Report on the Deliberation Results

August 14, 2025
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau,
Ministry of Health, Labour and Welfare

Brand Name	Doptelet Tablets 20 mg
Non-proprietary Name	Avatrombopag Maleate (JAN*)
Applicant	Swedish Orphan Biovitrum Japan Co., Ltd.
Date of Application	August 29, 2024

Results of Deliberation

In its meeting held on July 31, 2025, the First Committee on New Drugs concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

The re-examination period is the remainder of the re-examination period for the initial approval of the product (until March 26, 2031).

Approval Conditions

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

** Japanese Accepted Name (modified INN)*

Review Report

July 4, 2025
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	Doptelet Tablets 20 mg
Non-proprietary Name	Avatrombopag Maleate
Applicant	Swedish Orphan Biovitrum Japan Co., Ltd.
Date of Application	August 29, 2024
Dosage Form/Strength	Tablets: Each tablet contains avatrombopag maleate equivalent to 20 mg of avatrombopag.
Application Classification	Prescription drug, (4) Drug with a new indication and (6) Drug with a new dosage
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug II

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of persistent and chronic immune thrombocytopenia (ITP), and that the product 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 indications and dosage and administration shown below, with the following conditions.

Indications

○ Improvement of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo an elective invasive procedure
○ Persistent and chronic immune thrombocytopenia

(Underline denotes additions.)

Dosage and Administration

Improvement of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo an elective invasive procedure

The usual adult dose of avatrombopag is determined as follows and orally administered once daily after a meal for 5 days.

Platelet count before the start of treatment ≥40,000/μL and <50,000/μL: 40 mg
Platelet count before the start of treatment <40,000/μL: 60 mg

Persistent and chronic immune thrombocytopenia

The usual initial adult dose of avatrombopag is 20 mg, which is orally administered once daily after a meal. After starting the treatment, the dosage should be adjusted as appropriate according to the platelet count and symptoms of the patient. The maximum dose is 40 mg once daily.

(Underline denotes additions.)

Approval Conditions

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

Attachment

Review Report (1)

May 23, 2025

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 (PMDA).

Product Submitted for Approval

Brand Name	Doptelet Tablets 20 mg
Non-proprietary Name	Avatrombopag Maleate
Applicant	Swedish Orphan Biovitrum Japan Co., Ltd.
Date of Application	August 29, 2024
Dosage Form/Strength	Tablets: Each tablet contains avatrombopag maleate equivalent to 20 mg of avatrombopag.

Proposed Indications

○ Improvement of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo an elective invasive procedure

○ Chronic idiopathic thrombocytopenic purpura

(Underline denotes additions.)

Proposed Dosage and Administration

Improvement of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo an elective invasive procedure

The usual adult dose of avatrombopag is determined as follows and orally administered once daily after a meal for 5 days.

Platelet count before the start of treatment ≥40,000/μL and <50,000/μL: 40 mg

Platelet count before the start of treatment <40,000/μL: 60 mg

Chronic idiopathic thrombocytopenic purpura

The usual initial adult dose of avatrombopag is 20 mg, which is orally administered once daily after a meal. After starting the treatment, the dosage should be adjusted as appropriate according to the platelet count and symptoms of the patient. The maximum dose is 40 mg once daily.

(Underline denotes additions.)

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List of Abbreviations

See Appendix.

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

Immune thrombocytopenia (ITP) is an acquired autoimmune disease involving the production of autoantibodies against platelet membrane glycoproteins. Binding of these autoantibodies to platelets and megakaryocytes leads to increased phagocytosis and destruction of platelets by splenic macrophages and reduced platelet production by megakaryocytes, thereby resulting in thrombocytopenia. ITP is a designated intractable disease in Japan.

Avatrombopag maleate (hereinafter referred to as "avatrombopag") is an orally available small-molecule thrombopoietin (TPO) receptor agonist that was developed by Yamanouchi Pharmaceutical Co., Ltd. Avatrombopag promotes the proliferation of hematopoietic stem cells, and megakaryocytic differentiation and maturation of these cells, by partially activating the endogenous TPO signaling pathway through binding to the TPO receptor, consequently increasing platelet count.

In Japan, avatrombopag was approved for the indication of "improvement of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo an elective invasive procedure" in March 2023.

Outside Japan, avatrombopag has been approved for the indications of "thrombocytopenia in patients with chronic liver disease who are scheduled to undergo an elective invasive procedure" and "chronic immune thrombocytopenia in patients who have had an insufficient response to conventional therapies" since 2018. As of May 2025, avatrombopag has been approved in 15 countries or regions including Europe and the US.

In Japan, the applicant has recently filed an application for partial changes of approved items to add the indication of "chronic idiopathic thrombocytopenic purpura" and an additional dosage for this indication based on the results of a Japanese phase III study in patients with chronic ITP as the pivotal data.

2. Quality and Outline of the Review Conducted by PMDA

This is an application for an additional indication and an additional dosage. No data relating to quality have been submitted.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

Although this is an application for an additional indication and an additional dosage, no additional study results on non-clinical pharmacology have been submitted because the study results on the platelet-increasing effect of avatrombopag had been evaluated at the time of the initial approval of avatrombopag.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Although this is an application for an additional indication and an additional dosage, no additional study results on non-clinical pharmacokinetics (PK) have been submitted because the data had been evaluated at the time of the initial approval of avatrombopag.

5. Toxicology and Outline of the Review Conducted by PMDA

This is an application for an additional indication and an additional dosage. No data on toxicity studies have been 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 III study in patients with chronic ITP (Study AVA-ITP-307 [Study 307]) used tablets that were identical in formulation to the commercial drug product in Japan.

The plasma concentration of avatrombopag was measured using liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS), with a lower limit of quantitation of 0.848 or 1.000 ng/mL.

6.2 Clinical pharmacology

6.2.1 Population PK and population PK/PD analyses (CTD 5.3.3.5-1, CTD 5.3.3.5-2)

Population pharmacokinetic (PK) and population PK/pharmacodynamic (PD) analyses were performed using the data obtained from phase I studies in non-Japanese and Japanese healthy adults (Studies 477-CL-001, 477-CL-002, 501-PK-902, E5501-A001-001, E5501-A001-005, E5501-A001-006, E5501-A001-007, E5501-A001-017, E5501-A001-018, E5501-A001-019, E5501-G000-008, and E5501-G000-010), and foreign phase II studies (Studies 501-CL-003 and 501-CL-004) and foreign phase III studies (Study 302 and Study E5501-G000-305 [Study 305][1)]) in non-Japanese patients with chronic ITP. For the population PK analysis, plasma avatrombopag concentration data obtained at a total of 17067 points in 475 healthy subjects (including 13 Japanese subjects) and 102 non-Japanese patients with chronic ITP were used. For the population PK/PD analysis, platelet count data obtained at a total of 1724 points in 97 non-Japanese patients with chronic ITP were used. Population PK and population PK/PD analyses of Study 307 in Japanese patients with chronic ITP were also performed using plasma avatrombopag concentration data obtained at a total of 200 points and platelet count data obtained at a total of 619 points, respectively, in 19 Japanese patients with chronic ITP.

The PK and PK/PD of avatrombopag were described by a 1-compartment model with first-order absorption and a model that takes the platelet maturation process into account, respectively (Figure 1).

1) A foreign eltrombopag-controlled phase III study to investigate the efficacy and safety of avatrombopag in patients with chronic ITP. This study was terminated early because patient registration was difficult.

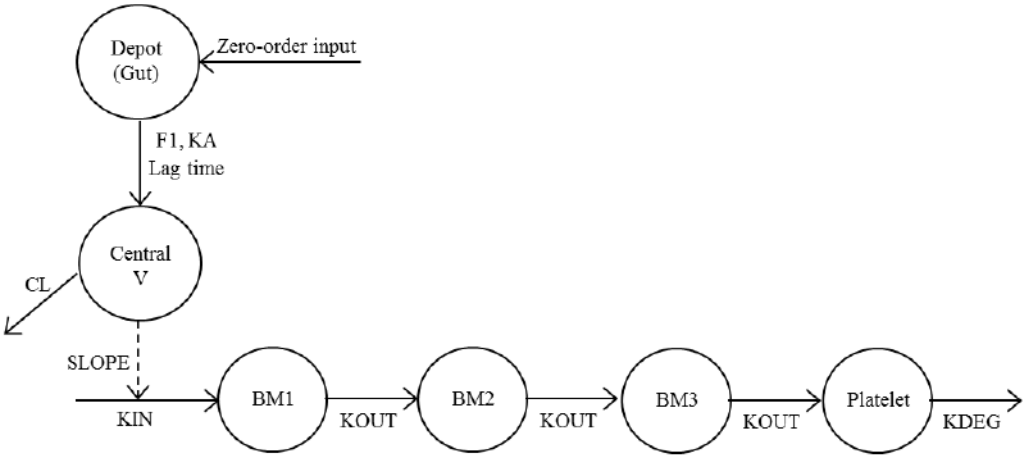

Figure 1. Outline of the population PK/PD structural model

F1, factor for bioavailability; KA, first-order absorption rate constant; V, volume of distribution; CL, clearance; SLOPE, avatrombopag plasma concentration related to the increase in production of platelet precursors through a linear proportionality constant; BM1, precursor production compartment; BM2 and BM3, maturation compartments; KIN, zero-order production rate of platelet precursors; KOUT, first-order maturation rate constant of platelet precursors; KDEG, first-order degradation rate constant of platelets.

Table 1 shows the covariates incorporated in the final population PK and population PK/PD models and their distribution.

Table 1. Covariates incorporated in the final models and their distribution

Model	Covariate incorporated in the final model (parameters affected)	Distribution of covariate
PK[a]	Body weight at baseline (CL/F1, V/F1)	74.0 [42.1, 161] kg[c]
	Concomitant use of strong or moderate dual CYP2C9 and CYP3A4 inducers (CL/F1)	Present in 14 subjects and absent in 563 subjects
	Concomitant use of strong or moderate CYP2C9 inhibitors (CL/F1)	Present in 72 subjects and absent in 505 subjects
	Concomitant use of strong or moderate CYP3A4 inhibitors (CL/F1)	Present in 71 subjects and absent in 506 subjects
	Health status (CL/F1)	Healthy in 475 subjects and chronic ITP in 102 subjects
	Formulation (KA, F1)	Oral suspension in 67 subjects, formulation in the early development stage in 125 subjects,[d] and commercial formulation in 385 subjects
PK/PD[b]	Baseline platelet count (KIN)	20.0 [1.00, 50.0] 10^9/L[c]
	History of splenectomy (SLOPE)	Present in 30 subjects and absent in 67 subjects
	Concomitant use of corticosteroids (KOUT)	Present in 40 subjects and absent in 57 subjects

a: The following factors were assessed as candidate covariates: age, sex, race, ethnicity, body weight at baseline, health status, food, formulation, laboratory data at baseline (creatinine clearance, eGFR, and serum albumin), and concomitant use of interacting drugs (inhibitors or inducers of CYP3A and/or CYP2C9, and inducers or inhibitors of P-glycoprotein [P-gp]).

b: The following factors were assessed as candidate covariates: concomitant use of drugs for the treatment of chronic ITP (corticosteroids, azathioprine, mycophenolate mofetil, danazol, cyclosporine A, etc.), history of splenectomy, and baseline platelet count.

c: Median [minimum, maximum].

d: The formulation in the early development stage was further classified based on the batch number (Batch No. [redacted] used in 54 subjects and other batches used in 71 subjects).

Table 2 shows the PK parameters following administration of avatrombopag 20 mg once daily in non-Japanese and Japanese patients with chronic ITP, estimated using the constructed population PK model.[2)]

[2)] PK parameters in Japanese patients with chronic ITP were estimated using the population PK model that was updated at the time of application in Europe. The update included fixation of the allometry coefficient (0.75) of body weight for CL/F1, simplification of the covariate model of the formulation for KA (disregard of the classification of the formulation in the early development stage with Batch No. [redacted] and the commercial formulation), and the introduction of inter-occasion variability for F1. The main objective of this update was to improve the stability of the model, and the estimates of major parameters including CL/F1 and V/F1 were similar before and after the update.

Table 2. Estimated PK parameters of avatrombopag based on the population PK model

	N	$C_{max,ss}$ (ng/mL)	$AUC_{0\text{-}24h,ss}$ (ng·h/mL)	CL/F1 (L/h)
Non-Japanese patients with chronic ITP (Studies 302 and 305)	42	152 (76.3)	3040 (77.9)	6.58 (77.9)
Japanese patients with chronic ITP (Study 307)	12	263 (37.2)	4991 (35.0)[a]	5.22 (14.6)[a]

Geometric mean (geometric coefficient of variation %)

a: The inter-occasion variability of F1 was considered in the estimation of $AUC_{0\text{-}24h,ss}$, but not in the estimation of CL/F1.

Given that body weight was a significant covariate for apparent total clearance (CL/F1) and apparent volume of distribution (V/F1) (Table 1) and that avatrombopag is a substrate of cytochrome P450 (CYP) 2C9 and CYP3A4, the effects of body weight and concomitant use of CYP2C9 and CYP3A4 inducers or inhibitors on the PD of avatrombopag were investigated through simulation using the constructed population PK/PD model. The basic scenario for simulation was as follows: baseline platelet count, 20,000/μL; body weight, 74 kg; no concomitant drugs; starting dose of avatrombopag, 20 mg once daily; and the number of patients, 500. The proportion of patients achieving the target platelet count (50,000-200,000/μL) at Week 10 of treatment with avatrombopag in the basic scenario was compared to those in other scenarios with different conditions (body weight, concomitant drugs, dose per administration, and dosing frequency). Table 3 shows the results. For all scenarios, simulation was performed assuming that the dose of avatrombopag would not be adjusted after the start of treatment and that all patients would be treated at a fixed dose.

Table 3. Estimated proportion of patients achieving the target platelet count based on the population PK/PD model

Scenario[a]	Proportion of patients achieving the target platelet count (%)[b]
Basic (body weight 74 kg, no concomitant drugs, avatrombopag 20 mg once daily)	53.4
+ Body weight 55 kg	55.2
+ Body weight 110 kg	50.2
+ Concomitant use of strong or moderate CYP2C9 inhibitors	53.4
+ Concomitant use of strong or moderate CYP3A4 inhibitors	52.6
+ Concomitant use of strong or moderate dual CYP2C9 and CYP3A4 inhibitors	46.2
+ Concomitant use of strong or moderate dual CYP2C9 and CYP3A4 inducers	45.8
+ Concomitant use of strong or moderate dual CYP2C9 and CYP3A4 inhibitors + avatrombopag 20 mg 3 times a week	51.6
+ Concomitant use of strong or moderate dual CYP2C9 and CYP3A4 inducers + avatrombopag 40 mg once daily	54.4

a: The symbol "+" denotes a change from the basic scenario. The dose of avatrombopag has not been adjusted in any scenario after the start of treatment.

b: The proportion of patients who achieved the target platelet count (50,000-200,000/μL) at Week 10 of treatment with avatrombopag.

6.R Outline of the review conducted by PMDA

6.R.1 Differences in PK between Japanese and non-Japanese patients

The applicant's explanation about differences in the PK of avatrombopag between Japanese and non-Japanese patients with chronic ITP:

The exposure to avatrombopag ($C_{max,ss}$ and $AUC_{0\text{-}24h,ss}$) estimated using the population PK model was higher in Japanese patients (Study 307) than in non-Japanese patients (Studies 302 and 305) (Table 2). Given that the mean body weight of Japanese patients enrolled in Study 307 was 60.16 kg and the mean body weight of non-Japanese patients enrolled in Studies 302 and 305 were 81.90 kg and 77.34 kg, respectively, the above difference in exposure is considered attributable to the difference in body weight. However, the results of simulation using the population PK/PD model did not show a clear difference in the proportion of patients

achieving the target platelet count between subjects with a body weight of 55 kg and 110 kg (Table 3). It is therefore unlikely that differences in PK between Japanese and non-Japanese patients will affect the platelet-increasing effect.

On the basis of the presented simulation investigation results, PMDA has concluded that there are no clinically relevant differences in the PK of avatrombopag between Japanese and non-Japanese patients.

6.R.2 Rationale for and justification of the dose adjustment algorithm

The applicant's explanation about the rationale for and justification of the dose adjustment algorithm at the proposed dosage and administration:

In Study E5501-G000-302 (Study 302), in which several formulations with different strengths (5, 10, and 20 mg tablets) were available, the dosing frequency was fixed at once daily and the dose was adjusted within a range of 5 to 40 mg. The commercial formulation consists only of 20 mg tablets. Therefore, Study 307 adopted the dose adjustment algorithm developed based on simulation using the population PK/PD model [see Section 6.2.1] so that the total dose per week could be adjusted within a range of 20 to 280 mg, as in Study 302, by combining the doses that can be administered using 20 mg tablets at different dosing frequencies (Table 5 and Table 6).

The change in platelet count over time with dose adjustment based on the algorithm shown in Table 6 was simulated[3)] using the population PK/PD model. The proportion of patients achieving the target platelet count was expected to be 85.2% to 86.4% by Week 8 to Week 14, which supported justification of the dose adjustment algorithm.

On the basis of the presented simulation investigation results, PMDA concluded that the dose adjustment algorithm at the proposed dosage and administration is justified from the viewpoint of PD.

6.R.3 Pharmacokinetic interactions

The applicant's explanation about the appropriateness of the starting dose of avatrombopag when used concomitantly with strong or moderate inhibitors or inducers of CYP2C9 and CYP3A4:

According to the results of simulation using the population PK/PD model (Table 3), the proportion of patients achieving the target platelet count with the concomitant use of avatrombopag and strong or moderate dual CYP2C9 and CYP3A4 inhibitors or inducers (46.2% for inhibitors and 45.8% for inducers) was lower than with the basic scenario (53.4%), suggesting that the concomitant use of these CYP inhibitors and inducers may affect the PD of avatrombopag. The proportion of patients achieving the target platelet count became 51.6% with the concomitant use of avatrombopag and strong or moderate dual CYP2C9 and CYP3A4 inhibitors by changing the dosage of avatrombopag to 20 mg 3 times a week (dose level 3), and it became 54.4% with the concomitant use of avatrombopag and strong or moderate dual CYP2C9 and CYP3A4 inducers by changing the dosage of avatrombopag to 40 mg once daily (dose level 6). It was estimated that both of these proportions

[3)] The conditions for simulation were as follows: baseline platelet count, 20,000/μL; body weight, 74 kg; no concomitant drugs; the starting dose of avatrombopag, 20 mg once daily; the number of patients, 500.

would be similar to that of the basic scenario. In view of the above, the dosage at the start of treatment with avatrombopag, when used concomitantly with strong or moderate dual CYP2C9 and CYP3A4 inhibitors or inducers, should be 20 mg 3 times a week (dose level 3) for inhibitors and 40 mg once daily (dose level 6) for inducers.

PMDA asked the applicant to explain whether it is necessary to decrease the dose level of avatrombopag when starting treatment with strong or moderate dual CYP2C9 and CYP3A4 inhibitors during treatment with avatrombopag.

The applicant's explanation:
In clinical studies in patients with chronic ITP, none of the subjects concomitantly used strong or moderate dual CYP2C9 and CYP3A4 inhibitors with avatrombopag at the maximum dose. However, Japanese and foreign post-marketing reports of avatrombopag administered for the approved indication have not raised any safety concerns that may be related to drug interactions. In addition, healthcare professionals will be advised to take precautions to ensure that the platelet count is measured approximately once every 4 weeks during treatment with avatrombopag, even after the count has stabilized. Thus, the dose of avatrombopag will be adjusted based on periodic monitoring of the platelet count, even if treatment with strong or moderate dual CYP2C9 and CYP3A4 inhibitors is started. It is therefore unnecessary to decrease the dose level of avatrombopag.

PMDA's view:
In view of the results of simulation using the population PK/PD model, when used concomitantly with strong or moderate dual CYP2C9 and CYP3A4 inhibitors or inducers, the starting doses of avatrombopag 20 mg 3 times a week (dose level 3) for inhibitors and avatrombopag 40 mg once daily (dose level 6) for inducers are justified.

In case treatment with strong or moderate dual CYP2C9 and CYP3A4 inhibitors is started during treatment with avatrombopag, there is little need to prespecify a reduction to a lower dose level of avatrombopag because the dose will be adjusted based on periodic monitoring of platelet counts, even after the platelet count has stabilized, during treatment with avatrombopag. However, given that the change in exposure to avatrombopag in combination with fluconazole is relatively large, namely, approximately 2-fold (see the Review Report of "Doptelet Tablets 20 mg," dated February 8, 2023), it is necessary to provide a precautionary statement in the package insert to ensure that the platelet count should be measured every week until the count has stabilized.

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

The applicant submitted efficacy and safety evaluation data, in the form of results data from the pivotal 2 clinical studies shown in Table 4 [for PK, see Section 6].

Table 4. Summary of the pivotal clinical studies

Data category	Region	Study identifier	Phase	Population	N	Outline of dosage regimen	Primary endpoints
Evaluation	Japanese	AVA-ITP-307	III	Patients with chronic ITP	19	Avatrombopag 20 mg was orally administered once daily as the starting dose. The dose and dosing frequency were subsequently adjusted depending on the platelet count of each patient (minimum dose, 20 mg once weekly; maximum dose, 40 mg once daily).	Efficacy Safety
Reference	Foreign	E5501-G000-302	III	Patients with chronic ITP	49	Avatrombopag 20 mg or placebo was orally administered once daily as the starting dose. The dose was subsequently adjusted depending on the platelet count of each patient (minimum dose, 5 mg; maximum dose, 40 mg).	Efficacy Safety

7.1 Japanese phase III study (Study AVA-ITP-307; CTD 5.3.5.2-1, CTD 5.3.5.2-2; June 2022 to ongoing [data cutoff, [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted at 19 Japanese study sites to investigate the efficacy and safety of avatrombopag in Japanese patients with chronic[4)] ITP (target sample size, 19 subjects[5)]).

This study consisted of a screening period of up to 4 weeks, a core phase of 26 weeks, and an extension phase. The core phase was divided into a titration period (6 weeks from the start of treatment with avatrombopag), a concomitant ITP medication reduction period[6)] (the subsequent 12 weeks), and a maintenance period (the last 8 weeks).

The dosage regimen was as follows: Avatrombopag was orally administered once daily after a meal. Treatment was started at 20 mg, and the dose and dosing frequency of avatrombopag were adjusted according to Table 5 and Table 6 to maintain the platelet count within the target range (≥50,000/μL and <200,000/μL).

Table 5. Adjustment level for the dose and dosing frequency of avatrombopag

Dose and dosing frequency	Dose level
40 mg once daily	6
40 mg 3 times a week AND 20 mg on the 4 remaining days of each week	5
20 mg once daily	4
20 mg 3 times a week	3
20 mg twice a week OR 40 mg once weekly	2
20 mg once weekly	1

4) Defined as a duration >12 months from diagnosis.

5) The primary endpoint of this study was the cumulative number of weeks with a platelet response. Assuming that the results of the primary endpoint follow a normal distribution with a mean value of 12.0 weeks and a standard deviation of 8.75 weeks in reference to the results of Study 302, the sample size required for the lower limit of the 95% CI for the mean value of the primary endpoint to exceed the threshold of 8.02 weeks was calculated to be 19 subjects.

6) Dose reduction of concomitant ITP medication was considered at the investigator's discretion only when the platelet count was >200,000/μL. The dose of concomitant ITP medication was reduced based on the following instructions: (1) The dose should be reduced at ≥14-day intervals; (2) If ≥2 concomitant drugs are used, the dose of only 1 drug should be reduced at a time; (3) Unless continued low-dose steroid treatment is considered preferable in the judgement of the investigator, it is recommended to discontinue treatment with the first drug before reducing the dose of the second drug.

Table 6. Adjustment method for the dose and dosing frequency of avatrombopag

Platelet count	Dose adjustment or action
<50,000/μL (after ≥2 weeks of treatment with avatrombopag)	Increase 1 dose level per Table 5. To confirm the effect of the regimen after the change, maintain the same regimen for at least 2 weeks.
≥50,000/μL and <200,000/μL	Maintain the current dose and dosing frequency.
≥200,000/μL and ≤400,000/μL	Decrease 1 dose level per Table 5. To confirm the effect of the regimen after the change, maintain the same regimen for at least 2 weeks.
>400,000/μL	Stop avatrombopag. Increase platelet monitoring to twice weekly. When platelet count is less than 150,000/μL, decrease 1 dose level per Table 5 and reinitiate therapy.
<50,000/μL (after 4 weeks of treatment with avatrombopag 40 mg once daily)	Discontinue avatrombopag.
>400,000/μL (after 2 weeks of treatment with 20 mg once weekly)	Discontinue avatrombopag.

Patients with chronic ITP aged ≥18 years who met the following main inclusion criteria were eligible for the study:

- Platelet count <30,000/μL[7)]
- Insufficient response to a previous ITP treatment, in the opinion of the Investigator

Patients who met the following main exclusion criteria were ineligible for the study:

- Having undergone splenectomy or received treatment with rituximab within 12 weeks before the start of treatment with avatrombopag
- Having received long-term treatment with corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine A, danazol, vinca alkaloids, or cyclophosphamide within 4 weeks before the start of treatment with avatrombopag
- Having received treatment with immunoglobulin (intravenous immunoglobulin [IVIg] and anti D immunoglobulin [anti-D Ig]), eltrombopag, or romiplostim (genetical recombination) (romiplostim), rescue therapy with corticosteroids, or platelet transfusion within 1 week before the start of treatment with avatrombopag

Use of the following concomitant ITP medications was permitted during the study period: corticosteroids or azathioprine if these had been used at a stable dose for at least 4 weeks before enrollment in the study; and mycophenolate mofetil, cyclosporine A, or danazol if these had been used at a stable dose for at least 12 weeks before enrollment in the study. Use of vinca alkaloids, cyclophosphamide, rituximab, splenectomy, or TPO receptor agonists (eltrombopag and romiplostim) for ITP treatment was prohibited during the core phase.

The following patients were allowed to receive rescue therapy (additional ITP treatment[8)] or a dose increase of concomitant ITP medication). In case rescue therapy was performed ≥4 times or continued for >3 weeks, treatment with avatrombopag was discontinued.

- Patients who developed life-threatening thrombocytopenia, such as a platelet count <10,000/μL

7) The mean value of 2 measurements, one taken at screening and the other taken before the start of administration on the start day of the study treatment, with an interval of ≥48 hours and ≤2 weeks after the first measurement. However, the platelet count should not exceed 35,000/μL at either measurement time point.

8) Corticosteroids, immunoglobulin (IVIg and anti-D Ig), mycophenolate mofetil, azathioprine, danazol, cyclosporine A, or platelet transfusion.

- Patients who developed major bleeding
- Patients who had clinical signs or symptoms suggesting potential bleeding (e.g., wet purpura)

(1) Core phase

Nineteen enrolled subjects received avatrombopag, and all of these subjects were included in the safety analysis set and the full analysis set (FAS). The FAS was used as the primary efficacy analysis population. Treatment with avatrombopag was discontinued in 4 subjects. The reasons for discontinuation were "use of prohibited concomitant drugs" (2 subjects), "adverse events" (1 subject), and "insufficient efficacy at the maximum dose (dose level 6)" (1 subject). The median [minimum, maximum] duration of exposure to avatrombopag was 26.14 [11.0, 26.3] weeks.

Table 7 shows the results of the primary efficacy endpoint, the cumulative number of weeks with a platelet response (defined as the cumulative number of weeks with platelet count ≥50,000/μL in the absence of rescue therapy during the 26-week core phase; the same applies hereinafter). The lower limit of the 95% confidence interval (CI) of the mean number exceeded the predetermined threshold of 8.02 weeks.[9)]

Table 7. Cumulative number of weeks with a platelet response (FAS)

	Overall (N = 19)
Cumulative number of weeks with a platelet response[a] (weeks)	13.47 ± 9.002 [9.13, 17.80] 16.57 [0.0, 25.1]

Upper row, mean ± standard deviation [95% CI]; lower row, median [minimum, maximum].

a: Missing platelet assessments at any given time point was considered to be a nonresponse at that time point. Subjects who used rescue therapy and subjects who discontinued the study were considered not to have any platelet responses for all subsequent weeks after rescue therapy or discontinuation.

Table 8 shows the results of other main endpoints.

Table 8. Results of other main endpoints (FAS)

Main endpoints		Overall (N = 19)
Proportion of patients with a platelet response (platelet count ≥50,000/μL) at Week 1[a] (%)		63.2 (12)
Proportion of patients with dose reduction or discontinuation of concomitant ITP medication[b] (%)		55.6 (5/9)
Proportion of patients with a durable platelet response[c] (%)		42.1 (8)
Duration of continuous platelet response (platelet count ≥50,000/μL)[d] (weeks)		7.0 [0.0, 25.1]
Proportion of patients who received rescue therapy (%)		26.3 (5)
Incidence of bleeding events[e] based on the WHO bleeding scale[f] (%)	Grade 0	21.1 (4)
	Grade 1	73.7 (14)
	Grade 2	5.3 (1)
	Grade 3	0 (0)
	Grade 4	0 (0)

Proportion (n), proportion (number of applicable subjects / number of subjects analyzed), median [minimum, maximum].

a: Subjects with missing platelet counts at Day 8 or use of a rescue therapy before or on Day 8 were considered platelet non-responders.

b: Proportion of patients in whom the dose of concomitant ITP medication was reduced without an increase in the daily total dose from baseline or treatment with concomitant ITP medication was discontinued in the core phase.

c: Durable platelet response was defined as platelet count ≥50,000/μL at ≥6 of the visits in the last 8 weeks of the 26-week core phase in the absence of rescue therapy.

d: Duration while a platelet response was observed in the absence of rescue therapy.

e: Tabulation of the highest-grade event per patient among the ITP-related bleeding events (including bleeding, contusion, and petechial bleeding).

f: Grade 0, no bleeding; Grade 1, petechial bleeding; Grade 2, mild blood loss (clinically significant); Grade 3, gross blood loss; Grade 4, debilitating blood loss.

9) The threshold was set as "8.02 weeks" based on the results of the cumulative number of weeks with a platelet response (mean [95% CI], 11.2 [8.02, 14.38] weeks) in the eltrombopag group of the Japanese phase II/III study of eltrombopag (Study TRA108109; *J Thromb Haemost*. 2012;5:799-806).

The safety results are as follows: The incidence of all adverse events was 94.7% (18 of 19 subjects). Adverse events that occurred in ≥3 subjects were Coronavirus disease 2019 [COVID-19] and upper respiratory tract inflammation (3 subjects each).

There were no deaths.

Serious adverse events were observed in 15.8% (3 of 19) of subjects (autoimmune hepatitis, diffuse large B-cell lymphoma, and heavy menstrual bleeding in 1 subject each). A causal relationship to avatrombopag was ruled out for all of these events.

An adverse event leading to discontinuation of treatment with avatrombopag was observed in 5.3% (1 of 19) of subjects (autoimmune hepatitis). A causal relationship to avatrombopag was ruled out.

(2) Extension phase

Fifteen subjects who completed the core phase and entered the extension phase were included in the FAS. The FAS was used as the efficacy analysis population. Nineteen subjects who received at least 1 dose of avatrombopag in the core phase or the extension phase and in whom safety evaluation was performed were included in the safety analysis set. As of the data cutoff time point, 12 subjects were in the study and 3 subjects had discontinued the study. The reasons for discontinuation were “insufficient efficacy at the maximum dose (dose level 6)” (1 subject), “investigator discretion” (1 subject), and “significant medical condition” (1 subject). The median [minimum, maximum] duration of exposure to avatrombopag throughout the core phase and the extension phase was 61.71 [11.0, 111.1] weeks, and 73.7% (14 of 19) of subjects received treatment for ≥52 weeks.

Figure 2 shows the efficacy results on the change in platelet count over time in the extension phase.

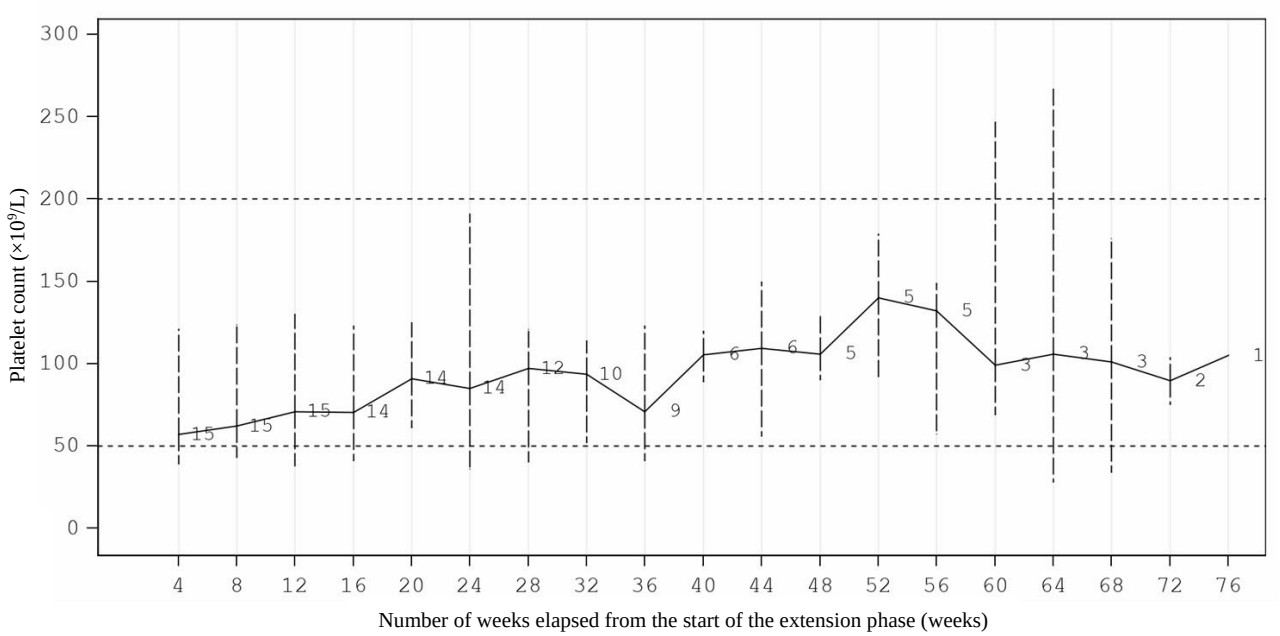

Figure 2. Change in platelet count over time (median [first quartile, third quartile]) in the extension phase (FAS)

Values on the plot: Number of subjects analyzed at each measurement time point

The safety results are as follows: The incidence of all adverse events was 100% (19 of 19 subjects). Adverse events that occurred in ≥3 subjects were COVID-19 (4 subjects), and insomnia, nasopharyngitis, oropharyngitis, and upper respiratory tract infection (3 subjects each).

There were no deaths.

Serious adverse events were observed in 26.3% (5 of 19) of subjects (autoimmune hepatitis, diffuse large B-cell lymphoma, heavy menstrual bleeding, colorectal cancer, and sepsis/ileus). A causal relationship to avatrombopag was ruled out for all of these events.

An adverse event leading to discontinuation of treatment with avatrombopag was observed in 5.3% (1 of 19) of subjects (autoimmune hepatitis). A causal relationship to avatrombopag was ruled out.

7.2 Foreign phase III study (Study E5501-G000-302; CTD 5.3.5.1-3 (reference data); February 2012 to November 2013[10])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted at 35 foreign study sites to investigate the efficacy and safety of avatrombopag in non-Japanese patients with chronic[4] ITP (target sample size, 45 subjects[11] [15 subjects in the placebo group and 30 subjects in the avatrombopag group]).

[10] Only 1 subject continued the study until [redacted] 20[redacted].

[11] The distribution of the cumulative number of weeks with a platelet response, the primary endpoint of this study, was assumed (0 weeks, 80% in the placebo group and 7% in the avatrombopag group [the same order applies hereinafter]; 1 week, 20% and 0%; 2 weeks, 0% and 7%; 3 weeks, 0% and 7%; 4 weeks, 0% and 80%) in reference to the results of the foreign phase II study in patients with chronic ITP (Study 501-CL-003). With a 2-sided significance level of 5%, an allocation ratio of 1:2 (placebo:avatrombopag), and a dropout rate of 15%, the sample size required to demonstrate the superiority of avatrombopag over placebo with >95% power using the Wilcoxon rank sum test was calculated to be 45 subjects (15 subjects in the placebo group and 30 subjects in the avatrombopag group).

This study consisted of a screening phase of up to 4 weeks, a core phase of 26 weeks, and an extension phase of up to 76 weeks. The core phase was divided into a titration period (6 weeks from the start of treatment with avatrombopag), a concomitant ITP medication reduction period [12)] (the subsequent 12 weeks), and a maintenance period (the last 8 weeks).

The enrolled patients were randomized to the placebo or the avatrombopag group in a 1:2 ratio using the following stratification factors: splenectomy status, baseline platelet count (≤15,000/μL, or >15,000/μL and <30,000/μL), and use of concomitant ITP medication at baseline.

The dosage regimen was as follows: Placebo or avatrombopag was orally administered once daily after a meal. Treatment was started at 20 mg, and the dose of the study drug was adjusted every 2 weeks as shown in Table 9 to maintain the platelet count within the target range (≥50,000/μL and <200,000/μL).[13)] After completing the core phase, patients were allowed to choose to enter the extension phase or discontinue the study treatment. Patients who did not enter the extension phase entered a dose-tapering period of up to 4 weeks and a follow-up period of 30 days. In the dose-tapering period, patients visited the study site once weekly, and the study drug was down-titrated 1 dose level per week until the treatment could be discontinued. During this period, to prevent the recurrence of thrombocytopenia, subsequent upward titration or addition of concomitant ITP medication was considered at the investigator's discretion during the dose-tapering period.

Table 9. Adjustment method for the dose of the study drug

Platelet count	Adjustment method
<50,000/μL	Increase 1 dose level: 5 mg to 10 mg, 10 mg to 20 mg, 20 mg to 30 mg, or 30 mg to 40 mg.
≥50,000/μL and ≤150,000/μL	Maintain the current dose.
>150,000/μL and ≤250,000/μL	Reduce 1 dose level: 10 mg to 5 mg, 20 mg to 10 mg, 30 mg to 20 mg, or 40 mg to 30 mg.
>250,000/μL	Interrupt treatment with avatrombopag and measure the platelet count twice weekly. If the platelet count decreases to ≤150,000/μL, resume treatment at a 1-level lower dose. 10 mg to 5 mg, 20 mg to 10 mg, 30 mg to 20 mg, or 40 mg to 30 mg.

Patients with chronic ITP aged ≥18 years who met the following main inclusion criteria were eligible for the study:

- Platelet count <30,000/μL[7)]
- Having received ≥1 line of treatment for ITP in the past

Patients who met the following main exclusion criteria were ineligible for the study:

- Having undergone splenectomy or received treatment with rituximab within 12 weeks before the start of the study treatment
- Having received treatment with romiplostim, eltrombopag, cyclophosphamide, vinca alkaloids,

[12)] Dose reduction of concomitant ITP medication was considered at the investigator's discretion only when the platelet count was >150,000/μL. The dose of concomitant ITP medication was reduced based on the following guidance: (1) The dose should be reduced at ≥2-week intervals; (2) If ≥2 concomitant drugs are used, the dose of only 1 drug should be reduced at a time; (3) Unless continued low-dose steroid treatment is considered preferable in the judgement of the investigator, it is recommended to discontinue treatment with the first drug before reducing the dose of the second drug; (4) The dose should not be reduced by more than 25% to 50% of the original dose within 2 weeks.

[13)] When the platelet count was <50,000/μL or >250,000/μL, the dose could be adjusted every week.

corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine A, or danazol within 4 weeks before the start of the study treatment

- Having received treatment with immunoglobulin (IVIg and anti-D Ig) within 1 week before the start of the study treatment

Use of the following concomitant ITP medications was permitted during the study period: corticosteroids or azathioprine if these had been used at a stable dose for at least 4 weeks before enrollment in the study; and mycophenolate mofetil, cyclosporine A, or danazol if these had been used at a stable dose for at least 12 weeks before enrollment in the study. Use of vinca alkaloids, cyclophosphamide, rituximab, splenectomy, or TPO receptor agonists (eltrombopag and romiplostim) for ITP treatment was prohibited during the core phase.

The following patients were allowed to receive rescue therapy (additional ITP treatment[8)] or a dose increase of concomitant ITP medication). In case rescue therapy was performed ≥3 times or continued for ≥3 weeks, the study treatment was discontinued.

- Patients who developed life-threatening thrombocytopenia, such as a platelet count <10,000/μL
- Patients who developed major bleeding
- Patients who had clinical signs or symptoms suggesting potential bleeding (e.g., wet purpura)

(1) Core phase

Forty-nine randomized subjects (17 subjects in the placebo group and 32 subjects in the avatrombopag group; the same order applies hereinafter) received the study drug, and all of these subjects were included in the FAS and the safety analysis set. The FAS was used as the primary efficacy analysis population. Treatment with the study drug was discontinued in 26 subjects (16 and 10 subjects). The reasons for discontinuation were "insufficient efficacy" (15 and 7 subjects), "adverse events" (0 and 3 subjects), and "withdrawal of consent" (1 and 0 subjects). The median [minimum, maximum] duration of exposure to the study drug was 6.00 [2.1, 29.9] weeks and 26.00 [3.7, 31.1] weeks.

Table 10 shows the results of the primary efficacy endpoint, the cumulative number of weeks with a platelet response. The results demonstrated the superiority of avatrombopag over placebo.

Table 10. Cumulative number of weeks with a platelet response in patients with chronic ITP (FAS)

	Placebo (N = 17)	Avatrombopag (N = 32)	*P* value[a]
Cumulative number of weeks with a platelet response[b] (weeks)	0.1 ± 0.49 0.0 [0, 2]	12.0 ± 8.75 12.4 [0, 25]	<0.0001

Upper row, mean ± standard deviation; lower row, median [minimum, maximum].

a: Wilcoxon rank sum test, 2-sided significance level of 0.05.

b: Missing platelet assessments at any given time point was considered to be a nonresponse at that time point. Subjects who used rescue therapy and subjects who discontinued the study were considered not to have any platelet responses for all subsequent weeks after rescue therapy or discontinuation.

Table 11 shows the results of other main endpoints.

Table 11. Results of other main endpoints (FAS)

Main endpoints		Placebo (N = 17)	Avatrombopag (N = 32)
Proportion of patients with a platelet response (platelet count ≥50,000/μL) at Week 1[a] (%)		0 (0)	65.6 (21)
Patients with a reduction in concomitant ITP medication from baseline[b] (%)		0 (0/7)	33.3 (5/15)
Proportion of patients with a durable platelet response[c] (%)		0 (0)	34.4 (11)
Duration of continuous platelet response (platelet count ≥50,000/μL)[d] (weeks)		0.0 [0, 2]	4.4 [0, 25]
Proportion of patients who received rescue therapy (%)		11.8 (2)	21.9 (7)
Incidence of bleeding events[e] based on the WHO bleeding scale[f] (%)	Grade 0	47.1 (8)	56.3 (18)
	Grade 1	52.9 (9)	34.4 (11)
	Grade 2	0 (0)	6.3 (2)
	Grade 3	0 (0)	3.1 (1)
	Grade 4	0 (0)	0 (0)

Proportion (n), proportion (number of applicable subjects / number of subjects analyzed), median [minimum, maximum].

a: Subjects with missing platelet counts at Day 8 or use of a rescue therapy before or on Day 8 were considered platelet nonresponders.

b: Proportion of patients in whom the dose of concomitant ITP medication was reduced without an increase in the daily total dose from baseline or treatment with concomitant ITP medication was discontinued in the core phase.

c: Durable platelet response was defined as platelet count ≥50,000/μL at ≥6 of the visits in the last 8 weeks of the 26-week core phase in the absence of rescue therapy.

d: Duration while a platelet response (platelet count ≥50,000/μL) was observed in the absence of rescue therapy.

e: Tabulation of the highest-grade event per patient among all bleeding events.

f: Grade 0, no bleeding; Grade 1, petechial bleeding; Grade 2, mild blood loss (clinically significant); Grade 3, gross blood loss; Grade 4, debilitating blood loss.

The safety results are as follows: The incidence of all adverse events was 58.8% (10 of 17 subjects) in the placebo group and 96.9% (31 of 32 subjects) in the avatrombopag group. Table 12 shows the incidences of adverse events that occurred in ≥10% of subjects in either group.

Table 12. Incidences of adverse events that occurred in ≥10% of subjects in either group (safety analysis set)

MedDRA PT	Placebo (N = 17)	Avatrombopag (N = 32)
Headache	11.8 (2)	37.5 (12)
Contusion	23.5 (4)	31.3 (10)
Upper respiratory tract infection	5.9 (1)	18.8 (6)
Arthralgia	0 (0)	12.5 (4)
Epistaxis	17.6 (3)	12.5 (4)
Fatigue	5.9 (1)	12.5 (4)
Gingival bleeding	0	12.5 (4)
Petechiae	5.9 (1)	12.5 (4)

Incidence % (n)

There were no deaths.

Serious adverse events were observed in 5.9% (1 of 17) of subjects in the placebo group (idiopathic thrombocytopenic purpura) and 28.1% (9 of 32) of subjects in the avatrombopag group (thrombocytopenia/mouth haemorrhage, food poisoning/vomiting, nausea/vomiting/headache, polyserositis, urinary tract infection/platelet count decreased/epistaxis/petechiae, cerebrovascular accident, headache, uterine haemorrhage, and deep vein thrombosis in 1 subject each). Deep vein thrombosis, vomiting, headache, nausea, epistaxis, petechiae, platelet count decreased, and cerebrovascular accident observed in the avatrombopag group were assessed as causally related to the study drug.

Adverse events leading to discontinuation of the study treatment were observed in 9.7% (3 of 32) of subjects in the avatrombopag group (polyserositis, cerebrovascular accident, and headache in 1 subject each). Cerebrovascular accident and headache were assessed as causally related to the study drug.

(2) Extension phase

Thirty-nine subjects who entered the extension phase and in whom the platelet count was measured at least once during the extension phase were included in the modified full analysis set (mFAS). The mFAS was used as the efficacy analysis population. Forty-seven subjects who received at least 1 dose of avatrombopag in the core phase or the extension phase and in whom safety evaluation was performed at least once were included in the safety analysis set. Of the 39 subjects who entered the extension phase, 9 subjects discontinued the study. The reasons for discontinuation were "adverse events" (3 subjects), "patient's personal reason" (3 subjects), "insufficient efficacy" (2 subjects), and "lost to follow-up" (1 subject). The median [minimum, maximum] duration of exposure to avatrombopag throughout the core phase and the extension phase was 44.00 [7.9, 75.7] weeks, and 29.8% (14 of 47) of subjects received treatment for ≥52 weeks.

Figure 3 shows the efficacy results on the change in platelet count over time.

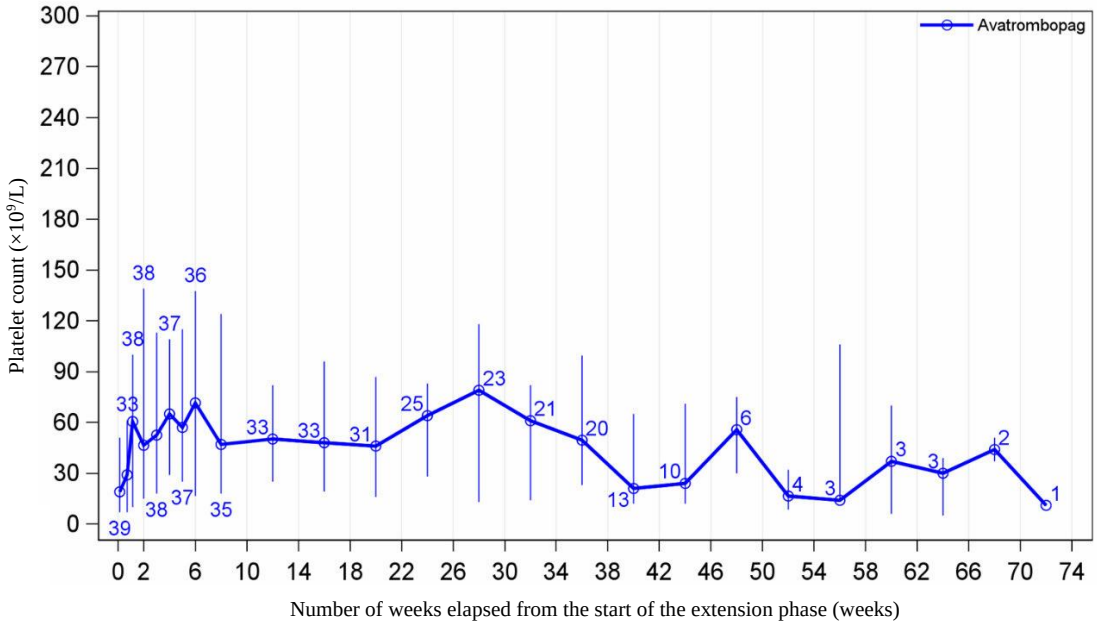

Figure 3. Change in platelet count over time (median [first quartile, third quartile]) in the extension phase (mFAS)

Values on the plot: Number of subjects analyzed at each measurement time point

The safety results are as follows: The incidence of all adverse events was 95.7% (45 of 47 subjects). Table 13 shows the incidences of adverse events that occurred in ≥10% of subjects.

There were no deaths.

Serious adverse events were observed in 31.9% (15 of 47) of subjects (thrombocytopenia/dizziness, thrombocytopenia/mouth haemorrhage, thrombocytopenia, erosive duodenitis/gastritis haemorrhagic, food poisoning/vomiting, gingival bleeding/platelet count decreased/headache, nausea/vomiting/headache, polyserositis, urinary tract infection/platelet count decreased/epistaxis/petechiae, alanine aminotransferase

increased/aspartate aminotransferase increased/gamma-glutamyltransferase increased, intervertebral disc disorder, chronic myelomonocytic leukaemia/deep vein thrombosis, cerebrovascular accident, uterine haemorrhage, and jugular vein thrombosis). Dizziness, deep vein thrombosis, jugular vein thrombosis, vomiting, headache, nausea, epistaxis, petechiae, platelet count decreased, and cerebrovascular accident were assessed as causally related to the study drug.

Adverse events leading to discontinuation of the study treatment were observed in 12.8% (6 of 47) of subjects (erosive duodenitis/gastritis haemorrhagic, polyserositis, chronic myelomonocytic leukaemia, cerebrovascular accident, dizziness, and headache). Cerebrovascular accident, dizziness, and headache were assessed as causally related to the study drug.

Table 13. Incidences of adverse events that occurred in ≥10% of subjects (core phase and extension phase; safety analysis set)

MedDRA PT	Avatrombopag (N = 47)
Contusion	40.4 (19)
Headache	29.8 (14)
Upper respiratory tract infection	23.4 (11)
Thrombocytopenia	19.1 (9)
Epistaxis	17.0 (8)
Gingival bleeding	17.0 (8)
Fatigue	14.9 (7)
Petechiae	14.9 (7)
Pharyngitis	12.8 (6)
Arthralgia	10.6 (5)
Hypertension	10.6 (5)
Nasopharyngitis	10.6 (5)

Incidence % (n)

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

(1) Development strategy for avatrombopag and design of the Japanese phase III study (Study 307)

The applicant's explanation about the development strategy for avatrombopag in Japan and the design of Study 307:

The development of avatrombopag in patients with chronic ITP was first initiated outside Japan. At the time when the development program of avatrombopag in Japan was formulated, the foreign phase III study (Study 302) had already been completed. Therefore, Study 307 was separately planned in Japan to evaluate the efficacy and safety of avatrombopag in Japanese patients.

There were no differences in the PK between Japanese and non-Japanese patients affecting the platelet-increasing effect (see the Review Report of "Doptelet Tablets 20 mg," dated February 8, 2023), and intrinsic and extrinsic ethnic factors are unlikely to affect the evaluation of efficacy of avatrombopag even when differences in the diagnosis and treatment algorithms for ITP between Japan and overseas are taken into account. Based on these and other findings, the applicant considered that the efficacy and safety of avatrombopag in Japanese patients could be evaluated based on the result of Study 307, with reference to the results of Study 302, using a design similar to Study 302 except for an open-label, uncontrolled setting. The open-label, uncontrolled setting was adopted in view of the following points:

- At the planning stage of Study 307, TPO receptor agonists similar to avatrombopag had already been

approved and were widely used in Japan. Therefore, the conduct of Study 307 as a placebo-controlled study was considered to make it difficult to obtain consent from patients.

- The conduct of a confirmatory study using an approved TPO receptor agonist as the comparator was considered infeasible from the viewpoint of the required sample size.[14)]

The primary endpoint of Study 307 was aligned with that of Study 302, which was the "cumulative number of weeks with a platelet response (defined as the cumulative number of weeks when the platelet count was ≥50,000/μL in the absence of rescue therapy during a 26-week period)." The treatment goal of chronic ITP is not to normalize the platelet count, but to maintain a sufficient platelet count to prevent serious bleeding (*Blood Adv*. 2019;3:3829-3866, *Blood Adv*. 2019;3:3780-3817), and a platelet count of ≥50,000/μL can be the target platelet count for the prevention of serious bleeding. In addition, achieving a platelet response for a cumulative period of ≥8.02 weeks is considered to be of clinical significance in reference to the cumulative number of weeks with a platelet response (platelet count ≥50,000/μL) (mean [95% CI], 11.2 [8.02, 14.38] weeks) in the Japanese phase II/III study of eltrombopag in patients with chronic ITP (Study TRA108109). Therefore, this number of weeks was set as the threshold for the primary endpoint.

PMDA asked the applicant to further explain the justification of evaluating the efficacy of avatrombopag using the threshold in view of the differences in patient characteristics between Study TRA108109 of eltrombopag and Study 307, and the differences in the medical environment at the times when these studies were conducted.

The applicant's explanation:
The patient characteristics differed between Study TRA108109 and Study 307 with respect to the time from the diagnosis of ITP (≥12 months in Study 307 and ≥6 months in Study TRA108109) and the requirements for the previous treatment regimen. The main baseline characteristics that differed between the study populations are the proportion of subjects with a history of splenectomy (10.5% [2 of 19 subjects] in Study 307 and 73% [11 of 15 subjects] in the eltrombopag group in Study TRA108109), use of concomitant ITP medication (47.4% [9 of 19 subjects] in Study 307 and 80% [12 of 15 subjects] in the eltrombopag group in Study TRA108109), and the baseline platelet count (median, 18,000/μL in Study 307 and 21,000/μL in the eltrombopag group in Study TRA108109). However, the results of these 2 studies do not suggest that these baseline characteristics influenced the platelet-increasing effect. Differences in the medical environment at the time when these studies were conducted include whether TPO receptor agonists were available for use, because no TPO receptor agonists had been approved in Japan at the time when Study TRA108109 started. In Study 307, a washout period was established for patients who had used TPO receptor agonists before participating in the study and the use of TPO receptor agonists was prohibited during the study. Therefore, the effect of the difference in the approval status of TPO receptor agonists on the efficacy evaluation is considered to be small. Thus, it is justified to evaluate the efficacy in Japanese patients in Study 307 based on the threshold established from the results of the cumulative number of weeks with a platelet response in the eltrombopag group in Study TRA108109,

[14)] In reference to the results of the previous clinical studies of avatrombopag, the proportion of subjects achieving durable platelet response was assumed to be 40% in the eltrombopag group and 45% in the avatrombopag group. Based on this assumption, with a non-inferiority margin of 15% and a 1-sided significance level of 2.5%, the sample size required to demonstrate the non-inferiority of avatrombopag to eltrombopag with ≥92% power was calculated to be 286 subjects (143 subjects per group).

even if differences in the patient characteristics and medical environment between the studies are taken into account.

(2) Results of efficacy evaluation

The applicant's explanation about the efficacy of avatrombopag:

The results of Study 307 demonstrated the platelet-increasing effect of avatrombopag. All of the bleeding events observed in the core phase of Study 307 were Grade 1, except in 1 subject (Grade 2), and there were no bleeding events classified as Grade 3 or 4 on the World Health Organization (WHO) bleeding scale (Table 8).

In the avatrombopag group in Study 302, which was the basis of the design of Study 307, the cumulative number of weeks with a platelet response and the proportion of patients with a platelet response at Week 1 were similar to those in Study 307 (Table 7, Table 8, Table 10, and Table 11). In Study 302, the incidence of all bleeding events (Grade 1-4 on the WHO bleeding scale) adjusted for exposure duration[15)] was lower in the avatrombopag group (2 subjects/100 person-weeks) than in the placebo group (6 subjects/100 person-weeks), suggesting that avatrombopag suppresses the occurrence of bleeding symptoms.

In patients enrolled in Study 307, compared with those enrolled in Study 302, age and the baseline platelet count were higher, body weight was lower, and the proportion of patients with a history of splenectomy was lower. However, these differences in patient characteristics do not affect the results of the efficacy evaluation [see Section 7.R.1 (3)]. Intrinsic and extrinsic ethnic factors are also unlikely to affect the efficacy evaluation of avatrombopag [see Sections 6.R.1 and 7.R.1 (1)]. In view of these, and based on the similarity in platelet response between Study 302 and Study 307, avatrombopag can be expected to suppress the occurrence of bleeding symptoms in Japanese patients, as seen in the patient population of Study 302.

(3) Baseline characteristics that affect efficacy

The applicant's explanation about baseline characteristics that affect the efficacy of avatrombopag:

Subgroup analysis by patient characteristics was performed on the primary endpoint in Study 307, namely the cumulative number of weeks with a platelet response. Table 14 shows the results. Although there are limitations to the interpretation of the results due to the limited number of subjects analyzed, all subgroups showed results that do not differ substantially from the results in the overall population. The results suggest that none of the baseline characteristics significantly affect the efficacy evaluation of avatrombopag.

[15)] Adjusted for the total exposure duration in each group (147.87 person-weeks in the placebo group and 714.85 person-weeks in the avatrombopag group).

Table 14. Cumulative number of weeks with a platelet response by baseline characteristics in Study 307 (FAS; core phase)

			Avatrombopag (N = 19)
Body weight	<61.07 kg (median)		13.5 ± 9.1 (9)
	≥61.07 kg (median)		13.5 ± 9.4 (10)
Baseline platelet count	≤15,000/μL		11.9 ± 7.5 (8)
	>15,000/μL		14.6 ± 10.1 (11)
History of splenectomy	Present		10.0 ± 9.9 (2)
	Absent		13.9 ± 9.1 (17)
Concomitant ITP medication	Present		11.2 ± 8.8 (9)
	Absent		15.5 ± 9.1 (10)
Prior treatment for ITP	Corticosteroids	Present	12.2 ± 8.7 (13)
		Absent	16.2 ± 9.8 (6)
	Eltrombopag	Present	12.2 ± 9.5 (15)
		Absent	18.1 ± 5.1 (4)
	Romiplostim	Present	5.9 ± 4.1 (2)
		Absent	14.4 ± 9.1 (17)
	Rituximab	Present	12.9 ± 9.0 (4)
		Absent	13.6 ± 9.3 (15)
	IVIg	Present	15.3 ± 7.1 (5)
		Absent	12.8 ± 9.7 (14)
	Danazol	Present	- (0)
		Absent	13.5 ± 9.0 (19)
	Immunosuppressants	Present	5.9 ± 4.1 (2)
		Absent	14.4 ± 9.1 (17)
	Hemostatics (excluding TPO receptor agonists)	Present	- (0)
		Absent	13.5 ± 9.0 (19)

Mean ± standard deviation (n); -, not applicable.

(4) Long-term efficacy

The applicant's explanation about the long-term efficacy of avatrombopag:

In Study 307, a total of 73.7% (14 of 19) of subjects received treatment with avatrombopag for ≥52 weeks. The median [minimum, maximum] duration of exposure to avatrombopag, combining the core and extension phases, was 61.71 [11.0, 111.1] weeks. Although 3 subjects discontinued the study in the extension phase, the platelet count was maintained in the target range both in the core phase and the extension phase (Figure 2 and Figure 4). The incidence of all bleeding events (Grade 1-4 on the WHO bleeding scale) observed in the extension phase of Study 307 was 73.3% (11 of 15 subjects). However, all of these bleeding events were Grade 1 on the WHO bleeding scale, except events in 2 subjects (Grade 2 on the WHO bleeding scale). There were no bleeding events classified as Grade 3 or 4 on the WHO bleeding scale (Table 15). Thus, the platelet-increasing effect of avatrombopag in Japanese patients was maintained over a long period of time, and bleeding events did not tend to increase in incidence or severity with increasing duration of treatment.

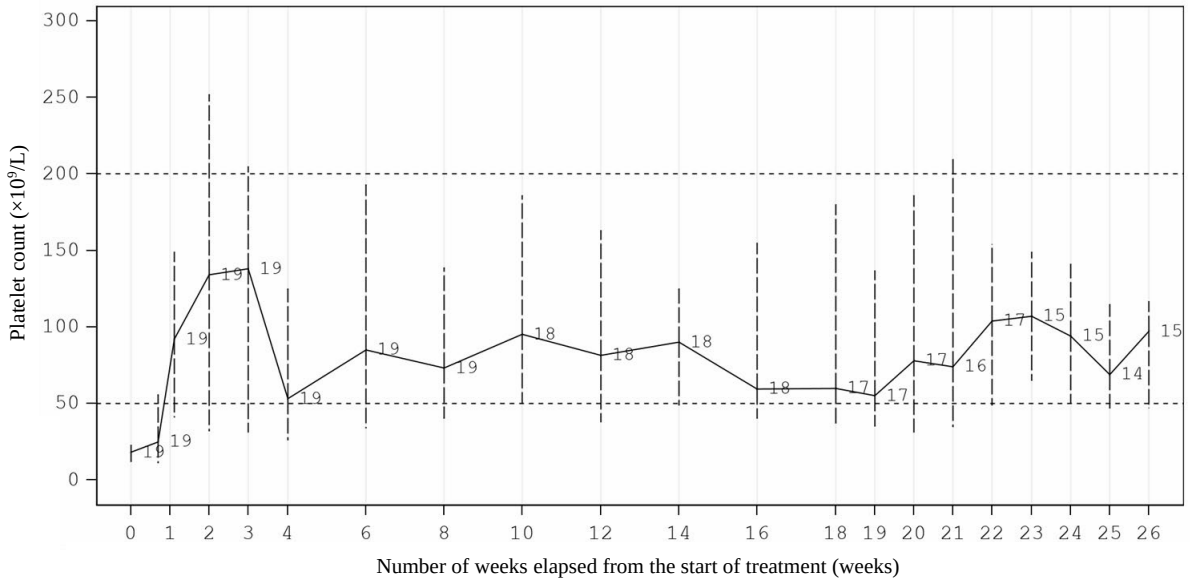

Figure 4. Change in platelet count over time (median [first quartile, third quartile]) in the core phase of Study 307 (FAS)

Values on the plot: Number of subjects analyzed at each measurement time point

Table 15. Incidence of bleeding events in the extension phase of Study 307 (FAS)

		Avatrombopag (N = 15)
Incidence of bleeding events[a] based on the WHO bleeding scale[b] (%)	Grade 0	26.7 (4)
	Grade 1	60.0 (9)
	Grade 2	13.3 (2)
	Grade 3	0 (0)
	Grade 4	0 (0)

Proportion % (n)

a: Tabulation of the highest-grade event per patient among the ITP-related bleeding events (including bleeding, contusion, and petechial bleeding).

b: Grade 0, no bleeding; Grade 1, petechial bleeding; Grade 2, mild blood loss (clinically significant); Grade 3, gross blood loss; Grade 4, debilitating blood loss.

PMDA's view:

Given that TPO receptor agonists had already been widely used in Japan at the time when avatrombopag was developed, and considering the rarity of patients with ITP, it was unavoidable to conduct an open-label, uncontrolled study to investigate the efficacy of avatrombopag in Japanese patients. The efficacy of avatrombopag in Japanese patients can be evaluated based on the results of Study 307 in view of the following points:

- Platelet count, used to assess the primary endpoint, is an objective measure. From the viewpoint of maintaining a sufficient platelet count to prevent serious bleeding, the clinical significance of the therapeutic effect can be evaluated based on the cumulative number of weeks with a platelet response.
- In Study 302, which had the same inclusion criteria as Study 307, the cumulative number of weeks with a platelet response (median) in the placebo group was 0 weeks. Therefore, the subjects of Study 307 are considered to be the patient population whose platelet response cannot be expected without additional treatment.

The results of Study 307 showed that the lower limit of the 95% CI for the mean cumulative number of weeks with a platelet response, the primary endpoint, exceeded the prespecified threshold. Since there are no

differences in patient characteristics that may substantially affect efficacy evaluation between Study TRA108109, which was used to establish the threshold for the primary endpoint, and Study 307, the threshold was deemed justified. It can therefore be concluded that the results of Study 307 demonstrated that avatrombopag exhibits a platelet-increasing effect capable of preventing serious bleeding in Japanese patients. In addition, there were no differences in patient characteristics that may affect efficacy between Study 307 and Study 302, and the results of the primary endpoint and main secondary endpoints in Study 307 did not clearly differ from those in the avatrombopag group in Study 302. Taken all together, avatrombopag can also be expected to prevent the occurrence of bleeding symptoms in Japanese patients. Although there are limitations to the interpretation of the results because the number of patients per subgroup in Study 307 and the number of Japanese patients treated for a long period were limited, no baseline characteristics that significantly affect the efficacy of avatrombopag or concerns about long-term efficacy have been identified.

7.R.2 Safety

As a result of the review based on the information presented below and the foreign post-marketing safety information,[16)] PMDA considers that no new safety concerns of avatrombopag have been identified compared with approved TPO receptor agonists. Therefore, PMDA has concluded that the safety of avatrombopag in Japanese patients is acceptable if appropriate measures such as adjustment of the dose and dosing frequency of avatrombopag and treatment interruption are taken under the supervision of physicians with adequate experience in the treatment of blood disorders.

7.R.2.1 Safety profile of avatrombopag

The applicant's explanation about the safety profile of avatrombopag:

Table 16 shows the incidences of adverse events in Studies 307 and 302. In the core phase of Study 302, the incidence of all adverse events adjusted for the duration of exposure to the study drug[15)] was similar in the avatrombopag group (4.3 subjects/100 person-weeks) and the placebo group (6.6 subjects/100 person-weeks). The incidences of other adverse events were also similar in these groups. There were no clear differences in the incidences of adverse events in the avatrombopag group between Study 307 and Study 302 throughout the core phase and the extension phase.

Table 16. Incidences of adverse events in Studies 307 and 302 (safety analysis set)

	Core phase[a]			Core phase and extension phase[b]	
	Study 307	Study 302		Study 307	Study 302
	Avatrombopag (N = 19)	Placebo (N = 17)	Avatrombopag (N = 32)	Avatrombopag (N = 19)	Avatrombopag (N = 47)
All adverse events	94.7 (18)	58.8 (10)	96.9 (31)	100 (19)	95.7 (45)
Death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Serious adverse events	15.8 (3)	5.9 (1)	28.1 (9)	26.3 (5)	31.9 (15)
Adverse events leading to discontinuation of the study treatment	5.3 (1)	0 (0)	9.4 (3)	5.3 (1)	12.8 (6)
Adverse events for which a causal relationship to the study drug cannot be ruled out	15.8 (3)	17.6 (3)	62.5 (20)	21.1 (4)	66.0 (31)

Incidence % (n)

a: The median [minimum, maximum] exposure duration (weeks) was 26.14 [11.0, 26.3] in Study 307, 6.0 [2.1, 29.9] in the placebo group in Study 302, and 26.0 [3.7, 31.1] in the avatrombopag group in Study 302.

b: The median [minimum, maximum] exposure duration (weeks) was 61.71 [11.0,111.1] in Study 307 and 44.00 [7.9,75.7] in Study 302.

16) Based on the periodic safety update report (PSUR) ([redacted], 20[redacted] to [redacted], 20[redacted]).

Eltrombopag, an approved TPO receptor agonist, has an inhibitory effect on uridine diphosphate-glucuronosyltransferase (UGT) 1A1 and organic anion transporting polypeptide (OATP) 1B1, which is associated with liver function test abnormalities. Therefore, healthcare professionals are advised that hepatic dysfunction is a clinically significant adverse reaction to eltrombopag. In contrast, avatrombopag does not have such an inhibitory effect, and the results of Japanese and foreign clinical studies of avatrombopag do not suggest that avatrombopag is associated with a risk of liver disorder.

PMDA has concluded that the results of Studies 307 and 302 have not suggested any clear safety concern associated with avatrombopag treatment in patients with chronic ITP. However, taking into account information on approved TPO receptor agonists and other related information, thromboembolic adverse events, rebound thrombocytopenia after treatment discontinuation, and the risks of increased bone marrow reticulin and bone marrow fibrosis as well as the progression of hematological malignancy such as myelodysplastic syndrome will be further examined in the subsequent sections.

7.R.2.2 Thromboembolic adverse events

Given that patients with chronic ITP are at risk of developing thromboembolic adverse events (*Can J Neurol Sci*. 2021;48:38-46) and that thromboembolic adverse events have been reported in ITP patients on treatment with approved TPO receptor agonists, PMDA asked the applicant to explain thromboembolic adverse events associated with treatment with avatrombopag.

The applicant's explanation:

In Study 307, although there were no thromboembolic adverse events[17)] in the core phase, 2 non-serious thromboembolic adverse events (peripheral arterial occlusive disease and stroke) were observed in 1 subject in the extension phase. This subject had concurrent diabetes mellitus and hypertension, and was using romiplostim and prednisolone as concomitant ITP medications. Treatment with avatrombopag was discontinued after onset of serious sepsis and peripheral arterial occlusive disease. A causal relationship to avatrombopag was ruled out for peripheral arterial occlusive disease, but not for stroke.

According to the results of the integrated analysis (Group 4),[18)] 11 thromboembolic adverse events were observed in 9 subjects in the avatrombopag group (cerebrovascular accident in 2 subjects, and deep vein thrombosis, jugular vein thrombosis, portal vein thrombosis, pulmonary embolism, myocardial infarction/retinal artery occlusion/transient ischaemic attack, superficial thrombophlebitis, and pelvic venous thrombosis in 1 subject each). Cerebrovascular accident in 1 subject, and deep vein thrombosis, jugular vein thrombosis, pulmonary embolism, portal vein thrombosis, myocardial infarction, retinal artery occlusion, and transient ischaemic attack were assessed as causally related to the study drug. The subject with portal vein thrombosis showed an increase in platelet count of >400,000/μL.

17) Events classified under the standardised MedDRA query (SMQ) "embolic and thrombotic events."
18) Integrated analysis of Studies 302, 305, 501-CL-003, and 501-CL-004 (22 subjects in the placebo group and 128 subjects in the avatrombopag group).

In Study 307, when the platelet count exceeded 400,000/μL, treatment with avatrombopag was temporarily interrupted. An increase in the platelet count to >400,000/μL was observed in 5 subjects. None of these subjects had thromboembolic adverse events.

Thrombosis and thromboembolism (portal vein thrombosis) were identified as events requiring caution at the time of approval of the approved indication, and the package insert advises of these events as clinically significant adverse drug reactions. In view of the results of Study 307, etc., the following precautionary statements will be added:

- Treatment with avatrombopag may cause stroke and arterial and venous thromboembolism.
- After administration of avatrombopag, the platelet count should be measured on a regular basis. If the platelet count exceeds the target treatment level, dose reduction or interruption of avatrombopag should be considered.

PMDA's view:

In view of the incidence of thromboembolic adverse events in Study 307 and the integrated analysis (Group 4), the risk of thromboembolic adverse events associated with avatrombopag can be managed on the premise that the dose and dosing frequency of avatrombopag are adjusted under the supervision of physicians with adequate experience in the treatment of blood disorders, as with approved TPO receptor agonists. However, given that thromboembolic adverse events for which a causal relationship to avatrombopag was not ruled out were observed after administration of avatrombopag in Study 307 and the integrated analysis (Group 4), and that the relationship between the occurrence of thromboembolic adverse events and the increase in platelet count was not clear, the increase in platelet count caused by avatrombopag should be minimized to the extent necessary, as with approved TPO receptor agonists. Therefore, PMDA concluded that healthcare professionals should be advised that the platelet count should be measured on a regular basis after administration of avatrombopag, and that dose reduction or interruption of avatrombopag should be considered if the platelet count exceeds the target treatment level.

7.R.2.3 Rebound thrombocytopenia after treatment discontinuation

The applicant's explanation about the rebound thrombocytopenia (recurrence of thrombocytopenia) after discontinuation of treatment with avatrombopag:

In ITP patients receiving an approved TPO receptor agonist, the rebound thrombocytopenia[19)] is observed after discontinuation of the drug. The rebound thrombocytopenia was not observed in Study 307. However, in 3 of 4 subjects who discontinued treatment with avatrombopag in the study, the platelet count had already decreased to near the baseline level at the time when the treatment was discontinued or the dose was tapered. In the remaining subject, the platelet count decreased to near the baseline level within 1 week after the start of dose tapering.

[19)] Defined as a decrease in platelet count of <10,000/μL with a decrease of >10,000/μL from baseline occurring after discontinuation of the study treatment and up to 30 days after the last dose of the study drug.

According to the results of the integrated analysis (Group 4), the rebound thrombocytopenia was observed in 11 subjects in the avatrombopag group. The rebound thrombocytopenia occurred in 1 to 4 weeks after discontinuation of treatment with avatrombopag, but resolved with measures such as additional treatment in 10 of the 11 subjects. Serious bleeding was not observed in any of the 11 subjects. In both Studies 307 and 302, the platelet count decreased to near the baseline level in many patients within approximately 1 week after treatment with avatrombopag was discontinued or the dose was tapered.

Thus, since the platelet count may decrease after discontinuation of treatment with avatrombopag, the package insert will advise that the platelet count should be frequently measured for approximately 4 weeks after treatment discontinuation.

PMDA's view:
Considering the time to onset of the rebound thrombocytopenia in the clinical studies of avatrombopag, healthcare professionals should be advised that the platelet count should be frequently measured for approximately 4 weeks after treatment discontinuation. In clinical studies, while serious bleeding was not observed after discontinuation of treatment with avatrombopag, the platelet count decreased to near the baseline level promptly after treatment discontinuation in many patients. In view of this, attention should be paid to bleeding regardless of the rebound thrombocytopenia after discontinuation of treatment with avatrombopag. Therefore, it is necessary that healthcare professionals be advised that bleeding is a clinically significant adverse reaction to avatrombopag, as with approved TPO receptor agonists.

7.R.2.4 Risks of increased bone marrow reticulin and bone marrow fibrosis as well as the progression of hematological malignancy such as myelodysplastic syndrome

The applicant's explanation about the risks of increased bone marrow reticulin and bone marrow fibrosis as well as the progression of hematological malignancy such as myelodysplastic syndrome associated with avatrombopag:
It is known that TPO receptor agonists may increase the risks of increased bone marrow reticulin, the formation of reticular fibers and the development of fibrosis in the bone marrow, as well as the progression of hematological malignancies such as myelodysplastic syndromes. In Study 307, there were no bone marrow pathology-related adverse events,[20)] but a neoplasm-related adverse event[21)] was observed in 1 subject (diffuse large B-cell lymphoma). A causal relationship between the observed event and avatrombopag was ruled out.

According to the results of the integrated analysis (Group 4), there were no bone marrow pathology-related adverse events, and neoplasm-related adverse events were observed in 6 subjects (chronic lymphocytic leukaemia, chronic myelomonocytic leukaemia, lipoma, myelofibrosis, myeloproliferative neoplasm, and skin papilloma in 1 subject each). Myelofibrosis was assessed as causally related to the study drug. In the patient

[20)] Events classified under the SMQ "blood premalignant disorders," excluding those classified under the MedDRA system organ class (SOC) "neoplasms benign, malignant and unspecified (incl cysts and polyps)."
[21)] Events classified under the MedDRA SOC "neoplasms benign, malignant and unspecified (incl. cysts and polyps)."

with myelofibrosis, although an increase in reticulin fibers in the bone marrow was identified by bone marrow biopsy after the end of treatment with avatrombopag, reticulin may have already accumulated at baseline.

In view of the above, precautionary statements will be provided in the package insert to ensure that blood tests should be performed before the start of treatment with avatrombopag to carefully monitor for abnormalities in blood cell morphology, and to ensure that blood tests should also be performed approximately once every 4 weeks during treatment with avatrombopag to monitor for abnormalities in blood cell morphology and decreases in blood cells. In addition, healthcare professionals will be advised that myelofibrosis, which is considered to be associated with long-term treatment with TPO receptor agonists, is a clinically significant adverse reaction to avatrombopag, as with approved TPO receptor agonists.

PMDA's view:
Avatrombopag may pose risks of increased bone marrow reticulin and bone marrow fibrosis as well as the progression of hematological malignancies such as myelodysplastic syndromes, as with approved TPO receptor agonists. Therefore, a precautionary statement should be provided in the package insert to ensure that blood tests should be performed before the start of treatment with avatrombopag and approximately once every 4 weeks during treatment. Given that myelofibrosis for which a causal relationship to avatrombopag could not be ruled out was observed in the integrated analysis (Group 4), the package insert should list myelofibrosis as a clinically significant adverse reaction to avatrombopag. In addition, it is necessary to provide a precautionary statement that TPO receptor agonists may aggravate existing hematological malignancies in the "Important Precautions" section, as with approved TPO receptor agonists.

7.R.3 Clinical positioning

The applicant's explanation about the clinical positioning of avatrombopag in the treatment of ITP:
In Japan, corticosteroids are the first-line treatment for ITP. For patients who have had an insufficient response or intolerance to corticosteroids, TPO receptor agonists, rituximab, or splenectomy are recommended as a second-line treatment (*Jpn J Clin Hematol*. 2019;60:877-896). In addition, fostamatinib sodium hydrate (fostamatinib) and efgartigimod alfa (genetical recombination) (efgartigimod) have recently been approved for the treatment of ITP in patients who have had an insufficient response to other ITP treatments such as corticosteroids.

The TPO receptor agonist avatrombopag stimulates the signaling pathway by binding to a site different from the TPO-binding site, consequently increasing platelet production. Based on the results of Study 307 and related data, which have demonstrated the efficacy and safety of avatrombopag for the treatment of chronic ITP in patients who have had an insufficient response to other ITP treatments such as corticosteroids, avatrombopag is considered to be positioned similarly to approved TPO receptor agonists.

In the strategy of ITP treatment with TPO receptor agonists, if an adequate response cannot be obtained with 1 TPO receptor agonist, switching to another TPO receptor agonist is considered. Currently in Japan, eltrombopag and romiplostim are approved TPO receptor agonists besides avatrombopag. Romiplostim is

administered by injection, whereas avatrombopag and eltrombopag are oral drugs. Other differences include that eltrombopag requires dietary restrictions such as administration under fasting conditions and that it is associated with a concern about hepatic dysfunction. In medical practice, an appropriate drug will be selected for each patient taking into account factors such as dosage and the patient's condition.

PMDA's view:
Given that the results of Study 307 have demonstrated the efficacy and safety of avatrombopag in patients with chronic ITP who were considered to have an insufficient response to previous ITP treatment, and other information [see Sections 7.R.1 and 7.R.2], it is meaningful to make avatrombopag available in medical practice as a treatment option with a clinical positioning similar to that of approved TPO receptor agonists for these patients. As no clinical study results comparing the efficacy and safety of avatrombopag with those of approved TPO receptor agonists are available, it is expected that, in medical practice, an appropriate drug would be selected for each patient, taking into account factors such as the characteristics and safety profile of each drug as well as the individual patient's condition.

7.R.4 Target population and indications

The applicant's explanation about the justification of including "chronic idiopathic thrombocytopenic purpura" in the target population and indications of avatrombopag:
In Japan, approved TPO receptor agonists are indicated for patients with ITP lasting ≥6 months from the estimated onset or diagnosis. Study 307 enrolled patients with ITP lasting ≥12 months from diagnosis in accordance with the treatment guidelines of the American Society of Hematology (ASH)/British Committee for Standards in Haematology (*Blood Adv*. 2019;3:3829-3866), thus no data are available for patients with ITP lasting 6 to 12 months from diagnosis. However, it is considered justified to define the target population of avatrombopag as patients with ITP lasting ≥6 months from diagnosis in view of the following points:

- In patients enrolled in Study 307, the duration from diagnosis to the first dose of avatrombopag ranged from 514 to approximately 7400 days, and no specific trends are observed between the duration and efficacy or safety. Therefore, duration from diagnosis is not considered to significantly affect the efficacy or safety of avatrombopag.
- A foreign prospective observational study in ITP patients has reported that the efficacy and safety of avatrombopag were similar in patients with newly diagnosed ITP or persistent ITP (duration 3-12 months from diagnosis) and patients with chronic ITP (duration >12 months from diagnosis) (*Am J Hematol*. 2024;99:155-162).

Based on the above, the indication of "chronic idiopathic thrombocytopenic purpura" is justified. The efficacy and safety of avatrombopag for the treatment of chronic ITP in patients who have had an insufficient response to previous ITP treatment have been demonstrated in Study 307 and other studies. Therefore, the package insert will advise that the target population of avatrombopag is patients who have had an insufficient response or intolerance to other treatments and who are considered at high risk of bleeding based on the platelet count and clinical symptoms even after receiving existing treatments.

PMDA's view:

Study 307 did not enroll patients with ITP lasting 6 to 12 months from diagnosis, and therefore there are limitations in estimating the efficacy and safety of avatrombopag in these patients based on the results of Study 307. However, based on the findings from Study 307 and foreign clinical studies indicating that the efficacy and safety of avatrombopag are unlikely to differ substantially depending on the duration from diagnosis, it is acceptable to select chronic ITP patients, including those with persistent ITP lasting 6 to 12 months from diagnosis, as the target population of avatrombopag, provided that the package insert advises that the efficacy and safety of avatrombopag have not been established in patients with ITP lasting 6 to 12 months from diagnosis.

In addition, it is acceptable to define the target population of avatrombopag as patients who have had an insufficient response to or tolerability problems with other treatments and are considered at high risk of bleeding even after receiving existing treatments, as with approved TPO receptor agonists.

Based on the above, the statements of Indications and Precautions Concerning Indications should be specified as follows:

Indications (excerpt)

Chronic idiopathic thrombocytopenic purpura

Precautions Concerning Indications (excerpt)

- Avatrombopag should be used in patients who do not have an adequate response to or may have a tolerability problem with other treatments.
- Avatrombopag should be used in patients who are considered at high risk of bleeding based on the platelet count and clinical symptoms.
- The efficacy and safety of avatrombopag have not been established in patients with idiopathic thrombocytopenic purpura lasting 6 to 12 months from diagnosis.

7.R.5 Dosage and administration

The applicant's explanation about the dosage and administration and the dose adjustment criteria:

(1) Dosage and administration

In the foreign phase II study in patients with chronic ITP (Study 501-CL-003), avatrombopag 2.5 to 20 mg was administered for 28 days. A dose-dependent increase in platelet count was confirmed in the study, and the proportion of responders[22)] in the avatrombopag 20 mg group was statistically significantly higher than that in the placebo and avatrombopag 2.5 mg groups. The results of simulation using the population PK/PD model [see Section 6.2.1] estimated that the proportion of patients whose platelet count is maintained in the target range was expected to be 86% at the maximum dose of 40 mg. Based on these study and analysis results, results

22) The sum of the proportion of patients whose platelet count was <30,000/μL at baseline and reached ≥50,000/μL on Day 28, and the proportion of patients on steroids whose platelet count was ≥30,000/μL and <50,000/μL at baseline and increased by ≥20,000/μL from baseline on Day 28.

of Study 302, and the approved dosage for chronic ITP outside Japan, the dosage regimen selected in Study 307 was avatrombopag at a starting dose of 20 mg administered orally once daily after a meal, followed by dose adjustment up to a maximum of 40 mg.

The results of Study 307 demonstrated the efficacy of avatrombopag in patients with chronic ITP and showed that its safety is acceptable. Therefore, it is justified to use the dosage regimen in Study 307 as the dosage and administration of avatrombopag in patients with chronic ITP.

(2) Dose adjustment criteria

In Study 307, dose adjustment criteria based on the platelet count (Table 5 and Table 6) were established to maintain the platelet count within the target range. Figure 5 shows the distribution of weekly avatrombopag dose levels up to Week 26 in Study 307. The mean cumulative number of weeks with a platelet response by dose level at Week 26 was within the range of 10 to 24 weeks, except in patients at dose level 6 whose condition was severe (Table 17).

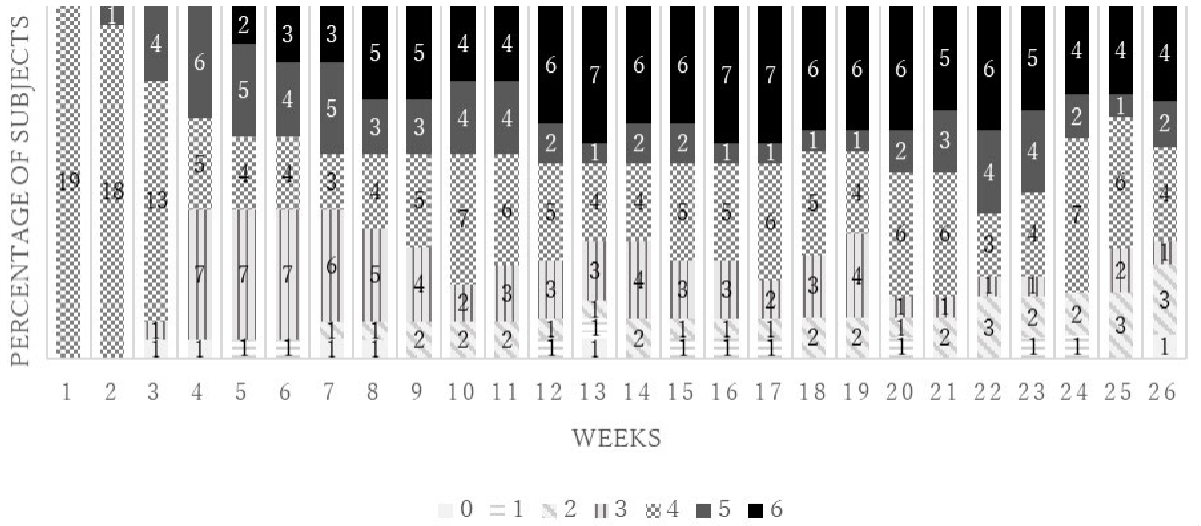

Figure 5. Distribution of avatrombopag dose levels in Study 307 (core phase)

Dose level 0: Treatment suspension

Table 17. Results of the primary endpoint by dose level at Week 26 in Study 307 (FAS; core phase)

Dose level	1 (0 subjects)	2 (3 subjects)	3 (1 subject)	4 (4 subjects)	5 (2 subjects)	6 (4 subjects)
Cumulative number of weeks with a platelet response (weeks)	0	22.33 ± 2.79	23.86	10.61 ± 12.29	17.36 ± 4.34	7.11 ± 7.30

Mean ± standard deviation

There were no clear differences by dose level in the proportion of subjects achieving a durable platelet response[23)] nor the incidence or severity of bleeding events based on the WHO bleeding scale. Although the results should be carefully interpreted because of the limited number of patients at each dose level, the platelet-increasing effect was maintained up to Week 26 by using the specified dose adjustment criteria. Based on the

[23)] Defined as a platelet count of ≥50,000/μL at ≥6 of the visits in the last 8 weeks of the 26-week core phase in the absence of rescue therapy.

above, it is justified to use the dose adjustment criteria selected in Study 307 as dose adjustment criteria for avatrombopag in patients with chronic ITP.

The frequency of platelet count monitoring and dose adjustment should be the same as specified in Study 307. Specifically, the platelet count should be measured every week until the count stabilizes and the dosage should be adjusted every 2 weeks. Once the dosage is changed, it should be maintained for at least 2 weeks. If the platelet count is <50,000/μL or >400,000/μL, the dose may be adjusted every week. In 8 of the 19 subjects enrolled in Study 307 whose platelet counts were maintained at ≥50,000/μL for at least 4 weeks without dose adjustment, subsequent doses were examined at 4-week intervals and the platelet count could be maintained at ≥50,000/μL. Therefore, once the platelet count has stabilized, it can be controlled by measuring it approximately once every 4 weeks, as with approved TPO receptor agonists. The above precautions regarding the frequency of platelet count monitoring and dose adjustment will be included in the Precautions Concerning Dosage and Administration section.

The criterion for treatment interruption due to an excessive increase in platelet count in Study 307 was set as >400,000/μL, as with the approved dosage in the US, because the post-marketing treatment experience in patients with chronic ITP accumulated in the US and other countries have not raised any particular safety concerns associated with avatrombopag. To prevent a rapid and significant decrease in platelet count to <50,000/μL after treatment interruption, the treatment was resumed at a 1-level lower dose if the platelet count decreased to <150,000/μL. In Study 307, the platelet count increased to >400,000/μL during the study period in 5 patients (4 subjects with treatment suspension and 1 subject with dose reduction). Of the 4 subjects with treatment suspension, 3 subjects, excluding 1 who had completed the core phase, resumed treatment with avatrombopag after the platelet count decreased to <150,000/μL, as specified. In all of these patients, the platelet counts were maintained in the target range during most of the remaining study period, without any adverse events including thromboembolism. Thus, the above treatment interruption criteria and method of treatment resumption will be specified in the Precautions Concerning Dosage and Administration section.

The criteria for treatment discontinuation due to inadequate response will be the same as specified in Study 307. A statement will be provided in the Precautions Concerning Dosage and Administration section to ensure that appropriate measures such as treatment discontinuation should be taken if the platelet count is <50,000/μL after 4 weeks of treatment with avatrombopag 40 mg once daily.

PMDA's view:
Given the efficacy and acceptable safety of avatrombopag demonstrated in Study 307 and other information, it is justified to use the dosage regimen and dose adjustment criteria selected in Study 307 as the dosage and administration and dose adjustment criteria of avatrombopag for patients with chronic ITP. However, according to the results of the integrated analysis (Group 4), thromboembolic adverse events were observed even in patients with a platelet count within the target range. Therefore, even if the platelet count is within the target range, dose reduction should be considered as appropriate to secure the minimum effective dose to reduce the

risk of bleeding, as with approved TPO receptor agonists. It is necessary to include a precautionary statement regarding this point.

Based on the above and in view of the review in Section 6.R.3, the statements of Dosage and Administration and Precautions Concerning Dosage and Administration of avatrombopag for patients with chronic ITP should be specified as follows:

Dosage and Administration (excerpt)
The usual initial adult dose of avatrombopag is 20 mg, which is orally administered once daily after a meal. After starting the treatment, the dosage should be adjusted as appropriate according to the platelet count and symptoms of the patient. The maximum dose is 40 mg once daily.

Precautions Concerning Dosage and Administration (excerpt)

- Avatrombopag should be used at the minimum effective dose.
- The dosage of avatrombopag should be adjusted every 2 weeks depending on the platelet count until the count stabilizes (≥50,000/μL for at least 4 weeks without dose adjustment) in reference to the table below. The same dosage should be maintained for at least 2 weeks. If the platelet count is <50,000/μL or >400,000/μL, the dose may be adjusted once a week.

Dosage	Level
40 mg once daily	6
40 mg on 3 days of each week, and 20 mg on the remaining 4 days of the week	5
20 mg once daily	4
20 mg 3 times a week	3
20 mg twice weekly or 40 mg once weekly	2
20 mg once weekly	1

* If avatrombopag is administered at a lower frequency than once daily, avoid administration on consecutive days and use a consistent method on a weekly basis.

Platelet count	Adjustment method
<50,000/μL	Increase 1 dose level. If the platelet count does not increase to an appropriate level to avoid the risk of clinically significant bleeding, even after 4 weeks of treatment at the maximum dose of 40 mg once daily, take appropriate measures such as discontinuation of treatment with avatrombopag.
≥50,000/μL and <200,000/μL	Maintain the current dose level. Consider dose reduction as appropriate to secure the minimum dosage required to decrease the risk of bleeding.
≥200,000/μL and ≤400,000/μL	Decrease 1 dose level.
>400,000/μL	Interrupt treatment with avatrombopag and measure the platelet count twice weekly. After treatment interruption, if the platelet count decreases to <150,000/μL, resume treatment at a 1-level lower dose. If the platelet count is >400,000/μL, even after 2 weeks of treatment at the minimum dose of 20 mg once weekly, discontinue treatment with avatrombopag.

- During treatment with avatrombopag, the platelet count should be measured every week until the count stabilizes (≥50,000/μL for at least 4 weeks without dose adjustment). Even after the platelet count has stabilized, the count should be measured approximately once every 4 weeks.
- Coadministration of avatrombopag with strong or moderate dual CYP2C9 and CYP3A4 inhibitors

causes an increase in the plasma concentration of avatrombopag. When administered in combination with these drugs, the initial dose of avatrombopag should be 20 mg 3 times a week. If treatment with strong or moderate dual CYP2C9 and CYP3A4 inhibitors is started during treatment with avatrombopag, the platelet count should be measured every week until the count stabilizes (≥50,000/μL for at least 4 weeks without dose adjustment).

- Coadministration of avatrombopag with strong or moderate dual CYP2C9 and CYP3A4 inducers causes a decrease in the plasma concentration of avatrombopag. When administered in combination with these drugs, the initial dose of avatrombopag should be 40 mg once daily.

7.R.6 Post-marketing investigations

The applicant does not plan any additional pharmacovigilance activities, except for early post-marketing phase vigilance, for the present application. Taking the points described below into account as well, PMDA considers that no new post-marketing investigations are required at present. Therefore, PMDA has concluded that the applicant's response to perform early post-marketing phase vigilance and routine pharmacovigilance activities without conducting post-marketing surveillance of avatrombopag is justified.

- No new concerns have been identified based on the incidences of adverse events in Study 307 and other studies, as well as foreign post-marketing safety information,[16)] compared with approved TPO receptor agonists. Therefore, the safety of avatrombopag in patients with chronic ITP is considered acceptable if periodic monitoring including platelet count measurement is performed [see Section 7.R.2].
- In Japan, sufficient use experience and safety information on TPO receptor agonists in patients with chronic ITP have been accumulated, and no particular concerns have been identified regarding the safety of TPO receptor agonists.

However, if new issues requiring further post-marketing investigation of avatrombopag are identified, additional pharmacovigilance activities such as post-marketing surveillance should immediately be considered.

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 inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA 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) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, 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 avatrombopag has efficacy in the treatment of patients with chronic ITP, and that avatrombopag has acceptable safety in view of its benefits. Avatrombopag is clinically meaningful because it offers a new treatment option for patients with chronic ITP.

PMDA has concluded that avatrombopag may be approved if avatrombopag is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

July 4, 2025

Product Submitted for Approval

Brand Name	Doptelet Tablets 20 mg
Non-proprietary Name	Avatrombopag Maleate
Applicant	Swedish Orphan Biovitrum Japan Co., Ltd.
Date of Application	August 29, 2024

List of Abbreviations

See Appendix.

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 below. 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).

At the Expert Discussion, the expert advisors supported the PMDA's conclusions concerning the efficacy, safety, clinical positioning, dosage and administration, and post-marketing investigations of avatrombopag described in Review Report (1).

1.1 Indications

At the Expert Discussion, the expert advisors supported the PMDA's conclusion described in Section "7.R.4 Target population and indications," which includes the inclusion of patients with ITP lasting ≥6 months from diagnosis[24)] in the target population of avatrombopag.

In response to the change of the name of the designated intractable disease "idiopathic thrombocytopenic purpura" to "immune thrombocytopenia" (Public Notice No. 382 of the Ministry of Health, Labour and Welfare, 2024), a notification titled "Handling of the Term "Immune Thrombocytopenia" in Approved Information of Drugs and Electronic Package Inserts, etc." (PSB/PED Notification No. 0701-2, PSB/PSD Notification No. 0701-1, dated July 1, 2025) was issued after preparation of the Review Report (1). This notification states that the disease name "idiopathic thrombocytopenic purpura" in the approved information of drugs and other materials should be changed to "immune thrombocytopenia."

[24)] In the indications of approved drugs for ITP treatment, patients were classified as having chronic ITP based on the criteria established by the Research Study Team for Blood Coagulation Abnormalities, Research on rare and intractable diseases, Health and Labour Sciences Research Grants from the Ministry of Health, Labour and Welfare of Japan, in which acute ITP was defined as disease cured within 6 months after estimated onset or diagnosis, and chronic ITP as disease persisting for ≥6 months after estimated onset or diagnosis.

PMDA concluded that the indications of the product should also be revised under such circumstances. The latest ITP treatment guideline (*Jpn J Clin Hematol*. 2019;60:877-896) and other materials define patients with ITP lasting 3 to 12 months from the estimated onset or diagnosis as having persistent ITP and patients with ITP lasting ≥12 months from the diagnosis as having chronic ITP. In view of this, PMDA also concluded that the product should be indicated for the following patient populations, based on the duration from diagnosis: patients with persistent ITP lasting ≥6 months from diagnosis and patients with chronic ITP.

Based on the above, PMDA concluded that the statements of Indications and Precautions Concerning Indications should be specified as follows:

Indications (excerpt)
Persistent and chronic immune thrombocytopenia

Precautions Concerning Indications (excerpt)

- Avatrombopag should be administered to patients with immune thrombocytopenia lasting ≥6 months from diagnosis.
- Avatrombopag should be used in patients who do not have an adequate response to or may have a tolerability problem with other treatments.
- Avatrombopag should be used in patients who are considered at high risk of bleeding based on the platelet count and clinical symptoms.
- The efficacy and safety of avatrombopag have not been established in patients with immune thrombocytopenia lasting 6 to 12 months from diagnosis.

Based on the above, PMDA instructed the applicant to specify the Indications and Precautions Concerning Indications sections as described above. The applicant responded appropriately.

1.2 Risk management plan (draft)

In view of the review in Section "7.R.6 Post-marketing investigations" of the Review Report (1) and the comments of the expert advisors at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for the product should include the safety specification presented in Table 18, and that the applicant should conduct the additional pharmacovigilance activity and risk minimization activity presented in Table 19.

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

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Thrombosis/thromboembolism • Myelofibrosis • Bleeding	• Progression of hematological malignancy	• None
Efficacy specification		
• None		

Only the information related to the present application is provided.

Table 19. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance	• Provision of information collected through early post-marketing phase vigilance

Only the information related to the present application is provided.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indications and dosage and administration shown below, with the following approval conditions. Although this is an application for a drug with a new indication and a new dosage, the remainder of the re-examination period for the initial approval of the product is more than 4 years. Therefore, the re-examination period for the present application should be specified as the remaining period (until March 26, 2031).

Indications

○ Improvement of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo an elective invasive procedure

○ Persistent and chronic immune thrombocytopenia

(Underline denotes additions.)

Dosage and Administration

Improvement of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo an elective invasive procedure

The usual adult dose of avatrombopag is determined as follows and orally administered once daily after a meal for 5 days.

Platelet count before the start of treatment ≥40,000/μL and <50,000/μL: 40 mg

Platelet count before the start of treatment <40,000/μL: 60 mg

Persistent and chronic immune thrombocytopenia

The usual initial adult dose of avatrombopag is 20 mg, which is orally administered once daily after a meal. After starting the treatment, the dosage should be adjusted as appropriate according to the platelet count and symptoms of the patient. The maximum dose is 40 mg once daily.

(Underline denotes additions.)

Approval Conditions

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

Appendix

List of Abbreviations

Anti-D Ig	Anti D immunoglobulin
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h,ss}$	AUC from time 0 to 24 hours at steady state
Avatrombopag	Avatrombopag Maleate
CI	Confidence interval
CL/F1	Apparent total clearance
$C_{max,ss}$	Maximum plasma concentration at steady state
COVID-19	Coronavirus disease 2019
CYP	Cytochrome P450
Doptelet	Doptelet Tablets 20 mg
Efgartigimod	Efgartigimod alfa (genetical recombination)
eGFR	Estimated glomerular filtration rate
Eltrombopag	Eltrombopag olamine
FAS	Full analysis set
F1	Factor for bioavailability
Fostamatinib	Fostamatinib sodium hydrate
ITP	Immune thrombocytopenia
IVIg	Intravenous immunoglobulin
KA	First-order absorption rate constant
KIN	Zero-order production rate of platelet precursors
KOUT	First-order maturation rate constant of platelet precursors
LC-MS/MS	Liquid chromatography coupled with tandem mass spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified full analysis set
PD	Pharmacodynamics
P-gp	P-glycoprotein
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PSUR	Periodic safety update report
PT	Preferred Term
Romiplostim	Romiplostim (genetical recombination)
SLOPE	Avatrombopag plasma concentration related to the increase in production of platelet precursors through a linear proportionality constant
SMQ	Standardised MedDRA queries
SOC	System organ class
Study 302	Study E5501-G000-302
Study 305	Study E5501-G000-305
Study 307	Study AVA-ITP-307
TPO	Thrombopoietin
V/F1	Apparent volume of distribution
WHO	World Health Organization