Report on the Deliberation Results

March 6, 2024
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Vyvgart for Intravenous Infusion 400 mg
Non-proprietary Name	Efgartigimod Alfa (Genetical Recombination) (JAN*)
Applicant	Argenx Japan K.K.
Date of Application	June 13, 2023

Results of Deliberation

In its meeting held on February 29, 2024, 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 Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 10 years.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because data from Japanese clinical studies are very limited, the applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product until data are accrued from a certain number of patients, in order to identify the characteristics of treated patients, collect data on the safety and efficacy of the product as early as possible, and take necessary measures to ensure its proper use.

**Japanese Accepted Name (modified INN)*

This English translation of this Japanese review report is intended to serve as reference material made available for the convenience of users. In the event of any inconsistency between the Japanese original and this English translation, the Japanese original shall take precedence. PMDA will not be responsible for any consequence resulting from the use of this reference English translation.

Review Report

February 15, 2024
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	Vyvgart for Intravenous Infusion 400 mg
Non-proprietary Name	Efgartigimod Alfa (Genetical Recombination)
Applicant	Argenx Japan K.K.
Date of Application	June 13, 2023
Dosage Form/Strength	Injection: Each 20-mL vial contains 400 mg of efgartigimod alfa (genetical recombination)
Application Classification	Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage
Items Warranting Special Mention	Orphan drug (Orphan Drug Designation No. 554 of 2022 [*R4 yaku*]; PSEHB/PED Notification No. 1216-1 dated December 16, 2022, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
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 chronic idiopathic thrombocytopenic purpura, 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

○ Generalized myasthenia gravis (only in patients who do not sufficiently respond to steroids or nonsteroidal immunosuppressants)
○ Chronic idiopathic thrombocytopenic purpura

(Underline denotes additions.)

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Dosage and Administration

Generalized myasthenia gravis

The usual adult dosage is 10 mg/kg of efgartigimod alfa (genetical recombination) administered as an intravenous infusion over 1 hour once weekly for 4 doses per cycle. This treatment cycle is repeated.

Chronic idiopathic thrombocytopenic purpura

The usual adult dosage is 10 mg/kg of efgartigimod alfa (genetical recombination) administered as an intravenous infusion over 1 hour once weekly or every other week. The treatment should be started once weekly for 4 weeks. Thereafter, the treatment may be adjusted to every-other-week administration according to the patient's platelet count and clinical symptoms.

(Underline denotes additions.)

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because data from Japanese clinical studies are very limited, the applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product until data are accrued from a certain number of patients, in order to identify the characteristics of treated patients, collect data on the safety and efficacy of the product as early as possible, and take necessary measures to ensure its proper use.

Attachment

Review Report (1)

November 13, 2023

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	Vyvgart for Intravenous Infusion 400 mg
Non-proprietary Name	Efgartigimod Alfa (Genetical Recombination)
Applicant	Argenx Japan K.K.
Date of Application	June 13, 2023
Dosage Form/Strength	Injection: Each 20-mL vial contains 400 mg of efgartigimod alfa (genetical recombination)

Proposed Indications

○ Generalized myasthenia gravis (only in patients who do not sufficiently respond to steroids or nonsteroidal immunosuppressants)

○ Primary immune thrombocytopenia

(Underline denotes additions.)

Proposed Dosage and Administration

Generalized myasthenia gravis

The usual adult dosage is 10 mg/kg of efgartigimod alfa (genetical recombination) administered as an intravenous infusion over 1 hour once weekly for 4 doses per cycle. This treatment cycle is repeated.

Primary immune thrombocytopenia

The usual adult dosage is 10 mg/kg of efgartigimod alfa (genetical recombination) administered as an intravenous infusion over 1 hour once weekly or every other week. The treatment should be started once weekly, and may be adjusted to every-other-week administration according to the patient's platelet count and clinical symptoms.

(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

Idiopathic thrombocytopenic purpura is an acquired autoimmune disease characterized by low platelet counts caused by factors including accelerated platelet phagocytosis/destruction by splenic macrophages and suppressed platelet production by megakaryocytes, as a result of production of autoantibodies against platelet membrane glycoproteins and their binding to platelets and megakaryocytes. In Europe and the US, idiopathic thrombocytopenic purpura is commonly known as primary immune thrombocytopenia (ITP) (*Blood.* 2009;113:2386-93).

Efgartigimod alfa is a human immunoglobulin G1 (IgG1) Fc fragment engineered to increase its affinity to the neonatal Fc receptor (FcRn) discovered by argenx BV (Belgium). The amino acid residues in the CH2 and CH3 domains of the Fc fragment are modified. Efgartigimod alfa binds to FcRn, inhibiting the binding of endogenous IgG and FcRn and preventing endogenous IgG recycling, which leads to acceleration of lysosomal degradation of endogenous IgG, thereby transiently reducing IgG concentrations. In Japan, Vyvgart for Intravenous Injection (Vyvgart) was approved in January 2022 for the indication of "generalized myasthenia gravis (only for patients who do not sufficiently respond to steroids or nonsteroidal immunosuppressants)." Outside Japan, as of October 2023, Vyvgart has been approved in 7 countries and regions including the US and Europe for the treatment of generalized myasthenia gravis.

Recently, an application for partial change has been filed using data including the results from a global phase III study, which demonstrated the efficacy and safety of Vyvgart in the treatment of primary immune thrombocytopenia. As of October 2023, Vyvgart has not been approved in any countries or regions for the indication of primary immune thrombocytopenia.

Efgartigimod alfa was designated as an orphan drug on December 16, 2022, with an intended indication of "chronic idiopathic thrombocytopenic purpura" (Orphan Drug Designation No. 554 of 2022 [*R4 yaku*]; PSEHB/PED Notification No. 1216-1 dated December 16, 2022, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare).

2. Quality and Outline of the Review Conducted by PMDA

Although the present application relates to a new indication and new dosage, a drug substance manufactured by a manufacturing process that is different from that of the approved drug substance used in the commercialized formulation, and a formulation using the drug substance in question were used in non-clinical and clinical studies; therefore, as data relating to quality, the applicant submitted data on the comparability between the approved drug substance and the drug substance used in the non-clinical and clinical studies, and between the commercial formulation and formulations used in these studies. The review of data identified no particular problems.

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

3.1 Primary pharmacodynamics

3.1.1 Effects on reduced-platelet mouse model (CTD 4.2.1.1-1)

To investigate the effect of efgartigimod alfa on inhibiting platelet count reduction induced by administration of anti-CD41 antibodies, after intraperitoneal administration of anti-CD41 antibodies to male mice (N = 10/group) on Days 1 to 3, efgartigimod alfa (approximately 50 mg/kg), wild-type Fc (approximately 50 mg/kg), IgG (approximately 1 g/kg), or solvent (phosphate buffered saline [PBS]) was intravenously administered 24 hours before the initial administration of anti-CD41 antibodies and on Day 2. On Days 2, 3, and 4, the change from baseline in platelet count was evaluated. On and after Day 3, there was less platelet count reduction in the efgartigimod alfa group than in the wild-type Fc group or solvent group. The decrease in the platelet count reduction in the efgartigimod alfa group was similar to that in the IgG group.

3.R Outline of the review conducted by PMDA

The applicant's explanation about the pharmacology of efgartigimod alfa in primary ITP:

It is considered that in patients with primary ITP, platelet count reduction is caused by accelerated macrophage-mediated platelet phagocytosis and suppressed platelet production by megakaryocytes, resulting from binding of pathogenic IgG autoantibodies to the membrane glycoproteins on platelets and their progenitor cells, megakaryocytes (e.g., *Br J Haematol.* 2009;146:585-96, *Cleve Clin J Med.* 2011;78:358-73). While it is known that FcRn is involved in the transport and homeostasis of endogenous IgG (*J Clin Invest.* 2018;128:4372-86), efgartigimod alfa has been shown to have a higher binding affinity to human FcRn compared with the human wild-type Fc fragment, and it has the effect of reducing endogenous IgG concentrations (see Review Report of Vyvgart for Intravenous Infusion 400 mg, dated November 17, 2021). A study in the reduced-platelet mouse model demonstrated that efgartigimod alfa inhibits platelet count reduction. Based on the above, efgartigimod alfa competitively inhibits binding of endogenous IgG and FcRn, promoting IgG degradation, which leads to reduction in endogenous IgG concentrations, thereby inhibiting platelet count reduction in patients with primary ITP.

Based on the applicant's explanation, PMDA considers that a reduced platelet count in patients with primary ITP can be improved by the efgartigimod alfa-mediated inhibitory effect on FcRn to reduce endogenous IgG concentrations.

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

Although the present application relates to a new indication and a new dosage, no new data were submitted because the non-clinical pharmacokinetic data have been evaluated at the time of initial approval.

5. Toxicity and Outline of the Review Conducted by PMDA

Because the present application relates to a new indication and a new dosage, no data relating to toxicity testing were submitted.

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

Unless otherwise specified, pharmacokinetic (PK) parameters are expressed as mean or mean ± standard deviation.

6.1 Summary of biopharmaceutic studies and associated analytical methods

Despite the fact that the formulation used in the foreign phase II study (Study 1603) used a drug substance prepared from a cell line different from that used for the commercial formulation and the formulation used in the global phase III studies (Studies 1801 and 1803), comparability between the pre- and post-change in the cell line has been demonstrated (see Review Report of Vyvgart for Intravenous Infusion 400 mg, dated November 17, 2021). Despite the fact that part of Studies 1801 and 1803 used a formulation that is different from the commercial formulation in terms of the manufacturing scale, etc., comparability between the formulation in question and the commercial formulation has been demonstrated.

The serum concentration of efgartigimod alfa was measured by enzyme-linked immunosorbent assay (ELISA). The lower limit of quantitation was 200 or 300 ng/mL. The anti-drug antibodies (ADAs) against efgartigimod alfa in serum were measured by ELISA, with the sensitivity to detect ADAs being 25.0 to 100 ng/mL. Neutralizing antibodies against efgartigimod alfa in serum were measured by electrochemiluminescence immunoassay and the detection sensitivity was 1.17 μg/mL.

6.2 Clinical pharmacology

6.2.1 Foreign phase II study (Study ARGX-113-1603, CTD 5.3.5.1-1 [March 2017 to May 2019])

Study ARGX-113-1603 consisted of a double-blind period and an open-label treatment period in which patients who had relapsed[1)] during the double-blind period were eligible to receive treatment. In the double-blind period, efgartigimod alfa 5 or 10 mg/kg was administered to patients with primary ITP as an intravenous infusion over ≥2 hours, weekly for 3 weeks for a total of 4 doses. Table 1 shows the PK parameters of efgartigimod alfa, and Table 2 shows the percent change from baseline over time in serum total IgG concentration.

Table 1. PK parameters after administration of multiple intravenous doses of efgartigimod alfa

Dose (mg/kg)	N	Dose number	C_{trough}[a] (μg/mL)	C_{max} (μg/mL)	t_{max}[b] (h)	$AUC_{0\text{-}168h}$ (μg·h/mL)	$t_{1/2}$ (h)
5	13	1	5.262 ± 2.473	127.7 ± 49.22[c]	2.46[c]	4528 ± 1239[c]	—
	13	2	5.845 ± 2.022	122.8 ± 53.98	2.47	4719 ± 1755	—
	13	3	7.041 ± 2.776	95.61 ± 27.42	2.50	4460 ± 1462	—
	13	4	6.265 ± 3.044	121.7 ± 37.80	2.50	4887 ± 1325	127.7 ± 35.99
10	13	1	8.143 ± 2.074	194.7 ± 39.96[c]	2.38[c]	8299 ± 1737[c]	—
	13	2	9.353 ± 3.759[c]	175.5 ± 27.20[c]	2.38[d]	7420 ± 843.7[d]	—
	13	3	12.92 ± 4.903[d]	155.0 ± 35.58[c]	2.33[c]	7226 ± 1601[e]	—
	13	4	10.92 ± 5.723[d]	194.6 ± 45.68[d]	2.38[e]	8491 ± 1695[c]	124.3 ± 47.43[f]

a, Measured 7 days after administration (before the next dose); b, Median; c, N = 12; d, N = 11; e, N = 10; f, N = 9; "—," not calculated

[1)] Relapse was defined as during the follow-up period up to 21 weeks, (1) platelet count decreased to below 30,000/μL; or (2) platelet counts never reached ≥30,000/μL

Table 2. Percent change from baseline over time in serum total IgG concentration (%)[a]

Timepoint (after start of treatment)	Efgartigimod alfa 5 mg/kg	Efgartigimod alfa 10 mg/kg	Placebo
Week 1	−36.0 ± 10.09 [13]	−41.3 ± 10.26 [13]	−0.1 ± 14.30 [12]
Week 2	−51.1 ± 10.24 [13]	−55.6 ± 8.43 [12]	3.5 ± 11.43 [12]
Week 3	−53.4 ± 10.51 [12]	−60.8 ± 6.26 [11]	0.8 ± 13.87 [11]
Week 4	−57.2 ± 9.31 [12]	−60.2 ± 8.78 [10]	1.8 ± 12.68 [12]
Week 6	−36.3 ± 13.79 [11]	−31.2 ± 20.86 [9]	5.2 ± 11.52 [10]
Week 8	−22.2 ± 18.07 [9]	−14.2 ± 20.79 [8]	6.6 ± 14.94 [8]
Week 10	−17.1 ± 16.51 [9]	0.9 ± 23.03 [9]	1.7 ± 10.52 [8]

Mean ± standard deviation [N]

a, Baseline serum total IgG concentrations are 9915.4 ± 3202.48 μg/mL (efgartigimod alfa 5 mg/kg), 10581.5 ± 5127.59 μg/mL (efgartigimod alfa 10 mg/kg), and 11669.2 ± 2447.26 μg/mL (placebo)

In the double-blind period, 6 of 13 subjects in the efgartigimod alfa 5 mg/kg group and 3 of 13 subjects in the efgartigimod alfa 10 mg/kg group were ADA positive.[2)] Neutralizing antibodies were not evaluated.

6.2.2 Global phase III study (Study ARGX-113-1801, CTD 5.3.5.1-2 [December 2019 to February 2022])

Efgartigimod alfa 10 mg/kg was intravenously administered for over ≥1 hour for 24 weeks to patients with chronic primary ITP and those with persistent primary ITP.[3)] Treatment was to be started once weekly; after Week 4 up to Week 15, it was permissible to adjust the dosing frequency to once weekly or every other week according to the platelet count and other factors. After Week 16 up to Week 23, the dose was to be administered at the same frequency as at Week 15, or the frequency at the time of the last visit. Table 3 shows the PK parameters of efgartigimod alfa, and Table 4 shows the percent change from baseline over time in serum total IgG concentration.

[2)] Patients who had tested negative for ADAs at baseline and had ADAs detected after treatment with efgartigimod alfa (treatment-induced ADA positive patients); and patients who had tested positive for ADAs at baseline and had a ≥4-fold increase in ADA titer after treatment with efgartigimod alfa (treatment-boosted ADA positive patients)

[3)] Persistent ITP, ≥3 months and ≤12 months from diagnosis; chronic ITP, >12 months from diagnosis

Table 3. PK parameters after administration of multiple intravenous doses of efgartigimod alfa

Dosing frequency	Timepoint (after the start of treatment)	Japanese		Non-Japanese	
		C_{trough} (μg/mL)	C_{max} (μg/mL)	C_{trough} (μg/mL)	C_{max} (μg/mL)
Once weekly	Initial dose	—	222 ± 47.6 [5]	—	230 ± 85.1 [74]
	Week 1	6.53 ± 2.40 [5]	247 ± 83.6 [5]	10.6 ± 5.84 [63]	230 ± 72.1 [74]
	Week 2	8.03 ± 3.22 [4]	223 ± 62.8 [4]	12.6 ± 7.24 [62]	235 ± 64.4 [68]
	Week 3	10.7 ± 3.22 [4]	212 ± 62.6 [5]	17.9 ± 30.4 [59]	254 ± 126 [71]
Once weekly	Week 16	6.07, 7.99[a] [2]	148, 235[a] [2]	12.1 ± 7.31 [50]	235 ± 58.6 [52]
	Week 17	5.00, 14.3[a] [2]	150, 256[a] [2]	12.1 ± 7.81 [48]	232 ± 61.4 [50]
	Week 18	6.44, 9.80[a] [2]	158, 264[a] [2]	12.9 ± 7.75 [47]	243 ± 57.5 [50]
	Week 19	6.92, 8.50[a] [2]	150, 287[a] [2]	13.0 ± 8.84 [45]	229 ± 95.6 [46]
	Week 20	7.39[a] [1]	163[a] [1]	17.0 ± 30.2 [40]	220 ± 64.6 [45]
	Week 21	7.70[a] [1]	158, 343[a] [2]	13.0 ± 7.93 [40]	232 ± 48.6 [45]
	Week 22	7.59, 15.0[a] [2]	188, 208[a] [2]	12.2 ± 7.80 [47]	229 ± 68.1 [49]
	Week 23	4.67, 7.09[a] [2]	162, 174[a] [2]	12.8 ± 8.41 [43]	249 ± 102 [43]
	Week 24	—	—	—	190[a] [1]
Every other week	Week 16	—	—	2.47, 9.13[a] [2]	281 ± 66.6 [3]
	Week 17	2.52[a] [1]	305[a] [1]	2.86 ± 0.532 [4]	220 ± 35.6 [5]
	Week 18	—	—	2.71 ± 1.91 [3]	184, 221[a] [2]
	Week 19	3.01[a] [1]	275[a] [1]	2.88 ± 0.918 [3]	395 ± 325 [4]
	Week 20	—	—	2.56 ± 1.71 [3]	192 ± 18.6 [4]
	Week 21	2.63[a] [1]	299[a] [1]	3.37 ± 1.57 [3]	256 ± 48.1 [4]
	Week 22	—	—	2.57 ± 1.46 [4]	164 ± 8.18 [4]
	Week 23	3.10[a] [1]	270[a] [1]	3.01 ± 1.06 [4]	219 ± 35.3 [4]

Mean ± standard deviation [N]; a, individual value; "—," not calculated

Table 4. Percent change from baseline over time in serum total IgG concentration (%)[a]

Dosing frequency	Timepoint (after the start of treatment)	Japanese	Non-Japanese
Once weekly	Week 1	−35.836 ± 7.0298 [5]	−40.110 ± 6.4747 [72]
	Week 2	−55.224 ± 4.8170 [5]	−52.281 ± 29.7261 [68]
	Week 3	−59.537 ± 8.5575 [5]	−55.238 ± 49.9643 [69]
Once weekly or every other week	Week 4	−61.752 ± 2.6643 [4]	−59.969 ± 30.1504 [60]
	Week 8	−68.869 ± 5.1539 [4]	−61.398 ± 30.0113 [60]
	Week 12	−71.448 ± 2.0058 [3]	−62.201 ± 29.1436 [54]
	Week 16	−72.273, −71.612[b] [2]	−65.784 ± 13.4645 [55]
Once weekly	Week 17	−72.079, −70.696[b] [2]	−65.733 ± 14.3269 [51]
	Week 19	−72.430, −69.645[b] [2]	−61.485 ± 29.3806 [47]
	Week 21	−72.011, −64.603[b] [2]	−61.206 ± 23.4028 [46]
	Week 23	−71.091, −70.444[b] [2]	−63.619 ± 21.1350 [44]
Every other week	Week 17	−64.017[b] [1]	−65.682 ± 5.3249 [4]
	Week 19	−64.017[b] [1]	−64.226 ± 9.9290 [3]
	Week 21	−63.285[b] [1]	−61.679 ± 10.1963 [4]
	Week 23	−56.485[b] [1]	−63.852 ± 9.3508 [4]

Mean ± standard deviation [N]

a, The baseline serum total IgG concentration was 8296 ± 9858 μg/mL for Japanese patients and 10380 ± 30980 μg/mL for non-Japanese patients; b, individual values

The proportion of ADA positive patients[2)] was 3.5% (3 of 86 subjects). The proportion of neutralizing antibody-positive patients was 1.2% (1 of 85 subjects).

6.2.3 Population PK analysis (CTD 5.3.3.5-4)

A population PK analysis was performed on serum efgartigimod alfa concentration data (N = 86; 3320 timepoints) from Study 1801, which was conducted in patients with primary ITP (NONMEM Version 7.5.0). The major baseline demographics and disease characteristics, and disposition of the analysis set were as follows: sex (47 females and 39 males), race (80 Caucasian patients, 5 Asian patients [all Japanese], and 1

patient categorized as other race), concomitant use of corticosteroids (14 patients used, 72 patients did not use), body weight (median [Min, Max], the same applies hereinafter in the paragraph): 77.6 kg [36.7, 136]; estimated glomerular filtration rate (eGFR): 96.8 mL/min/1.73 m^2 [30.8, 137]; albumin: 45 g/L [31, 53]; and alkaline phosphatase (ALP): 73.5 U/L [27, 155].

In this analysis, the population PK model, which was created from clinical study data on healthy subjects and patients with myasthenia gravis, was used as the base model, which was then updated using data obtained from patients with ITP. In the base model, the PK of efgartigimod alfa was described by a 3-compartment model assuming 2 peripheral compartments (peripheral volume of distribution [V2], [V3]) and clearance (total clearance [CL]) from the central compartment (central volume of distribution [V1]). After updating the model, among covariate effects included in the base model (effects of body weight on CL, V1, V2, and V3; effects of eGFR on CL; effects of sex on V1; and effects of albumin on CL), the effect of albumin on CL was excluded from the final model.

As a result of the review on the final model, the area under the serum concentration-time curve at steady state (AUC_{ss}) was estimated to be higher in patients with an eGFR of 56.1 mL/min/1.73 m^2 (5th percentile) by 26.7% and lower in patients with an eGFR of 127.3 mL/min/1.73 m^2 (95th percentile) by 11.2% compared with patients with an eGFR of 96.8 mL/min/1.73 m^2 (median)[4)]; compared with patients weighing 77.6 kg (median), AUC_{ss} was estimated to be lower in patients weighing 46.9 kg (5th percentile) by 19.5%, and higher in patients weighing 113.0 kg (95th percentile) by 17.6%. Sex did not have a clinically meaningful effect on the PK parameters of efgartigimod alfa.

[4)] Body weight was fixed at 77.6 kg, the median.

6.2.4 Population PK/PD analysis (CTD 5.3.3.5-4)

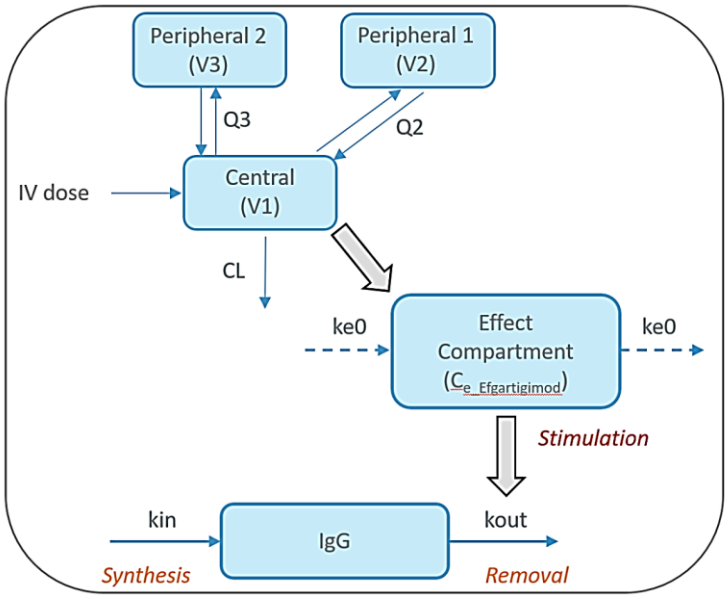


Figure 1. Outline of population PK/PD model

V1, volume of distribution of the central compartment; V2, peripheral volume of distribution (volume of the second compartment); V3, peripheral volume of distribution (volume of the third compartment); Q2, inter-compartmental clearance between V1 and V2; Q3, inter-compartmental clearance between V1 and V3; CL, total clearance by efgartigimod alfa; $C_{e\_Efgartigimod}$, the concentration of efgartigimod alfa in the effect compartment; IgG, serum total IgG; k_{eo}, equilibrium rate constant in the effect compartment; k_{in}, serum total IgG generation rate constant; k_{out}, serum total IgG elimination rate constant

A population PK/pharmacodynamic (PD) analysis was performed on serum efgartigimod alfa concentration data and serum total IgG concentration data (N = 131; 2487 timepoints) from Study 1801, which was conducted in patients with primary ITP (NONMEM Version 7.5.0). The major baseline demographics and disease characteristics, and disposition of the analysis set were as follows: sex (71 females and 60 males), race (121 Caucasian patients, 8 Asian patients [all Japanese], 1 patient categorized as other race, and 1 unknown), concomitant use of corticosteroids (34 patients used and 97 patients did not use), body weight (median [Min, Max], the same applies hereinafter in the paragraph): 76.4 kg [36.7, 136], eGFR: 93.4 mL/min/1.73 m^2 [30.8, 137], albumin: 45 g/L [31, 53], ALP: 72 U/L [27, 161], and aspartate aminotransferase (AST): 18 U/L [9, 34].

In this analysis, a population PK/PD model, which was created from clinical study data on healthy subjects and patients with myasthenia gravis, was used as the base model, which was then updated using data obtained from patients with ITP. In the base model, the change in serum total IgG concentration after the administration of efgartigimod alfa was described by an indirect response model with effect compartment. The relationship between the efgartigimod alfa concentration ($C_{e\_Efgartigimod}$) and serum total IgG elimination rate constant (k_{out}) in the effect compartment was modeled using a maximum effect model containing E_{max} and half-maximal effective concentration (EC_{50}) as parameters (Figure 1). After updating the model, all covariate effects included in the base model (effects of ALP, race, and concomitant use of corticosteroids on baseline serum total IgG concentration, effects of AST on k_{out}, and effects of body weight on EC_{50}) were excluded from the final model.

6.R Outline of the review conducted by PMDA

6.R.1 Rationale for selection of the dosage regimens in Study 1801

The applicant's explanation of the rationale for selecting the dosage regimen of efgartigimod alfa in Study 1801:

Because efgartigimod alfa is intended to increase platelet count by reducing IgG, the dosage regimen was selected based on the percent change from baseline in serum total IgG concentration. A model was created using data from Study 1603 to describe the relationship between the serum total IgG concentration following administration of efgartigimod alfa and change in platelet count. However, there was marked variation in the interindividual platelet count; in addition, it was difficult to fully explain the interindividual variation based on the data from Study 1603. Therefore, there were limitations to select the dosage regimen of efgartigimod alfa for Study 1801 on the basis of the simulation of platelet count change.

In Study 1603, following administration of efgartigimod alfa once weekly for 3 weeks, the maximum percent reduction from baseline in serum total IgG concentration was greater at efgartigimod alfa 10 mg/kg than at efgartigimod alfa 5 mg/kg. Both efgartigimod alfa 5 mg/kg and 10 mg/kg have acceptable safety and were well tolerated [see Table 2 and Section "7.1 Foreign phase II study"]. Based on the results, efgartigimod alfa 10 mg/kg, which is expected to be more clinically effective than 5 mg/kg, was selected as the study dose for Study 1801. In addition, since primary ITP is a chronic disease, the protocol specified that every-other-week administration was permissible depending on the patient's response to treatment (e.g., platelet count). This allows patients on long-term treatment to select a treatment option with less frequent administration.

Simulations of serum total IgG concentrations following 26-week multiple intravenous dose treatment of efgartigimod alfa with 4 different dosage regimens were performed using the population PK/PD model created from clinical study data in healthy subjects to support the justification of the dosage regimen in Study 1801 (Figure 2). The maximum percent reduction from baseline in serum total IgG concentration following administration of efgartigimod alfa 10 mg/kg once weekly was higher than that of efgartigimod alfa 5 mg/kg once weekly. When the dosing frequency for efgartigimod alfa 10 mg/kg was decreased to every other week, the maximum percent reduction from baseline in serum total IgG concentration at steady state was similar to that for the once-weekly administration of efgartigimod alfa 5 mg/kg. In Study 1603, there were patients who achieved complete response[5)] among those receiving efgartigimod alfa 5 mg/kg once weekly and those receiving 10 mg/kg once weekly (Table 6); therefore, it was considered that when dosing frequency was changed to every other week after 4 weeks of treatment according to the patient's platelet count and clinical symptoms, increased platelet count is expected to be maintained in some cases.

[5)] Platelet count ≥100,000/μL, confirmed by 2 separate consecutive measurements ≥7 days apart, and the absence of bleeding

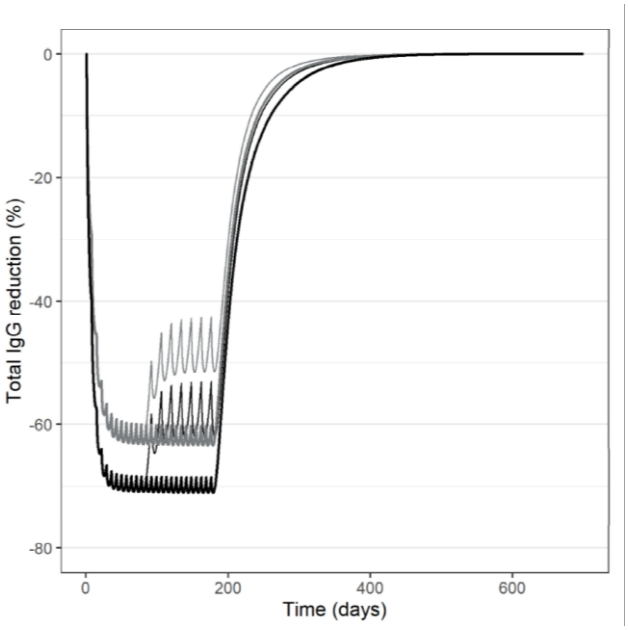


Figure 2. Percent reduction from baseline over time in serum total IgG concentration after administration of multiple intravenous doses of efgartigimod alfa for 26 weeks

Gray bold line, efgartigimod alfa 5 mg/kg once weekly
Black bold line, efgartigimod alfa 10 mg/kg once weekly
Gray solid line, efgartigimod alfa 5 mg/kg once weekly for the first 12 weeks, and thereafter, every other week administration for a total of 7 doses
Black solid line, efgartigimod alfa 10 mg/kg once weekly for the first 12 weeks, and thereafter, every other week administration for a total of 7 doses

PMDA's view:

The applicant explained that although the expected efficacy of efgartigimod alfa is to improve the platelet count, there were limitations at the time of designing Study 1801 to evaluate the dosage regimen of efgartigimod alfa based on the change in platelet count. This explanation by the applicant is understood, and given the mechanism of action of efgartigimod alfa, setting the study dosage regimen of efgartigimod alfa in Study 1801 based on the percent reduction from baseline in serum total IgG concentration can be regarded as rational.

6.R.2 Differences in PK/PD between Japanese and non-Japanese populations

The applicant's explanation about the differences in PK/PD of efgartigimod alfa between Japanese and non-Japanese populations:

The change in mean PK parameters over time after intravenous administration of efgartigimod alfa 10 mg/kg once weekly (during the first 3 weeks of treatment and then from Week 16 to Week 23, during which dosing frequency was fixed again) in Japanese and non-Japanese populations, respectively, was as follows: C_{max}, 163 to 251 μg/mL and 220 to 254 μg/mL; trough drug serum concentration (C_{trough}), 5.88 to 11.3 μg/mL and 10.6 to 17.9 μg/mL (Table 3), indicating that values are similar between populations. The median values of PK parameters and their 90% confidence intervals [90% CI] estimated by the population PK analysis [see Section "6.2.3 Population PK analysis"] in the Japanese and non-Japanese populations, respectively, are as follows: maximum serum concentration at steady state ($C_{max,ss}$), 197 μg/mL [172, 223] and 230 μg/mL [222,

237]; trough drug serum concentration at steady state ($C_{trough,ss}$), 8.55 μg/mL [7.05, 10.05] and 11.22 μg/mL [10.10, 12.34]; AUC_{ss}, 4780 μg·h/mL [4584, 4975] and 6186 μg·h/mL [5860, 6513]. The exposure (AUC_{ss}) was lower in the Japanese population than in the non-Japanese population, which is considered attributable primarily to a difference in body weight for the following reasons:

- The population PK analysis based on Study 1801 data [see Section "6.2.3 Population PK analysis"] estimated that the exposure tended to decrease with decrease in body weight when the administered efgartigimod alfa dose was determined based on body-weight conversion.
- In Study 1801, the median body weight of Japanese subjects (47.3 kg) was lower than that of non-Japanese subjects (78.0 kg). The estimated AUC_{ss} of Japanese subjects did not differ significantly from that of non-Japanese subjects when comparing AUC_{ss} between subjects of similar weights.
- In the population PK analysis based on clinical study results data in healthy subjects and patients with myasthenia gravis, race was not identified as a covariate that has a significant impact on PK parameters of efgartigimod alfa.

The PD data show the following: in Study 1801, the change over time in serum total IgG concentration after intravenous administration of efgartigimod alfa 10 mg/kg once weekly in the Japanese population was similar to that in the non-Japanese population (Table 4). The median values of PD parameters and their 90% confidence intervals [90% CI] at steady state estimated by the population PK/PD analysis [see Section "6.2.4 Population PK/PD analysis"] in the Japanese and non-Japanese populations, respectively, are as follows: area under the effect-time curve at steady state ($AUEC_{ss}$), 1086 g·h/L [1011, 1160] and 1167 g·h/L [1100, 1235]; and maximum percent reduction in serum total IgG concentration, 74.0% [72.0%, 75.9%] and 72.1% [70.8%, 73.4%], indicating no differences between populations.

PMDA's view:

Although only limited data from Japanese patients are available, which precludes strict interpretation of the results, based on the submitted study data and evaluation results, the exposure after intravenous administration of efgartigimod alfa 10 mg/kg once weekly to patients with primary ITP was lower in Japanese than in non-Japanese patients, which was primarily attributable to the difference in body weight. Given that there is no significant difference in the change in serum total IgG concentration over time between Japanese and non-Japanese populations, the difference in exposure between Japanese and non-Japanese population is unlikely to have had a significant impact on efficacy; however, this issue should be further discussed taking into account efficacy and other results from clinical studies [see Section "7.R.2.3 Efficacy in Japanese patients"].

6.R.3 Immunogenicity

The applicant's explanation of immunogenicity of efgartigimod alfa:

In Studies 1801 and 1803, the proportion of ADA positive subjects[2)] was 4.1% (5 of 124 subjects) and that of neutralizing antibody-positive subjects was 0.8% (1 of 124 subjects). During the treatment with efgartigimod alfa, serum total IgG concentration decreased; therefore, it was considered that ADAs of the IgG isotype also decrease during treatment with efgartigimod alfa, and ADAs are not readily detected during treatment. For this reason, an immunogenicity evaluation was planned during the follow-up period after completion of treatment

(in Study 1801, 4 weeks after the completion of treatment; in Study 1803, 4 or 8 weeks after the completion of treatment). In the pooled data from Studies 1801 and 1803 (N = 124), only 35 subjects completed the immunogenicity evaluation during the follow-up period as of the data cut-off date (August 10, 2022). Among the 35 subjects, the proportion of ADA positive subjects[2)] and neutralizing antibody-positive subjects was 5.7% (2 of 35 subjects) and 2.9% (1 of 35 subjects), respectively.

The effects of ADAs on the PK and PD of efgartigimod alfa were evaluated. The results of the integrated analysis of Studies 1801 and 1803 show that the C_{trough} of efgartigimod alfa (Figure 3) and percent reduction from baseline in serum total IgG concentration in treatment-induced ADA positive subjects,[6)] treatment-boosted ADA positive subjects,[7)] and treatment-unaffected ADA positive subjects[8)] did not differ significantly from those in ADA negative subjects.[9)] In Study 1801, 1 subject tested positive for neutralizing antibodies; however, it was after the completion of efgartigimod alfa treatment when this subject developed neutralizing antibodies; therefore, effects on PK and PD were not evaluated.

[6)] Patients who had tested negative for ADAs at baseline and had ADAs detected after treatment with efgartigimod alfa
[7)] Patients who had tested positive for ADAs at baseline and had a ≥4-fold increase in ADA titer after treatment with efgartigimod alfa
[8)] Patients who had tested positive for ADAs at baseline and had ADAs detected after treatment with efgartigimod alfa
[9)] The treatment-boosted ADA positive subjects, treatment-induced ADA positive subjects, and treatment-unaffected ADA positive subjects (7 subjects in total) developed ADAs during the treatment period of efgartigimod alfa

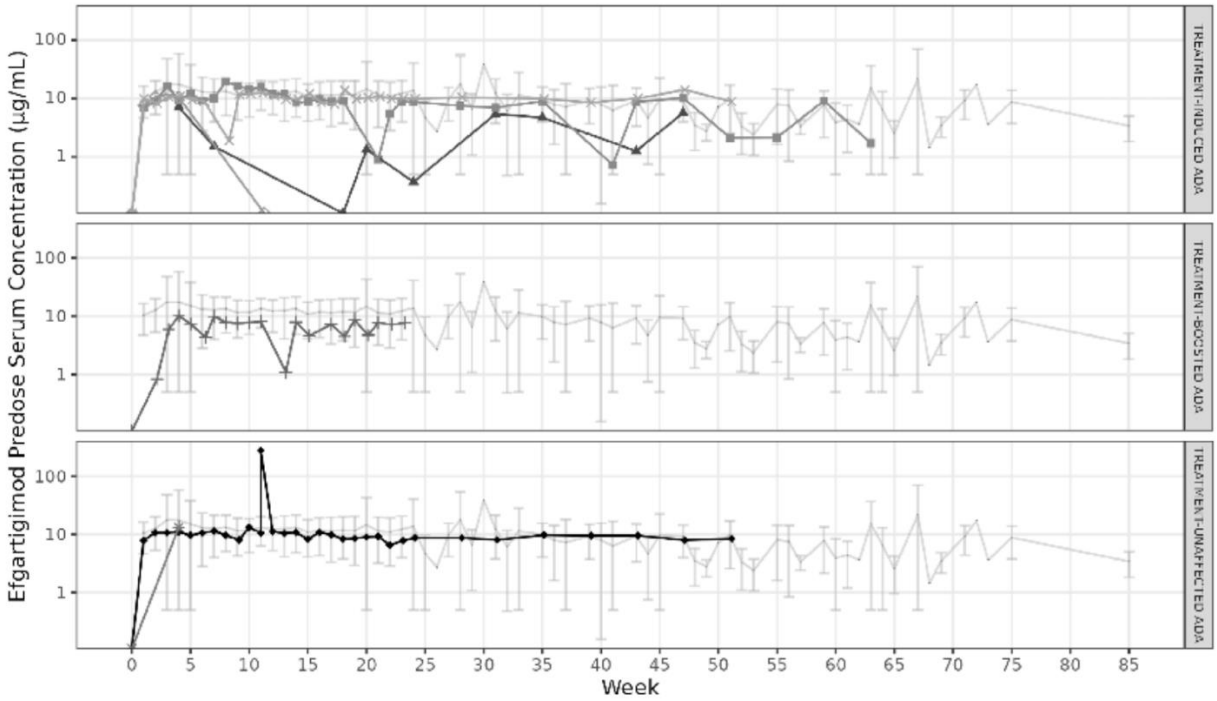


Figure 3. Change in C_{trough}[a] of efgartigimod alfa over time in treatment-induced ADA positive subjects, treatment-boosted ADA positive subjects, and treatment-unaffected ADA positive subjects in Study 1801

Upper graph: Symbols "■, ×, ▲, and ◊" indicate treatment-induced ADA positive subjects,[6] Symbol "–" indicates ADA negative subjects

Middle graph: Symbol "+" indicates treatment-boosted ADA positive subjects,7) Symbol "–" indicates ADA negative subjects

Bottom graph: Symbols "♦ and ∗" indicate treatment-unaffected ADA positive subjects,8) Symbol "–" indicates ADA negative subjects

a, Values of ADA negative subjects are expressed as mean ± standard deviation; values of ADA positive subjects are individual values of each subject

The effects of ADAs on the safety of efgartigimod alfa were evaluated. Of the 5 subjects[2] who tested positive for ADAs in Studies 1801 and 1803, 1 subject experienced a hypersensitivity-related adverse event; however this event was noted before the development of ADAs, suggesting no relationship between ADAs and the hypersensitivity-related adverse event.

The effects of ADAs on the efficacy of efgartigimod alfa were evaluated. The results of the analysis of integrated data from Studies 1801 and 1803 showed that the proportion of patients who achieved a sustained platelet count response (defined as platelet counts of ≥50,000/µL on ≥4 of the 6 visits between Weeks 19 and 24) was 25.4% (29 of 114 subjects) in ADA negative subjects, 25.0% (1 of 4 subjects) in treatment-induced ADA positive subjects,[6] 0% (0 of 1 subject) in treatment-boosted ADA positive subjects,[7] and 0% (0 of 2 subjects) in treatment-unaffected ADA positive subjects.[8] There was no trend towards decreasing platelet counts associated with emergence of ADAs in subjects who developed ADAs. The subject who tested positive for neutralizing antibodies in Study 1801 did not show a sustained platelet count response, while no platelet count decrease was noted associated with the emergence of neutralizing antibodies.

In view of the above, there are no clear effects of ADA production on the PK, PD, safety, or efficacy of efgartigimod alfa.

Based on the applicant's explanation, PMDA accepted that the PK, PD, safety, and efficacy of efgartigimod alfa are not affected by the presence or absence of ADAs, and PMDA considers that immunogenicity is unlikely to become a clinical problem.

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 3 main clinical studies presented in Table 5 [for PK and PD, see Section "6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA"].

Table 5. Outline of main clinical studies

Data	Location	Study ID	Phase	Study population	Number of subjects randomized[a]	Summary of dosage regimen	Main endpoints
Evaluation	Foreign	1603	II	Patients with primary ITP	38	Double-blind period: Placebo, efgartigimod alfa 5 or 10 mg/kg was administered as once-weekly IV infusions for 3 weeks Open-label treatment period: Efgartigimod alfa 10 mg/kg was administered in cycles of once-weekly IV infusions for 3 weeks followed by a ≥4 week-rest period, up to 12 months maximum	Safety Efficacy PK PD
	Global	1801	III	Patients with chronic or persistent primary ITP	131 (8)	Placebo or efgartigimod alfa 10 mg/kg was administered as once-weekly or every-other-week IV infusions, for 24 weeks	Efficacy Safety
	Global	1803	III	Patients with chronic or persistent primary ITP	101[b] (5)	Efgartigimod alfa 10 mg/kg was administered as once-weekly or every-other-week IV infusions, up to 4 years	Safety Efficacy

a, The number of Japanese patients is shown in parentheses
b, Number of patients enrolled

7.1 Foreign phase II study (Study ARGX-113-1603, CTD 5.3.5.1-1 [March 2017 to May 2019])

A randomized, double-blind, placebo-controlled study was conducted at 19 study centers outside Japan to evaluate the safety, efficacy, PK, and PD of efgartigimod alfa in patient with primary ITP (target sample size, approximately 36 subjects after randomization [12 subjects/group]).

This study consisted of (1) a double-blind period (including 2-week screening period, 3-week treatment period, and 8-week follow-up period) and (2) an open-label treatment period (up to 12 months). Patients who completed the 8-week follow-up period without receiving rescue treatment were given the option to participate in an extended follow-up period of up to 13 weeks. Patients who relapsed[1)] during the double-blind period were given the option to participate in the open-label treatment period.

(1) Double-blind period

The enrolled patients were assigned to the placebo, efgartigimod alfa 5 or 10 mg/kg group.

Patients were to receive placebo, efgartigimod alfa 5 or 10 mg/kg as once-weekly intravenous infusions over ≥2 hours for 3 weeks. The recommended maximum dose in patients weighing ≥120 kg was up to 1200 mg per infusion.

The key inclusion criteria were patients with primary ITP[10] aged ≥18 years to ≤85 years who met the following requirements:

- Patients whose platelet counts <30,000/μL[11] and who have not experienced major bleeding in the 4 weeks prior to screening
- Patients who have been receiving standard of care treatment for ITP (oral corticosteroids and/or oral immunosuppressants,[12] and/or thrombopoietin [TPO] receptor agonist[13]) that has been stable in terms of dose and frequency for ≥4 weeks prior to screening

Patients including the following conditions were excluded: patients who had had prior treatment with recombinant TPO; patients who had received rituximab or other anti-CD20 antibodies within 6 months prior to screening; patients who had received blood transfusion or been treated with intravenous immunoglobulin (IVIg), or intravenous anti D immunoglobulin (IV anti-D Ig) within 4 weeks prior to screening; patients who had had a serious infection within 8 weeks prior to screening; patients with past or ongoing human immunodeficiency virus (HIV) positivity, hepatitis C virus (HCV) positivity, or hepatitis B virus (HBV) positivity; patients with history of thrombosis or embolism within 12 months prior to screening; patients with angina pectoris.

The ITP treatment drugs administered at screening were to be administered concomitantly without modifying the dosage regimen throughout the treatment period. If complete response (platelet count ≥100,000/μL, confirmed on 2 consecutive measurements at least 7 days apart, with absence of bleeding) is achieved, the dose of the concomitant ITP drug may be decreased by up to 25% in the follow-up period.

Throughout the study period, patients may receive rescue treatment (dose increase or increase in the dosing frequency of concomitant ITP treatment drug, or initiation of new treatment for ITP [IVIg, IV anti-D Ig, high-dose corticosteroids, platelet transfusion]) if necessary, at the discretion of the investigator.

All 38 randomized subjects (12 subjects, 13 subjects, and 13 subjects in the placebo group, efgartigimod alfa 5 mg/kg group, and efgartigimod alfa 10 mg/kg group, respectively; the same applies hereinafter) received at least 1 dose of the study drug, and were included in the safety analysis set. Of the randomized subjects, all 38 subjects had at least 1 platelet measurement after the start of study drug treatment, and were included in the full analysis set (FAS), which was the primary efficacy analysis set. Thirty two subjects completed the 8-week follow-up period, and 14 subjects (2 subjects, 6 subjects, and 6 subjects) participated in the extended follow-

[10] Patients with confirmed diagnosis of ITP according to the diagnostic criteria in the 2011 American Society of Hematology (ASH) guidelines for ITP
[11] The mean of 2 measurements at least 1 day apart during the screening period. Individual measurements must be <35,000/μL.
[12] Azathioprine (2.5 mg/kg/day maximum), danazol (15 mg/kg/day maximum), mycophenolate mofetil (3 g/day maximum), and mycophenolate sodium (2160 mg/day maximum)
[13] Eltrombopag olamine (75 mg/day maximum) and romiplostim (10 μg/kg/week maximum)

up period. Six subjects (4 subjects, 0 subjects, and 2 subjects) discontinued the study with reasons for discontinuation being "inadequate effect" (3 subjects total; 3 subjects, 0 subjects, and 0 subjects), "withdrawal of consent" (2 subjects total; 1 subject, 0 subjects, and 1 subject), and "other reasons" (1 subject total; 0 subjects, 0 subjects, and 1 subject). Patients who received 4 doses of the study drug were 11 of 12 subjects, 13 of 13 subjects, and 11 of 13 subjects; while patients who received 3 doses of the study drug were 1 of 12 subjects, 0 of 13 subjects, and 2 of 13 subjects.

In the FAS, 0 of 12 subjects, 2 of 13 subjects, and 0 of 13 subjects were <3 months from diagnosis; 3 of 12 subjects, 1 of 13 subjects, and 4 of 13 subjects were ≥3 months and ≤12 months from diagnosis; 9 of 12 subjects, 10 of 13 subjects, and 9 of 13 subjects were >12 months from diagnosis. One of 12 subjects, 2 of 13 subjects, and 3 of 13 subjects had a history of splenectomy; 11 of 12 subjects, 11 of 13 subjects, and 8 of 13 subjects had prior ITP treatments; and 8 of 12 subjects, 12 of 13 subjects, and 11 of 13 subjects were receiving concomitant ITP treatment drugs.

Table 6 shows the results for main efficacy endpoints.

Table 6. Results for main efficacy endpoints (Double-blind period, FAS)

		Placebo (N = 12)	Efgartigimod alfa 5 mg/kg (N = 13)	Efgartigimod alfa 10 mg/kg (N = 13)
Proportion of patients with initial response[a]		33.3 (4)	23.1 (3)	38.5 (5)
Proportion of patients who achieved the following at any time during the study period				
Complete response[b]		0 (0)	15.4 (2)	23.1 (3)
Response[c]		16.7 (2)	23.1 (3)	15.4 (2)
No response[d]		66.7 (8)	46.2 (6)	53.8 (7)
Proportion of patients whose platelet count increased to ≥50,000/μL at any time during the study period		50.0 (6)	53.8 (7)	53.8 (7)
Proportion of patients requiring rescue treatment		8.3 (1)	46.2 (6)	30.8 (4)
Change from baseline[e] in platelet count (per μL)	Week 3	10,600 ± 29,400 (10)	27,300 ± 62,710 (11)	21,200 ± 33,560 (10)
	End of follow-up period	9,400 ± 13,330 (7)	31,100 ± 61,090 (8)	55,500 ± 114,280 (10)
Proportion of patients assessed as Grade 0 according to the WHO bleeding scale	Baseline	66.7 (8)	53.8 (7)	61.5 (8)
	Week 3	50.0 (6)	61.5 (8)	69.2 (9)
	End of follow-up period	41.7 (5)	46.2 (6)	69.2 (9)
SMOG index of the ITP-BAT	Baseline	0.0 [0, 1] (12)	0.0 [0, 1] (13)	0.0 [0, 2] (13)
	Week 3	0.0 [0, 1] (11)	0.0 [0, 1] (12)	0.0 [0, 1] (11)
	End of follow-up period	0.0 [0, 1] (8)	0.0 [0, 1] (9)	0.0 [0, 1] (10)

Proportion in % (n); median [Min, Max] (N); mean ± standard deviation (N)

a, Platelet count ≥30,000/μL and/or at least doubling of the baseline count and absence of bleeding at any time during the study

b, Platelet count ≥100,000/μL, confirmed on 2 consecutive measurements taken ≥7 days apart, and absence of bleeding

c, Platelet count ≥30,000/μL and <100,000/μL, and >2-fold increase in platelet count from baseline, confirmed on 2 consecutive measurements taken ≥7 days apart, and absence of bleeding

d, Platelet count <30,000/μL, or less than doubling of the baseline count, or bleeding

e, 18,300 ± 12,290/μL (N = 12) in the placebo group, 17,300 ± 12,050/μL (N = 12) in the efgartigimod alfa 5 mg/kg group, and 15,300 ± 9,090/μL (N = 13) in the efgartigimod alfa 10 mg/kg group.

The incidence of all adverse events in the double-blind period[14] was 58.3% (7 of 12) of subjects in the placebo group, 69.2% (9 of 13) of subjects in the efgartigimod alfa 5 mg/kg group, and 84.6% (11 of 13) of subjects in the efgartigimod alfa 10 mg/kg group. Table 7 shows adverse events occurring in ≥10% of subjects in any group.

Table 7. Adverse events occurring in ≥10% of subjects in any group (Safety analysis set)

MedDRA PT	Placebo (N = 12)	Efgartigimod alfa 5 mg/kg (N = 13)	Efgartigimod alfa 10 mg/kg (N = 13)
Vomiting	0 (0)	0 (0)	15.4 (2)
Headache	16.7 (2)	7.7 (1)	0 (0)
Petechiae	8.3 (1)	15.4 (2)	15.4 (2)
Purpura	0 (0)	15.4 (2)	7.7 (1)
Haematoma	0 (0)	23.1 (3)	15.4 (2)
Hypertension	8.3 (1)	0 (0)	15.4 (2)

Incidence, % (n)

There were no reports of death.

Other serious adverse event (thrombocytopenia) occurred in 7.7% (1 of 13) of subjects in the efgartigimod alfa 10 mg/kg group. A causal relationship to the study drug was denied.

An adverse event leading to study drug treatment discontinuation was thrombocytopenia in 7.7% (1 of 13) of subjects in the efgartigimod alfa 10 mg/kg group.

(2) Open-label treatment period

Of the patients who had received ≥3 doses of the study drug and had been followed for ≥2 weeks in the double-blind period, those who had relapsed[1] were eligible to receive treatment in the open-label treatment period.

Patients were to receive efgartigimod alfa 10 mg/kg as once-weekly intravenous infusions for 3 weeks (treatment period), followed by a ≥4-week follow-up period. This treatment cycle was to be repeated if the patient met all of the following, and the patient was to be followed for up to 12 months. For patients weighing ≥120 kg, the recommended dose was up to 1200 mg per infusion.

- The patient received ≥3 doses of efgartigimod alfa and had ≥4 weeks of follow-up in the previous treatment cycle
- The patient whose platelet counts were measured in the treatment and follow-up periods of the previous cycle, and reached a platelet count of at least twice that measured on the day of the first efgartigimod alfa treatment (≥2 consecutive measurements, ≥1 day apart but ≤7 days in between the measurements)
- The patient is on the same concomitant ITP therapy as in the previous treatment cycle (dose increase or dosing frequency increase is allowed)
- The patient is relapsing[1], and absence of bleeding

[14] From the first treatment day in the double-blind period to the first treatment day in the open-label treatment period

Twelve patients who relapsed[1)] in the double-blind period (4 subjects, 2 subjects, and 6 subjects, in the placebo, efgartigimod alfa 5 mg/kg, and efgartigimod alfa 10 mg/kg groups, respectively; the same applies hereinafter) entered the open-label treatment period. The number of patients who participated in the subsequent cycles were 12 subjects in Cycle 1 (4 subjects, 2 subjects, and 6 subjects), 3 subjects in Cycle 2 (1 subject, 1 subject, and 1 subject), and 1 subject in Cycle 3 (0 subjects, 0 subjects, and 1 subject). In Cycle 1, all subjects received 4 doses of efgartigimod alfa.

Table 8 shows the results for the efficacy endpoints in Cycle 1.

Table 8. Results for efficacy endpoints (Open-label treatment period [Cycle 1], FAS)

		Placebo-efgartigimod alfa 10 mg/kg (N = 4)	Efgartigimod alfa 5 mg/kg-10 mg/kg (N = 2)	Efgartigimod alfa 10 mg/kg-10 mg/kg (N = 6)
Proportion of patients with initial response[a]		25.0 (1)	0 (0)	16.7 (1)
Proportion of patients who achieved the following at any time during the study period				
Complete response[b]		25.0 (1)	0 (0)	0 (0)
Response[c]		0 (0)	0 (0)	16.7 (1)
No response[d]		25.0 (1)	0 (0)	83.3 (5)
Proportion of patients whose platelet count increased to ≥50,000/μL at any time during the study period		75.0 (3)	50.0 (1)	50.0 (3)
Proportion of patients requiring rescue treatment		0 (0)	0 (0)	50.0 (3)
Change from baseline[e] in platelet count (per μL)	Week 3	25,300 ± 47,350 (4)	5,000 (1)	−9,100 ± 19,920 (6)
	End of 8-week rest period	14,300 ± 37,580 (3)	2,000 (1)	−6,500 ± 26,870 (3)
Proportion of patients assessed as Grade 0 according to the WHO bleeding scale	Baseline	75.0 (3)	0 (0)	83.3 (5)
	Week 3	75.0 (3)	0 (0)	66.7 (4)
	End of 8-week rest period	50.0 (2)	50.0 (1)	33.3 (2)
SMOG index of the ITP-BAT	Baseline	0.0 [0, 1] (4)	0.5 [0, 1] (2)	0.5 [0, 2] (6)
	Week 3	0.0 [0, 0] (4)	0.0 [NA] (1)	0.0 [0, 1] (6)
	End of 8-week rest period	0.0 [0, 1] (3)	0.0 [NA] (1)	0.0 [0, 0] (3)

Proportion, % (n); median [Min, Max] (N); mean ± standard deviation (N)
NA, not calculated
Subjects in the placebo-efgartigimod alfa 10 mg/kg group, efgartigimod alfa 5 mg/kg-10 mg/kg group, and efgartigimod alfa 10 mg/kg-10 mg/kg group received placebo, efgartigimod alfa 5 mg/kg, and efgartigimod alfa 10 mg/kg, respectively, in the double-blind period.
a, Platelet count ≥30,000/μL or at least doubling of the baseline count and absence of bleeding at any time during the study
b, Platelet count ≥100,000/μL, confirmed on 2 consecutive measurements taken ≥7 days apart, and absence of bleeding
c, Platelet count ≥30,000/μL and <100,000/μL, and >2-fold increase in platelet count from baseline, confirmed on 2 consecutive measurements taken ≥7 days apart, and absence of bleeding
d, Platelet count <30,000/μL, or less than doubling of the baseline count, or bleeding
e, 18,500 ± 11,500/μL (N = 4) in the placebo-efgartigimod alfa 10 mg/kg group, 15,000/μL (N = 1) in the efgartigimod alfa 5 mg/kg-10 mg/kg group, and 34,600 ± 26,970/μL (N = 6) in the efgartigimod alfa 10 mg/kg-10 mg/kg group

The overall incidence of adverse events in the open-label treatment period[15)] was 58.3% (7 of 12) of subjects. ALT increased was the only adverse event that occurred in some subjects (16.7%, 2 of 12) of subjects.

There were no reports of death.

15) From the first treatment day in the open-label treatment period to the last visit

Other serious adverse events (pneumonia, uterine polyp) occurred in 16.7% (2 of 12) of subjects, and a causal relationship to the study drug was denied.

No adverse events led to treatment discontinuation of the study drug.

7.2 Phase III studies

7.2.1 Global phase III study (Study ARGX-113-1801, CTD 5.3.5.1-2 [December 2019 to February 2022])

A randomized, double-blind, placebo-controlled study was conducted at 71 study centers in and outside Japan to evaluate the efficacy and safety of efgartigimod alfa in patients with chronic or persistent[3)] primary ITP (target sample size,[16)] 117 patients with chronic primary ITP and a maximum of 39 patients with persistent primary ITP).

This study consisted of a screening period lasting approximately 2 weeks, a 24-week treatment period, and a 4-week follow-up period.

In each type of primary ITP, chronic or persistent, enrolled patients were randomized 1:2 to receive placebo or efgartigimod alfa, with past splenectomy and concomitant ITP drug use at baseline as the stratification factors.[17)] Patients who had completed 24 weeks of treatment were given an option to participate in the long-term extension study (Study 1803).

Patients were to receive placebo or efgartigimod alfa 10 mg/kg as an intravenous infusion over ≥1 hour. The treatment was to be started as once-weekly infusions, and dosing frequency could be adjusted to once-weekly or every-other-week infusions from Week 4 up to Week 15 based on the criteria in Table 9. From Week 16 to Week 23, the study drug was to be administered at the same fixed dosing frequency as at Week 15 or the frequency at the last treatment visit. The recommended maximum dose for patients weighing ≥120 kg was up to 1200 mg per infusion.

Table 9. Criteria to adjust dosing frequency of study drug

Adjustment criteria	Dosing frequency
If one of the following is met: • Platelet counts of ≥100,000/μL for ≥3 of 4 consecutive visits • Platelet counts of ≥100,000/μL for 3 consecutive visits	Switch from once weekly to every other week
If one of the following is met: • Platelet counts of <100,000/μL on 2 consecutive visits • Platelet counts of <30,000/μL at 1 visit • Received rescue treatment	Switch from every other week to once weekly

16) Based on the data from clinical studies for the approved ITP drugs (*Lancet.* 2008;371:395-403, *Lancet.* 2011;377:393-402, *Am J Hematol.* 2018;93:921-30), of patients with chronic primary ITP, it was assumed that 30% of the efgartigimod alfa group and 5% of the placebo group would achieve a sustained platelet count response. With a significance level of 0.025 (one-sided), a randomization ratio of 1:2 (placebo:efgartigimod alfa), 117 patients were required to achieve a minimum of 90% statistical power to detect the superiority of efgartigimod alfa to placebo; therefore, a target sample size of 117 was selected for patients with chronic primary ITP (39 subjects in the placebo group and 78 subjects in the efgartigimod alfa group). For patients with persistent primary ITP, a target sample size of 39 maximum was selected based on study feasibility. Enrollment of patients was to be ended when 117 patients with chronic primary ITP had been randomized.

17) Stratified randomization was not performed for the Japanese population due to the small sample size.

If platelet counts exceeded 400,000/μL, study drug treatment was to be interrupted, and the treatment was to be resumed at every-other-week frequency after confirming that the platelet count had dropped below 150,000/μL.

Key inclusion criteria were patients with chronic or persistent primary ITP[18] aged ≥18 years who met the following requirements:

- Patients whose platelet counts <30,000/μL[19]
- Patients who had received at least 1 type of treatment for ITP, and met one of the following:
  - Patients who had received at least 1 type of treatment for ITP in the past, and who were receiving at least 1 type of prespecified ITP drug at the time of screening (oral corticosteroids, oral immunosuppressants, danazol/dapsone, fostamatinib, oral TPO receptor agonists) that had been stable in terms of dose and frequency for ≥4 weeks prior to randomization
  - Patients who had received at least 2 types of ITP treatment in the past, and had not been receiving ITP treatment drugs for ≥4 weeks (or ≥6 months for anti-CD20 antibodies) prior to randomization

Ineligible patients including the following were excluded: patients who had had prior treatment with rituximab or other anti-CD20 antibodies within 6 months prior to randomization; patients who had undergone splenectomy within 4 weeks prior to randomization; patients who had received romiplostim, immunoglobulin (Ig), or plasmapheresis; patients who had received anticoagulants or blood transfusions; patients with past or ongoing HBV positivity (excluding those who tested negative to HBV deoxyribonucleic acid [DNA]), HCV antibody positivity (excluding those who tested negative to HCV ribonucleic acid [RNA]), or HIV positivity; and patients with thrombosis or embolism within 12 months prior to randomization. The ITP treatment drugs administered at screening were to be administered concomitantly without modifying the dosage regimen throughout the treatment period except for oral TPO receptor agonists and fostamatinib. For patients who had been taking concomitant oral TPO receptor agonists or fostamatinib, dose modification was allowed according to the approved dosage regimen. If the patient responded inadequately to study drug treatment at Week 12 or thereafter (platelet counts <30,000/μL at all visits in the recent 4 weeks), prespecified addition or dose increase of ITP drug was allowed.

In the treatment period, patients with a platelet count of <30,000/μL who met any of the following were allowed to receive rescue treatment (intravenous methylprednisolone [1 g/day maximum for 1-3 days], oral dexamethasone [40 mg/day maximum for 1-3 days], oral prednisone [1 mg/kg/day maximum for 1-2 days], IVIg [1 g/kg/day maximum for 1-2 days], IV anti-D Ig [50–75 μg/kg/day maximum for 1-2 days], or platelet transfusion). Patients who received rescue treatment ≥4 times were to discontinue from study drug treatment.

- At immediate risk of bleeding, or presence of clinically significant bleeding or wet purpura
- Requiring emergency surgery

[18] Patients with confirmed diagnosis of ITP according to the diagnostic criteria in the 2011 ASH guidelines at least 3 months prior to randomization, and whose diagnosis has been supported by the investigator based on the response to prior ITP treatment other than TPO receptor agonists

[19] The mean of 3 measurements during screening and at randomization. Individual measurements must be ≤35,000/μL.

Overall population

All 131 randomized subjects (45 subjects and 86 subjects in the placebo and efgartigimod alfa groups, respectively: the same applies hereinafter) were included in the FAS. Data on patients with chronic primary ITP in the FAS ("FAS-Chronic," 118 subjects total [40 subjects and 78 subjects]) were used for the analysis of primary endpoints. All 131 randomized subjects had at least 1 dose of the study drug and were included in the safety analysis set. Of 106 subjects (39 subjects and 67 subjects) who completed the study, 101 subjects (38 subjects and 63 subjects) participated in Study 1803. Twenty-five subjects (6 subjects and 19 subjects) discontinued from the study, with the reason for discontinuation being "inadequate effect" (3 subjects total; 2 subjects and 1 subject), "withdrawal of consent" (16 subjects total; 3 subjects and 13 subjects), "adverse events" (3 subjects total; 0 subjects and 3 subjects), "pregnancy" (1 subject total; 0 subjects and 1 subject), "investigator's decision" (1 subject total; 1 subject and 0 subjects), and "protocol deviation" (1 subject total; 0 subjects and 1 subject). The median treatment duration [Min, Max] (from the first dose of the study drug to the completion or early termination of the study) was 169.0 days [18, 172] in the placebo group and 169.0 days [22, 183] in the efgartigimod alfa group.

Table 10 shows the baseline demographics and disease characteristics of patients in the safety analysis set.

Table 10. Baseline demographics and disease characteristics of patients (Safety analysis set)

		Placebo (N = 45)	Efgartigimod alfa (N = 86)
Age (years)		55.0 [18, 82]	47.0 [19, 85]
Male (%)		46.7 (21)	45.3 (39)
Body weight (kg)		71.00 [45.8, 119.3]	77.60 [36.7, 135.9]
Time since diagnosis (years)		6.07 [0.5, 53.4]	4.15 [0.3, 54.1]
≥3 months and ≤12 months (persistent) (%)		11.1 (5)	9.3 (8)
>12 months (chronic) (%)		88.9 (40)	90.7 (78)
Baseline platelet count (/μL)		12,000 [2,000, 31,000]	17,000 [0,000, 51,000]
Baseline WHO bleeding scale (%)	Grade 0	35.6 (16)	51.2 (44)
	Grade 1	55.6 (25)	44.2 (38)
	Grade 2	8.9 (4)	4.7 (4)
Number of prior ITP treatment (treatment types)		3.0 [1, 7]	3.0 [1, 9]
Use of prior ITP treatment by type (%)	Corticosteroids	88.9 (40)	95.3 (82)
	TPO receptor agonist	64.4 (29)	55.8 (48)
	IVIg or IV anti-D Ig	64.4 (29)	48.8 (42)
	Splenectomy	37.8 (17)	37.2 (32)
	Anti-CD20 antibodies	31.1 (14)	36.0 (31)
	Other immunosuppressants	40.0 (18)	24.4 (21)
	Danazol	13.3 (6)	11.6 (10)
	Fostamatinib	2.2 (1)	3.5 (3)
	Dapsone	4.4 (2)	1.2 (1)
	Other	4.4 (2)	2.3 (2)
Concomitant ITP drug used[20] (%)		48.9 (22)	50.0 (43)
Use of concomitant ITP treatment drug by type (%)	Corticosteroids	26.7 (12)	25.6 (22)
	TPO receptor agonist	20.0 (9)	23.3 (20)
	Immunosuppressants	13.3 (6)	9.3 (8)
	Danazol	2.2 (1)	2.3 (2)

Median [Min, Max]; proportion (n)

[20] Although concomitant use of IVIgs or rituximab was prohibited, there were reports of concomitant use of IVIg and rituximab in 1 subject in the efgartigimod alfa group, and IVIg in 2 subjects in the placebo group. It was confirmed that in all of the subjects, treatment had ended before the washout period prior to randomization, which was specified in the protocol.

The proportion of patients whose ITP treatment regimen was intensified (addition of treatment or dose increase) after the start of study drug treatment was 17.8% (8 of 45) of subjects and 8.1% (7 of 86) of subjects in the placebo and efgartigimod alfa groups, respectively (the same applies hereinafter). The proportion of patients who received rescue therapy was 48.9% (22 of 45) of subjects and 33.7% (29 of 86) of subjects, and the specific therapies were as follows: corticosteroids: 28.9% (13 of 45) of subjects and 29.1% (25 of 86) of subjects; IVIg: 40.0% (18 of 45) of subjects and 15.1% (13 of 86) of subjects; and platelet transfusion: 13.3% (6 of 45) of subjects and 2.3% (2 of 86) of subjects.

Table 11 shows the primary efficacy endpoint, the proportion of patients with chronic primary ITP who achieved a sustained platelet count response (defined as platelet counts of ≥50,000/μL on ≥4 of the 6 visits between Weeks 19 and 24; the same applies hereinafter). The results showed a significantly higher achievement in the efgartigimod alfa group than in the placebo group.

Table 11. Proportion of patients with chronic primary ITP who achieved a sustained platelet count response (FAS-Chronic, overall population)

	Placebo (N = 40)	Efgartigimod alfa (N = 78)	Odds ratio vs placebo [95% CI][b]	*P*-value[b]
Proportion of patients who achieved a sustained platelet count response[a]	5.0 (2)	21.8 (17)	4.884 [1.007, 43.591]	0.0316

Proportion of patients, % (n)

a, Patients who experienced intercurrent events (discontinuation of study drug treatment for 24 weeks during the treatment period, rescue treatment at and after Week 12, or intensification of concomitant ITP treatment drugs due to lack of efficacy or adverse events) were considered to be non-achievement of sustained platelet count response. When a platelet count measurement was missing for reasons other than the intercurrent events described above, before evaluating as to whether a sustained platelet count response was achieved, the missing value was to be imputed with ≥50,000/μL, if the timepoints immediately before and after the missing data were within the treatment period and platelet counts at both timepoints were ≥50,000/μL; otherwise, the missing value was to be imputed with <50,000/μL.

b, The Cochran-Mantel-Haenszel test with history of splenectomy, baseline concomitant use of ITP treatment drugs, baseline platelet count (<15,000/μL or ≥15,000/μL) as stratification factors. Significance level 5% (two-sided)

Table 12 shows the results for key secondary endpoints.

Table 12. Results for key secondary endpoints (Overall population)

Key secondary endpoints	Analysis population	Placebo	Efgartigimod alfa
Disease control duration[a] in patients with chronic primary ITP (number of weeks over the 24-week period)	FAS-Chronic	0.00 [0.0, 14.0] (40)	2.00 [0.0, 24.0] (78)
The proportion of patients with chronic/persistent primary ITP who achieved a sustained platelet count response[b] (%)	FAS	6.7 (3/45)	25.6 (22/86)
Number of WHO-classified Grade ≥1 bleeding events in patients with chronic/persistent primary ITP[c]	FAS	5.0 [0, 24] (45)	4.0 [0, 24] (86)
Proportion of patients with chronic/persistent primary ITP who achieved platelet counts ≥50,000/μL in ≥6 of 8 visits between Weeks 17 and 24[d] (%)	FAS	6.7 (3/45)	22.1 (19/86)

Median [Min, Max] (N); proportion of patients (n/N)

a, The cumulative number of weeks during which a platelet count of ≥50,000/μL was maintained in the treatment period. For patients who developed intercurrent events (discontinuation of study drug treatment for 24 weeks during the treatment period, or intensification of concomitant ITP treatment drugs due to lack of efficacy or adverse events), platelet counts <50,000/μL were to be used as platelet count data after the intercurrent events. For patients who developed intercurrent events (rescue treatment), platelet counts <50,000/μL were to be used as platelet count data for 4 weeks after the rescue treatment. For all missing platelet count data other than those described above, the missing value was to be imputed with ≥50,000/μL, if the timepoints immediately before and after the missing data were within the treatment period and platelet counts at both timepoints were ≥50,000/μL; otherwise, the missing value was to be imputed with <50,000/μL.

b, Defined as platelet counts of ≥50,000/μL on ≥4 of the 6 visits between Weeks 19 and 24. The data were handled according to a rule equivalent to that described in Note a to Table 11.

c, For patients who developed intercurrent events (intensification of concomitant ITP treatment), missing bleeding event data after the intercurrent event were not to be imputed. For patients who developed intercurrent events (rescue treatment), missing bleeding event data for 4 weeks after the rescue treatment were not to be imputed. For missing bleeding event evaluation other than the cases of intercurrent events shown above, if the timepoints immediately before and after the missing evaluation for bleeding events were within the treatment period and no bleeding events occurred at either timepoint, the missing evaluation was imputed as no bleeding events; otherwise, the missing evaluation was imputed as bleeding events present.

d, The data were handled according to a rule equivalent to that described in Note a to Table 11.

The overall incidence of adverse events was 95.6% (43 of 45) of subjects in the placebo group and 93.0% (80 of 86) of subjects in the efgartigimod alfa group. Table 13 shows the incidence of adverse events occurring in ≥5% of subjects in either group.

Table 13. Incidence of adverse events occurring in ≥5% of subjects in either group (Safety analysis set, overall population)

MedDRA PT	Placebo (N = 45)	Efgartigimod alfa (N = 86)
Blood urine present	37.8 (17)	36.0 (31)
Contusion	13.3 (6)	19.8 (17)
Haematuria	15.6 (7)	16.3 (14)
Headache	13.3 (6)	16.3 (14)
Petechiae	26.7 (12)	15.1 (13)
Haematoma	24.4 (11)	9.3 (8)
Epistaxis	17.8 (8)	9.3 (8)
Mouth haemorrhage	17.8 (8)	8.1 (7)
Purpura	8.9 (4)	8.1 (7)
COVID-19	6.7 (3)	8.1 (7)
Anaemia	6.7 (3)	7.0 (6)
Asthenia	0 (0)	7.0 (6)
Ecchymosis	13.3 (6)	5.8 (5)
Heavy menstrual bleeding	6.7 (3)	5.8 (5)
Nausea	4.4 (2)	5.8 (5)
Hypertension	0 (0)	5.8 (5)
Gingival bleeding	13.3 (6)	4.7 (4)
Diarrhoea	8.9 (4)	3.5 (3)
Neutropenia	6.7 (3)	2.3 (2)
Oral blood blister	6.7 (3)	2.3 (2)
Pain in extremity	11.1 (5)	1.2 (1)

Incidence, % (n)

There were no reports of death.

Serious adverse events occurred in 15.6% (7 of 45) of subjects in the placebo group (haematuria, COVID-19, anaemia, road traffic accident, immune thrombocytopenia, acute kidney disease/appendicitis, mouth haemorrhage in 1 subject each) and 8.1% (7 of 86) of subjects in the efgartigimod alfa group (thrombocytopenia [2 subjects]; chronic myelomonocytic leukaemia, headache, abdominal pain/musculoskeletal chest pain/vaginal haemorrhage, cytomegalovirus infection, iron deficiency anaemia [1 subject each]). A causal relationship to the study drug was denied for all these events.

Adverse events led to study drug treatment discontinuation in 2.2% (1 of 45) of subjects in the placebo group (COVID-19) and 4.7% (4 of 86) of subjects in the efgartigimod alfa group (thrombocytopenia, chronic myelomonocytic leukaemia, bronchitis, urticaria [1 subject each]). A causal relationship to the study drug was denied for all these events.

Japanese population

Of the 8 randomized subjects (3 subjects in the placebo group and 5 subjects in the efgartigimod alfa group), 5 subjects (2 subjects in the placebo group and 3 subjects in the efgartigimod alfa group) completed Study 1801 and participated in Study 1803. Three subjects (1 subject in the placebo group and 2 subjects in the efgartigimod alfa group) discontinued from the study, with the reason for discontinuation being "withdrawal of consent" for all 3 subjects.

The proportion of patients whose concomitant ITP treatment regimen was intensified after the start of study drug treatment was 0% (0 of 3) of subjects in the placebo group and 20.0% (1 of 5) of subjects in the efgartigimod alfa group. The proportion of patients who received rescue therapy was 33.3% (1 of 3) of subjects in the placebo group and 0% (0 of 5) of subjects in the efgartigimod alfa group. Corticosteroids and IVIg were administered to the subject.

Table 14 shows the primary efficacy endpoint, the proportion of patients with chronic primary ITP who achieved a sustained platelet count response.

Table 14. Proportion of patients with chronic primary ITP who achieved a sustained platelet count response (FAS-Chronic, Japanese population)

	Placebo (N = 3)	Efgartigimod alfa (N = 5)
Proportion of patients who achieved a sustained platelet count response[a]	0 (0)	40.0 (2)

Proportion of patients, % (n)

a, Defined as platelet counts of ≥50,000/μL on ≥4 of the 6 visits between Weeks 19 and 24. The data were handled according to a rule equivalent to that described in Note a to Table 11.

Table 15 shows results for the key secondary endpoints.

Table 15. Results for key secondary endpoints (Japanese population)

Key secondary endpoints	Analysis population	Placebo (N = 3)	Efgartigimod alfa (N = 5)
Disease control duration[a] in patients with chronic primary ITP (number of weeks over the 24-week period)	FAS-Chronic	0.00 [0.0, 4.0] (3)	0.00 [0.0, 24.0] (5)
The proportion of patients with chronic/persistent primary ITP who achieved a sustained platelet count response[b] (%)	FAS	0 (0/3)	40.0 (2/5)
Number of WHO-classified Grade ≥1 bleeding events in patients with chronic/persistent primary ITP[c]	FAS	1.0 [0, 5] (3)	4.0 [0, 8] (5)
Proportion of patients with chronic/persistent primary ITP who achieved platelet counts ≥50 × 10^9/L in ≥6 of 8 visits between Weeks 17 and 24[d] (%)	FAS	0 (0/3)	40.0 (2/5)

Median [Min, Max] (N); proportion of patients (n/N)
a to d, The data were handled according to a rule equivalent to that described in Notes a through d to Table 12.

The overall incidence of adverse events was 66.7% (2 of 3) of subjects in the placebo group and 80.0% (4 of 5) of subjects in the efgartigimod alfa group. Table 16 shows the incidence of all adverse events.

Table 16. Incidence of all adverse events (Safety analysis set, Japanese population)

MedDRA PT	Placebo (N = 3)	Efgartigimod alfa (N = 5)
Diarrhoea	33.3 (1)	20.0 (1)
Purpura	33.3 (1)	20.0 (1)
Haemorrhoids	0 (0)	20.0 (1)
Malaise	0 (0)	20.0 (1)
Impetigo	0 (0)	20.0 (1)
Contusion	0 (0)	20.0 (1)
Skin abrasion	0 (0)	20.0 (1)
Paraesthesia	0 (0)	20.0 (1)
Peroneal nerve palsy	0 (0)	20.0 (1)
Dry skin	0 (0)	20.0 (1)
Immune thrombocytopenia	33.3 (1)	0 (0)
Haemorrhoidal haemorrhage	33.3 (1)	0 (0)
Headache	33.3 (1)	0 (0)

Incidence, % (n)

There were no reports of death. No adverse events led to discontinuation of study drug treatment.

Serious adverse events occurred in 33.3% (1 of 3) of subjects in the placebo group (immune thrombocytopenia), and a causal relationship to the study drug was denied.

7.2.2 Global phase III extension study (Study ARGX-113-1803, CTD 5.3.5.2-1 [ongoing since June 2020, data cut-off in September 2022])

An open-label, extension study was conducted at 59 study centers in and outside Japan to evaluate the long-term safety and efficacy of efgartigimod alfa in patients who had completed the treatment period of Study 1801.

This study consisted of up to 4 years of treatment followed by an 8-week follow-up period. Subjects who had completed the first 52 weeks of treatment were given an option to participate in subsequent 52-week treatment cycles for up to 3 cycles. The study was to be discontinued when efgartigimod alfa became available commercially or through a drug supply program.

Patients were to receive efgartigimod alfa 10 mg/kg as an intravenous infusion over ≥1 hour. The dosing frequency could be adjusted to once-weekly or every-other-week infusions based on criteria similar to those for Study 1801 (Table 9). The recommended maximum dose for patients weighing ≥120 kg was up to 1200 mg per infusion.

If platelet counts exceeded 400,000/μL, study drug treatment was to be interrupted, and the treatment was to be resumed at a frequency of every other week after confirming that the platelet count had dropped to <150,000/μL. If platelet counts were <30,000/μL at all visits during Week 8 to Week 11, the study was to be discontinued.

Key inclusion criteria were patients with primary ITP who had completed the 24-week treatment period in Study 1801.

Patients were to continue to receive concomitant ITP drugs administered at the start of Study 1803 (oral corticosteroids, oral immunosuppressants, danazol/dapsone, fostamatinib, oral TPO receptor agonists). While the dose adjustment of oral TPO receptor agonists and fostamatinib according to the approved dosage regimens remained permissible, addition or dose increase of ITP drugs became unacceptable. Dose reduction or discontinuation of concomitant ITP drugs was allowed at the discretion of the investigator, only when platelet counts exceeded 100,000/μL.

Patients with a platelet count of <30,000/μL who had met any of the following were allowed to receive rescue treatment (intravenous methylprednisolone [1 g/day maximum for 1-3 days], oral dexamethasone [40 mg/day maximum for 1-3 days], oral prednisone [1 mg/kg/day maximum for 1-2 days], IVIg [1 g/kg/day maximum for 1-2 days], IV anti-D Ig [50-75 μg/kg/day maximum for 1-2 days], or platelet transfusion).

- At immediate risk of bleeding, or presence of clinically significant bleeding or wet purpura
- Requiring emergency surgery

Overall population

A total of 101 subjects of Study 1801 participated in Study 1803 (38 subjects who had received placebo in Study 1801 [P-efgartigimod alfa group] and 63 subjects who had received efgartigimod alfa in Study 1801 [efgartigimod-efgartigimod group]), and all the subjects were included in the FAS. The FAS was the efficacy analysis set. All the 101 subjects who had been in Study 1801 and received at least 1 dose of efgartigimod alfa in Study 1803 were included in the safety analysis set (38 subjects and 63 subjects in the P-efgartigimod alfa group and efgartigimod-efgartigimod group, respectively; the same applies hereinafter). As of the data cut-off date, 4 subjects (1 subject and 3 subjects) completed the study, 46 subjects (14 subjects and 32 subjects) continued to receive study treatment. A total of 51 subjects (23 subjects and 28 subjects) discontinued the study for the following reasons: “inadequate effect” (23 subjects total; 11 subjects and 12 subjects), “withdrawal of consent” (20 subjects total; 7 subjects and 13 subjects), “investigator's decision” (4 subjects total; 3 subjects and 1 subject), “death” (3 subjects total; 2 subjects and 1 subject), and “other” (1 subject total; 0 subjects and

1 subject). The median number of doses of efgartigimod alfa [Min, Max] was 14.0 doses [3, 64] in the P-efgartigimod alfa group and 24.0 doses [3, 71] in the efgartigimod-efgartigimod group. The median treatment duration [Min, Max] was 116.0 days [71, 339] in the P-efgartigimod alfa group and 281.0 days [85, 359] in the efgartigimod-efgartigimod group. The proportion of patients who received every-other-week infusions was 23.7% (9 of 38) of subjects in the P-efgartigimod alfa group and 34.9% (22 of 63) of subjects in the efgartigimod-efgartigimod group. The median cumulative number of weeks of every-other-week infusions [Min, Max] was 8.0 weeks [4, 12] in the P-efgartigimod alfa group and 15.0 weeks [2, 24] in the efgartigimod-efgartigimod group.

The proportion of patients who received rescue treatment was 36.8% (14 of 38) of subjects in the P-efgartigimod alfa group and 25.4% (16 of 63) of subjects in the efgartigimod-efgartigimod group. The specific therapies in the P-efgartigimod alfa group and the efgartigimod-efgartigimod group, respectively, were as follows: corticosteroids: 23.7% (9 of 38) of subjects and 17.5% (11 of 63) of subjects; IVIg: 23.7% (9 of 38) of subjects and 7.9% (5 of 63) of subjects; platelet transfusion: 13.2% (5 of 38) of subjects and 1.6% (1 of 63) of subjects.

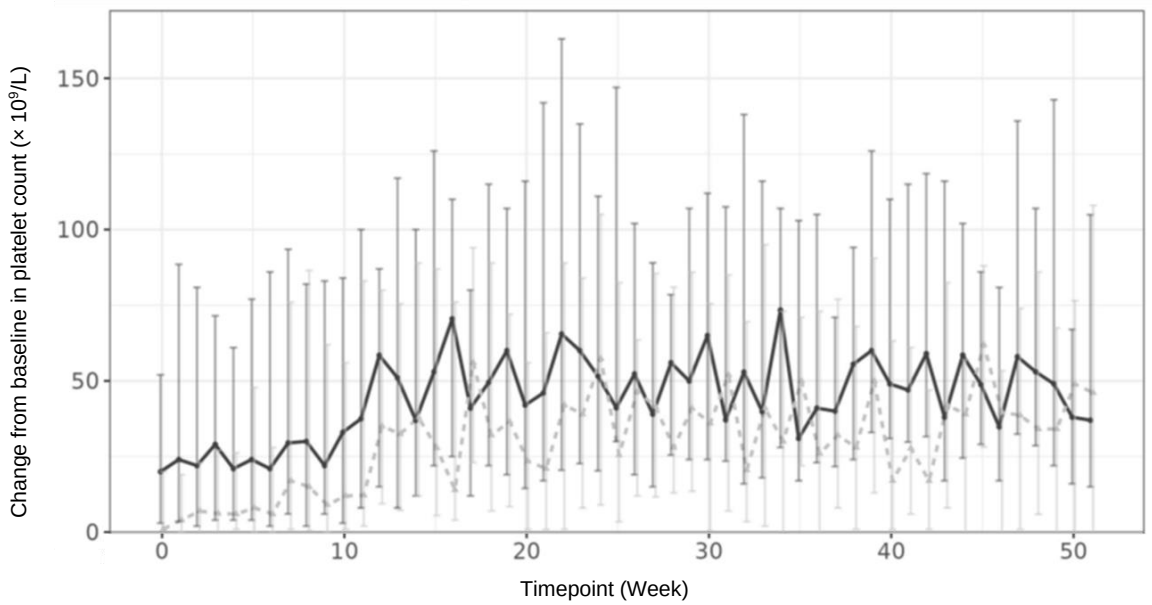
Table 17 shows the proportion of patients who achieved a sustained platelet count response in every 6 week-period (defined as platelet counts of ≥50,000/μL on ≥4 of the 6 visits). The efficacy analysis was performed on 77 subjects (30 subjects in the P-efgartigimod alfa group and 47 subjects in the efgartigimod-efgartigimod group) who had completed the first 52 weeks of treatment or discontinued the study before Week 51 as of the data cut-off date.

Table 17. The proportion of patients who achieved a sustained platelet count response in every 6-week period (FAS, overall population)

	P-efgartigimod alfa	Efgartigimod-efgartigimod
Weeks 1-6	23.7 (9/38)	33.3 (21/63)
Weeks 7-12	28.9 (11/38)	31.7 (20/63)
Weeks 13-18	23.7 (9/38)	33.3 (21/63)
Weeks 19-24	26.3 (10/38)	36.5 (23/63)
Weeks 25-30	21.1 (8/38)	41.3 (26/63)
Weeks 31-36	22.2 (8/36)	38.1 (24/63)
Weeks 37-42	20.0 (7/35)	39.3 (22/56)
Weeks 43-48	21.9 (7/32)	25.0 (12/48)

Proportion, % (n/N)
Handling of missing platelet count data: if both timepoints immediately before and after the timepoint for missing data were within the treatment period and the platelet counts were ≥50,000/μL at both timepoints, the missing value was imputed with ≥50,000/μL; otherwise, the missing value was imputed with <50,000/μL.

Figure 4 shows the change from baseline (i.e., at the start of study drug treatment in Study 1801) in platelet count over time.



Timepoint (Week)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Efgartigimod-efgartigimod (N)	63	60	61	60	59	57	55	52	49	50	50	50	46	39	41	39	38	37
P-efgartigimod alfa (N)	38	37	37	38	35	35	35	31	32	29	29	26	21	20	19	20	19	19

Timepoint (Week)	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
Efgartigimod-efgartigimod (N)	38	39	38	39	38	38	36	28	27	29	32	30	31	28	30	26	30	26
P-efgartigimod alfa (N)	18	17	18	17	18	13	18	16	16	16	17	16	16	17	16	15	15	15

Timepoint (Week)	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51
Efgartigimod-efgartigimod (N)	31	25	26	25	26	23	24	19	22	20	19	21	17	18	15	19
P-efgartigimod alfa (N)	13	15	14	16	11	12	13	12	13	12	12	9	11	8	8	7

Figure 4. Change from baseline in platelet count over time (median [first quartile, third quartile]) (FAS)

Black solid line, efgartigimod-efgartigimod group; gray dotted line, P-efgartigimod alfa group

The overall incidence of adverse events[21)] was 94.7% (36 of 38) of subjects in the P-efgartigimod alfa group and 90.5% (57 of 63) of subjects in the efgartigimod-efgartigimod group. Table 18 shows the incidence of adverse events occurring in ≥5% in either group.

[21)] Adverse events occurring after administration of the first dose of efgartigimod alfa in Study 1803 and by 60 days followingthe final dose of efgartigimod alfa

Table 18. The incidence of adverse events occurring in ≥5% in either group (Safety analysis set, overall population)

MedDRA PT	P-efgartigimod alfa (N = 38)	Efgartigimod-efgartigimod (N = 63)
Blood urine present	47.4 (18)	38.1 (24)
COVID-19	15.8 (6)	22.2 (14)
Petechiae	15.8 (6)	17.5 (11)
Contusion	7.9 (3)	11.1 (7)
Headache	7.9 (3)	11.1 (7)
Haematoma	13.2 (5)	7.9 (5)
Gingival bleeding	7.9 (3)	7.9 (5)
Arthralgia	0 (0)	7.9 (5)
Anaemia	15.8 (6)	6.3 (4)
Iron deficiency anaemia	10.5 (4)	6.3 (4)
Mouth haemorrhage	7.9 (3)	6.3 (4)
Haematuria	7.9 (3)	6.3 (4)
Upper respiratory tract infection	0 (0)	6.3 (4)
Epistaxis	18.4 (7)	4.8 (3)
Ecchymosis	13.2 (5)	4.8 (3)
Diarrhoea	7.9 (3)	4.8 (3)
Purpura	7.9 (3)	4.8 (3)
Influenza-like illness	5.3 (2)	3.2 (2)
Hypertension	5.3 (2)	3.2 (2)
Back pain	5.3 (2)	1.6 (1)
Conjunctival haemorrhage	5.3 (2)	0 (0)
Pyrexia	5.3 (2)	0 (0)
Myalgia	5.3 (2)	0 (0)
Osteoporosis	5.3 (2)	0 (0)

Incidence, % (n)

Deaths were reported in 5.3% (2 of 38) of subjects in the P-efgartigimod alfa group (cerebral haemorrhage and pulmonary fibrosis in 1 subject each) and 1.6% (1 of 63) of subjects in the efgartigimod-efgartigimod group (femur fracture), and a causal relationship to efgartigimod alfa was denied for all these cases.

Other serious adverse events occurred in 10.5% (4 of 38) of subjects in the P-efgartigimod alfa group (acute respiratory failure/systemic inflammatory response syndrome, lung neoplasm malignant, headache/nausea/vomiting, basal cell carcinoma in 1 subject each) and 11.1% (7 of 63) of subjects in the efgartigimod-efgartigimod group (rectal haemorrhage/haemoglobin decreased, gastritis, diarrhoea/vomiting, chronic kidney disease, myocardial infarction, COVID-19/COVID-19 pneumonia, platelet count decreased in 1 subject each). A causal relationship to efgartigimod alfa was denied for all these cases.

An adverse event (chronic kidney disease) led to treatment discontinuation of efgartigimod alfa in 1.6% (1 of 63) of subjects in the efgartigimod-efgartigimod group, and a causal relationship to efgartigimod alfa was ruled out for the event.

Japanese population

Five Japanese patients in Study 1801 entered Study 1803 (2 subjects in the P-efgartigimod alfa group and 3 subjects in the efgartigimod-efgartigimod group) and were included in the FAS. The FAS was the safety analysis set. As of the data cut-off date, 3 subjects (1 subject and 2 subjects in the P-efgartigimod alfa group and efgartigimod-efgartigimod group, respectively; the same applies hereinafter) continued to receive study

treatment. Two subjects (1 subject and 1 subject) discontinued from the study for "inadequate effect" (1 subject total; 0 subjects and 1 subject) and "withdrawal of consent" (1 subject total; 1 subject and 0 subjects). The median number of doses of efgartigimod alfa [Min, Max] was 24.5 doses [8, 41] in the P-efgartigimod alfa group and 37.0 doses [11, 47] in the efgartigimod-efgartigimod group. The median treatment duration [Min, Max] was 183.0 days [57, 309] in the P-efgartigimod alfa group and 287.0 days [134, 530] in the efgartigimod-efgartigimod group. No subjects in the P-efgartigimod alfa group and 2 of 3 subjects in the efgartigimod-efgartigimod group received every-other-week infusions. The median cumulative number of weeks of every-other-week infusions [Min, Max] was 10.0 weeks [4, 16].

No Japanese subjects received rescue treatment.

Table 19 shows the proportion of patients who achieved a sustained platelet count response in every 6 week-period (defined as platelet counts of ≥50,000/μL on ≥4 of the 6 visits). The efficacy analysis was performed on 3 subjects (1 subject in the P-efgartigimod alfa group and 2 subjects in the efgartigimod-efgartigimod group) who had completed the first 52 weeks of treatment or discontinued the study before Week 51 as of the data cut-off date.

Table 19. The proportion of patients who achieved a sustained platelet count response in every 6-week period (FAS, Japanese population)

	P-efgartigimod alfa	Efgartigimod-efgartigimod
Weeks 1-6	0 (0/2)	66.7 (2/3)
Weeks 7-12	0 (0/2)	66.7 (2/3)
Weeks 13-18	0 (0/2)	66.7 (2/3)
Weeks 19-24	0 (0/2)	66.7 (2/3)
Weeks 25-30	0 (0/2)	66.7 (2/3)
Weeks 31-36	0 (0/2)	66.7 (2/3)
Weeks 37-42	0 (0/2)	50.0 (1/2)
Weeks 43-48	0 (0/1)	50.0 (1/2)

Proportion, % (n/N)
Handling of missing platelet count data: if both timepoints immediately before and after the timepoint for missing data were within the treatment period and the platelet counts were ≥50,000/μL at both timepoints, the missing value was imputed with ≥50,000/μL; otherwise, the missing value was imputed with <50,000/μL.

The overall incidence of adverse events[21)] was 50.0% (1 of 2) of subjects in the P-efgartigimod alfa group (purpura/abdominal pain upper/constipation/ligament sprain/muscle spasms/epistaxis/acne) and 100.0% (3 of 3) of subjects in the efgartigimod-efgartigimod group (purpura/seizure/urinary occult blood, diarrhoea/rash maculo-papular, urticaria).

There were no reports of death or other serious adverse events. No adverse events led to treatment discontinuation of efgartigimod alfa.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical positioning

The applicant's explanation of clinical positioning of efgartigimod alfa:

Primary ITP is an acquired autoimmune disease characterized by suppression of platelet aggregation and blood coagulation caused by binding of IgG autoantibodies to platelets and megakaryocytes, which accelerates removal of platelets by splenic macrophages, suppresses megakaryocyte platelet production, leading to impaired platelet function. The goal for treatment of primary ITP is to maintain a safe platelet count that can prevent serious bleeding, rather than correcting platelet count to normal levels (*Blood.* 2009;113:2386-93, *Blood Adv.* 2019;3:3829-66, *Blood Adv.* 2019;3:3780-817). In Japan, based on the "Reference guide for management of adult idiopathic thrombocytopenic purpura (ITP): 2019 revised version" [in Japanese] (hereinafter referred to as the "2019 ITP reference guide"), corticosteroids are administered as the first-line therapy to patients whose platelet count does not increase adequately after eradication of *H.pylori*, and patients at a high risk for bleeding among those who tested negative for *H.pylori*, to suppress excessive immune response. The second-line therapies recommended for patients who had an inadequate response to or were intolerant to corticosteroids are TPO receptor agonists, which promote platelet production in the bone marrow; rituximab, which induces B cell depletion to impair antibody production, thereby preventing platelet destruction; and splenectomy. No randomized studies have been conducted to compare the second-line therapies. A treatment option is selected taking into account factors including the characteristics of each therapy and the patient's condition such as comorbidities, age, and lifestyle. Furthermore, for patients for whom the second-line therapies are ineffective, or who are refractory to the second-line therapies due to comorbidities, after thorough evaluation of the need for treatment, the use of the following third-line therapies is considered: mycophenolate mofetil, cyclosporin, azathioprine, vinca alkaloid, cyclophosphamide, and other immunosuppressants, danazol, and diaphenylsulfone. Fostamatinib, which inhibits signal transduction of the Fc-activating receptor and B-cell receptor, thereby suppressing platelet destruction, is another treatment option.

Efgartigimod alfa binds to FcRn, inhibiting the binding of IgG and FcRn, promoting IgG degradation and reducing IgG autoantibody levels in blood. The mechanism of action of efgartigimod alfa is different from that of approved ITP drugs. The results of Study 1801 suggest that efgartigimod alfa is expected to show efficacy in patients with primary ITP who have received prior ITP treatment regardless of the number or types of prior ITP therapies, and regardless of the use of concomitant ITP drugs [see Section "7.R.2.2 Baseline demographics and disease characteristics that have impacts on efficacy"]. Therefore, efgartigimod alfa can be a treatment option for patients who have responded inadequately to existing therapies, either as the second-line or further-line therapies, alone or in combination with existing treatment.

PMDA's view:

In the global phase III study in patients with chronic/persistent primary ITP who had previously received at least 1 type of ITP drug (e.g., corticosteroids, TPO receptor agonists, rituximab), the efficacy and safety of efgartigimod alfa have been demonstrated [see Sections "7.R.2 Efficacy" and "7.R.3 Safety"]. Therefore, it is considered that efgartigimod alfa can be clinically positioned as one of the drugs that can be administered alone or in combination with existing therapies to patients who are assessed to be at high risk of bleeding after

treatment with existing ITP therapy based on the platelet counts and clinical symptoms and therefore require further treatment. However, there are no data from clinical studies that directly compared efgartigimod alfa with other ITP drugs used as second-line or further-line therapies. Therefore, in clinical practice, efgartigimod alfa should be selected by physicians with thorough knowledge and experience in ITP treatment only after fully considering the characteristics and other aspects of efgartigimod alfa and other treatment options.

7.R.2 Efficacy

7.R.2.1 Efficacy in global phase III studies

(1) Appropriateness of the primary endpoints

The applicant's explanation of the appropriateness of the primary endpoints in the global phase III studies:

The goal of treatment for ITP is to maintain a platelet count sufficient to prevent serious bleeding, rather than returning the platelet count to normal levels (*Blood*. 2009;113:2386-93, *Blood Adv*. 2019;3:3829-66, *Blood Adv*. 2019;3:3780-817). In most cases, target platelet counts that can prevent serious bleeding will be ≥30,000/μL. Under circumstances that require prevention of mucocutaneous bleeding, which is a typical symptom of ITP, or patients who are at major risk of bleeding, a platelet count of 50,000/μL may be one of the thresholds that provides adequate hemostasis (*Blood Adv*. 2019;3:3780-817, 2019 ITP reference guide, *N Engl J Med*. 2002;346:995-1008). In addition, given that the efficacy of existing ITP drugs had been evaluated in confirmatory studies where the primary endpoint was a target platelet count of ≥50,000/μL, a platelet count of 50,000/μL was selected as the threshold for achieving the primary endpoint in Study 1801. The primary endpoint was defined as "the proportion of patients who achieved a sustained platelet count response (defined as platelet counts of ≥50,000/μL on ≥4 of the 6 visits between Weeks 19 and 24)" to reduce the effect of intraindividual platelet count fluctuations between timepoints to appropriately evaluate the duration of efficacy.

PMDA's view:

Japan's 2019 ITP reference guide and the US practice guidelines for ITP (*Blood Adv*. 2019;3:3780-817) recommend as a treatment goal maintaining a platelet count that can prevent serious bleeding (typically ≥30,000/μL) in patients with chronic or persistent primary ITP, rather than normalizing the platelet count. The primary endpoint for Study 1801 also focuses on maintenance of the platelet count at a certain level, which is similar to the treatment goal recommended in the guidelines; and the threshold for platelet count response (platelet counts 50,000/μL) is considered to be a more conservative value from the perspective of achieving a platelet count that can prevent serious bleeding. Therefore, the primary endpoint is a reasonable measure to allow evaluation of treatment effect in patients with chronic or persistent primary ITP.

(2) Efficacy in global phase III study (Study 1801)

The between-group difference in the proportion of patients with chronic primary ITP who achieved a sustained platelet count response, the primary endpoint of Study 1801, was smaller than the estimated between-group difference in the study plan.[16)] PMDA asked the applicant to explain whether it is possible to claim that the results of Study 1801 demonstrated the clinically meaningful efficacy of efgartigimod alfa.

The applicant's explanation:

At the time of planning Study 1801, the proportion of patients with chronic primary ITP who achieved a sustained platelet count response, the primary endpoint, was estimated to be 5% for the placebo group, because it was not expected that a sustained platelet count would be achieved in the placebo group, and a clinically meaningful between-group difference of 25% (i.e., achievement in 30% of patients in the efgartigimod alfa group) was estimated based on the clinical study results of approved ITP drugs (romiplostim, eltrombopag olamine, and fostamatinib) as well as between-group differences (35%-40%) in the expected response rate at the time of planning. The results of Study 1801 showed that the between-group difference in the proportion of patients who achieved a sustained platelet count response was 16.8% (21.8% in the efgartigimod alfa group and 5.0% in the placebo group), which was smaller than the estimated between-group difference in the study plan. The clinical studies of approved ITP drugs differ from Study 1801 in terms of the definition of the primary endpoint, handling of data in the analysis when patients undergo rescue treatment, or intensification of concomitant ITP treatment, frequency of platelet count measurement, and other factors; therefore, these differences in study design may have affected the results. In addition, it is considered that the proportion of patients who achieved a sustained platelet count response was higher in patients with persistent primary ITP, patients with no prior splenectomy, and patients who had received fewer prior ITP drugs. The difference in the proportions of such patients between the clinical studies used as the base for estimation and Study 1801 may have led to a smaller between-group difference in the proportion of patients who achieved a sustained platelet count response than the estimated difference in the study plan. One of the substantial differences between Study 1801 and the clinical studies of approved ITP drugs used as the basis for estimation was that in Study 1801, patients who had prior TPO receptor agonist treatment were eligible. However, the between-group difference in the proportion of patients who achieved a sustained platelet count response in Study 1801 was similar to the between-group difference in the response rate (15.8%) in the clinical study of fostamatinib conducted in patients with at least 1 prior ITP therapy including TPO receptor agonists. In addition to the above results, given that eligible patients in Study 1801 had at least 1 prior ITP therapy including TPO receptor agonists and were still at increased risk for bleeding regardless of existing treatment; and that the target platelet count as the primary endpoint is considered a conservative threshold for hemostasis, the between-group difference observed in Study 1801 is clinically meaningful and demonstrated the platelet-increasing effect of efgartigimod alfa.

Reduction of bleeding symptoms is a treatment goal of efgartigimod alfa. The number of World Health Organization (WHO)-classified Grade ≥1 bleeding events (median) in patients with chronic/persistent primary ITP was evaluated as a secondary endpoint. The results were 5.0 in the placebo group and 4.0 in the efgartigimod alfa group, indicating that the incidence did not differ greatly between the groups (Table 12). The proportion of patients with WHO-classified Grade ≥1 bleeding events was 91.1% (41 of 46) of subjects in the placebo group and 77.9% (56 of 86) of subjects in the efgartigimod alfa group, indicating a lower incidence in the efgartigimod alfa group. Among these patients, the proportion of patients with WHO-classified Grade ≥2 bleeding events was 20.0% (9 of 45) of subjects in the placebo group and 20.9% (18 of 86) of subjects in the efgartigimod alfa group, indicating no significant difference between the groups. WHO-classified Grade 3 bleeding events occurred in 2 subjects in the placebo group and 1 subject in the efgartigimod alfa group, with

each subject experiencing only 1 bleeding event. The median number [Min, Max] of WHO-classified Grade ≥1 bleeding events was as follows: among patients who had not achieved a sustained platelet count response: 6.0 [0, 24] in the placebo group (N = 42) and 5.0 [0, 24] in the efgartigimod alfa group (N = 64); among patients who had achieved a sustained platelet count response: 2.0 [0, 2] in the placebo group (N = 3) and 2.0 [0, 14] in the efgartigimod alfa group (N = 22), indicating that those who had achieved a sustained platelet count response experienced fewer bleeding events. The results suggested a relationship between the increase in platelet count and reduction in bleeding symptoms. The above findings indicate that efgartigimod alfa has an effect in maintaining platelet counts that can prevent bleeding events.

The applicant explained that patients with chronic primary ITP were selected as the main analysis population for assessing efficacy in Study 1801 because spontaneous remission is rare in patients with chronic primary ITP (*Br J Haematol*. 2023;201:1005-6). PMDA asked the applicant to explain the efficacy of efgartigimod alfa in patients with persistent primary ITP.

The applicant's explanation:
Chronic and persistent primary ITP is classified according to the time since diagnosis and there is no significant pathophysiological difference; in addition, given the mechanism of action of efgartigimod alfa, its efficacy is not likely to be affected by disease duration. Based on these and other factors, it was considered that if clinically meaningful efficacy is demonstrated for both types of patients with primary ITP (chronic/persistent), and efficacy in the chronic primary ITP group tends to be similar to the efficacy in the persistent primary ITP group, it would be possible to use data from Study 1801 to explain the efficacy of efgartigimod alfa in patients with persistent primary ITP.

Table 20 shows the results for key efficacy endpoints in the chronic/persistent primary ITP group, chronic primary ITP group, and persistent primary ITP group in Study 1801. The results for the chronic primary ITP group did not differ greatly from those for the chronic/persistent primary ITP group. In both the placebo and efgartigimod alfa groups, baseline platelet counts tended to be higher, the proportion of prior splenectomy tended to be lower, and prior ITP treatments tended to be fewer in the persistent primary ITP group compared with those in the chronic primary ITP group (Table 21). These differences were considered to be attributable to the shorter time since diagnosis in patients with persistent primary ITP.

Based on the above, efgartigimod alfa is expected to demonstrate efficacy in patients with persistent primary ITP in addition to patients with chronic primary ITP.

Table 20. Results for efficacy endpoints by chronic vs persistent primary ITP

	Chronic/persistent primary ITP (FAS)		Chronic primary ITP (FAS-Chronic)		Persistent primary ITP	
	Placebo (N = 45)	Efgartigimod alfa (N = 86)	Placebo (N = 40)	Efgartigimod alfa (N = 78)	Placebo (N = 5)	Efgartigimod alfa (N = 8)
Proportion of patients who achieved a sustained platelet count response[a] (%)	6.7 (3)	25.6 (22)	5.0 (2)	21.8 (17)	20.0 (1)	62.5 (5)
Disease control duration[b] (number of weeks over the 24-week period)	0.0 [0, 22]	3.0 [0, 24]	0.0 [0, 14]	2.0 [0, 24]	1.0 [0, 22]	18.5 [1, 23]
Number of WHO-classified Grade ≥1 bleeding events	5.0 [0, 24]	4.0 [0, 24]	5.5 [0, 24]	4.5 [0, 24]	2.0 [0, 22]	1.0 [0, 10]
Proportion of patients who achieved platelet counts ≥50,000/μL in ≥6 of 8 visits between Weeks 17 and 24 (%)	6.7 (3)	22.1 (19)	5.0 (2)	18.0 (14)	20.0 (1)	62.5 (5)
Proportion of patients who achieved overall platelet count response[c] (Week 24)	15.6 (7)	48.8 (42)	15.0 (6)	44.9 (35)	20.0 (1)	87.5 (7)
Proportion of patients who received rescue treatment	48.9 (22)	33.7 (29)	47.5 (19)	37.2 (29)	60.0 (3)	0 (0)

Median [Min, Max] (N); proportion of patients (n)
a, Achieving a platelet count of ≥50,000/μL on ≥4 of the 6 visits between Weeks 19 and 24
b, The cumulative number of weeks during which a platelet count of ≥50,000/μL was maintained in the treatment period
c, Achieving a platelet count of ≥50,000/μL on ≥4 occasions during the treatment period

Table 21. Baseline demographics and disease characteristics of patients: chronic vs persistent primary ITP

		Chronic primary ITP (FAS-Chronic)		Persistent primary ITP	
		Placebo (N = 40)	Efgartigimod alfa (N = 78)	Placebo (N = 5)	Efgartigimod alfa (N = 8)
Age (years)		53.5 [18, 82]	47.0 [19, 85]	62.0 [28, 81]	43.0 [19, 68]
Male (%)		45.0 (18)	42.3 (33)	60.0 (3)	75.0 (6)
Body weight (kg)		71.15 [45.8, 119.3]	77.00 [36.7, 135.9]	69.00 [54.2, 91.1]	93.35 [43.4, 113.5]
Time since diagnosis (years)		6.42 [1.4, 53.4]	4.74 [1.0, 54.1]	0.52 [0.5, 0.6]	0.40 [0.3, 0.9]
Baseline platelet count (/μL)		13,620 ± 9,036 (40)	16,730 ± 10,349 (78)	19,200 ± 9,935 (5)	23,130 ± 6,357 (8)
WHO bleeding Grade (%)	Grade 0	35.0 (14)	51.3 (40)	40.0 (2)	50.0 (4)
	Grade 1	57.5 (23)	43.6 (34)	40.0 (2)	50.0 (4)
	Grade ≥2	7.5 (3)	5.1 (4)	20.0 (1)	0 (0)
Number of prior ITP treatment (treatment types)		4.0 [1, 7]	3.0 [1, 9]	1.0 [1, 2]	1.0 [1, 4]
Use of prior ITP treatment by type (%)	Corticosteroids	90.0 (36)	94.9 (74)	80.0 (4)	100.0 (8)
	TPO receptor agonist	70.0 (28)	60.3 (47)	20.0 (1)	12.5 (1)
	IVIg or IV anti-D Ig	67.5 (27)	52.6 (41)	40.0 (2)	12.5 (1)
	Splenectomy	42.5 (17)	39.7 (31)	0 (0)	12.5 (1)
	Anti-CD20 antibodies	35.0 (14)	39.7 (31)	0 (0)	0 (0)
	Other immunosuppressants	45.0 (18)	26.9 (21)	0 (0)	0 (0)
	Danazol	15.0 (6)	12.8 (10)	0 (0)	0 (0)
	Fostamatinib	2.5 (1)	3.8 (3)	0 (0)	0 (0)
	Dapsone	5.0 (2)	1.3 (1)	0 (0)	0 (0)
	Other	5.0 (2)	2.6 (2)	0 (0)	0 (0)
Concomitant ITP drug used (%)		50.0 (20)	51.3 (40)	40.0 (2)	37.5 (3)
Use of concomitant ITP treatment drug by type (%)	Corticosteroids	25.0 (10)	26.9 (21)	40.0 (2)	12.5 (1)
	TPO receptor agonist	22.5 (9)	24.4 (19)	0 (0)	12.5 (1)
	Immunosuppressants	15.0 (6)	0 (0)	0 (0)	0 (0)
	Danazol	2.5 (1)	2.6 (2)	0 (0)	0 (0)

Proportion, % (n); median [Min, Max]; mean ± standard deviation (N)

PMDA's view:
In Study 1801, given that the proportion of patients with chronic primary ITP who achieved a sustained platelet count response, the primary endpoint, was significantly higher in the efgartigimod alfa group than in the placebo group, and that the effect of maintaining platelet counts is evaluated using a more conservative threshold for hemostasis, a certain level of increased platelet count can be maintained by efgartigimod alfa in patients who require further treatment after being treated with at least 1 type of ITP treatment drug. Although there was no clear between-group difference in the number of WHO-classified Grade bleeding events, a secondary endpoint, the data suggest that the number of WHO-classified bleeding events tends to be fewer in patients who achieved a sustained platelet count response than in patients who did not. Based on this and other data, efgartigimod alfa has been shown to be effective in maintaining platelet counts that can prevent bleeding.

As for efficacy by staging classification of primary ITP, patients with persistent primary ITP are more likely to achieve spontaneous remission compared with patients with chronic primary ITP; in Study 1801, which was conducted on a limited scale, if the main analysis population contains a small number of patients with persistent primary ITP, it would be difficult to interpret the results of a comparison between groups. Therefore, it is reasonable that the applicant used a study design in which patients with chronic primary ITP were used as the analysis population for the primary endpoint, and efficacy in patients with persistent primary ITP will be evaluated by comparing the results of patients with chronic primary ITP. The results of Study 1801 showed that in both the placebo and efgartigimod alfa groups, the proportion of patients who achieved a sustained platelet count response was higher in the persistent primary ITP group than in the chronic primary ITP group, suggesting that the persistent primary ITP group may have contained a number of patients who achieved spontaneous remission. Although the limited number of patients studied precludes a strict interpretation, the results for key efficacy endpoints in the efgartigimod alfa group were more favorable compared with placebo, suggesting the efficacy of efgartigimod alfa. In addition, given that there were no differences in baseline demographics and disease characteristics between patients with persistent primary ITP and those with chronic primary ITP that could have a clear impact on the comparison of the placebo and efgartigimod alfa groups in Study 1801 [see Section "7.R.2.2 Baseline demographics and disease characteristics that have impacts on efficacy"], it is possible to evaluate efficacy in patients with chronic primary ITP and those with persistent primary ITP based on the results for overall patients in Study 1801.

Based on the above, efgartigimod alfa can be expected to show clinically meaningful efficacy in patients with chronic or persistent primary ITP who are at an increased risk of bleeding despite previous treatment with existing ITP drugs. The details of the above decision by PMDA will be finalized taking into comments from the Expert Discussion.

7.R.2.2 Baseline demographics and disease characteristics that have impacts on efficacy

The applicant's explanation about the baseline demographics and disease characteristics that may affect the efficacy of efgartigimod alfa:
Table 22 shows the body weight category, baseline platelet count, the number of prior ITP treatment types, the types of prior ITP treatment, presence of concomitant ITP treatment drugs, and the proportion of patients who

achieved a sustained platelet count response by concomitant ITP drug type in Study 1801. Because the number of patients in each subgroup is small, interpretation of the results is difficult; however, the proportion of patients who achieved a sustained platelet count response was higher in the efgartigimod alfa group than in the placebo group in each subgroup, suggesting that efgartigimod alfa can be expected to show efficacy. In Study 1801, information on *H.pylori* infection and its eradication therapy was not gathered; therefore, the effect of *H.pylori* eradication therapy was not evaluated.

Table 22. The proportion of patients who achieved a sustained platelet count response by baseline demographics and disease characteristics (Study 1801, FAS)

Baseline demographics and disease characteristics			Placebo (N = 45)	Efgartigimod alfa (N = 86)
Body weight[a]	<50 kg		0 (0/2)	14.3 (1/7)
	≥50 kg and <75 kg		12.5 (3/24)	21.4 (6/28)
	≥75 kg and <120 kg		0 (0/19)	30.6 (15/49)
Baseline platelet count	<15,000/μL		4.0 (1/25)	21.6 (8/37)
	≥15,000/μL		10.0 (2/20)	28.6 (14/49)
Number of prior ITP treatment (treatment types)	<3		12.5 (2/16)	29.6 (8/27)
	≥3		3.4 (1/29)	23.7 (14/59)
Types of prior ITP treatment used	Corticosteroids	Yes	7.5 (3/40)	26.8 (22/82)
		No	0 (0/5)	0 (0/4)
	TPO receptor agonist	Yes	10.3 (3/29)	25.0 (12/48)
		No	0 (0/16)	26.3 (10/38)
	Splenectomy	Yes	0 (0/17)	18.8 (6/32)
		No	10.7 (3/28)	29.6 (16/54)
	Anti-CD20 antibodies	Yes	7.1 (1/14)	25.8 (8/31)
		No	6.5 (2/31)	25.5 (14/55)
	Immunosuppressants	Yes	0 (0/18)	14.3 (3/21)
		No	11.1 (3/27)	29.2 (19/65)
	Danazol	Yes	0 (0/6)	10.0 (1/10)
		No	7.7 (3/39)	27.6 (21/76)
Use of concomitant ITP drug	Yes		4.2 (1/24)	19.6 (9/46)
	No		9.5 (2/21)	32.5 (13/40)
Types of concomitant ITP drug used	Corticosteroids	Yes	0 (0/13)	17.4 (4/23)
		No	9.4 (3/32)	28.6 (18/63)
	TPO receptor agonist	Yes	8.3 (1/12)	25.0 (6/24)
		No	6.1 (2/33)	25.8 (16/62)
	Immunosuppressants	Yes	14.3 (1/7)	22.2 (2/9)
		No	5.3 (2/38)	26.0 (20/77)

Proportion, % (n/N)
a, There were 2 subjects weighing ≥120 kg in the efgartigimod alfa group, and both were excluded from the analysis.

PMDA's view:

Although the limited number of patients in each subgroup analysis precludes a strict interpretation, given that the proportion of patients who achieved a sustained platelet count response was higher in the efgartigimod alfa group than in the placebo group regardless of baseline demographics and disease characteristics of patients such as baseline platelet count, types or number of prior ITP treatments, and use of concomitant ITP drugs and their types, currently available data have identified no baseline demographics and disease characteristics that raise concerns for the efficacy of efgartigimod alfa in patients with chronic/persistent primary ITP.

7.R.2.3 Efficacy in Japanese patients

The applicant's explanation of efficacy in Japanese patients:

No differences in PK and PD between Japanese and non-Japanese populations that may cause clinical problems have been identified in terms of intrinsic ethnic factors [see Section "6.R.2 Differences in PK/PD between Japanese and non-Japanese populations"]. There are no significant differences between Japanese and non-Japanese populations in terms of extrinsic ethnic factors including diagnostic criteria for primary ITP, morbidity, and available drugs, except that in Japan eradication therapy is recommended for patients who tested positive for *H.pylori*, and disease names as well as staging classification based on the time since onset or diagnosis differ between Japan and other countries (2019 ITP reference guide, *Blood Adv.* 2019;3:3829-66, *Oncol Res Treat.* 2018;41 Suppl 5:1-30).

Study 1801 enrolled 8 Japanese patients (3 subjects in the placebo group and 5 subjects in the efgartigimod alfa group), all of whom had chronic primary ITP. Table 23 shows the results for key efficacy endpoints in Japanese and non-Japanese populations of patients with chronic primary ITP, and Table 24 shows the baseline demographics and disease characteristics of patients in the populations. In both Japanese and non-Japanese populations, the proportion of patients who achieved a sustained platelet count response was higher in the efgartigimod alfa group than in the placebo group (Table 23). The results for other efficacy endpoints are also shown in Table 23. The results in the Japanese population tended to be similar to those in the non-Japanese population regarding disease control duration, the proportion of patients who achieved a sustained platelet count response, and the proportion of patients who achieved platelet counts ≥50,000/μL in at least 6 of 8 visits between Weeks 17 and 24. The results demonstrated that a certain level of increase in platelet count can be maintained. In the Japanese population, the number of WHO-classified Grade ≥1 bleeding events was 4.0 in the efgartigimod alfa group, which was more than in the placebo group, 1.0, although strict interpretation of results is difficult due to the small number of patients studied. WHO-classified Grade ≥1 bleeding events occurred in 3 subjects in the efgartigimod alfa group (2 subjects were Grade 1 and 1 subject was Grade 2) and 2 subjects in the placebo group (1 subject each was Grade 1 and Grade 2). One subject each in the efgartigimod alfa and placebo groups completed Study 1801 and entered Study 1803, while 2 subjects in the efgartigimod alfa group and 1 subject in the placebo group discontinued the study due to "withdrawal of consent" between Day 45 and Day 56. One of the 2 subjects in the placebo group who experienced bleeding events had a baseline platelet count of ≥15,000/μL and had received rescue treatment, while all the 3 subjects in the efgartigimod alfa group had a baseline platelet count of <15,000/μL and did not receive rescue treatment.

In the Japanese population, patients weighed less and the proportion of patients who had undergone splenectomy was lower than those in the non-Japanese population. Other baseline demographics and disease characteristics that may have affected efficacy including time since diagnosis and baseline platelet counts in the Japanese population did not differ markedly from those in the non-Japanese population (Table 24). Based on the subgroup analysis results by baseline demographics and disease characteristics (Table 22), efgartigimod alfa can be expected to show efficacy regardless of the body weight category or prior splenectomy.

Table 23. Results for key efficacy endpoints in Japanese and non-Japanese populations (FAS-Chronic)

	Japanese population		Non-Japanese population	
	Placebo (N = 3)	Efgartigimod alfa (N = 5)	Placebo (N = 37)	Efgartigimod alfa (N = 73)
Proportion of patients who achieved a sustained platelet count response[a] (%)	0 (0)	40.0 (2)	5.4 (2)	20.5 (15)
Disease control duration[b] (number of weeks over the 24-week period)	0.0 [0, 4]	0.0 [0, 24]	0.0 [0, 14]	2.0 [0, 24]
Number of WHO-classified Grade ≥1 bleeding events	1.0 [0, 5]	4.0 [0, 8]	6.0 [0, 24]	5.0 [0, 24]
Proportion of patients who achieved platelet counts ≥50,000/μL in ≥6 of 8 visits between Weeks 17 and 24 (%)	0 (0)	40.0 (2)	5.4 (2)	16.4 (12)
Proportion of patients who achieved overall platelet count response[c] (Week 24)	33.3 (1)	40.0 (2)	13.5 (5)	45.2 (33)
Proportion of patients who received rescue treatment	33.3 (1)	0 (0)	48.6 (18)	39.7 (29)

Median [Min, Max]; proportion of patients (n)
a, Achieving a platelet count of ≥50,000/μL on ≥4 of the 6 visits between Weeks 19 and 24
b, The cumulative number of weeks during which a platelet count of ≥50,000/μL was maintained in the treatment period
c, Achieving a platelet count of ≥50,000/μL on at least 4 occasions during the treatment period

Table 24. Baseline demographics and disease characteristics of patients: Japanese population and non-Japanese population (FAS-Chronic)

		Japanese population		Non-Japanese population	
		Placebo (N = 3)	Efgartigimod alfa (N = 5)	Placebo (N = 37)	Efgartigimod alfa (N = 73)
Age (years)		75.0 [69, 78]	45.0 [22, 54]	50.0 [18, 82]	47.0 [19, 85]
Male (%)		33.3 (1)	40.0 (2)	45.9 (17)	42.5 (31)
Body weight (kg)		52.40 [45.8, 52.4]	47.30 [36.7, 82.9]	72.00 [48.0, 119.3]	77.10 [45.2, 135.9]
Time since diagnosis (years)		1.71 [1.6, 53.4]	10.21 [2.2, 22.5]	6.61 [1.4, 46.6]	4.65 [1.0, 54.1]
Baseline platelet count (/μL)		18,330 ± 10,017 (3)	10,200 ± 5,891 (5)	13,240 ± 8,993 (37)	17,180 ± 10,462 (73)
WHO bleeding Grade (%)	Grade 0	66.7 (2)	40.0 (2)	32.4 (12)	52.1 (38)
	Grade 1	0 (0)	60.0 (3)	62.2 (23)	42.5 (31)
	Grade ≥2	33.3 (1)	0 (0)	5.4 (2)	5.5 (4)
Number of prior ITP treatment (treatment types)		3.0 [2, 5]	3.0 [1, 5]	4.0 [1, 7]	3.0 [1, 9]
Use of prior ITP treatment by type (%)	Corticosteroids	100.0 (3)	100.0 (5)	89.2 (33)	94.5 (69)
	TPO receptor agonist	100.0 (3)	80.0 (4)	67.6 (25)	58.9 (43)
	IVIg or IV anti-D Ig	66.7 (2)	20.0 (1)	67.6 (25)	54.8 (40)
	Splenectomy	33.3 (1)	0 (0)	43.2 (16)	42.5 (31)
	Anti-CD20 antibodies	0 (0)	40.0 (2)	37.8 (14)	39.7 (29)
	Other immunosuppressants	0 (0)	20.0 (1)	48.6 (18)	27.4 (20)
	Danazol	33.3 (1)	20.0 (1)	13.5 (5)	12.3 (9)
	Fostamatinib	0 (0)	0 (0)	2.7 (1)	4.1 (3)
	Dapsone	0 (0)	0 (0)	5.4 (2)	1.4 (1)
	Other	0 (0)	0 (0)	5.4 (2)	2.7 (2)
Concomitant ITP drug used (%)		33.3 (1)	60.0 (3)	51.4 (19)	50.7 (37)
Use of concomitant ITP treatment drug by type (%)	Corticosteroids	33.3 (1)	60.0 (3)	27.0 (10)	26.0 (19)
	TPO receptor agonist	0 (0)	60.0 (3)	29.7 (11)	27.4 (20)
	Immunosuppressants	0 (0)	0 (0)	16.2 (6)	11.0 (8)
	Danazol	0 (0)	0 (0)	2.7 (1)	2.7 (2)

Proportion, % (n); median [Min, Max]; mean ± standard deviation (n)

The above data indicate that efficacy in Japanese patients with chronic primary ITP can be evaluated based on the results for overall patients with chronic primary ITP in Study 1801. It is expected that efgartigimod alfa

will maintain increased platelet count levels that can prevent serious bleeding also in Japanese patients with chronic primary ITP; and efficacy in patients with persistent primary ITP tended to be similar to that with chronic primary ITP; therefore, efgartigimod alfa is expected to show efficacy in Japanese patients with chronic or persistent primary ITP.

PMDA's view:
No differences were found in terms of intrinsic or extrinsic ethnic factors between Japanese and non-Japanese populations that may cause significant problems in conducting a global study in patients with primary ITP [see Section "6.R.2 Differences in PK/PD between Japanese and non-Japanese populations"], and the efficacy results in the Japanese population are similar to those in the non-Japanese population among patients with chronic primary ITP who participated in Study 1801. Although Japanese patients with persistent primary ITP were not enrolled in Study 1801, taking into account the discussions in Section "7.R.2.1 Efficacy in global phase III studies", efgartigimod alfa is expected to maintain increased platelet count levels at which serious bleeding can be prevented in Japanese patients with chronic or persistent primary ITP.

7.R.2.4 Long-term efficacy

The applicant's explanation of long-term efficacy:
In Study 1803, in the first 52 weeks of study drug treatment, the median cumulative treatment period [Min, Max] of efgartigimod alfa was 116 days [71, 339] in the P-efgartigimod alfa group (N = 38), who were assigned to the placebo group in Study 1801, and 449 days [188, 699] in the efgartigimod-efgartigimod group (N = 63), who were assigned to the efgartigimod alfa group in Study 1801. In the P-efgartigimod alfa group, 23.7% (9 of 38) of subjects achieved a sustained platelet response as of Week 6, and 21.9%(7 of 32) of subjects roughly maintained a sustained platelet count response up to Week 48 (Table 17). In the efgartigimod-efgartigimod group, a sustained platelet count response was maintained up to Week 48 in Study 1803 (Table 17). In the overall population, a sustained platelet count response was achieved in 60.0% (33 of 55) of subjects who had completed Week 24 and in 61.3% (19 of 31) of subjects who had completed Week 48. In patients who achieved a sustained platelet count response, a platelet count response was maintained during long-term treatment.

The time course of platelet counts in long-term treatment is as shown in Figure 4. Although it should be noted that there were subjects whose treatment was discontinued due to inadequate response, throughout the first 52 weeks, the change from baseline in platelet count (mean ± standard error) in the P-efgartigimod alfa group ranged from 23,060 ± 7,301 to 80,640 ± 27,939/μL, and that in the efgartigimod-efgartigimod group ranged from 38,830 ± 7,761 to 107,690 ± 17,025/μL. WHO-classified Grade ≥1 bleeding events occurred in 83.3% (25 of 30) of subjects in the P-efgartigimod alfa group and 78.7% (37 of 47) of subjects in the efgartigimod-efgartigimod group, and all the events were Grade 1 or 2 in severity. There were no trends towards an increasing incidence and severity of bleeding events with increasing duration of treatment.

Based on the results of Study 1803, PMDA considered that for patients with chronic/persistent primary ITP whose platelet count was increased by efgartigimod alfa, long-term treatment with efgartigimod alfa can also be expected to show efficacy.

7.R.3 Safety

Given that no new concerns have been raised in relation to the present application regarding the incidence of adverse events in the clinical studies conducted in Japan and other countries as well as the following discussions, based on the efficacy of efgartigimod alfa demonstrated in Section "7.R.2 Efficacy," PMDA concluded that efgartigimod alfa has clinically acceptable safety in patients with chronic/persistent primary ITP, provided that appropriate steps including dosing frequency adjustment, dose interruption, or treatment discontinuation of efgartigimod alfa are taken by a physician with sufficient experience in the treatment of blood diseases. After the product launch of efgartigimod alfa for the approved indication, a serious case of anaphylactic shock was reported; currently, therefore, additional safety measures are under discussion.

7.R.3.1 Safety profiles of efgartigimod alfa

The applicant's explanation about the safety profiles of efgartigimod alfa:

Table 25 shows a summary of the safety data in Study 1801 and the integrated analysis[22)] of Studies 1801 and 1803. The main adverse events occurring at a higher incidence in the efgartigimod alfa group than in the placebo group in Study 1801 were asthenia, contusion, hypertension, and headache. In the integrated analysis for Studies 1801 and 1803, in relation to the aforementioned events, there were no reports of serious adverse events for which a causal relationship to the study drug could not be ruled out, with the majority of events being Grade 1 or 2 according to the Common Terminology Criteria for Adverse Events (CTCAE). Given that there are no concerns associated with the mechanism of action of efgartigimod alfa in relation to these events, it was determined that no new risks of efgartigimod alfa have been identified for the indication of the present application. As of the data cut-off date for Study 1803, 9 subjects had not completed the 12-month follow-up period. No deaths, serious adverse events, or CTCAE Grade ≥3 adverse events had occurred in these subjects as of Month 12.

No significant differences were noted in the safety profile of efgartigimod alfa between the overall population and Japanese population in Study 1801. There was no trend towards increasing specific risks in Japanese patients.

[22)] The analysis was performed on adverse events occurring from the first dose of efgartigimod alfa up to 60 days after the final dose in 124 subjects who had received at least 1 dose of efgartigimod alfa in Study 1801 and/or Study 1803. The median [Min, Max] duration of treatment of efgartigimod alfa was 253.0 days [22, 699].

Table 25. Summary of safety data in global phase III studies (Safety analysis set)

	Study 1801				Integrated analysis for Studies 1801 and 1803 (N = 124)
	Overall		Japanese		
	Placebo (N = 45)	Efgartigimod alfa (N = 86)	Placebo (N = 3)	Efgartigimod alfa (N = 5)	
All adverse events	95.6 (43) [17.87]	93.0 (80) [13.56]	66.7 (2) [7.61]	80.0 (4) [8.91]	95.2 (118) [10.21]
Adverse events for which a causal relationship to the study drug could not be ruled out	22.2 (10) [0.94]	17.4 (15) [0.79]	0 (0) [0]	20.0 (1) [1.19]	16.1 (20) [0.47]
Death	0 (0) [0]	0 (0) [0]	0 (0) [0]	0 (0) [0]	2.4 (3) [0.03]
Serious adverse events	15.6 (7) [0.42]	8.1 (7) [0.32]	33.3 (1) [0.95]	0 (0) [0]	15.3 (19) [0.29]
CTCAE Grade ≥3 adverse events	20.0 (9) [0.68]	12.8 (11) [0.58]	33.3 (1) [0.95]	0 (0) [0]	21.0 (26) [0.52]
Adverse events leading to dose interruption	13.3 (6) [0.47]	14.0 (12) [0.34]	0 (0) [0]	0 (0) [0]	24.2 (30) [0.43]
Adverse events leading to treatment discontinuation	2.2 (1) [0.05]	4.7 (4) [0.11]	0 (0) [0]	0 (0) [0]	4.0 (5) [0.05]

Proportion, % (n) [incidence rate per person-year]

Table 26 shows the incidence of adverse events by onset time in the integrated analysis for Studies 1801 and 1803. There was no increase in the incidence of adverse events and no new adverse events associated with long-term continuous treatment with efgartigimod alfa.

Table 26. Incidence of adverse events by onset time in the integrated analysis for Studies 1801 and 1803

	Onset time							
Week	1-12	13-24	25-36	37-48	49-60	61-72	73-84	85-96
Number of subjects analyzed	124	110	92	73	57	44	22	11
All adverse events	83.9 (104)	69.1 (76)	65.2 (60)	52.1 (38)	50.9 (29)	34.1 (15)	18.2 (4)	0 (0)
Adverse events for which a causal relationship to the study drug could not be ruled out	12.1 (15)	6.4 (7)	3.3 (3)	2.7 (2)	0 (0)	2.3 (1)	4.5 (1)	0 (0)
Death	0 (0)	0 (0)	1.1 (1)	0 (0)	1.8 (1)	2.3 (1)	0 (0)	0 (0)
Serious adverse events	3.2 (4)	4.5 (5)	6.5 (6)	4.1 (3)	5.3 (3)	2.3 (1)	0 (0)	0 (0)
CTCAE Grade ≥3 adverse events	5.6 (7)	6.4 (7)	7.6 (7)	11.0 (8)	7.0 (4)	2.3 (1)	0 (0)	0 (0)
Adverse events leading to dose interruption	8.1 (10)	5.5 (6)	12.0 (11)	9.6 (7)	5.3 (3)	2.3 (1)	4.5 (1)	0 (0)
Adverse events leading to treatment discontinuation	1.6 (2)	1.8 (2)	1.1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Proportion, % (n)

PMDA's view:

Based on the applicant's explanation, the safety profile of efgartigimod alfa relating to the indication of the present application did not reveal problems that were more serious than those identified in the review conducted for the approval of the previous indication. There were no differences leading to clinical problems between the overall and Japanese populations in the clinical studies in patients with chronic/persistent primary ITP.

Infections, infusion reactions and other adverse events of special interest that were evaluated based on the pharmacological actions of efgartigimod alfa as well as the data previously submitted for the initial approval will be discussed in the next and subsequent sections.

7.R.3.1.1 Infection-related adverse events

The applicant's explanation about infection-related adverse events associated with efgartigimod alfa treatment: Treatment with efgartigimod alfa decreases IgG concentrations in blood, which may increase the risk of infections.

Table 27 shows the incidence of infection-related adverse events[23)] in Study 1801 and the integrated analysis for Studies 1801 and 1803. The incidence was higher in the efgartigimod alfa group than in the placebo group in Study 1801. Serious adverse events occurred in 2 subjects in the efgartigimod alfa group in Study 1801 (2 cases; cytomegalovirus infection, erysipelas), and 2 subjects in the integrated analysis for Studies 1801 and 1803 (3 cases; COVID-19, COVID-19 pneumonia, erysipelas). A causal relationship to efgartigimod alfa was denied for all cases. In the integrated analysis for Studies 1801 and 1803, adverse events led to treatment discontinuation in 1 subject (1 case; bronchitis), and a causal relationship to efgartigimod alfa was denied. In the integrated analysis for Studies 1801 and 1803, adverse events led to dose interruption in 20 subjects, 18 of which were due to COVID-19.

The incidence of opportunistic infection[24)] was 6.7% (3 of 45) of subjects (3 events) in the placebo group and 11.6% (10 of 86) of subjects (16 events) in the efgartigimod alfa group in Study 1801, and 23.8% (24 of 101) of subjects (29 events) in Study 1803. The main adverse events reported in the efgartigimod alfa groups in both studies were COVID-19 and influenza. In addition to the cases of COVID-19 and COVID-19 pneumonia mentioned above, 1 subject developed systemic inflammatory response syndrome (1 event), which was classified as a serious adverse event. This patient, a male aged 4[redacted] years, developed acute respiratory failure, systemic inflammatory response syndrome, brain oedema, and anaemia at Week 64 (3 days after receiving the latest dose of efgartigimod alfa) and was hospitalized. The patient developed a cerebral haemorrhage on the second day of hospitalization, which led to death. The investigator considered that because the patient went out hunting 2 days before hospitalization, this was most likely the cause of the events; therefore, a causal relationship to efgartigimod alfa was denied.

In the integrated analysis for Studies 1801 and 1803, there was no trend towards an increasing incidence of infection-related adverse events by onset time associated with long-term continuous treatment with efgartigimod alfa.

[23)] Medical Dictionary for Regulatory Activities (MedDRA) System organ class (SOC) "Infections and infestations"
[24)] MedDRA Standardised MedDRA queries (SMQ) (broad) "opportunistic infections"

Table 27. Incidence of infection-related adverse events in global phase III studies (Safety analysis set)

	Study 1801		Integrated analysis for Studies 1801 and 1803 (N = 124)
	Placebo (N = 45)	Efgartigimod alfa (N = 86)	
All adverse events	22.2 (10) [0.62]	29.1 (25) [0.97]	41.1 (51) [0.86]
Adverse events for which a causal relationship to the study drug could not be ruled out	2.2 (1)	2.3 (2)	1.6 (2)
Serious adverse events	4.4 (2)	2.3 (2)	1.6 (2)
CTCAE Grade ≥3 adverse events	4.4 (2)	2.3 (2)	1.6 (2)
Adverse events leading to dose interruption	4.4 (2)	9.3 (8)	16.1 (20)
Adverse events leading to treatment discontinuation	2.2 (1)	1.2 (1)	0.8 (1)
Main adverse events			
COVID-19	6.7 (3)	8.1 (7)	20.2 (25)
Influenza	0 (0)	2.3 (2)	4.0 (5)
Nasopharyngitis	0 (0)	0 (0)	4.0 (5)
Upper respiratory tract infection	2.2 (1)	2.3 (2)	4.0 (5)
Pulpitis dental	2.2 (1)	1.2 (1)	3.2 (4)
Rhinitis	2.2 (1)	2.3 (2)	2.4 (3)
Urinary tract infection	4.4 (2)	2.3 (2)	2.4 (3)
Bronchitis	0 (0)	1.2 (1)	1.6 (2)
Respiratory tract infection viral	0 (0)	2.3 (2)	1.6 (2)
Tonsillitis	0 (0)	2.3 (2)	1.6 (2)

Proportion, % (n) [incidence rate per person-year]

Table 28 shows the results of the subgroup analysis of infection-related adverse events by the use/non-use and types of concomitant ITP drugs in Study 1801. The results showed no clear effects by the use/non-use and types of concomitant ITP drugs.

Table 28. Incidence of infection-related adverse events by the use/non-use and types of concomitant ITP drugs (Study 1801, safety analysis set)

Baseline demographics and disease characteristics			Placebo	Efgartigimod alfa
Use of concomitant ITP drugs	Yes		20.8 (5/24)	32.6 (15/46)
	No		23.8 (5/21)	25.0 (10/40)
Types of concomitant ITP drug used	Corticosteroids	Yes	15.4 (2/13)	17.4 (4/23)
		No	25.0 (8/32)	33.3 (21/63)
	TPO receptor agonist	Yes	33.3 (4/12)	41.7 (10/24)
		No	18.2 (6/33)	24.2 (15/62)
	Immunosuppressants	Yes	0 (0/7)	33.3 (3/9)
		No	26.3 (10/38)	28.6 (22/77)

Proportion, % (n/N)

Infection risks associated with efgartigimod alfa in the clinical studies conducted in patients with primary ITP did not tend to be significantly higher than those in the clinical studies conducted in patients with generalized myasthenia gravis; and cautionary statements are already provided in the package insert regarding the risk of infections occurring or worsening, as well as the need to exercise caution regarding patients with an active infection. Therefore, no additional cautionary statements will be necessary for expanding the indications to include primary ITP.

A total of 10 cases of infection-related[23)] adverse reactions (10 serious and 0 unknown/non-serious cases) were reported in Japan[25)] as post-marketing safety information for efgartigimod alfa with common events being pneumonia (3 cases) and COVID-19 (2 cases), and no events led to death. Outside Japan,[26)] a total of 64 cases of infection-related adverse reactions (18 serious and 46 non-serious cases) were reported with common events being COVID-19 (19 cases), urinary tract infection (9 cases), and pneumonia (6 cases), and no events lead to death.

PMDA considers that the following response by the applicant is appropriate:
Since the cautionary statements are already provided in the package insert of efgartigimod alfa regarding the risks associated with efgartigimod alfa treatment, and determining from the incidence of infection-related adverse events in the clinical studies, the applicant considers no additional cautionary statements will be necessary for expanding the indications to include primary ITP.

7.R.3.1.2 Infusion reactions

The applicant's explanation about the incidence of infusion reactions associated with efgartigimod alfa treatment:
Table 29 shows the incidence of infusion reactions[27)] in Study 1801 and data from the integrated analysis for Studies 1801 and 1803. No significant differences exist between the treatment groups in Study 1801. In the integrated analysis for Studies 1801 and 1803, concerning infusion reactions, there were no deaths, serious adverse events, or CTCAE Grade ≥3 adverse events. No adverse events led to treatment discontinuation. An adverse event (infusion related reaction) leading to dose interruption in 1 subject in the efgartigimod alfa group in Study 1801 was classified as a CTCAE Grade 1 event, and the outcome was reported as "resolved." In Studies 1801 and 1803, there were no reports of anaphylaxis. While Studies 1801 and 1803 had no rules on the premedication to prevent hypersensitivity reactions, prophylactic drugs was administered to 2 subjects each in the placebo and efgartigimod alfa groups in Study 1801 at the discretion of the physician.

In the integrated analysis for Studies 1801 and 1803, there was no trend towards an increasing incidence of infusion reactions by onset time associated with long-term continuous treatment with efgartigimod alfa.

[25)] The cases were evaluated based on 862 patients, the estimated number of patients treated, in the Periodic Safety Update Report (from January 20, 2022 to June 16, 2023).
[26)] The cases were evaluated based on 4784 patients, the estimated number of patients treated, in the Periodic Benefit-Risk Evaluation Report (PBRER) (from December 17, 2022 to June 16, 2023).
[27)] Adverse events classified within MedDRA SMQ (broad) "hypersensitivity," "anaphylactic reaction," or "extravasation events (excluding implants)" occurring within 48 hours of administration (or within 2 days if time of onset for the adverse event is unknown)

Table 29. Incidence of infusion reactions in global phase III studies (Safety analysis set)

	Study 1801		Integrated analysis for Studies 1801 and 1803 (N = 124)
	Placebo (N = 45)	Efgartigimod alfa (N = 86)	
All adverse events	11.1 (5) [0.26]	11.6 (10) [0.39]	9.7 (12) [0.26]
Main adverse events			
Pruritus	2.2 (1)	3.5 (3)	3.2 (4)
Infusion related reaction	0 (0)	1.2 (1)	1.6 (2)
Cough	0 (0)	2.3 (2)	2.4 (3)

Proportion, % (n) [incidence rate per person-year]

No particular concerns have been raised regarding infusion reactions caused by efgartigimod alfa in the clinical studies conducted in patients with primary ITP, and a cautionary statement has already been provided concerning infusion reactions associated with administration of efgartigimod alfa; therefore, no additional cautionary statements will be necessary for expanding the indications to include primary ITP.

A total of 2 cases of adverse reactions of MedDRA SOC "immune system disorders" (1 serious and 1 non-serious cases) were reported in Japan[25] as post-marketing safety information for efgartigimod alfa, and no events lead to death. One case of anaphylactic shock, classified as a serious adverse event, was reported. Twenty minutes after administration of the first dose of efgartigimod alfa, this patient experienced symptoms of hot flush in the face, rash, and discomfort, and other symptoms including blood pressure decreased were noted. Efgartigimod alfa treatment was discontinued, and the patient was treated. The events disappeared within the same day, and the patient was discharged from the hospital on the following day. Three cases of adverse reaction of MedDRA SOC "immune system disorders" (1 serious and 2 non-serious cases) were reported outside Japan, and none of the events in the class led to death. One case of a serious event (sensitisation) was reported.

PMDA's view:

The applicant stated that since a cautionary statement on infusion reactions when administering efgartigimod alfa has already been provided in the package insert, and determining from the incidence of infusion reactions in the clinical studies, no additional cautionary statements will be necessary for expanding the indications to include primary ITP. The applicant's response to the issue is appropriate. A serious case of anaphylactic shock was reported in the post-marketing period; therefore, it should be cautioned in an appropriate manner that anaphylaxis (including anaphylactic shock) may also occur after administration of efgartigimod alfa for the indication of primary ITP.

7.R.3.2 Risk of thrombosis or thromboembolism

PMDA asked the applicant to explain the risk of developing thromboembolism associated with efgartigimod alfa treatment.

The applicant's explanation:
Because patients with primary ITP are reported to be at a higher risk for thromboembolic-related adverse events (*Br J Haematol.* 2021;194:822-34, *Blood.* 2020;136(Supplement 1):9-10), patients with history of thrombotic or embolic events in the preceding 12 months were excluded from Studies 1603, 1801, and 1803.

In Studies 1603 and 1801, no thromboembolic-related adverse events[28)] were reported. In Study 1803, 3 cases of thromboembolic-related adverse events occurred in 2 subjects (myocardial infarction, superficial vein thrombosis). The patient who developed myocardial infarction was a female aged 6[redacted] years, who had comorbidities including diabetes mellitus, hypertension, and hyperlipidaemia, and was taking eltrombopag olamine, a concomitant ITP drug. At Week 49 (7 days after receiving the latest dose of efgartigimod alfa), the patient developed a myocardial infarction, which was classified as a serious adverse event, requiring interruption of efgartigimod alfa doses and inpatient care. Two days after the onset, the patient recovered and resumed treatment with efgartigimod alfa. The patient participated in Study 1803 as of the data cut-off date. At the time when the patient experienced the myocardial infarction, the platelet count was 433,000/μL. A causal relationship to efgartigimod alfa was denied by the investigator. The other patient, a male aged 4[redacted] years, developed 2 cases of superficial vein thrombosis, during Weeks 10 and 14 (the following day after receiving the latest dose of efgartigimod alfa on both occasions). Both cases were non-serious and symptoms resolved without efgartigimod alfa administration being interrupted. The cases were attributed to intravenous administration procedures, and a causal relationship to efgartigimod alfa was denied.

In Studies 1801 and 1803, study drug treatment was to be temporarily interrupted if the platelet count exceeded 400,000/μL, and treatment was to be resumed at a dosing frequency of every other week after confirming that the platelet count had decreased to <150,000/μL. Nine subjects (2 subjects in the placebo group and 7 subjects in the efgartigimod alfa group) in Study 1801 and 13 subjects in Study 1803 exceeded 400,000/μL. All 7 subjects in the efgartigimod alfa group in Study 1801 exceeded 400,000/μL only once. The maximum values ranged from 431,000 to 696,000/μL, and the platelet count was within the normal range (<450,000/μL) in 2 of 7 subjects. In Study 1803, the platelet count exceeded 400,000/μL only once in 8 of 13 subjects with the maximum values ranging from 404,000 to 524,000/μL, and 4 of the 8 subjects had a platelet count within the normal range (<450,000/μL). The platelet count exceeded 400,000/μL multiple times in 5 of 13 subjects, with the maximum values ranging from 403,000 to 699,000/μL. No thromboembolic-related adverse events occurred in any of these subjects. The platelet count increased in 2 of 7 subjects in the efgartigimod alfa group in Study 1801 and 6 of 13 subjects in Study 1803 after receiving rescue treatment.

Taken together, the above findings indicated no clear risks of thromboembolic-related adverse events associated with efgartigimod alfa treatment or no clear risks associated with increasing platelet count; therefore, it will not be necessary to include cautionary statements regarding thromboembolism. The package insert will include a cautionary statement to the effect that the dose should be interrupted when the platelet count exceeds

[28)] MedDRA SMQ (narrow) "embolic and thrombotic events"

400,000/μL and resumed when the count decreases to below 150,000/μL, equivalent to that in the protocol for clinical studies.

PMDA's view:
In Studies 1603 and 1801, there have been no reports of thromboembolic-related adverse events, while a causal relationship to efgartigimod alfa was denied for the thromboembolic-related adverse events reported in Study 1803. In general, although the risk of thromboembolism may increase with increasing platelet count, efgartigimod alfa, based on its mechanism of action, is unlikely to cause an excessive increase in the platelet count; in addition, given that the platelet count is measured on a regular basis and dosing frequency is adjusted in an appropriate manner according to the platelet count and other factors, it will not be necessary at this time to include any specific cautionary statements in the package insert regarding thromboembolism. The decision above will be finalized, taking into account the comments from the Expert Discussion.

7.R.4 Intended patient population and indication of efgartigimod alfa

The applicant's explanation about the intended patient population and indication of efgartigimod alfa:
Studies 1801 and 1803 demonstrated the efficacy and safety of efgartigimod alfa in patients with chronic/persistent primary ITP who did not adequately respond to or were not tolerant to at least 1 type of prior treatment. Therefore, the "Precautions concerning indication" section should include cautionary statements to the effect that efgartigimod alfa should be used in patients who did not adequately respond to or were not tolerant to prior treatment and who remain at a higher risk for bleeding based on the platelet count and clinical symptoms despite preexisting treatment. In Europe and the US, the disease name "primary immune thrombocytopenia" and the classification of disease stages ("newly diagnosed," within 3 months of onset; "persistent," duration of 3-12 months; and "chronic," duration of >12 months) are well established (*Blood.* 2009;113:2386-93). However, the indication will be changed to "chronic idiopathic thrombocytopenic purpura" according to the disease name that has historically been used in Japan, "idiopathic thrombocytopenic purpura" and its staging classification ("acute" if cured within 6 months from estimated onset time or diagnosis; "chronic" if prolonged ≥6 months from estimated onset time or diagnosis).

PMDA's view:
Studies 1801 and 1803 demonstrated the efficacy and safety of efgartigimod alfa in patients with chronic/persistent primary ITP who had responded inadequately to or who were not tolerant to ≥1 type of prior treatment [see Sections "7.R.2 Efficacy" and "7.R.3 Safety"]. Based on this and other factors, PMDA considers it is appropriate that the applicant plans to define patients who responded inadequately to or were intolerant to other treatments, and those who remain at a higher risk for bleeding based on the platelet count and clinical symptoms despite preexisting treatment, as the intended patient population of efgartigimod alfa.

On the basis of the applicant's explanation, it is appropriate to define "chronic idiopathic thrombocytopenic purpura" as the indication, equivalent to that for the approved ITP drugs.

Accordingly, PMDA considers that the indication and the "Precautions concerning indication" section should be as shown below; however, the final decision will be made, taking account of comments from the Expert Discussion.

Indications (excerpt for the indication relating to the present application)
Chronic idiopathic thrombocytopenic purpura

Precautions Concerning Indications (excerpt for the indication relating to the present application)

Efgartigimod alfa should be administered to patients who are considered appropriate to receive the treatment based on the clinical practice guidelines and other latest information, only if:

- the patient does not respond adequately to or is considered to be intolerant to other treatments
- the patient is at a high risk for bleeding based on the platelet count and clinical symptoms

7.R.5 Dosage and administration

In view of the discussions in Sections 7.R.5.1 and 7.R.5.2, PMDA concluded that the dosage and administration and the "Precautions concerning dosage and administration" section should be as shown below. The details of cautionary statements including the appropriateness of dosage and administration, time period required to determine if efgartigimod alfa treatment is inadequate, adjustment of dosing frequency or dose interruption criteria for efgartigimod alfa, and monitoring frequency, will be finalized taking into account the comments from the Expert Discussion.

Dosage and administration (excerpt for dosage and administration relating to the present application)
The usual adult dosage is 10 mg/kg of efgartigimod alfa (genetical recombination) administered as an intravenous infusion over 1 hour once weekly or every other week. The treatment should be started once weekly for 4 weeks. Thereafter, the treatment may be adjusted to every-other-week administration according to the patient's platelet count and clinical symptoms.

Precautions Concerning Dosage and Administration (excerpt for dosage and administration relating to the present application)

- Efgartigimod alfa should be used at the minimally required dosing frequency for treatment.
- Platelet count should be measured once weekly for the first 4 weeks of treatment or until the platelet count stabilizes, and thereafter, on a regular basis according to platelet count response and clinical symptoms.
- The dosing frequency of efgartigimod alfa should be adjusted according to the table below and based on the platelet count response and clinical symptoms.

Platelet count	Dosing frequency
If stable at ≥100,000/μL	Administer every other week.
If stable at ≥30,000/μL and <100,000/μL	If on every-other-week administration: Consider switching to once-weekly administration according to the patient's condition. If on once-weekly administration: Administer once weekly.
If decreased to <30,000/μL	Administer once weekly.
If ≥400,000/μL	Interrupt doses. Continue platelet count measurement. If platelet count decreases to ≤150,000/μL, resume efgartigimod alfa treatment on an every-other-week administration schedule.

- Consider discontinuation of efgartigimod alfa treatment if the platelet count does not increase to a level that is sufficient to prevent a clinically significant bleeding risk after 12 weeks of administration of efgartigimod alfa.

7.R.5.1 Appropriateness of dosage and administration

The applicant's explanation about the rationale for selection of the dosage regimen and its appropriateness:
Based on the population PK/PD model (CTD 5.3.3.5-1) constructed using clinical study data from healthy subjects and patients with generalized myasthenia gravis, results of Study 1603 in patients with primary ITP, and other data, the study dosage regimen in Study 1801 was as follows: starting treatment of efgartigimod alfa 10 mg/kg once-weekly, and at Week 4 and thereafter, the dosing frequency can remain at once-weekly or be changed to every-other-week administration according to the platelet count and other factors to allow selection of a less frequent dosing option in long-term treatment [see Section "6.R.1 Rationale for selection of the dosage regimens in Study 1801"].

In Study 1801, the reduction in serum total IgG concentration almost peaked approximately 1 week after the fourth dose (Week 3) in the weekly administration of efgartigimod alfa 10 mg/kg. At and after Week 4, 6.5% (3 of 46) of subjects in the placebo group and 17.4% (15 of 86) of subjects in the efgartigimod alfa group switched to every-other-week administration, among which, 1 subject in the placebo group and 10 subjects in the efgartigimod alfa group were on every-other-week administration during the weeks of fixed dosing frequency (from Week 16 to Week 23). The proportion of patients who achieved a sustained platelet count response from Week 16 to Week 23 by dosing frequency was 9.4% (3 of 32) of subjects in the placebo group and 22.8% (13 of 57) of subjects in the efgartigimod alfa group for once-weekly administration, and 0.0% (0 of 1) of subject in the placebo group and 90.0% (9 of 10) of subjects in the efgartigimod alfa group for every-other-week administration. The proportion with a sustained platelet count response was higher in the efgartigimod alfa group than in the placebo group regardless of dosing frequency. In Study 1801, of the 22 subjects who achieved a sustained platelet count response in the efgartigimod alfa group, 13 subjects received once-weekly administration and 9 subjects received every-other-week administration during the weeks of fixed dosing frequency (from Week 16 to Week 23).

In Study 1803, 30.7% (31 of 101) of subjects received at least 1 dose of efgartigimod alfa at a frequency of every-other-week, and the cumulative treatment duration (mean ± standard deviation) on the every-other-week dosing schedule in the subjects in question was 43.7 ± 29.5% of the overall treatment period. Of the subjects who achieved a sustained platelet count response in Study 1801, 11 of 13 subjects who continued once-weekly administration and 7 of 9 subjects who continued every-other-week administration, generally maintained a sustained platelet count response up to the data cut-off date of Study 1803.

Based on the above, it was considered appropriate to start treatment of efgartigimod alfa at 10 mg/kg once-weekly and continue treatment by adjusting the dosing frequency to once weekly or every other week according to the platelet count and the patient's condition.

The Studies 1801 and 1803 had defined that the dosing frequency at and after Week 4 is adjustable according to the platelet count and other factors (Table 9), and dose interruption and resumption in response to platelet count increase. PMDA asked the applicant to explain whether it is necessary to provide information in the package insert on platelet count criteria and the monitoring frequency recommended to facilitate dosing frequency adjustment and dose interruption/resumption of efgartigimod alfa.

The applicant's explanation about the dosing frequency adjustment criteria for efgartigimod alfa:
In Studies 1801 and 1803, the efficacy and acceptable safety of efgartigimod alfa were demonstrated based on the regimen adjusted according to the criteria for dosing frequency presented in Table 9, indicating the appropriateness of the adjustment criteria.

In Studies 1801 and 1803, the doses were to be interrupted when the platelet count had increased to >400,000/μL, and treatment could be resumed after confirming that the platelet count had decreased to <150,000/μL, at a frequency of every-other-week administration. In addition, treatment was to be resumed at once-weekly administration if (1) rescue treatment was given before the platelet count had increased to >400,000/μL, and if the platelet count decreased to <150,000/μL within 4 weeks after the rescue treatment, and (2) if the platelet count at the time of resuming treatment was <30,000/μL. Although platelet counts of >400,000/μL were reported in 7 subjects in the efgartigimod alfa group in Study 1801 and 13 subjects in Study 1803, no safety concerns have been identified due to an increase in the platelet count associated with efgartigimod alfa [see Section "7.R.3.2 Risk of thrombosis or thromboembolism"], and therefore, the criteria for dose interruption and resumption are shown to be justifiable. In addition, 1 subject in the efgartigimod alfa group in Study 1801 whose platelet count did not decrease to <150,000/μL until the end of study was excluded, and among the remaining 19 subjects, 8 subjects resumed treatment every other week, 8 subjects resumed treatment once weekly because the platelet count exceeded 400,000/μL after rescue treatment, and 1 subject resumed treatment once weekly because the platelet count before resuming treatment was <30,000/μL. The remaining 2 subjects resumed treatment every other week or once weekly because the platelet count exceeded 400,000/μL multiple times under different circumstances.

The frequency of platelet count monitoring was specified as once weekly throughout the entire study period in Study 1801, while in Study 1803, the frequency of platelet count monitoring was specified as once weekly after the start of administration up to Week 25, and thereafter, the platelet count was to be measured every other week in patients on every-other-week administration. No particular problems arose in terms of efficacy or safety. Accordingly, the platelet count should be measured once weekly for the first 4 weeks of treatment or until the platelet count stabilizes, and thereafter, on a regular basis as determined by the physician according to the patient's condition.

Based on the above, the package insert will include the following information regarding the recommended steps for the adjustment of dosing frequency and dose interruption/resumption of efgartigimod alfa.

- Efgartigimod alfa should be used at the minimally required dosing frequency for treatment
- The dosing frequency should be adjusted according to the platelet count response and clinical symptoms.

- If the platelet count stabilizes at ≥100,000/μL when administered once weekly, switch to every-other-week administration.
- If the platelet count stabilizes at ≥30,000/μL and <100,000/μL when administered every other week, switch to once weekly administration.
- If the platelet count becomes ≥400,000/μL, interrupt doses of efgartigimod alfa. If it decreases to ≤150,000/μL, resume treatment every other week.

- It is recommended to measure the platelet count on a regular basis until the platelet count stabilizes.

PMDA's view:

In Study 1801, the efficacy and acceptable safety of efgartigimod alfa were demonstrated following the adjustment criteria for dosing frequency presented in Table 9. In addition, the data suggested that efgartigimod alfa shows efficacy regardless of dosing frequency, once weekly or every-other-week administration during the weeks of fixed dosing frequency. Given these findings, it is appropriate to start treatment of efgartigimod alfa at 10 mg/kg once-weekly and the dosing frequency at and after Week 4 to be adjusted according to the patient's platelet count and other factors to once weekly or every other week, equivalent to those specified in the Studies 1801 and 1803. Given that there are no clear differences between the Japanese and non-Japanese populations in terms of PK and PD, and no clear differences in the efficacy and safety between the Japanese and non-Japanese populations in Study 1801 [see Sections "6.R.2 Differences in PK/PD between Japanese and non-Japanese populations," "7.R.2.3 Efficacy in Japanese patients," and "7.R.3 Safety"], PMDA concluded that it is appropriate to select the dosage regimen for Japanese patients with chronic/persistent primary ITP that is equivalent to those used in Studies 1801 and 1803.

The applicant's plan to provide information in the package insert regarding the adjustment criteria for dosing frequency according to the platelet count used in Study 1801 is appropriate. However, in the treatment of primary ITP, given that the target platelet count that can prevent serious bleeding varies depending on the patient's condition, it is difficult to define uniform criteria, and that it is recommended to use efgartigimod alfa at the minimally required dosing frequency for treatment. Therefore, adjustment of the dosing frequency and other measures should be determined by the physician according to the patient's condition and by referring to the criteria. The following plan from the applicant regarding the frequency of platelet count measurement is appropriate: the platelet count should be measured once weekly for the first 4 weeks of treatment or until the platelet count stabilizes, and thereafter, on a regular basis as determined by the physician according to the patient's condition.

7.R.5.2 Decision on continuation or discontinuation of treatment in patients with inadequate response to efgartigimod alfa

PMDA asked the applicant to explain the timing for making a decision on whether to discontinue treatment in patients with an inadequate response to efgartigimod alfa.

The applicant's explanation:
The Study 1801 allowed the use of rescue treatment if the platelet count was <30,000/μL and the subject was at an immediate risk of bleeding in the treatment period, and study treatment should be discontinued if rescue treatment was given ≥4 times. The Study 1803 had specified that study treatment should be discontinued if the platelet count was <30,000/μL at all of the 4 visits immediately preceding Visit 12 (Day 78). Consequently, in Study 1801, 11.1% (5 of 45) of subjects in the placebo group and 9.3% (8 of 86) of subjects in the efgartigimod alfa group, and 25.7% (26 of 101) of subjects in Study 1803 discontinued study drug treatment because of "inadequate response" as the primary reason.

In Study 1801, the platelet count increased quickly within 1 week of the start of administration of efgartigimod alfa, and the change from baseline (least squares mean ± standard error) at Week 1 was −894 ± 8,494/μL in the placebo group and 22,151 ± 6,127/μL in the efgartigimod alfa group.

Table 30 shows the results for the post-hoc analysis of the cumulative proportion of patients who achieved a platelet count response (platelet count of ≥30,000/μL or platelet count at least twice that measured at baseline) over time in Study 1801. While 65.1% of patients who achieved a platelet count response by Week 3 and approximately 80% of subjects by Week 11, some patients (4.7%) achieved a platelet count response at Week 14 or later. All the 22 patients who achieved a sustained platelet count response in the efgartigimod alfa group in Study 1801 achieved a platelet count response by Week 9.

Table 30. The cumulative proportion of patients who achieved a platelet count response over time (Study 1801, FAS)

After start of treatment	Placebo (N = 45)	Efgartigimod alfa (N = 86)
Week 1	20.0 (9)	48.8 (42)
Week 2	35.6 (16)	58.1 (50)
Week 3	44.4 (20)	65.1 (56)
Week 4	46.7 (21)	65.1 (56)
Week 5	48.9 (22)	66.3 (57)
Week 6	51.1 (23)	68.9 (59)
Week 7	51.1 (23)	70.9 (61)
Week 8	53.3 (24)	74.4 (64)
Week 9	53.3 (24)	75.6 (65)
Week 10	53.3 (24)	75.6 (65)
Week 11	53.3 (24)	79.1 (68)
Week 12	53.3 (24)	79.1 (68)
Week 13	53.3 (24)	79.1 (68)
Week 14	55.6 (25)	80.2 (69)
Week 15	57.8 (26)	80.2 (69)
Week 16	57.8 (26)	81.4 (70)
Week 17	57.8 (26)	83.7 (72)
Week 18	60.0 (27)	83.7 (72)
Week 19	60.0 (27)	83.7 (72)
Week 20	60.0 (27)	83.7 (72)
Week 21	62.2 (28)	83.7 (72)
Week 22	62.2 (28)	83.7 (72)
Week 23	62.2 (28)	83.7 (72)
Week 24	62.2 (28)	83.7 (72)

Proportion, % (n)

Based on the above, it is recommended that the physicians should decide as to whether efgartigimod alfa is effective and whether to continue treatment around Week 12, as this timing is sufficient to identify a platelet count response in the majority of patients. The package insert should include a cautionary statement to the effect that discontinuation of efgartigimod alfa treatment should be considered if the platelet count has not increased to a level that is sufficient to prevent a clinically significant bleeding risk by Week 12.

PMDA's view:
When the platelet count is not expected to achieve a level that can prevent the risk of bleeding as a result of efgartigimod alfa treatment, treatment should be discontinued immediately, and other treatment option should be selected. The target platelet count that can prevent serious bleeding varies depending on the individual patient's condition, and it is difficult to establish uniform criteria to determine the effect; however, given that, according to the applicant's explanation, the majority of patients who achieved a platelet count of ≥30,000/μL or a platelet count at least twice that measured at baseline during the study period in Study 1801 had achieved at least these platelet count thresholds by Week 12, the applicant's plan to provide a cautionary statement to the effect that whether to continue efgartigimod alfa treatment should be decided by around Week 12 is appropriate.

7.R.6 Post-marketing investigations

The applicant's explanation:
The applicant plans to conduct a specified use-results survey to investigate the long-term safety of efgartigimod alfa in clinical use with infections and infusion reactions included in the safety specification covering all patients who will be receiving efgartigimod alfa (registration period, 2.5 years; follow-up period, 1.5 years; target sample size, 95 patients for safety analysis).

PMDA's view:
Because only a small number of Japanese patients with chronic idiopathic thrombocytopenic purpura were treated with efgartigimod alfa in the clinical studies, the applicant's plan to conduct post-marketing surveillance covering all patients with chronic idiopathic thrombocytopenic purpura who will have been receiving efgartigimod alfa is appropriate. The details of post-marketing surveillance, as well as the adequacy of the target sample size, identification of the safety specification, adequacy of risk classification, the appropriateness of pharmacovigilance activities and risk minimization activities will be finalized in accordance with the "Risk Management Plan Guidance" (PFSB/SD Notification No. 0411-1, and PFSB/ELD Notification No. 0411-2, dated April 11, 2012), taking into account the comments from the Expert Discussion.

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 5.3.5.1-2) 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 efgartigimod alfa has efficacy in the treatment of chronic idiopathic thrombocytopenic purpura, and that efgartigimod alfa has acceptable safety in view of its benefits. Efgartigimod alfa is clinically meaningful because it offers a new treatment option for patients with chronic idiopathic thrombocytopenic purpura who have responded inadequately to or are intolerant to existing treatments. PMDA considers that further discussions are necessary regarding the efficacy, indication, dosage and administration, post-marketing investigations and other issues related to efgartigimod alfa.

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

Review Report (2)

February 15, 2024

Product Submitted for Approval

Brand Name	Vyvgart for Intravenous Infusion 400 mg
Non-proprietary Name	Efgartigimod Alfa (Genetical Recombination)
Applicant	Argenx Japan K.K.
Date of Application	June 13, 2023

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).

1.1 Efficacy

The expert advisors supported the PMDA's conclusion concerning the efficacy of efgartigimod alfa presented in Section "7.R.2 Efficacy" in Review Report (1) as well as the following issues.

- Based on data including the results for the primary endpoint, the proportion of patients with chronic primary ITP who achieved a sustained platelet count response, and the results for secondary endpoints in the global phase III study (Study 1801), it is expected that efgartigimod alfa will maintain increased platelet count levels sufficient to prevent serious bleeding.
- Although the limited number of patients studied preclude a conclusive interpretation of the results on the efficacy in patients with persistent primary ITP, given that the staging classification of chronic and persistent primary ITP is based on time since diagnosis and no significant pathophysiological difference exists, and that the results for efficacy endpoints in the efgartigimod alfa group were more favorable compared with placebo, efgartigimod alfa is expected to demonstrate efficacy in patients with persistent primary ITP.

The following comment was made by the expert advisor regarding long-term efficacy:

In the global phase III extension study (Study 1803), a high proportion of subjects were discontinued from the study due to an "inadequate response" (22.8%, 23 of 101 subjects). Measures should be taken to avoid the misunderstanding that efgartigimod alfa is able to maintain long-term efficacy in all patients.

PMDA's view:
The Study 1803 had specified that the study drug should be discontinued if platelet counts were <30,000/μL at all visits during Week 8 to Week 11, which led to relatively many cases of study discontinuation due to inadequate response. PMDA also concluded that the "Precautions concerning dosage and administration" section of the package insert should include cautionary statements to the effect that whether to continue treatment needs to be assessed on a regular basis during the treatment period including long-term treatment; and not to continue treatment unnecessarily if a platelet count sufficient to prevent clinically significant bleeding is not achieved for 4 consecutive weeks.

Based on the above discussion, PMDA instructed the applicant to include the information above in the "Precautions concerning dosage and administration" section in the package insert, and the applicant responded to the request accordingly.

After the Expert Discussion, the applicant reported the following results:
In a global phase III study (Study 2004[29)]) of the subcutaneous formulation containing efgartigimod alfa as an active ingredient (Vyvdura Combination Subcutaneous Injection, hereinafter referred to as "Vyvdura"), the results for the primary endpoint, the proportion of patients with chronic primary ITP who achieved a sustained platelet count response, did not demonstrate the superiority of Vyvdura to placebo (16.2% [11 of 68] of subjects in the placebo group and 13.7% [17 of 124] of subjects in the Vyvdura group; $P = 0.5081$[30)]).

PMDA asked the applicant to explain the factors that prevented Study 2004 from demonstrating the efficacy of Vyvdura, which contains the same active ingredient as Vyvgart, and the influence of these factors on the efficacy of Vyvgart.

The applicant's explanation:
In Studies 2004 and 1801, the percent reduction in serum total IgG concentration over time when the study regimen for Vyvdura was administered to patients with chronic/persistent primary ITP was similar to that when the study regimen for Vyvgart was administered to the same study population. The inclusion and exclusion criteria for Study 2004 are almost the same as those for Study 1801, and the demographic characteristics and disease characteristics in both studies are similar, except for participating regions; therefore, it is unlikely that the study results were affected by the difference in the baseline demographics and disease characteristics of patients.

One of the reasons that Vyvdura did not demonstrate efficacy in Study 2004 was that the proportion of patients who achieved a sustained platelet count response in the placebo group (16.2%) was markedly higher than originally estimated (≤5%) at the time of study planning. Although it is not clear why the proportion of patients

[29)] Study 2004 used inclusion/exclusion criteria that were similar to those of Study 1801, and eligible patients were those with chronic/persistent primary ITP who received at least 1 type of prior ITP treatment, and had a platelet count of <30,000/μL at screening. The dosage regimen for Vyvdura (1000 mg once weekly or every other week) was selected as a regimen that can achieve a reduction in serum total IgG concentration equivalent to that achieved by Vyvgart 10 mg/kg.
[30)] A Cochran-Mantel-Haenszel test with/without prior splenectomy, use/non-use of concomitant ITP drug at baseline, baseline platelet count (<15,000/μL or ≥15,000/μL) as stratification factors, at a two-sided significance level of 5%

who achieved a sustained platelet count response in the placebo group was higher than expected, there were trends towards increasing change in platelet count from baseline in the placebo group, especially the group with concomitant ITP treatment, and in patient populations from the Middle East, Africa, and non-EU Central and East European countries. Therefore, the baseline demographics and disease characteristics of patients in these groups as well as factors including interventions may have influenced the comparison between groups. The proportion of patients who achieved a sustained platelet count response (13.7%) in the Vyvdura group in Study 2004 was lower than the estimated proportion (21.8%) at the time of study planning, and the change from baseline in the platelet count was less than that seen in the efgartigimod alfa group in Study 1801, although the reason for this has not been identified.

Study 2004 did not demonstrate the efficacy of Vyvdura compared with ITP drugs, and the reason for this was not identified; however, given that platelet count increased after patients were switched from placebo to Vyvgart in Study 1803 (P-efgartigimod alfa group) in addition to the results of Study 1801, the results of Study 2004 will not have an impact on the conclusion of the efficacy of Vyvgart when compared with ITP drugs.

PMDA's view:
The proportion of patients who achieved a sustained platelet count response in the placebo group in Study 2004 was higher than that estimated at the time of study planning, and the reason for this could not be identified based on the analysis results presented. Conversely, in phase III studies of other similar ITP drugs[31)] conducted in patients with prior treatment for ITP, equivalent to those in Study 2004, the proportion of patients in the placebo group who achieved a target representing a sustained platelet count increase ranged between 0% and 4.8%. Based on this, it may be possible that patients with ITP who were unlikely to achieve a sustained platelet increase without additional treatment may have not been enrolled in Study 2004 properly. Therefore, the results of Study 2004 are not regarded as data obtained from a patient population appropriately selected for assessing the efficacy of efgartigimod alfa. PMDA concluded that the results of Study 2004 alone will not raise questions about the conclusion on the efficacy of efgartigimod alfa.

Meanwhile, the proportion of patients who achieved a sustained platelet count response in the Vyvdura group in Study 2004 was lower than the estimated proportion at the time of study planning, and the definite reason for this has not been identified. The possibility that factors were present that could have affected the efficacy of efgartigimod alfa cannot be ruled out. Therefore, for the case of treatment discontinuation due to an inadequate response to efgartigimod alfa, instead of assessing efficacy at around Week 12 [see Section "7.R.5.2 Decision on continuation or discontinuation of treatment in patients with inadequate response to efgartigimod alfa" in Review Report (1)], discontinuation of treatment should be considered when the physician has determined that efgartigimod alfa is not expected to demonstrate efficacy based on the platelet count response, by Week 12 at the latest. Based on the above, PMDA concluded that the "Precautions concerning dosage and administration" section in the package insert should include a cautionary statement to the effect [see Section "1.4 Dosage and administration" in Review Report (2)].

[31)] Review Report of "Tavalisse Tablets 100 mg, Tavalisse Tablets 150 mg" (dated November 11, 2022), Review Report of "Romiplate for S.C. Injection 250 μg" (dated December 1, 2010)

1.2 Safety

The expert advisor made the following comments on the risk of thrombosis or thromboembolism:
While clinical studies of efgartigimod alfa have not indicated any clear risk of thromboembolism in patients with primary ITP, patients with primary ITP are at a higher risk for thromboembolism. Thus, because there are potential risks associated with an excessive increase in platelet count, and because thromboembolism is not always prevented by platelet count management, as well as for other reasons, the package insert should include a cautionary statement regarding the risk of thrombosis or thromboembolism.

In addition to the expert advisor's comments, and the fact that patients with a history of thrombosis or embolism were excluded from the clinical studies, albeit a small number, there were reports of an excessive increase in platelet count in patients receiving efgartigimod alfa in the clinical study. Therefore, PMDA concluded that the package insert should include cautionary statements to the effect that the risk of thrombosis or thromboembolism may be increased with an increase in platelet count; appropriate treatment should be given when abnormalities related to an increased risk of thrombosis or thromboembolism are noted after administration of efgartigimod alfa; and the safety of efgartigimod alfa treatment in patients with a history of thrombosis or embolism has not been evaluated. The expert advisors supported the PMDA's conclusion.

Based on the post-marketing safety information for efgartigimod alfa, a cautionary statement on shock and anaphylaxis was added to the "Clinically significant adverse reactions" section and others in the package insert.

1.3 Intended patient population and indication of efgartigimod alfa

Efgartigimod alfa offers a new treatment option for patients who are at a high risk for bleeding after being treated with at least 1 type of ITP drug based on the platelet count and clinical symptoms and require further treatment, as one of the drugs to be used alone or in combination with existing treatment (second-line or further line of therapies); therefore, it is meaningful to make the new treatment available to healthcare professionals. The PMDA's conclusion on clinical positioning of efgartigimod alfa was supported by the expert advisors.

Based on the disease name well established in Europe and the US (primary immune thrombocytopenia) and the staging classification (*Blood.* 2009;113:2386-93), the global phase III studies of efgartigimod alfa were conducted in patients with chronic/persistent primary ITP. However, based on the disease name that has historically been used in Japan (idiopathic thrombocytopenic purpura) and its staging classification, the indication should be "chronic idiopathic thrombocytopenic purpura," and the PMDA's conclusion was supported by the expert advisors.

In light of the above discussions, PMDA concluded that the indication and associated precautions in the package insert should be as follows, and the PMDA's conclusion was supported by the expert advisors.

Indications (excerpt for the indication relating to the present application)
Chronic idiopathic thrombocytopenic purpura

Precautions Concerning Indications (excerpt for the indication relating to the present application)

Efgartigimod alfa should be administered to patients who are considered appropriate to receive the treatment based on the clinical practice guidelines and other latest information, only if:

- the patient does not respond adequately to or is considered to be intolerant to other treatments
- the patient is at a high risk for bleeding based on the platelet count and clinical symptoms

1.4 Dosage and administration

The expert advisors supported the PMDA's conclusion regarding the dosage and administration of efgartigimod alfa, criteria for decision as to whether to continue or discontinue efgartigimod alfa treatment if the patient has not responded adequately to efgartigimod alfa, criteria for dosing frequency adjustment, and frequency of platelet count monitoring.

In light of the discussion in Section "1.1 Efficacy" in Review Report (2), PMDA concluded that the dosage and administration and associated precautions in the package insert should be as follows.

Dosage and administration (excerpt for dosage and administration relating to the present application)

The usual adult dosage is 10 mg/kg of efgartigimod alfa (genetical recombination) administered as an intravenous infusion over 1 hour once weekly or every other week. The treatment should be started once weekly for 4 weeks. Thereafter, the treatment may be adjusted to every-other-week administration according to the patient's platelet count and clinical symptoms.

Precautions Concerning Dosage and Administration (excerpt for dosage and administration relating to the present application)

- Efgartigimod alfa should be used at the minimally required dosing frequency for treatment.
- Platelet count should be measured once weekly for the first 4 weeks of treatment or until the platelet count stabilizes, and thereafter, on a regular basis according to platelet count response and clinical symptoms.
- The dosing frequency of efgartigimod alfa should be adjusted according to the table below and based on the platelet count response and clinical symptoms.

Platelet count	Dosing frequency
If decreased to <30,000/μL	If on every-other-week administration, switch to once-weekly administration.
If stable at ≥30,000/μL and <100,000/μL	If on every-other-week administration, consider switching to once-weekly administration according to the patient's condition.
If stable at ≥100,000/μL	If on once-weekly administration, switch to every-other-week administration.
If increased to ≥400,000/μL	Interrupt doses. Continue platelet count measurement. If platelet count decreases to ≤150,000/μL, resume efgartigimod alfa treatment at every-other-week administration.

- Evaluate the platelet count on a regular basis after the start of treatment. If the platelet count is not expected to increase to a level that is sufficient to prevent the risk of clinically significant bleeding, consider discontinuation of efgartigimod alfa treatment by Week 12 at the latest. Thereafter, assess whether treatment needs to be continued on a regular basis. Do not continue treatment unnecessarily if a platelet count sufficient to prevent bleeding is not achieved for 4 consecutive weeks.

1.5 Risk management plan (draft)

In view of the discussions presented in Section "7.R.6 Post-marketing investigations" in the Review Report (1) and comments from the expert advisers at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for efgartigimod alfa should include the safety specification presented in Table 31, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 32, and the specified use-results survey (all-case surveillance) presented in Table 33.

Table 31. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Infections • Shock, anaphylaxis • Infusion reaction	None	None
Efficacy specification		
None		

Table 32. 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 (chronic idiopathic thrombocytopenic purpura) • Specified use-results survey (long-term use) (generalized myasthenia gravis) • Specified use-results survey (long-term use) (chronic idiopathic thrombocytopenic purpura)	• Early post-marketing phase vigilance (chronic idiopathic thrombocytopenic purpura) • Prepare and disseminate an information leaflet for healthcare professionals (generalized myasthenia gravis) • Prepare and disseminate an information leaflet for healthcare professionals (chronic idiopathic thrombocytopenic purpura) • Prepare and disseminate an information leaflet for patients (generalized myasthenia gravis) • Prepare and disseminate an information leaflet for patients (chronic idiopathic thrombocytopenic purpura)

Underlines indicate activities related to the indication of the present application.

Table 33. Outline of the specified use-results survey (all-case surveillance) (draft)

Objective	To investigate safety and efficacy in clinical use
Survey method	Central registration method (all-case surveillance)
Population	Patients with chronic idiopathic thrombocytopenic purpura
Observation period	1.5 years
Planned sample size	137 patients (for safety analysis)
Main survey items	Baseline demographics and disease characteristics of patients (e.g., time of ITP diagnosis, medical history of thromboembolism), prior ITP treatment, treatment status of efgartigimod alfa, concomitant drugs, incidence of adverse events, platelet count, etc.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval conditions. Since efgartigimod alfa is designated as an orphan drug, the re-examination period is 10 years for the indication related to the present application and its dosage and administration.

Indications

- Generalized myasthenia gravis (only in patients who do not sufficiently respond to steroids or nonsteroidal immunosuppressants)
- Chronic idiopathic thrombocytopenic purpura

Dosage and administration

Generalized myasthenia gravis

The usual adult dosage is 10 mg/kg of efgartigimod alfa (genetical recombination) administered as an intravenous infusion over 1 hour once weekly for 4 doses per cycle. This treatment cycle is repeated.

Chronic idiopathic thrombocytopenic purpura

The usual adult dosage is 10 mg/kg of efgartigimod alfa (genetical recombination) administered as an intravenous infusion over 1 hour once weekly or every other week. The treatment should be started once weekly for 4 weeks. Thereafter, the treatment may be adjusted to every-other-week administration according to the patient's platelet count and clinical symptoms.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because data from Japanese clinical studies are very limited, the applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product until data are accrued from a certain number of patients, in order to identify the characteristics of treated patients, collect data on the safety and efficacy of the product as early as possible, and take necessary measures to ensure its proper use.

Appendix

List of Abbreviations

ADA	Anti-drug antibody
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ASH	American Society of Hematology
AST	Aspartate aminotransferase
AUC	Area under the serum concentration-time curve
AUC_{ss}	Area under the serum concentration-time curve at steady state
$AUC_{0\text{-}t}$	—
$AUEC_{ss}$	Area under the effect-time curve at steady state
CI	Confidence interval
CL	Total clearance
C_{max}	Maximum serum concentration
$C_{max,ss}$	Maximum serum concentration at steady state
COVID-19	Coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough drug serum concentration
$C_{trough,ss}$	Trough drug serum concentration at steady state
DNA	Deoxyribonucleic acid
EC_{50}	Half-maximal effective concentration
Efgartigimod alfa	Efgartigimod alfa (genetical recombination)
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
FAS	Full analysis set
FcRn	Neonatal Fc receptor
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency virus
Ig	Immunoglobulin
ITP	Immune thrombocytopenia
ITP-BAT	ITP-specific bleeding assessment tool
IVIg	Intravenous immunoglobulin
IV anti-D Ig	Intravenous anti D immunoglobulin
IWG	International Working Group on ITP
MedDRA	Medical Dictionary for Regulatory Activities
PBS	Phosphate buffered saline
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Pharmacodynamics
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PT	Preferred Term
RNA	Ribonucleic acid
SMOG	Skin, visible Mucosae, and Organs with Gradation of Severity
SMQ	Standardised MedDRA queries
SOC	System organ class
Study 1603	Study ARGX-113-1603
Study 1801	Study ARGX-113-1801
Study 1803	Study ARGX-113-1803
Study 2004	Study ARGX-113-2004
t_{max}	Time to maximum plasma concentration

$t_{1/2}$	Elimination half-life
TPO	Thrombopoietin
V1	Central volume of distribution
V2	Peripheral volume of distribution
V3	Peripheral volume of distribution
Vyvgart	Vyvgart for Intravenous Infusion 400 mg
WHO	World Health Organization