25 mg, dated August 17, 2010). Eye-related events (especially cataract) were thus investigated in Studies E1201 and E1202.

In Studies E1201 and E1202 (by Week 52), no onset or worsening of cataract was reported. Retinal detachment was a serious adverse event reported in 1 patient in Study E1201, but a causal relationship with eltrombopag was ruled out for the event because the patient had concomitant cytomegalovirus retinitis.

PMDA confirmed that no cataract occurred in Study E1201 or E1202 (by Week 52).

7.R.2.3.6 Thrombocytopenia after completion of treatment

The applicant's explanation:

A decrease in platelet count to baseline or lower after discontinuation of eltrombopag may cause bleeding. Eltrombopag treatment was discontinued in 13 patients in Study E1201 (by Week 52) and 4 patients in Study E1202 (by Week 52). No thrombocytopenia occurred after discontinuation.

PMDA confirmed that no thrombocytopenia occurred after discontinuation of eltrombopag in Study E1201 or E1202 (by Week 52).

7.R.2.3.7 Myelofibrosis

The applicant's explanation:

Eltrombopag and other TPO receptor agonists may form bone marrow reticulin fiber and promote fibrosis. Therefore, myelofibrosis was investigated using the European consensus scale and the Bauermeister scale in Studies E1201 and E1202.

Worsening of the fibrosis grade was observed in 3 and 2 patients in Studies E1201 and E1202, respectively. However, none of these patients were recognized by investigators to have an adverse event.

PMDA confirmed that no clinically significant myelofibrosis occurred in Studies E1201 and E1202 (by Week 52).

7.R.2.4 Foreign post-marketing safety information

The applicant's explanation about the post-marketing safety information of eltrombopag:

Since its first approval for treatment of chronic ITP in the US on November 20, 2008, eltrombopag has been approved for treatment of chronic ITP, hepatitis C virus infection-associated thrombocytopenia, or severe AA in ≥70 countries across the world, as of September 30, 2016. In the US, eltrombopag is also approved for chronic ITP in pediatric patients aged ≥1 year.

Based on the cumulative sales of each dosage form, the number of patients exposed to eltrombopag is approximately 76,568 person-years as of September 30, 2016. None of the safety measures taken by the regulatory authorities or marketing authorization holder (MAH) from October 1, 2015 through September 30, 2016 led to withdrawal from or suspension of the marketing authorization or rejection of the marketing authorization renewal.

PMDA confirmed that available foreign post-marketing data indicate no newly emerged safety concerns at present, other than known events in patients with ITP, which is the approved indication in Japan.

7.R.3 Clinical positioning

The applicant's explanation about clinical positioning of eltrombopag:

Therapeutic choice for AA depends on age, severity, availability of a donor, responsiveness to immunosuppressive therapy, etc. Bone marrow transplantation is the radical treatment of AA and is the first-line therapy for patients with slightly severe or greater AA aged <40 years who have a HLA-identical sibling donor (Table 5). In contrast, patients aged ≥40 years or have no matched donor are ineligible for transplantation (Reference Guide for Treatment of Aplastic Anemia 2016). ATG/CsA therapy is the standard care for patients with slightly severe or greater AA who are ineligible for transplantation (Reference Guide for Treatment of Aplastic Anemia 2016), but more effective therapy is needed in the clinical practice. Moreover, blood transfusion, although it is the mainstream treatment for patients with AA who are non-responders to or are ineligible for ATG therapy, is associated with risks of infections, refractoriness to platelet transfusion, etc., and therefore, other treatment options are awaited. In response, eltrombopag was designated as an orphan drug with a proposed indication of aplastic anemia on November 24, 2016 (Drug Designation No. 391 [*28 yaku*]).

Data from Study E1201 shows that eltrombopag improved pancytopenia and reduced the dependence on transfusion of patients with AA with an insufficient response to existing treatment. Data from Study E1202 demonstrated the greater therapeutic effect of eltrombopag combined with ATG/CsA therapy in ATG-therapy-naïve patients with AA than the existing treatment. There were no major safety concerns with eltrombopag in Studies E1201 and E1202. Therefore, eltrombopag, with its pharmacological effect on undifferentiated hematopoietic stem cells that promote hematopoiesis, is expected to be a new drug that will benefit patients with AA.

PMDA's view:

Data from Studies E1201 and E1202 demonstrated that eltrombopag is a new therapeutic option for patients with AA with an insufficient response to existing treatment and ATG-therapy-naïve patients with AA.

7.R.4 Indications

The applicant's explanation about the indications of eltrombopag:

Data from Study E1201 suggested the efficacy of eltrombopag in patients with AA with an insufficient response to existing treatment, while data from Study E1202 suggested the efficacy of eltrombopag combined with ATG/CsA in ATG-therapy-naïve patients with AA. Both studies revealed no significant safety concerns.

In general, ATG therapy is not for patients with mild AA requiring no blood transfusion. ATGs available in Japan are indicated for treatment of moderate or severe AA. Thus, eltrombopag is expected to be administered to ATG-therapy-naïve patients with moderate or severe AA. Meanwhile, the Reference Guide for Treatment of Aplastic Anemia 2016 notes that ATG therapy may be considered for patients with mild AA who have progressive cytopenia or those with a platelet count of ≤50,000/μL despite stable pancytopenia.

On the premise that eltrombopag is used under the supervision of a physician with adequate experience in the treatment of blood dyscrasia, the indication of eltrombopag should be defined as “aplastic anemia” without specifying severity. The package insert should advise that the use of eltrombopag be determined by referring to the latest treatment guidelines.

PMDA’s view:
Data from Study E1201 demonstrate the efficacy of eltrombopag in patients with AA with an insufficient response to existing treatment, while data from Study E1202 suggest that eltrombopag has promising efficacy in ATG-therapy-naïve patients with AA. Data from both studies indicate the acceptable safety of eltrombopag. Thus it is appropriate that the indication of eltrombopag be defined as aplastic anemia, and that healthcare professionals be advised to refer to the latest treatment guidelines for patient eligibility for the therapy so as to use eltrombopag for proper patients. The final decision on the indication of eltrombopag will be made taking into account the comments from the Expert Discussion.

7.R.5 Dosage and administration

Based on the reviews in Sections 7.R.5.1 and 7.R.5.2, PMDA considers that there is no particular problem in determining the dosage regimen of eltrombopag on the basis of Studies E1201 and E1202. The final decision will be made taking into account the comments from the Expert Discussion.

7.R.5.1 Patients with an insufficient response to or ineligible for existing treatment (Study E1201)

The applicant’s rationale for the dosage regimen in Study E1201:
The dosage regimen in Study E1201 were selected with a reference to those in Study 154 in patients with refractory severe AA.

The starting dose of eltrombopag in Study 154 was 50 mg (25 mg in East Asian patients), as was the case with treatment of chronic ITP in Europe and the US. The starting dose for East Asian patients was halved because in a foreign study, Study PMA112509 in patients with MDS/AML, the trough level of eltrombopag ≥100 mg was higher by approximately 60% in East Asian patients than in other patients. A comparison of trough levels between Japanese and Caucasian patients with chronic ITP showed a similar tendency (see Review Report for Revolade Tablets 12.5 and 25 mg, dated August 17, 2010). The trough levels following the administration of eltrombopag 50 mg were similar between the Japanese patients with chronic ITP and East Asian patients with MDS/AML. Therefore, 25 mg, a half the dose for non-East Asians, was selected as the starting eltrombopag dose in Study E1201, as that for East Asians in Study 154. The dose was increased by 25 mg every 2 weeks based on the platelet count until Week 26 (Table 7).

The maximum dose in Study 154 was 150 mg (75 mg in East Asian patients), which was higher than the maximum dose for patients with chronic ITP in western countries, 75 mg. Eltrombopag, in patients with chronic ITP, acts on megakaryocytes at the late differentiation phase (mainly megakaryocyte precursors). Meanwhile, in patients with hematopoietic failure such as AA, eltrombopag must stimulate hematopoietic progenitors and stem cells in the bone marrow microenvironment. While patients with chronic ITP have

normal hematopoietic function and bone marrow cell density, patients with AA have hypoplastic bone marrow. Considering that patients with AA require a higher dose of eltrombopag than those with chronic ITP, and the maximum dose was thus set at 150 mg (75 mg in East Asians). In Study 154, the eltrombopag dose was increased to 150 mg in most of patients responded hematologically (75 mg in East Asians) and was well tolerated. In view of the results from Study 154 and in expectation of further enhancement of therapeutic effects, the maximum daily dose in Study E1201 was set at 100 mg, the maximum dose that had been tolerated in Japanese healthy adult men. As a result, eltrombopag was increased to its maximum dose of 100 mg in 20 of 21 patients receiving eltrombopag in Study E1201. The remaining 1 patient discontinued eltrombopag on Day 37 after their laboratory data met the discontinuation criteria related to abnormal hepatic function tests. The patient received up to 75 mg of eltrombopag. The median of mean eltrombopag daily dose (min, max) was 88.6 mg (45, 95). The eltrombopag dose at each time point in Study E1201 is shown in Figure 1, and most of patients remaining on the therapy received eltrombopag 100 mg.

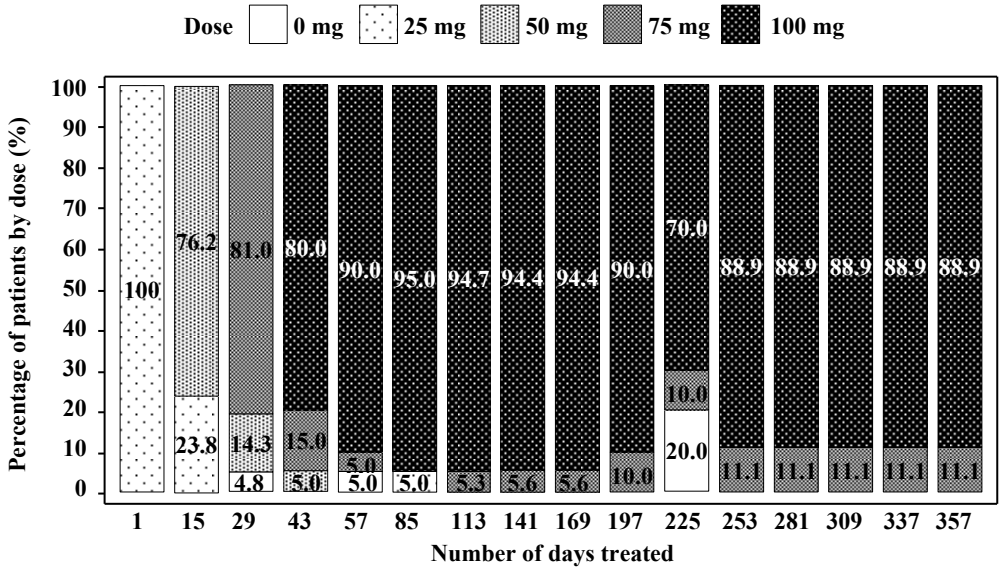

Figure 1. Eltrombopag dose at each time point in Study E1201

The data from Study E1201 have demonstrated the efficacy and safety of eltrombopag (Sections 7.R.1 and 7.R.2), and it was reasonable to refer to the Study E1201 data to determine the dosage regimen for patients with AA with an insufficient response to existing treatment. Information on dose adjustment will also be provided in the package insert.

PMDA's view:

There is no particular problem with the starting dose of 25 mg and the maximum dose of 100 mg for patients with AA with an insufficient response to existing treatment, based on data from Study E1201 which demonstrated the efficacy and safety of eltrombopag. Dose adjustment methods (e.g., increase by 25 mg every 2 weeks until Week 26 based on platelet count) should be communicated via the package insert.

7.R.5.2 Combination with ATG/CsA therapy (Study E1202)

The applicant's rationale for selection of the dosage regimen in Study E1202:
The dosage regimen in Study E1202 were selected with a reference to Study 150 in treatment-naïve patients with severe AA.

Platelet count begins to decrease markedly as soon as ATG/CsA therapy starts. Therefore, the starting dose in Study 150 was set at 150 mg (75 mg for East Asians) so that the high starting dose would recover the loss of platelets as early as possible [see Section "7.R.5.1 Patients with an insufficient response to or ineligible for existing treatment (Study E1201)"]. The maximum dose in Study E1201 was 100 mg. The geometric mean $AUC_{0-\tau}$ following administration of eltrombopag 150 mg in combination with equine ATG/CsA was 694 μg·h/mL, which was higher than the geometric means $AUC_{0-\tau}$ following administration at 150 mg in healthy adults (204 μg·h/mL) and patients with chronic ITP (252 μg·h/mL). The starting dose in Study E1202 was 75 mg, as was the case with East Asian patients in Study 150. The eltrombopag dose was decreased by 25 mg every 2 weeks until Week 26 based on platelet count (Table 11).

In 10 patients receiving eltrombopag in Study E1202, the median treatment duration (min, max) was 344.5 days (125, 355), and the median of mean daily dose (min, max) was 49.8 mg (27, 75). The eltrombopag dose at each time point in Study E1202 is shown in Figure 2. After transition to the extension phase, eltrombopag was reduced or suspended in 7 of 9 patients according to the dose adjustment criteria (Table 11). Of the 7, 1 patient discontinued the study due to relapse, and 6 patients remained suspension as of Week 52 with maintained PR. Due to possible underdose resulting from suspension, exposure outside the suspension period was also examined. The median of actual duration of eltrombopag therapy (min, max) was 251.0 days (125, 301), and the median of mean eltrombopag daily dose (min, max) was 68.8 mg (49, 75).

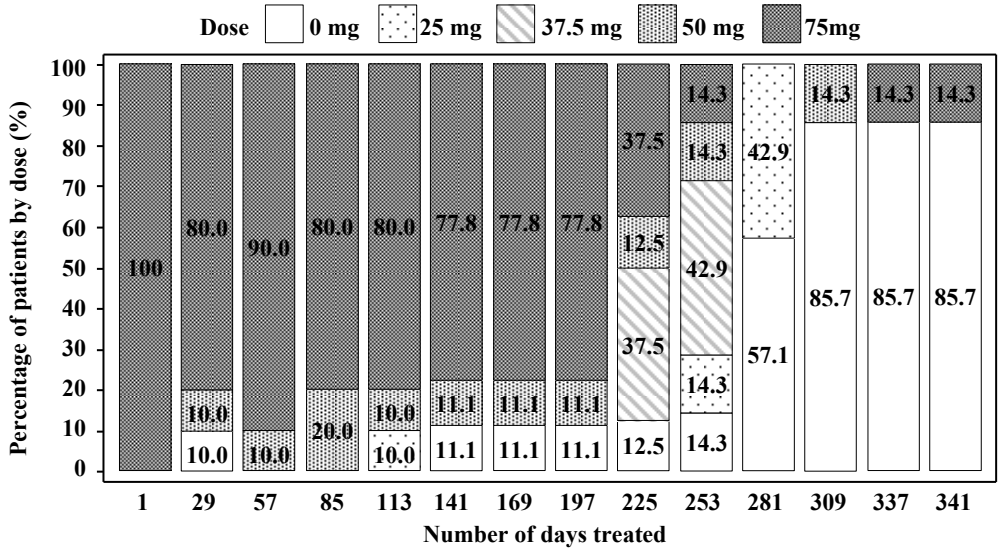

Figure 2. Eltrombopag dose at each time point in Study E1202

The data from Study E1202 have demonstrated the efficacy and safety of eltrombopag (Sections 7.R.1 and 7.R.2), and it was reasonable to refer to Study E1202 to determine the dosage regimen of eltrombopag with ATG/CsA therapy. The dose adjustment methods will also be provided in the package insert.

PMDA's view:

There is no particular problem with the starting dose of 75 mg for ATG-therapy-naïve patients with AA, based on the data from Study E1202, which demonstrated the efficacy and safety of eltrombopag. The dose adjustment methods (e.g., decrease by 25 mg every 2 weeks until Week 26 based on platelet count, reduce or suspend during improvement in tri-lineage blood cells) should be presented in the package insert.

7.R.6 Post-marketing investigations

The applicant plans to conduct a post-marketing specified drug use-results survey as shown in Table 22.

Table 22. Outline of specified drug use-results survey (draft)

Objective	**To evaluate the safety and efficacy of eltrombopag in long-term use in patients with AA in the clinical setting**
Survey method	**Central registration**
Population	**Patients with AA (patients with AA receiving or scheduled to receive ATG/CsA and patients with AA with an insufficient response to or ineligible for existing treatment)**
Target sample size	**110 patients (Safety analysis set: 100 patients)**
Survey period	**2 years (registration period: 12 months)**
Observation period	**1 year**
Main survey items	**• Patient characteristics (age, sex, concomitant disease, disease type classification, severity, prior treatment, etc.) • Details of eltrombopag therapy (daily dose, treatment period, reasons for dose modification or discontinuation) • Details of concomitant drugs and therapy (drug name/therapy name, treatment period, etc.) • Adverse events (onset date, seriousness, treatment, outcome, causal relationship with eltrombopag, etc.) • Laboratory data (blood biochemistry [AST, ALT, γ-GTP, bilirubin], hematological test [neutrophil count, hemoglobin, reticulocyte count, platelet count, MCV]) • Blood transfusion volume (platelet transfusion, red blood cell transfusion) • Efficacy (response status of patients with AA receiving or scheduled to receive ATG/CsA therapy; hematological response status of patients with AA with an insufficient response to or ineligible for existing treatment) • Clinical symptoms (presence or absence of anemia symptoms, bleeding symptoms, and signs of infections) • Key survey items: hepatic function disorder, thromboembolism**

PMDA's view:

Because of the limited number of Japanese patients treated with eltrombopag in Studies E1201 and E1202, data should be collected from more patients to investigate the safety and efficacy of eltrombopag. The following data are also subject to collection for investigation, but details will be finalized with consideration of comments from the Expert Discussion.

- Safety and efficacy of eltrombopag by patients characteristics
- Occurrence of hepatobiliary events, thromboembolic events, chromosome abnormality and hematological malignancy, kidney-related events, bleeding events, eye-related events (particularly cataract), thrombocytopenia after completion of treatment, and myelofibrosis
- Safety and efficacy of eltrombopag alone or in combination use with CsA

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection and assessment revealed no noteworthy issues. PMDA thus concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.2-1, CTD 5.3.5.2-2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that eltrombopag has efficacy in the treatment of aplastic anemia and that eltrombopag has acceptable safety in view of its benefits. PMDA has concluded that eltrombopag may be approved if eltrombopag is not considered to have any particular problems with its efficacy, safety, indications, dosage and administration, and post-marketing investigations, based on comments from the Expert Discussion.

Review Report (2)

July 19, 2017

Product Submitted for Approval

Brand Name	Revolade Tablets 12.5 mg, Revolade Tablets 25 mg
Nonproprietary Name	Eltrombopag Olamine
Applicant	Novartis Pharma K.K.
Date of Application	November 30, 2016

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized in the following. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc., concerning the product submitted for marketing approval, 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).

1.1 Efficacy, safety, indications, and dosage and administration

At the Expert Discussion, the expert advisors supported PMDA's conclusions on the issues presented in Sections "7.R.1 Efficacy," "7.R.2 Safety," "7.R.4 Indications," and "7.R.5 Dosage and administration" in the Review Report (1).

Based on comments from the Expert Discussion, PMDA accepts that the indication of eltrombopag relevant to AA be defined as per the applicant's proposal, as shown below. PMDA asked the applicant to revise the wording relevant to AA in the "Precautions for Indications," "Dosage and Administration," and "Precautions for Dosage and Administration" sections as shown below. The applicant responded properly and PMDA accepted it.

Indications

1. Chronic idiopathic thrombocytopenic purpura
2. Aplastic anemia

(Underline denotes additions.)

Precautions for Indications (only the part relevant to AA)

2. Aplastic anemia

Eltrombopag should be used for patients who are considered eligible for the treatment according to the latest information such as in the treatment guidelines (see the "CLINICAL STUDIES" section).

(Underline denotes additions.)

Dosage and Administration

1. Chronic idiopathic thrombocytopenic purpura

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 based on the patient's platelet count and condition. The maximum daily dose is 50 mg.

2. Aplastic anemia

Patients naïve to anti-thymocyte globulin

In combination with anti-thymocyte globulin, the usual adult dosage of eltrombopag is 75 mg once daily administered orally on an empty stomach (>2 hours before or after a meal). The dose may be reduced based on the patient's condition.

Patients with an insufficient response to existing treatment

The usual initial adult dosage of eltrombopag is 25 mg once daily administered orally on an empty stomach (>2 hours before or after a meal). The dose may be adjusted based on the patient's condition. The maximum daily dose is 100 mg.

(Underline denotes additions.)

Precautions for Dosage and Administration (only the parts relevant to AA)

4. Aplastic anemia

(1) Eltrombopag therapy requires regular blood and hepatic function tests throughout the therapy period. The dose of eltrombopag should be adjusted by reference to the guidelines below. The dose should be adjusted, when necessary, by 25 mg/day as a rule. The adjusted dose should be maintained for at least 2 weeks.

Patients naïve to anti-thymocyte globulin therapy

Because of a possible hepatic function disorder associated with anti-thymocyte globulin, eltrombopag should be started after a set period of time from anti-thymocyte globulin therapy (see the "CLINICAL STUDIES" section).

1) Before using an anti-thymocyte globulin, read the package insert of the concomitant drug carefully.
2) If the platelet count exceeds 200,000/μL, consider dose reduction of eltrombopag.
3) If the platelet count exceeds 400,000/μL, suspend eltrombopag. Once the platelet count decreases to below 200,000/μL after suspension, reinitiate eltrombopag at a dose 1 level lower than that before suspension as a rule.
4) If there is no improvement in blood cell counts by 26 weeks of therapy, discontinue eltrombopag.

Patients with an insufficient response to existing treatment

1) If the platelet count is below 50,000/μL, consider dose escalation.
2) If the platelet count is 100,000 to 200,000/μL, consider dose reduction.

3) If the platelet count exceeds 200,000/μL, suspend eltrombopag for at least 1 week. Once the platelet count decreases to below 50,000/μL after suspension, reinitiate eltrombopag at a dose 1 level lower than that before suspension as a rule.
4) If there is no improvement in blood cell counts by 16 weeks of therapy, discontinue eltrombopag.

(2) For patients who achieve tri-lineage response (i.e., platelet count exceeding 50,000/μL in transfusion independence, hemoglobin level exceeding 10 g/dL, and neutrophil count exceeding 1,000/μL) lasting at least 8 weeks, reduce the eltrombopag dose by up to 50%. If the response lasts at least 8 weeks at the reduced dose, suspend eltrombopag and monitor blood cell counts. If the platelet count drop to below 30,000/μL, hemoglobin to below 9 g/dL, or neutrophil count to below 500/μL after suspension, eltrombopag may be reinitiated at the dose used before suspension.

(Underline denotes additions.)

1.2 Risk management plan (draft)

The expert advisors supported the PMDA's conclusion in "7.R.6 Post-marketing investigations" in the Review Report (1).

In response, PMDA further concluded that the eltrombopag risk management plan (draft) should include the safety and efficacy specifications presented in Table 23 and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 24 and a specified drug use-results survey presented in Table 25.

Table 23. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	**Important potential risks**	**Important missing information**
• **Hepatic function disorder** • **Thromboembolism** • **Bleeding** • **Myelofibrosis**	• **Thrombotic microangiopathy** • **Hematopoietic malignancy** • **Renal tubular toxicity** • **Endosteal hyperostosis** • **Cataract**	• **Not applicable**
Efficacy specification		
• **Efficacy in patients with ITP in routine use** • **Efficacy in patients with AA in routine use**		

Table 24. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	**Additional risk minimization activities**
• **Early post-marketing phase vigilance (AA)** • **Use-results survey (ITP)** • **Specified drug use-results survey (AA)**	• **Provision of information obtained by the early post-marketing phase vigilance (AA)**

Table 25. Outline of specified drug use-results survey (draft)

Objective	**To evaluate the safety and efficacy of eltrombopag in long-term routine use in patients with AA**
Survey method	**Central registration**
Population	**Patients with AA (patients with AA naïve to ATG therapy or with an insufficient response to existing treatment)**
Target sample size	**400 patients (120 ATG-therapy-naïve patients with AA, 280 patients with AA with an insufficient response to existing treatment)**
Survey period	**4 years (registration period: 2 years)**
Observation period	**1 year**
Main survey items	**• Patient characteristics (age, sex, concomitant disease, disease type classification, severity, prior treatment, etc.)** **• Details of eltrombopag therapy (daily dose, treatment period, reasons for dose modification or discontinuation)** **• Details of concomitant drugs and therapy (drug name/therapy name, treatment period, etc.)** **• Adverse events (onset date, seriousness, treatment, outcome, causal relationship with eltrombopag, etc.)** **• Laboratory data (blood biochemistry [AST, ALT, γ-GTP, bilirubin], hematological test [neutrophil count, hemoglobin, reticulocyte count, platelet count, MCV])** **• Blood transfusion volume (platelet transfusion, red blood cell transfusion)** **• Efficacy (response status of patients with AA receiving or scheduled to receive ATG/CsA therapy; hematological response status of patients with AA with an insufficient response to or ineligible for existing treatment)** **• Clinical symptoms (presence or absence of anemia symptoms, bleeding symptoms, and signs of infections)** **• Key survey items: hepatic function disorder, thromboembolism**

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the proposed indication and dosage and administration modified as shown below, with the following condition. The product is an orphan drug, and the re-examination period of the product should be 10 years.

Indications

1. Chronic idiopathic thrombocytopenic purpura
2. Aplastic anemia

(Underline denotes additions.)

Dosage and Administration

1. Chronic idiopathic thrombocytopenic purpura

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 based on the patient's platelet count and condition. The maximum daily dose is 50 mg.

2. Aplastic anemia

Patients naïve to anti-thymocyte globulin

In combination with anti-thymocyte globulin, the usual adult dosage of eltrombopag is 75 mg once daily administered orally on an empty stomach (>2 hours before or after a meal). The dose may be reduced based on the patient's condition.

Patients with an insufficient response to existing treatment

The usual initial adult dosage of eltrombopag is 25 mg once daily administered orally on an empty stomach (>2 hours before or after a meal). The dose may be adjusted based on the patient's condition. The maximum daily dose is 100 mg.

(Underline denotes additions.)

Condition of Approval

The applicant is required to develop and appropriately implement a risk management plan.