Report on the Deliberation Results

August 29, 2022
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Eylea Intravitreal Injection 40 mg/mL
Non-proprietary Name	Aflibercept (Genetical Recombination) (JAN*)
Applicant	Bayer Yakuhin, Ltd.
Date of Application	October 20, 2021

Results of Deliberation

In its meeting held on August 25, 2022, 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 4 years.

Approval Condition

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

**Japanese Accepted Name (modified INN)*

Review Report

August 4, 2022
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	Eylea Intravitreal Injection 40 mg/mL
Non-proprietary Name	Aflibercept (Genetical Recombination)
Applicant	Bayer Yakuhin, Ltd.
Date of Application	October 20, 2021
Dosage Form/Strength	A solution for intravitreal injection containing 11.12 mg of Aflibercept (Genetical Recombination) per vial (0.278 mL)
Application Classification	Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug III

Results of Review

On the basis of the data submitted, PMDA has concluded that the efficacy of the product in the treatment of retinopathy of prematurity is expected, 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 approval condition.

Indications

Age-related macular degeneration with subfoveal choroidal neovascularization
Macular edema secondary to retinal vein occlusion
Choroidal neovascularization in pathologic myopia
Diabetic macular edema
Neovascular glaucoma
<u>Retinopathy of prematurity</u>

(Underline denotes additions.)

Dosage and Administration

● Age-related macular degeneration with subfoveal choroidal neovascularization

The initial dosage of Aflibercept (Genetical Recombination) is 2 mg (0.05 mL) administered by intravitreal injection once every month for 3 times consecutively (initial phase). In the subsequent maintenance phase, it is usually administered intravitreally once every 2 months. The dosing interval may be adjusted according to the patient's symptoms, but it should be ≥1 month.

● Macular edema secondary to retinal vein occlusion and choroidal neovascularization in pathologic myopia

The dosage of Aflibercept (Genetical Recombination) is 2 mg (0.05 mL) administered by intravitreal injection. The dosing interval should be ≥1 month.

● Diabetic macular edema

The dosage of Aflibercept (Genetical Recombination) is 2 mg (0.05 mL) administered by intravitreal injection once every month for 5 times consecutively. Then, it is usually administered intravitreally once every 2 months. The dosing interval may be adjusted according to the patient's symptoms, but it should be ≥1 month.

● Neovascular glaucoma

The dosage of Aflibercept (Genetical Recombination) is 2 mg (0.05 mL) administered by intravitreal injection. Retreatment with Aflibercept may be performed if necessary, with a dosing interval of ≥1 month.

● Retinopathy of prematurity

The dosage of Aflibercept (Genetical Recombination) is 0.4 mg (0.01 mL) administered by intravitreal injection. Retreatment with Aflibercept may be performed if necessary, with a dosing interval of ≥1 month.

(Underline denotes additions.)

Approval Condition

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

Attachment

Review Report (1)

July 5, 2022

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	Eylea Intravitreal Injection 40 mg/mL
Non-proprietary Name	Aflibercept (Genetical Recombination)
Applicant	Bayer Yakuhin, Ltd.
Date of Application	October 20, 2021
Dosage Form/Strength	A solution for intravitreal injection containing 11.12 mg of Aflibercept (Genetical Recombination) per vial (0.278 mL)

Proposed Indications

Age-related macular degeneration with subfoveal choroidal neovascularization
Macular edema secondary to retinal vein occlusion
Choroidal neovascularization in pathologic myopia
Diabetic macular edema
Neovascular glaucoma
Retinopathy of prematurity

(Underline denotes additions.)

Proposed Dosage and Administration

● Age-related macular degeneration with subfoveal choroidal neovascularization

The initial dosage of Aflibercept (Genetical Recombination) is 2 mg (0.05 mL) administered by intravitreal injection once every month for 3 times consecutively (initial phase). In the subsequent maintenance phase, it is usually administered intravitreally once every 2 months. The dosing interval may be adjusted according to the patient's symptoms, but it should be ≥1 month.

● Macular edema secondary to retinal vein occlusion and choroidal neovascularization in pathologic myopia

The dosage of Aflibercept (Genetical Recombination) is 2 mg (0.05 mL) administered by intravitreal injection. The dosing interval should be ≥1 month.

● Diabetic macular edema

The dosage of Aflibercept (Genetical Recombination) is 2 mg (0.05 mL) administered by intravitreal injection once every month for 5 times consecutively. Then, it is usually administered intravitreally once every 2 months. The dosing interval may be adjusted according to the patient's symptoms, but it should be ≥1 month.

● Neovascular glaucoma

The dosage of Aflibercept (Genetical Recombination) is 2 mg (0.05 mL) administered by intravitreal injection. Retreatment with Aflibercept may be performed if necessary, with a dosing interval of ≥1 month.

● Retinopathy of prematurity

The dosage of Aflibercept (Genetical Recombination) is 0.4 mg (0.01 mL) administered by intravitreal injection. Retreatment with Aflibercept may be performed if necessary, with a dosing interval of ≥1 month.

(Underline denotes additions.)

Table of Contents

List of Abbreviations

See Appendix.

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

Retinopathy of prematurity (ROP) is a disease of preterm infants. Following an arrest of retinal vascularization after birth, growth factors such as vascular endothelial growth factor (VEGF) are secreted by the avascular retina, resulting in pathological neovascularization, and fibrous tissue formed by neovascularization can lead to contraction and traction, resulting in retinal detachment or retinal degeneration. ROP can lead to severe visual impairment or blindness (*Lancet.* 2013; 382: 1445-57, *Journal of Japanese Ophthalmological Society.* 2012; 116: 683-702).

Although a standard of care for ROP, laser photocoagulation, is effective especially for peripheral retinal lesions, there are concerns about long-term ocular complications such as increases in high myopia and reductions in peripheral vision. Laser treatment often requires general anesthesia etc., and it may be difficult to perform laser photocoagulation in patients with systemic complications of prematurity (*N Eng J Med*. 2011; 364: 603-15, *Journal of Japanese Ophthalmological Society.* 2020; 124: 1013-9). In recent years, anti-VEGF therapy with intravitreal VEGF inhibitor has been used for ROP. In Japan, a VEGF inhibitor, ranibizumab has been approved for the indication of ROP.

Aflibercept (Genetical Recombination) (hereinafter referred to as aflibercept) is a recombinant glycoprotein consisting of sequences derived from human VEGF receptor extracellular domains fused to the Fc portion of human immunoglobulin G1. In Japan, Eylea, aflibercept solution for intravitreal injection, was approved for the indication of age-related macular degeneration with subfoveal choroidal neovascularization in September 2012, for the indication of macular edema secondary to central retinal vein occlusion in November 2013, for the indication of choroidal neovascularization in pathologic myopia in September 2014, for the indication of diabetic macular edema in November 2014, for the indication of macular edema secondary to retinal vein occlusion[1)] in June 2015, and for the indication of neovascular glaucoma in March 2020.

In the development of Eylea for ROP, as Eylea was expected to exert its effect for the treatment of ROP by inhibiting VEGF, a clinical study was initiated in September 2019. Claiming that the efficacy and safety of Eylea in the treatment of ROP have been shown, the applicant has now filed a partial change approval application for Eylea in Japan.

Outside Japan, an EU application for ROP was filed in November 2021 and is currently under review. As of May 2022, Eylea for the indication of ROP has not been approved in any country or region.

2. Quality and Outline of the Review Conducted by PMDA

Since the present application is intended for a new indication and a new dosage, no quality data have been submitted.

1) Eylea was approved for the indication of macular edema secondary to retinal vein occlusion to cover both central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) (obstruction at a branch of the retinal vein).

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

The present application is intended for a new indication and a new dosage. VEGF is known to play an important role also in the pathophysiology of ROP (*Br J Ophthalmol*. 2008; 92: 689-93, *Invest Ophthalmol Vis Sci*. 1996; 37: 290-9, *J AAPOS*. 1997; 1: 105-10). The results from studies on VEGF inhibition by aflibercept were previously evaluated as the non-clinical pharmacology data for the initial approval of aflibercept, and no new study data have been submitted.

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

Although the present application is intended for a new indication and a new dosage, the non-clinical pharmacokinetic data were previously evaluated for the initial approval of aflibercept, and no new study data have been submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

Since the present application is intended for a new indication and a new dosage, the toxicity data were previously evaluated for the initial approval of aflibercept, and no new study data have been submitted.

5.R Risk anticipated from the pharmacodynamic effect of aflibercept in ROP patients

PMDA asked the applicant to explain the reason for not conducting a toxicity study of aflibercept in juvenile animals with immature organ systems for the present application and the risk anticipated from the pharmacodynamic effect of aflibercept in ROP patients treated with aflibercept.

The applicant's explanation:

- Although a 3-month repeated intravenous dose toxicity study of aflibercept in young cynomolgus monkeys was conducted for the initial approval of aflibercept (The data submitted in the initial application, CTD 4.2.3.5.4-1), monkeys aged 2 to 2.5 years at baseline were used in this toxicity study. Thus, the effect of aflibercept on the immature organ systems of ROP patients has not fully been evaluated.
- With regard to toxicity studies in juvenile animals with immature organ systems, although intravitreal administration is technically difficult in juvenile mice, rats, and rabbits before eye opening, it seemed feasible to conduct a toxicity study of systemic administration of aflibercept in such juvenile mice, rats, and rabbits.
- On the other hand, the existing information indicated that as the risk theoretically anticipated from the pharmacodynamic effect of aflibercept (VEGF inhibition) in preterm infants, there are concerns about the effects of aflibercept on the nervous system (*Cell Mol Life Sci*. 2013; 70: 1763-78), respiratory system (*Am J Physiol Lung Cell Mol Physiol*. 2002; 283: L555-62, etc.), urinary system (*J Clin Invest.* 1997; 99: 2351-7), musculoskeletal system (*Nat Med*. 2003; 9: 669-76), and cardiovascular system (*Nat Med*. 2003; 9: 669-76, *Hypertension.* 2018; 71: e1-8). In addition, given that early safety information in clinical use was available from the off-label use of aflibercept in ROP patients, etc., a new toxicity study of aflibercept in juvenile animals with immature organ systems was considered unnecessary. According to the data from

the previously conducted toxicity studies that evaluated the systemic toxicity of aflibercept, including the above 3-month repeated intravenous dose study in young monkeys, there were no particular effects of aflibercept on the organ systems in which the above risk based on VEGF inhibition is a concern, at systemic exposures 17.9 to 19.4 times the human exposure (C_{max}) in ROP patients.

- According to the currently available data from global phase III studies of aflibercept in ROP patients (CTD 5.3.5.1.1, Study 20090; CTD 5.3.5.1.2, Study 20275), there were no clear effects of aflibercept on the organ systems in which the above risk based on VEGF inhibition is a concern. The risk anticipated from the pharmacodynamic effect of aflibercept is unlikely to become a clinically relevant problem in ROP patients treated with aflibercept.

PMDA's view:
Given the applicant's explanation, the present application submitted without conducting a toxicity study of aflibercept in juvenile animals with immature organ systems is acceptable. The safety of aflibercept in ROP patients will be discussed in Section 7.R.3, taking account of the clinical study data.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

No biopharmaceutic data have been submitted.

Free aflibercept (unbound to VEGF) and bound aflibercept (aflibercept-VEGF complex) concentrations in human plasma were measured using an enzyme-linked immunosorbent assay (ELISA) (Lower limit of quantitation [LLOQ], 15.6 ng/mL for free aflibercept, 31.3 ng/mL for bound aflibercept). Anti-aflibercept antibodies in human serum were determined using a bridging immunoassay, and neutralizing antibodies in human serum were determined using an ELISA.

6.2 Clinical pharmacology

The applicant submitted evaluation data, in the form of the results from a global phase III study in ROP patients (CTD 5.3.5.1.1, Study 20090).

6.2.1 Global phase III study (CTD 5.3.5.1.1, Study 20090)

Table 1 shows the plasma concentrations of free and bound aflibercept in Japanese and non-Japanese patients with ROP (75 subjects included in pharmacokinetic assessment) following bilateral or unilateral intravitreal administration[2)] of aflibercept 0.4 mg/eye [for the study design, see Section 7.1.1]. One subject was positive for anti-aflibercept antibodies, but negative for neutralizing antibodies.

2) Up to 2 additional 0.4-mg doses could be administered in each eye if there was presence of ROP requiring treatment, and the interval since the last dose of intravitreal aflibercept was 28 days or longer.

Table 1. Plasma concentrations of free and bound aflibercept in Japanese and non-Japanese patients with ROP following bilateral or unilateral[a)] intravitreal administration[b)] of aflibercept 0.4 mg/eye

Analyte	Population	Time since the first aflibercept administration					
		Day 1[c)]	Week 2	Week 4	Week 8	Week 12	Week 24
Free	Overall population	481 ± 885 (66/75) 0 - 4570	219 ± 359 (60/66) 0 - 2750	133 ± 205 (54/68) 0 - 923	16.1[d)] (1/3) 0 - 16.1	194[d)] (1/7) 0 - 194	－ (0/14) 0
	Japanese subgroup	800 ± 805 (10/10) 42.0 - 2450	230 ± 216 (10/10) 35.3 - 706	85.5 ± 127 (7/10) 0 - 426	16.1[d)] (1/1) 16.1	－ (0/1) 0	－ (0/2) 0
	Non-Japanese subgroup	432 ± 892 (56/65) 0 - 4570	217 ± 380 (50/56) 0 - 2750	141 ± 215 (47/58) 0 - 923	－ (0/2) 0	194[d)] (1/6) 0 - 194	－ (0/12) 0
Bound	Overall population	149 ± 166 (66/75) 0 - 968	1154 ± 677 (60/65) 0 - 2646	1336 ± 990 (61/67) 0 - 5887	1090[d)] (1/3) 0 - 1090	281 ± 297 (5/7) 0 - 803	131.3 ± 152.2 (9/14) 0 - 457
	Japanese subgroup	297 ± 314 (10/10) 45.6 - 968	1466 ± 578 (10/10) 633 - 2380	1622 ± 768 (10/10) 647 - 2868	1090[d)] (1/1) 1090	558[d)] (1/1) 558	265, 341[d)] (2/2) 265 - 341
	Non-Japanese subgroup	126 ± 119 (56/65) 0 - 576	1098 ± 683 (50/55) 0 - 2646	1286 ± 1021 (51/57) 0 - 5887	－ (0/2) 0	235 ± 296 (4/6) 0 - 803	102.7 ± 144.4 (7/12) 0 - 457

Unit: ng/mL, Upper row: Mean ± SD (No. of subjects with values above LLOQ/No. of evaluable subjects), Lower row: Min.-Max., －: No data
Values below LLOQ were substituted by 0.

a) Seventy-one subjects were bilaterally treated, and 4 subjects were unilaterally treated. Plasma free aflibercept concentrations at Day 1 and Weeks 2 and 4 in the 4 unilaterally treated subjects (all non-Japanese subjects) (Unit: ng/mL, mean ± SD [range] (No. of subjects with values above LLOQ/No. of evaluable subjects)) were 113 ± 102 [0-246] (3/4), 60.5 ± 27.9 [28.3-76.6] (3/3), and 22.3 ± 20.0 [0-38.4] (2/3), respectively, and plasma bound aflibercept concentrations were 112 ± 67.8 [26.5-172] (4/4), 635 ± 287 [398-954] (3/3), and 643 ± 185 [505-853] (3/3), respectively. Both concentrations were below LLOQ at later time points.

b) The number of doses of aflibercept given to each subject through Week 24 was 1 in 4 subjects, 2 in 55 subjects, 3 in 6 subjects, and 4 in 10 subjects. The first dose in one eye for subjects who received 1 dose of aflibercept; the first dose in both eyes for subjects who received 2 doses of aflibercept; the first dose in one eye and the first dose and 1 additional dose in the other eye for subjects who received 3 doses of aflibercept; and the first dose and 1 additional dose in both eyes for subjects who received 4 doses of aflibercept.

c) Approximately 24 hours after dosing

d) Individual values

6.R Pharmacokinetic profile of aflibercept in ROP patients

The applicant's explanation about differences in the pharmacokinetics of aflibercept between Japanese and non-Japanese ROP patients:

With regard to plasma concentrations of free and bound aflibercept in the Japanese and non-Japanese subgroups following bilateral or unilateral intravitreal administration of aflibercept 0.4 mg/eye in a global phase III study in ROP patients (CTD 5.3.5.1.1, Study 20090), although the plasma concentration of bound aflibercept tended to be slightly higher in the Japanese subgroup than in the non-Japanese subgroup (Table 1), the distributions of individual plasma free and bound aflibercept concentrations are as shown in Figure 1. The plasma free and bound aflibercept concentrations in Japanese patients with ROP largely fell within the concentration ranges in non-Japanese patients with ROP.

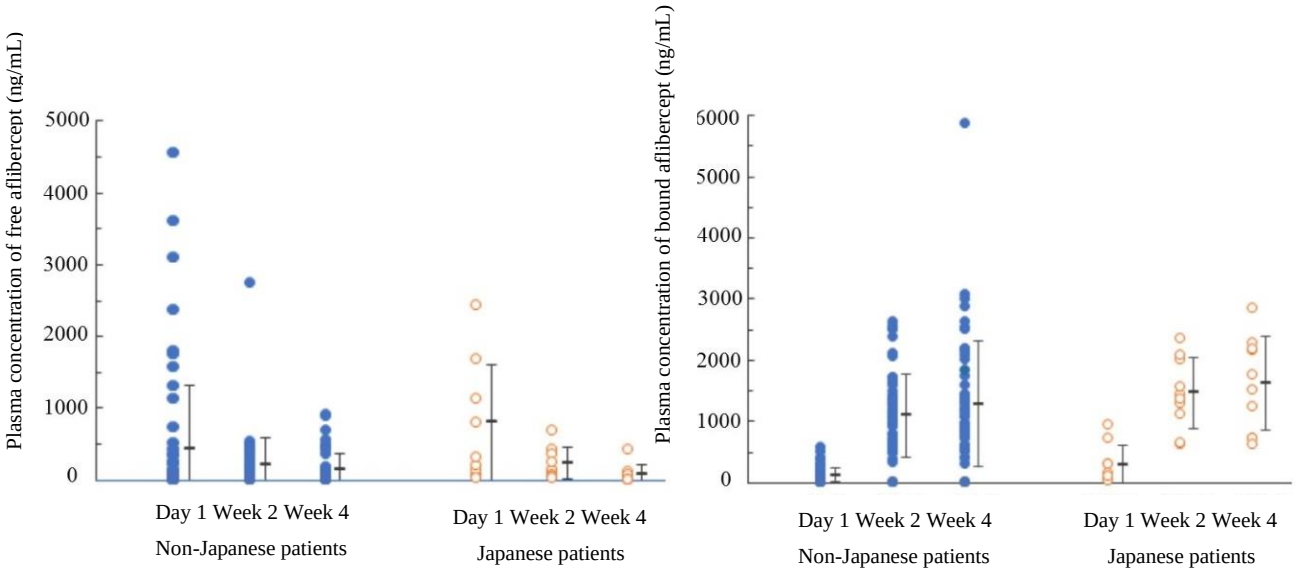

Figure 1. Distributions of plasma concentrations of free aflibercept (left figure) and bound aflibercept (right figure) in Japanese and non-Japanese patients with ROP following intravitreal administration of aflibercept (Distribution of individual values and mean ± SD, Study 20090)

In addition, the primary efficacy analysis in Japan for Study 20090 showed no major differences in efficacy between the overall population and the Japanese subgroup [see Section 7.R.2], and there were also no safety concerns unique to Japanese ROP patients in Study 20090 and a global phase III study (CTD 5.3.5.1.2, Study 20275) [see Section 7.R.3]. Based on the above, although aflibercept exposure tended to be slightly higher in Japanese ROP patients than in non-Japanese ROP patients, this difference is not considered clinically meaningful.

The applicant's explanation about differences in the pharmacokinetics of aflibercept between ROP patients and adult patients with the approved indication of exudative age-related macular degeneration (AMD):
Following a single unilateral intravitreal injection of aflibercept 2 mg/eye in non-Japanese patients with exudative AMD, the C_{max} values of plasma free aflibercept (3 subjects included in pharmacokinetic assessment) and bound aflibercept (6 subjects included in pharmacokinetic assessment) (mean ± SD) were 19.3 ± 22.8 ng/mL and 186 ± 74.8 ng/mL,[3)] respectively. The plasma free and bound aflibercept concentrations were higher in ROP patients (Table 1) than in patients with exudative AMD due to differences in the dose per body weight, etc. However, there were no major differences in the safety profile of aflibercept between ROP patients in Studies 20090 and 20275 and the adult patients [see Section 7.R.3], suggesting no safety concerns associated with increased aflibercept exposure in ROP patients.

PMDA's view:
With regard to differences in the pharmacokinetics of aflibercept between Japanese and non-Japanese patients with ROP, although the mean aflibercept exposure tended to be slightly higher in Japanese ROP patients than

3) In a foreign phase II extension study (Study 702.PK), plasma concentrations of free and bound aflibercept were determined in non-Japanese patients with exudative AMD with subfoveal CNV who completed foreign phase I studies (Studies 502 and 603) or a foreign phase II study (Study 508) (6 subjects included in pharmacokinetic assessment) following a single unilateral intravitreal injection of aflibercept 2 mg/eye (see Review Report on Eylea Intravitreal Injection 40 mg/mL and Eylea Intravitreal Injection Kit 40 mg/mL as of August 6, 2012).

in non-Japanese ROP patients, there were no marked differences in terms of individual values. Taking also into account that aflibercept is an antibody formulation to be injected intravitreally into the eye, with an expectation of its intraocular pharmacologic effect, and is considered insensitive to ethnic factors [see Section 7.R.1], no clinically relevant differences in the pharmacokinetics of aflibercept between Japanese and non-Japanese patients with ROP have been observed.

ROP patients showed higher aflibercept exposure than patients with exudative AMD. The safety of aflibercept in ROP patients will be discussed in Section 7.R.3, taking account of the clinical study data.

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 the results from the clinical studies presented in Table 2.

Table 2. Listing of efficacy and safety clinical studies

Data category	Geographical location	Study ID	Phase	Study population	Number of subjects enrolled[a)]	Dosage regimen	Main endpoints
Evaluation	Global	20090	III	ROP patients	113	Aflibercept group: Single bilateral or unilateral IVT injections of aflibercept 0.4 mg/eye. Up to 2 additional IVT injections could be administered in each eye if the retreatment criteria were met. Laser photocoagulation group: Bilateral or unilateral treatment with laser. Retreatment with laser could be administered if the retreatment criteria were met.	Efficacy Safety PK
		20275[b)]			89	No study treatment (aflibercept injection or laser photocoagulation) was administered. Subjects treated in Study 20090 were to be followed to 5 years of chronological age.	Safety Efficacy

a) The number of subjects who received study treatment for Study 20090; The number of subjects enrolled in Study 20275 for Study 20275
b) An extension study of Study 20090

7.1 Evaluation data

7.1.1 Global phase III study (1) (CTD 5.3.5.1.1, Study 20090 [September 2019 to February 2021])

A randomized, open-label, parallel-group study was conducted in 27 countries or regions[4)] including Japan to assess the efficacy, safety, and pharmacokinetics of aflibercept in ROP patients[5)] (target sample size, 102 subjects,[6)] 68 in the aflibercept group and 34 in the laser group) [for pharmacokinetic data, see Section 6.2.1].

4) Japan, Argentina, Austria, Belgium, Bulgaria, Brazil, Czech Republic, Spain, the UK, Greece, Hong Kong, Hungary, Israel, Italy, South Korea, Malaysia, Netherlands, Poland, Portugal, Romania, the Russian Federation, Singapore, Slovakia, Sweden, Turkey, Taiwan, Ukraine

5) Key inclusion criteria: gestational age at birth ≤32 weeks or birth weight ≤1500 g; body weight at baseline (day of treatment) ≥800 g; and treatment-naïve ROP classified according to the International Classification of Retinopathy of Prematurity (*Arch Ophthalmol*. 2005; 123: 991-9) in at least one eye with one of the following retinal findings: (a) Zone I Stage 1 plus, or 2 plus, or 3 or 3 plus (plus: findings of plus disease*), (b) Zone II Stage 2 plus or 3 plus (plus: findings of plus disease*), or (c) AP-ROP.
*Plus disease is characterized by dilation of posterior pole retinal veins and tortuosity of posterior pole retinal arterioles in ≥2 quadrants, and progresses at any stage.
At enrollment, ROP was to be graded by a central reading center.

6) In a global phase III study that evaluated the efficacy and safety of ranibizumab compared with laser photocoagulation in ROP patients (the RAINBOW study) (*Lancet*. 2019; 394: 1551-9), the response rate in the ranibizumab high dose group (0.2 mg/eye) was 80%. Considering that the response rate with aflibercept was greater than 80%, an estimated response rate of 85% for the aflibercept group in Study 20090 was assumed. With 68 subjects in the aflibercept group, a two-sided exact binomial test with a significance level of 5% would reject the null hypothesis of "the response rate in the aflibercept group ≤66%" with a power of 92.3%. Then, as the target sample size, at least 102 subjects were planned to be enrolled and randomized in a 2:1 ratio to aflibercept (68 subjects) or laser photocoagulation (34 subjects). A target sample size of 18 Japanese subjects was chosen (12 in the aflibercept group and 6 in the laser group).

Subjects randomized to aflibercept were to receive single bilateral or unilateral[7)] intravitreal (IVT) injections of aflibercept 0.4 mg/eye. If the retreatment criteria[8)] were met, up to 2 additional IVT injections of aflibercept 0.4 mg/eye could be administered in each eye. Rescue treatment with laser photocoagulation was permitted if the pre-specified conditions[9)] were met. Subjects randomized to laser photocoagulation were to be treated with laser photocoagulation[10)] bilaterally or unilaterally.[7)] Retreatment with laser photocoagulation could be administered if the retreatment criteria[11)] were met. Rescue treatment with intravitreal aflibercept 0.4 mg/eye was allowed if the pre-specified conditions[12)] were met. The observation period was from baseline to Week 24.[13)]

Of 118 randomized subjects (75 in the aflibercept group, 43 in the laser group), 113 subjects (75 subjects, 38 subjects) after excluding 5 subjects who were randomized to laser photocoagulation, but did not undergo laser treatment, were included in the full analysis set (FAS) and the safety analysis set. There were 9 study discontinuations (7 subjects, 2 subjects), and the main reasons for discontinuations were death (3 subjects, 0 subjects), adverse events (1 subject, 1 subject), consent withdrawal (1 subject, 1 subject), and the investigator's decision (1 subject, 0 subjects).

The primary endpoint of the proportion of subjects with absence of active ROP and unfavorable structural outcomes[14)] at 24 weeks after starting study treatment (the response rate)[15)] in the aflibercept group is shown in Table 3. The lower limit of its two sided 95% confidence interval (CI) was greater than the pre-specified threshold of 66%[16)] ($P = 0.0021$, binomial test), meeting the criterion for the success of the study. The response rate in the laser group [95% CI] was 84.2 [68.7, 94.0]% (32 of 38 subjects).[17)]

---

7) Both or one eyes of infants deemed eligible by the investigator were study eyes, and study eyes (both or one eyes) received study treatment according to each subject's randomization assignment.

8) Presence of ROP requiring treatment (with or without the retinal findings listed in 5)) and the interval since the last aflibercept injection ≥28 days.

9) If one of the following conditions was met.
- Worsening of ROP compared to the examination before the previous injection during the 27 days following that aflibercept injection
- Presence of ROP requiring treatment (with or without the retinal findings listed in 5)) after the subject already received a total of 3 aflibercept injections and the interval since the last IVT injection was ≥28 days

10) In case multiple sessions were necessary within 1 week from baseline (day of treatment), they were to be counted as a single treatment.

11) Presence of ROP requiring treatment (with or without the retinal findings listed in 5)) and fundus examination revealed laser treatment was incomplete as judged by the investigator.

12) If one of the following conditions was met.
- Worsening of ROP compared to the prelaser examination
- Persistence of ROP requiring treatment (with or without the retinal findings listed in 5)) 28 or more days after laser treatment

13) Up to Week 27 for subjects treated after Week 21.

14) Active ROP was defined as ROP requiring treatment with one of the retinal findings listed in 5), and unfavorable structural outcomes were defined as retinal detachment, macular dragging, macular fold, or retrolental opacity. The primary efficacy analysis was based on the investigator's assessments.

15) A subject who had 2 study eyes was considered a responder if both eyes responded to treatment. A subject who died was considered a non-responder. Eyes were considered non-responders if rescue treatment was given.
For subjects with missing data for the primary endpoint (only for eyes not having had an unfavorable structural outcome or rescue treatment before dropping out), missing data were imputed as follows.
- If at the last visit before dropping out the subject had no active ROP and Zone II was completely vascularized (aflibercept subjects) or laser treatment was completed (laser subjects), the respective eye was considered as responding.
- If the subject dropped out at or after week 16, the last ROP staging before dropping out was carried forward and used for determining the response in this eye.
- If the subject dropped out before Week 16, the missing information was imputed as follows:

If there was a clear documentation that the subject dropped out due to lack of efficacy, the respective eye was considered as non-responding; otherwise, a multiple imputation approach was used based on the subject's treatment group and the initial staging (Zone I versus II versus AP-ROP).

16) Referring to the point estimate of the response rate in the laser photocoagulation group (66.2% [45 of 68 subjects]) in a global phase III study that evaluated the efficacy and safety of ranibizumab compared with laser photocoagulation in ROP patients (the RAINBOW study), a threshold value of 66% was chosen.

17) Different primary efficacy analyses were planned for Japan and other countries or regions. The efficacy of aflibercept was to be assessed by comparison with the pre-specified threshold in Japan. The efficacy of aflibercept was to be assessed by comparison with laser photocoagulation as a control group in other countries or regions [see Section 7.R.2.1].

Table 3. Proportion of subjects with absence of active ROP and unfavorable structural outcomes at 24 weeks after starting study treatment (Response rate)
(Study 20090, FAS)

Treatment group	Aflibercept
Responders/Evaluable subjects	62/75
Response rate [95% CI][a)] (%)	82.7 [72.2, 90.4]
P-value[b)]	0.0021

a) Clopper-Pearson exact CI
b) A two-sided binomial exact test against a pre-specified threshold of 66%

The incidences of adverse events (including laboratory test abnormalities) were 93.3% (70 of 75 subjects) in the aflibercept group and 86.8% (33 of 38 subjects) in the laser group. There were 3 deaths in the aflibercept group (bronchopulmonary dysplasia and pneumothorax[18)]; bronchopulmonary dysplasia; and bronchiolitis [1 subject each]), and a causal relationship to study treatment (including rescue treatment) was denied for all those cases. Table 4 shows the incidence of serious adverse events other than deaths.

Table 4. Incidence of serious adverse events other than deaths (Study 20090, Safety analysis set)

Treatment group	Incidence	Breakdown
Aflibercept	32.0% (24 of 75 subjects)	Bronchiolitis [3 subjects]; retinal detachment and bronchopulmonary dysplasia [2 subjects]; and bronchopulmonary dysplasia and pneumothorax[a)]; cyanosis; inguinal hernia repair; retinal detachment and apnoea (1 subject[b)] and 0 subjects); gastrooesophageal reflux disease; gastroenteritis salmonella; postoperative adhesion and vomiting; pneumonia aspiration, retinal haemorrhage, and bronchiolitis; retinal detachment, retinal haemorrhage, and vitreous haemorrhage; macular degeneration; bronchiolitis and respiratory tract infection; COVID-19 and pneumonia; retinopathy of prematurity; concussion; mechanical ileus; intraocular pressure increased, corneal oedema, and overdose (1 subject,[c)] 1 subject,[c)] and 0 subjects); upper respiratory tract infection; retinoblastoma; and retinal detachment [1 subject each]
Laser	42.1% (16 of 38 subjects)	Retinal detachment [2 subjects] (1[b)] subject); bronchiolitis [2 subjects]; and pulmonary hypertension and obstructive airways disorder[a)]; intestinal prolapse[a)]; C-reactive protein increased and rhinitis; pharyngitis and respiratory distress; infantile apnoea; apnoea and pulmonary valve stenosis; respiratory arrest; inguinal hernia and abdominal adhesions; upper respiratory tract infection and conjunctivitis; infantile apnoea; spinal cord lipoma; and necrotising colitis [1 subject each]

Incidence (Number of subjects with event/Number of evaluable subjects)
Breakdown, [Number of subjects with event] (Number of subjects with event for which a causal relationship to study treatment could not be ruled out)
a) Japanese subject
b) Related to aflibercept
c) Related to injection procedure

The incidences of adverse events related to aflibercept in the study eyes were 4.0% (3 of 75 subjects) (retinal artery occlusion; retinal vascular disorder; and vitreous opacities [1 subject each]) in the aflibercept group and 2.6% (1 of 38 subjects) (retinal detachment) in the laser group, and non-ocular events were not reported in either treatment group. The incidences of adverse events related to injection procedure (if considered reasonably related to injection procedure) in the study eyes were 18.7% (14 of 75 subjects) and 0%, respectively, and those reported by ≥2 subjects in either treatment group were conjunctival haemorrhage (4 subjects, 0 subjects), retinal haemorrhage (3 subjects, 0 subjects), injection site haemorrhage (3 subjects, 0 subjects), and intraocular pressure increased (3 subjects, 0 subjects). The incidences of non-ocular adverse events related to injection procedure were 1.3% (1 of 75 subjects) and 0%, respectively. The incidences of adverse events related to laser photocoagulation in the study eyes were 1.3% (1 of 75 subjects) and 18.4% (7 of 38 subjects), respectively, and those reported by ≥2 subjects in either treatment group were retinal haemorrhage (0 subjects, 4 subjects). The incidences of non-ocular adverse events related to laser photocoagulation were 0% and 5.3% (2 of 38 subjects), respectively.

18) A Japanese subject

There were no clinically relevant changes in vital signs (blood pressure, heart rate, respiratory rate, body temperature).

7.1.2 Global phase III study (2) (CTD5.3.5.1.2, Study 20275 [ongoing since March 2020 ([redacted] 20[redacted] data cutoff[19])])

A long-term extension study was conducted in 24 countries or regions[20] including Japan to evaluate the long-term safety and efficacy of study treatment in ROP patients who completed a global phase III study (CTD5.3.5.1-1, Study 20090).[21]

In this study, no study treatment was to be administered, and subjects were to be followed to 5 years of age.

All of 89 subjects enrolled in the study (60 in the aflibercept group, 29 in the laser group) were included in the safety analysis set as of the data cutoff date. Sixty subjects (39 subjects, 21 subjects) completed 1 year chronological age visit.

As of the data cutoff date, the results of the primary endpoint of "binocular best-corrected visual acuity at 5 years of age" are not available. Though the final results of one of the secondary endpoints of "the proportion of subjects with absence of active ROP and unfavorable structural outcomes[14] at 1 year of age" also are not available, the number of subjects with absence of active ROP and unfavorable structural outcomes at 1 year of age as of the data cutoff date is shown in Table 5.

Table 5. Number of subjects with absence of active ROP and unfavorable structural outcomes at 1 year of age (Study 20275, as of the data cutoff date)

Treatment group	Aflibercept	Laser
Subjects who had 2 study eyes	36	19
Subjects with absence of active ROP and unfavorable structural outcomes in both eyes	35	17
Subjects with absence of active ROP and unfavorable structural outcomes in one eye only	1	0
Subjects who had 1 study eye	3	2
Subjects with absence of active ROP and unfavorable structural outcomes	3	2

Number of subjects

The incidences of adverse events (including laboratory test abnormalities)[22] were 48.3% (29 of 60 subjects) in the aflibercept group and 48.3% (14 of 29 subjects) in the laser group. No deaths were reported, and the incidence of serious adverse events other than deaths is shown in Table 6.

19) When ≥50% of subjects enrolled in Study 20275 completed 1 year chronological age visit, a data cutoff was performed.
20) Japan, Argentina, Belgium, Bulgaria, Brazil, Czech Republic, Spain, the UK, Greece, Hungary, Israel, Italy, South Korea, Malaysia, Netherlands, Portugal, Romania, the Russian Federation, Singapore, Slovakia, Sweden, Turkey, Taiwan, Ukraine
21) Patients who received study treatment in Study 20090 and less than 13 months of chronological age
22) Only adverse events that occurred during Study 20090 and remained unresolved at the start of Study 20275 or adverse events that occurred after the start of Study 20275 in subjects enrolled in Study 20275 were counted.

Table 6. Incidence of serious adverse events other than deaths (Study 20275, Safety analysis set)

Treatment group	Incidence	Breakdown
Aflibercept	11.7% (7 of 60 subjects)	Retinal detachment [2 subjects] (1 subject[a)]); and subdural haematoma[b)]; bronchopulmonary disease, gastroenteritis, and infantile spasms; retinopathy of prematurity; retinal neovascularisation and vitreous opacities; and cerebellar atrophy and retinoblastoma [1 subject each]
Laser	6.9% (2 of 29 subjects)	Cerebral palsy; and intellectual disability, cerebral palsy, deafness neurosensory, and dystonia [1 subject each]

Incidence (Number of subjects with event/Number of evaluable subjects)
Breakdown, [No. of subjects with event] (No. of subjects with event for which a causal relationship to study treatment could not be ruled out)
a) Related to aflibercept
b) Japanese subject

The incidences of adverse events related to aflibercept in the study eyes were 1.7% (1 of 60 subjects) (retinal detachment) and 0%, respectively, and non-ocular events were not reported in either treatment group. Adverse events related to injection procedure in the study eyes or non-ocular adverse events related to injection procedure were not reported in either treatment group. The incidences of adverse events related to laser photocoagulation in the study eyes were 3.3% (2 of 60 subjects) and 10.3% (3 of 29 subjects), respectively, and those reported by ≥2 subjects in either treatment group were myopia (1 subject, 2 subjects). Non-ocular events related to laser photocoagulation were not reported in either treatment group.

7.R Outline of the review conducted by PMDA

7.R.1 Intrinsic and extrinsic ethnic factors

PMDA asked the applicant to explain differences in intrinsic and extrinsic ethnic factors that influence the efficacy and safety of aflibercept between Japanese and non-Japanese populations and then the appropriateness of conducting phase III studies in ROP patients (CTD 5.3.5.1.1, Study 20090; CTD 5.3.5.1.2, Study 20275) as global studies including Japan.

The applicant's explanation:

Based on the following considerations, as there seem no major differences in intrinsic and extrinsic ethnic factors that influence the efficacy and safety of aflibercept between Japanese and non-Japanese populations, there should be no particular problem with conducting Studies 20090 and 20275 as global studies including Japan.

- Aflibercept is injected intravitreally into the eye. Aflibercept is a protein product, which does not undergo metabolism by drug metabolizing enzymes. Though neonatal Fc receptor (FcRn) plays an important role in the distribution and excretion of free and bound aflibercept in plasma, no ethnic differences in the expression of FcRn in preterm infants have been reported. It has been concluded that there are no major differences in plasma free and bound aflibercept concentrations between Japanese and non-Japanese adult patients with the approved indications (exudative AMD, CRVO, BRVO, diabetic macular edema [DME], myopic choroidal neovascularization [mCNV]) (CTD 1.13.1.03, the data submitted in the initial application; CTD 1.13.1.06, CTD 1.13.1.08, CTD 1.13.1.10, and CTD 1.13.1.12, the data submitted in the partial change application). Given these findings, there should be no clear ethnic differences in the pharmacokinetics of aflibercept in ROP patients.
- There seem no clear differences in the level of neonatal medical care and the criteria for screening of neonates for ROP among the main countries or regions participating in Study 20090 (*Retina and*

Vitreous Body. Japanese Ophthalmological Society; 2008.p52-5, *Klin Monbl Augenheilkd*. 2008; 225: 123-30, UK Retinopathy of Prematurity Guideline. Royal College of Paediatrics and Child Health; 2008).

- As to the diagnosis of ROP, the International Classification of Retinopathy of Prematurity (*Arch Ophthalmol*. 2005; 123: 991-9), which is used for ROP grading, is almost the same as the MHW classification in Japan (*Journal of Japanese Ophthalmological Society*. 2012; 116: 683-702). In addition, the International Classification of Retinopathy of Prematurity has commonly been used also in Japan in recent years (*Journal of the Japan Ophthalmologists Association*. 2014; 85: 1698-703).
- Concerning the prevalence of ROP, the reported incidences of ROP and ROP requiring treatment were 29.7% and 7.7%, respectively, among 560 premature infants born ≥22 and <35 weeks of gestational age in Japan (*Folia Japonica de Ophthalmologica Clinica.* 2017; 10: 482-5). On the other hand, the reported incidences of ROP and ROP requiring treatment were 24.1% and 4.4%, respectively, among 1784 premature infants with a gestational age of ≥22 and <32 weeks in Sweden (*Arch Ophthalmol*. 2012; 130: 1418-24), and the reported incidences of ROP and ROP requiring treatment were 27.6% and 3.5%, respectively, among 1222 premature infants with a gestational age of ≥22 and ≤40 weeks in Germany (*Graefes Arch Clin Exp Ophthalmol*. 2009; 247: 1251-62). Although the incidence of ROP requiring treatment tended to be slightly higher in Japan than in other countries, there seemed no major differences.
- In the treatment of ROP, there are no major differences in the indication for a standard of care, laser photocoagulation, and the treatment results between Japan and overseas, and a VEGF inhibitor, ranibizumab was approved in 2019 in both Japan and the EU, and has been a new treatment option (*Journal of Japanese Ophthalmological Society.* 2020; 124: 1013-19). With respect to the treatment criteria for ROP, treatment is recommended for Zone II stage 2 plus disease in the countries or regions (including Japan) other than Germany and the UK among 27 countries or regions that participated in Study 20090 (*Journal of Japanese Ophthalmological Society.* 2012; 116: 683-702, etc.), whereas the guidelines in Germany and the UK recommend that these eyes should be watched closely and treatment should be considered carefully when the disease worsens (*Ophthalmologe*. 2020; 117: 873-85, UK Retinopathy of Prematurity Guideline. Royal College of Paediatrics and Child Health; 2008). Thus, the investigators received prior training to ensure consistent decisions as to whether to treat ROP including Zone II Stage 2 plus disease, among the countries or regions participating in Study 20090.

PMDA's view:

Based on the applicant's explanation, as there are no clear differences in intrinsic and extrinsic ethnic factors that influence the efficacy and safety of aflibercept between Japanese and non-Japanese populations, there is no major problem with conducting Studies 20090 and 20275 as global studies including Japan.

The efficacy and safety of aflibercept in Japanese ROP patients, taking account of the results of both studies, will be discussed in Sections 7.R.2 and 7.R.3, respectively.

7.R.2 Efficacy

7.R.2.1 Design of Study 20090

PMDA asked the applicant to explain the rationale for the design of a global phase III study in ROP patients (CTD 5.3.5.1.1, Study 20090).

The applicant's explanation:

- Given that ROP is a rare disease with a limited number of patients etc., Study 20090 was initially designed as a single-arm study and planned to [redacted] based on [redacted] and [redacted], without [redacted]. Then, the study was re-designed as a randomized, open-label, laser-controlled, parallel-group study in ROP patients for the reasons below. Also, during the process of study planning, different primary efficacy analyses were planned for Japan and other countries or regions. In Japan, the efficacy of aflibercept was to be assessed using the later described primary endpoint, by demonstrating that the result in the aflibercept group was greater than the pre-specified threshold, while in other countries or regions, and the efficacy of aflibercept was to be assessed by comparison with laser photocoagulation as control.
  - ➢ At the time of designing Study 20090, laser photocoagulation was the standard of care for the treatment of Type 1 ROP[23)] and aggressive posterior retinopathy of prematurity (AP-ROP), i.e., the target diseases for the study (*Journal of Japanese Ophthalmological Society*. 2012; 116: 683-702). Meanwhile, the BEAT-ROP study of a VEGF inhibitor, bevacizumab, showed a trend towards increased efficacy of intravitreal bevacizumab as compared with conventional laser therapy for severe Zone I ROP and AP-ROP (*N Engl J Med*. 2011; 364: 603-15), and since then, the off-label use of intravitreal bevacizumab in these ROP patients have been reported in Japan and overseas (*Journal of Japanese Ophthalmological Society*. 2012; 116: 683-702). Although the procedure and prognosis of laser photocoagulation have been established, given that there are concerns about the risk of long-term ocular complications such as increased high myopia and reduced peripheral vision (*Journal of Japanese Ophthalmological Society*. 2020; 124: 1013-19), [redacted] was anticipated with the inclusion of laser photocoagulation as the control in Study 20090. Taking account of these points and given that ROP is a rare disease with a limited number of patients etc., Study 20090 was planned to be conducted as a single-arm study. Then, for the primary efficacy analysis in Japan, the success criterion for the study was to be defined, and the efficacy of aflibercept was to be assessed based on comparison with the pre-specified threshold using a frequentist method.
  - ➢ Outside Japan, [redacted], in addition to [redacted] of Study 20090 and a global phase III study (CTD 5.3.5.1.2, Study 20275), [redacted]

23) ROP with Zone I stage 1 plus disease, stage 2 plus disease, and stage 3 and stage 3 plus disease and Zone II stage 2 plus disease and stage 3 plus disease

[redacted].
In its course, to avoid [redacted], [redacted] and [redacted] in Study 20090. Given the above points etc., laser photocoagulation (a randomization ratio of 2:1 to receive aflibercept or laser photocoagulation) was included as a control group in Study 20090, and the efficacy of aflibercept was to be assessed by defining the success criterion[25)] for the comparison of aflibercept with laser photocoagulation in terms of the primary endpoint of the response probability estimated using a Bayesian statistical model. A fully masked study of IVT aflibercept compared to laser photocoagulation was considered technically not feasible because laser treatment produces burns and scars that are readily detectable. Thus, the study was to be conducted in an open-label manner.

- As described above, the study plan was developed in Japan and other countries or regions concurrently. In the end, Study 20090 was planned to be conducted by using laser photocoagulation as the control, including Japan. However, because of the limited number of ROP patients, it would be difficult, in terms of feasibility, to [redacted] based on [redacted] while [redacted]. Given these points etc., the above primary efficacy analysis plan for Japan, which was developed on the premise that the study is conducted as a single-arm study, was not changed, and the efficacy of aflibercept was to be assessed using the success criterion based on comparison with the pre-specified threshold.

- The primary endpoint for Study 20090 was defined as "the proportion of subjects with absence of active ROP and unfavorable structural outcomes[14)] at 24 weeks after starting study treatment," as in the RAINBOW study, a randomized study on ranibizumab versus laser photocoagulation in ROP patients (*Lancet.* 2019; 394: 1551-9), based on the following points.
  - The treatment goals for ROP are the prevention of severe active disease and avoidance of serious visual impairment (*Journal of Japanese Ophthalmological Society.* 2012; 116: 683-702, *Journal of Japanese Ophthalmological Society.* 2020; 124: 1013-19). "Absence of active ROP" is absence of ROP requiring treatment, suggesting well-controlled disease. Since the results of the ETROP study that evaluated the efficacy of early laser treatment versus conventional management in ROP patients (*Trans Am Ophthalmol Soc*. 2004; 102: 233-48; discussion 248-50) showed an association between unfavorable structural outcomes and the long-term prognosis for visual function, "absence of unfavorable structural outcomes" should suggest the preservation of good visual acuity. Based on the above, since the absence of both active ROP and unfavorable structural outcomes was considered clinically meaningful, the proportion of subjects with absence of these findings was to be evaluated as the primary endpoint.

24) [redacted] Study 20090 [redacted] Study [redacted] ([redacted]20[redacted]; [redacted]), [redacted] Study. These analysis results are not included in the clinical data package in Japan.

25) The primary endpoint was to be analyzed using a Bayesian statistical model with a noninformative prior probability distribution for the response probability for a single eye. Success of Study 20090 was to be concluded, if the response probability for aflibercept was greater than the one for laser minus 5 percentage points with at least 95% probability. This was the case if the lower limit of the two-sided 90% credible interval for the treatment difference (aflibercept − laser photocoagulation) was greater than −5%.

- ➢ Following ranibizumab injection in ROP patients, while the disease activity regressed within 4 weeks after the first treatment in many patients, many of recurrences occurred within 14 weeks after the first treatment (*JAMA Pediatr*. 2018; 172: 278-86). Given these findings and ROP stabilization at ≥14 weeks after the first treatment, 24 weeks after starting study treatment was selected as the timing of the primary endpoint.

- The success criterion for the primary efficacy analysis in Japan for Study 20090 was defined based on the results from the RAINBOW study of ranibizumab versus laser photocoagulation. If the response rate in the aflibercept group of Study 20090 was shown to be greater than the treatment success rate in the laser group of the RAINBOW study (66.2% [45 of 68 subjects]), the efficacy of aflibercept would be comparable or higher than that of laser therapy and considered clinically meaningful. Thus, a study design similar to that of the RAINBOW study (e.g., the study population [the location, stage, etc. of ROP lesion] and the primary endpoint) was selected for Study 20090, and success of the study was to be concluded if the lower limit of the two-sided 95% confidence interval for the response rate in the aflibercept group was greater than the threshold of 66% that was chosen, referring to the result in the laser group of the RAINBOW study.

PMDA's view:

- As to the design of Study 20090, although concerns about the risk of long-term ocular complications of laser photocoagulation such as increased high myopia and reduced peripheral vision are understandable, given that laser photocoagulation was the standard of care for ROP patients, i.e., the study population for Study 20090, at the time of initiating the study, and that laser photocoagulation was included as a control group also in the preceding RAINBOW study of ranibizumab, etc., there is no major problem with conducting Study 20090 as a laser-controlled study, including Japan.
- Then, with regard to the primary efficacy analysis in Japan for Study 20090, assessment based on comparison with laser photocoagulation as a control group may have been more appropriate, taking account of comparability. However, given the applicant's explanation (the number of ROP patients is limited, and there were restrictions on alternative study designs for efficacy assessment) etc., the planned analysis (efficacy assessment of aflibercept based on comparison with the pre-specified threshold that was chosen, referring to the result in the laser group of the RAINBOW study) is understandable.
- There is no particular problem with the primary endpoint chosen for Study 20090 of "the proportion of subjects with absence of active ROP and unfavorable structural outcomes [14)] at 24 weeks after starting study treatment." Although the success criterion for the primary efficacy analysis in Japan is understandable as the criterion based on the available information at the time of designing the study, the efficacy of aflibercept in the treatment of ROP, taking account of the results from Study 20090, will be discussed in Section 7.R.2.2.

7.R.2.2 Efficacy taking account of the results from Study 20090

In Study 20090, the lower limit of the two-sided 95% confidence interval for the primary endpoint in the aflibercept group was greater than the pre-specified threshold of 66%, and the success criterion for the primary

efficacy analysis in Japan was fulfilled, whereas the response rate in the laser group of Study 20090 was 84.2%, which was higher than 66.2%, i.e., the treatment success rate in the laser group of the RAINBOW study, which was used as a reference to choose the threshold value [see Section 7.1.1].

PMDA asked the applicant to explain the efficacy of aflibercept in the treatment of ROP based on the results from Study 20090, taking also account of the above point.

First, the applicant explained the factors contributing to the result that the response rate in the laser group of Study 20090 was higher than the treatment success rate in the laser group of the RAINBOW study and the interpretation of the results of the primary efficacy analysis in Japan, taking also account of this point, as follows:

- The response rate in the laser group of Study 20090 was higher than the treatment success rate in the laser group of the RAINBOW study. Given the following points, this may be attributable to differences in the study design (the criteria for retreatment with laser) and the incidence of deaths and patient characteristics (gestational age at birth and birth weight) in the laser group between the studies, the timing of Study 20090, etc.
  - Although the design of Study 20090 was largely similar to that of the RAINBOW study, there were some differences. Among which, as to the criteria for retreatment with laser, retreatment with laser was allowed at any time point in Study 20090,[11)] while retreatment was allowed up to Day 11 and a switch to rescue ranibizumab was considered treatment failure in the RAINBOW study. In the laser group of Study 20090, 2 were responders and 2 were non-responders among 4 retreated subjects. If assessed using the same criteria as in the RAINBOW study, these 2 responders would be considered treatment failure. Since retreatment with laser is performed at any time point after the first treatment in clinical practice, the criteria for retreatment with laser in Study 20090 reflected the treatment practice at medical institutions.
  - Since ROP patients are vulnerable to serious multi-organ comorbidities due to their underlying prematurity, they may die, regardless of study treatment, during the study period. For the primary endpoint of Study 20090 and the RAINBOW study, a subject who died was to be considered treatment failure. While 4 of 74 subjects (5.4%) died in the laser group of the RAINBOW study, no deaths were reported in the laser group of Study 20090.
  - Generally, infants with a lower gestational age at birth or a lower birth weight have an increased frequency of severe ROP such as Zone I disease characterized by incomplete vascularization (*Br J Ophthalmol*. 2002; 86: 1122-6, *Journal of Japanese Ophthalmological Society.* 2004; 108: 600-5), and the response rate with laser therapy tends to be lower in such severe cases (*Trans Am Ophthalmol Soc*. 2004; 102: 233-48, *N Engl J Med*. 2011: 364: 603-15). Table 7 shows the results of subgroup analyses of the response rate in Study 20090 and the treatment success rate in the RAINBOW study. The proportion of patients with a gestational age at birth of ≤24 weeks and the proportion of patients with a birth weight of ≤750 g tended to be lower in Study 20090 than in the RAINBOW study, and the response rate in the laser group of Study 20090 tended to be higher than the treatment success rate in

the laser group of the RAINBOW study among these patient subgroups. However, no clear factors contributing to the differences in the efficacy of laser treatment in the subgroups of patients with a gestational age at birth of ≤24 weeks or a birth weight of ≤750 g between the studies could be identified.

Table 7. Results of subgroup analysis of the primary endpoint in Study 20090 and in the RAINBOW study (Study 20090 [FAS] and the RAINBOW study [FAS])

		20090				RAINBOW			
		Aflibercept		Laser		Ranibizumab 0.2 mg		Laser	
		No. of evaluable subjects[a)]	Response rate[b)]	No. of evaluable subjects[a)]	Response rate[b)]	No. of evaluable subjects[a) c)]	Treatment success rate[d)]	No. of evaluable subjects[a) c)]	Treatment success rate[d)]
Overall population		75	82.7 (62)	38	84.2 (32)	70	80.0 (56)	68	66.2 (45)
Gender	Male	41 (54.7)	85.4 (35)	19 (50.0)	89.5 (17)	33 (47.1)	84.8 (28)	35 (51.5)	54.3 (19)
	Female	34 (45.3)	79.4 (27)	19 (50.0)	78.9 (15)	37 (52.9)	75.7 (28)	33 (48.5)	78.8 (26)
Gestational age at birth	≤24 weeks	6 (8.0)	66.7 (4)	4 (10.5)	100 (4)	29 (41.4)	75.9 (22)	27 (39.7)	44.4 (12)
	>24 weeks and <27 weeks	43 (57.3)	83.7 (36)	24 (63.2)	79.2 (19)	18 (25.7)	88.9 (16)	15 (22.1)	60.0 (9)
	≥27 weeks	26 (34.7)	84.6 (22)	10 (26.3)	90.0 (9)	23 (32.9)	78.3 (18)	26 (38.2)	92.3 (24)
Birth weight	≤750 g	32 (42.7)	81.3 (26)	17 (44.7)	76.5 (13)	36 (51.4)	80.6 (29)	35 (51.5)	51.4 (18)
	>750 g and <1000 g	22 (29.3)	86.4 (19)	14 (36.8)	92.9 (13)	15 (21.4)	73.3 (11)	11 (16.2)	72.7 (8)
	≥1000 g	21 (28.0)	81.0 (17)	7 (18.4)	85.7 (6)	16 (22.9)	81.3 (13)	15 (22.1)	86.7 (13)
Zone of ROP[e)]	Zone I (including AP-ROP)	42 (56.0)	76.2 (32)	18 (47.4)	66.7 (12)	28 (40.0)	67.9 (19)	23 (33.8)	60.9 (14)
	Zone II (including AP-ROP)	30 (40.0)	93.3 (28)	19 (50.0)	100.0 (19)	42 (60.0)	88.1 (37)	45 (66.2)	68.9 (31)
AP-ROP[e)]	Yes	21 (28.0)	71.4 (15)	11 (28.9)	54.5 (6)	10 (14.3)	40.0 (4)	8 (11.8)	62.5 (5)
	No	51 (68.0)	88.2 (45)	26 (68.4)	96.2 (25)	60 (85.7)	86.7 (52)	60 (88.2)	66.7 (40)

a) Number of evaluable subjects (Percentage of subjects in the subgroup in the overall population in each treatment group [%])
b) Response rate (%) (No. of responders)
c) Number of evaluable subjects with non-missing data (including imputed data) for the primary endpoint
d) Treatment success rate (%) (Number of subjects with treatment success)
e) MISSING for 2 subjects and NO GRADING for 1 subject in the aflibercept group and NO GRADING for 1 subject in the laser group in Study 20090

- Ranibizumab was approved for the indication of ROP in September 2019 in the EU and in November 2019 in Japan, and Study 20090 was initiated in September 2019 at around the same time as this approval. Thus, physicians with advanced skills in laser photocoagulation who do not hesitate to perform laser treatment, even if patients with severe ROP such as Zone I disease or ROP patients for whom general anesthesia may be difficult are randomized to laser treatment, may have participated in Study 20090.

- On the other hand, the response rate was 82.7% (62 of 75 subjects) in the aflibercept group of Study 20090, and the treatment success rate was 80.0% (56 of 70 subjects) in the ranibizumab 0.2 mg group of the RAINBOW study, showing similar results for the drug groups of the two studies. The criteria for retreatment with aflibercept or ranibizumab were similar between Study 20090 and the RAINBOW study. There were no major differences in the incidence of deaths, i.e., 3 of 75 subjects (4.0%) in the aflibercept group of Study 20090 and 4 of 74 subjects (5.4%) in the ranibizumab 0.2 mg group of the

RAINBOW study. According to the results of subgroup analyses of the response rate in the aflibercept group of Study 20090 and the treatment success rate in the ranibizumab 0.2 mg group of the RAINBOW study by gestational age at birth and birth weight (Table 7), the response rate tended to be slightly lower in the subgroup of patients with a gestational age at birth of ≤24 weeks in Study 20090, but there were no marked differences across other subgroups.

- The design of Study 20090 was largely similar to that of the RAINBOW study. For the primary efficacy analysis in Japan, the threshold value was chosen, referring to the treatment success rate in the laser group of the RAINBOW study. As described above, though differences in the study design and patient characteristics between Study 20090 and the RAINBOW study, etc., may have affected efficacy evaluation in the laser group of Study 20090, there were no such effects in the aflibercept group of Study 20090. Thus, the response rate in the laser group of Study 20090 was higher than the treatment success rate in the laser group of the RAINBOW study, which did not directly affect efficacy evaluation in the aflibercept group of Study 20090. It can be concluded that the efficacy of aflibercept is comparable or higher than that of laser photocoagulation because the success criterion for the primary efficacy analysis in Japan was met.
- With respect to a secondary endpoint of Study 20090, "requirement for intervention with a second treatment modality[26)] from baseline to Week 24," the proportion of subjects who required such intervention with a second treatment modality was 10.7% (8 of 75 subjects) in the aflibercept group and 13.2% (5 of 38 subjects) in the laser group. The proportion of patients who required intervention with a second treatment modality due to worsening of ROP or the presence of ROP requiring treatment tended to be lower in the aflibercept group than in the laser group, supporting the results of the primary endpoint.

Then, the applicant explained the efficacy of aflibercept in Japanese patients with ROP and the factors affecting the efficacy of aflibercept as follows:

- Regarding the efficacy of aflibercept in Japanese patients with ROP, Table 8 shows the results of the primary endpoint of Study 20090 in the Japanese subgroup. There were no major differences between the overall population and the Japanese subgroup, and consistent results between the overall population and the Japanese subgroup were obtained.

Table 8. Proportion of subjects with absence of active ROP and unfavorable structural outcomes at 24 weeks after starting study treatment (the response rate) in the overall population and Japanese and non-Japanese subgroups (Study 20090, FAS)

	Aflibercept		Laser	
	No. of responders/No. of evaluable subjects	Response rate [95% CI] [a)] (%)	No. of responders/No. of evaluable subjects	Response rate [95% CI] [a)] (%)
Overall population	62/75	82.7 [72.2, 90.4]	32/38	84.2 [68.7, 94.0]
Japanese subgroup	9/10	90.0 [55.5, 99.7]	5/6	83.3 [35.9, 99.6]
Non-Japanese subgroup	53/65	81.5 [70.0, 90.1]	27/32	84.4 [67.2, 94.7]

a) Clopper-Pearson exact CI

- With respect to the factors that may affect the efficacy of aflibercept, Table 7 shows the results of subgroup analysis of the primary endpoint of Study 20090 by patient characteristics. Although the response rate in the aflibercept group tended to be lower in the subgroup of patients with severe Zone I ROP (including

26) Rescue treatment and treatment with any other surgical or nonsurgical treatment for ROP (e.g., IVT anti-VEGF injection, ablative laser therapy, cryotherapy, or vitrectomy captured as concomitant therapies)

AP-ROP) and the subgroup of patients with AP-ROP, a similar trend was observed also in the laser group. A similar trend was reported also in the RAINBOW study of ranibizumab (*Lancet.* 2019; 394: 1551-9). The response rate in the aflibercept group tended to be lower also in the subgroup of patients with a gestational age at birth of ≤24 weeks. The possibility that the efficacy of aflibercept is relatively smaller in these subgroups cannot be ruled out. However, the interpretation of the results from the limited number of subjects has limitations. Based on the above, there were no major problems with the efficacy of aflibercept by patient characteristics.

Based on the above, the applicant explained the efficacy of aflibercept in the treatment of ROP, taking account of the results from Study 20090, as follows:

- The results of the primary efficacy analysis in Japan for Study 20090 showed that the efficacy of aflibercept is comparable or higher than that of laser photocoagulation in ROP patients including Japanese patients.
- Then, the risk of long-term ocular complications such as increased high myopia and reduced peripheral vision, which is a concern for laser photocoagulation, is considered low with aflibercept. Aflibercept is advantageous in terms of less time consuming, less burden on the infant, etc. [see Section 7.R.4]. Given these points, aflibercept is clinically meaningful for patients with ROP.
- Regarding the long-term efficacy of aflibercept in the treatment of ROP, though there was no particular problem with the efficacy of aflibercept up to 1 year of age (approximately 10 months from baseline in Study 20090)[19] in Study 20275 [see Section 7.1.2], the ongoing Study 20275 will be continued as a post-marketing clinical study, and visual function (best-corrected visual acuity, spherical equivalent refraction, etc.) will be evaluated until subjects are 5 years of age.

Then, PMDA asked the applicant to explain the rationale for the success criterion[25] for the primary efficacy analysis in the countries or regions other than Japan for Study 20090 and the results of the analysis.

First, the applicant explained the rationale for the success criterion for the primary efficacy analysis in the countries or regions other than Japan for Study 20090 as follows:

- Given that the risk of long-term ocular complications such as increased high myopia and reduced peripheral vision, which is a concern for laser photocoagulation, is considered low with anti-VEGF therapy, etc., aflibercept can be positioned as a treatment option for patients with ROP even if aflibercept and laser therapy have comparable effects on the primary endpoint of Study 20090. Thus, the success criterion for the primary efficacy analysis in the countries or regions other than Japan was defined as "response probability for aflibercept was greater than the one for laser minus 5 percentage points with at least 95% probability," and the non-inferiority of aflibercept to laser was to be tested.
- With the target sample size of 102 infants (68 in the aflibercept group and 34 in the laser group), the above success criterion for non-inferiority would be achieved with a power of 81%, assuming that the laser response probability in Study 20090 was similar to historic data and that the response probability for aflibercept in Study 20090 was 15% higher than that for laser, but not higher than 95%.

Subsequently, the applicant explained the results of the primary efficacy analysis in the countries or regions other than Japan for Study 20090 as follows:

- Regarding the results of the primary efficacy analysis in the countries or regions other than Japan for Study 20090, Table 9 shows the primary endpoint of "the proportion of subjects with absence of active ROP and unfavorable structural outcomes at 24 weeks after starting study treatment (the response probability)" estimated using a Bayesian statistical model. The probability that the treatment difference in the response probability (aflibercept − laser photocoagulation) is greater than −5% was 88.4%. The pre-defined success criterion (at least 95% probability) was not met, and the non-inferiority of aflibercept to laser treatment could not be concluded.

Table 9. Proportion of subjects with absence of active ROP and unfavorable structural outcomes at 24 weeks after starting study treatment (the response probability) (Study 20090, FAS)

	Aflibercept	Laser	Treatment difference[a)]
N	75	38	−
Response probability[b)] [90% credible interval] (%)	85.5 [78.0, 91.3]	82.1 [70.5, 90.8]	3.4 [-8.0, 16.2]
Probability that treatment difference is greater than −5% (%)	−	−	88.4

Analyzed using a Bayesian statistical model with a noninformative prior probability distribution for the response probability for a single eye.
a) Aflibercept − laser photocoagulation
b) Median of posterior distribution

- The pre-defined success criterion was not met, which may be attributable to the insufficient power of the study because the assumption at the time of designing the study that the response probability for aflibercept is 15% higher than that for laser was an overestimation. In Study 20090, although the response probability (the median of posterior distribution) for aflibercept (85.5%) was higher than that for laser (82.1%), the response probability for laser was higher than expected at the time of designing the study, resulting in no expected treatment difference.
- As described above, though the pre-defined success criterion for the primary efficacy analysis in the countries or regions other than Japan for Study 20090 was not met, given that the response probability (the median of posterior distribution) for aflibercept tended to be higher than that for laser, the results do not necessarily mean that aflibercept is less efficacious than laser photocoagulation. When the data from the laser group of Study 20090 are supplemented by the data from the laser group from historical controls in an analysis, the power of the analysis can be increased by including the results of the BEAT-ROP and RAINBOW studies. In this analysis, the same success criterion as the pre-defined success criterion for the primary efficacy analysis in the countries or regions other than Japan for Study 20090 was met.

PMDA's view:

- In Study 20090, the success criterion for the primary efficacy analysis in Japan was met because the lower limit of the two-sided 95% confidence interval for the primary endpoint in the aflibercept group was greater than the pre-specified threshold of 66%. On the other hand, the response rate in the laser group of Study 20090 was higher than the treatment success rate in the laser group of the RAINBOW study, which was used as a reference to choose the threshold value. The applicant explained that this did not directly affect efficacy evaluation in the aflibercept group of Study 20090, and that it can be concluded

from the results of the primary analysis that the efficacy of aflibercept is comparable or higher than that of laser photocoagulation. However, given the following points etc., efficacy evaluation based on the results of the primary analysis has limitations, and it is difficult to conclude that the efficacy of aflibercept in the treatment of ROP was shown just because the Japanese success criterion was met.

- In both the aflibercept and laser groups, the proportion of patients with a gestational age at birth of ≤24 weeks was particularly lower in Study 20090 than in the RAINBOW study [see Table 7], and there were differences in the characteristics of patients enrolled between the two studies. The possibility that such differences affected efficacy evaluation in the aflibercept group of Study 20090 based on comparison with the threshold value cannot be ruled out.
- There was a trend towards higher efficacy in the laser group of Study 20090 than in the laser group of the RAINBOW study among the subgroups of patients with a gestational age at birth of ≤24 weeks or a birth weight of ≤750 g. No factors contributing to these differences could be identified, and the possibility that this affected the efficacy evaluation of aflibercept cannot be ruled out.
- Although the applicant explained that physicians with advanced skills in laser photocoagulation may have participated in Study 20090 following the expansion of the indication for ranibizumab to include ROP, if there were differences in the background against which the study was conducted, such as the level of the investigator's skills in laser photocoagulation, between Study 20090 and the RAINBOW study, it is not appropriate to assess the efficacy of aflibercept based on comparison with the threshold value that was chosen, referring to the result in the laser group of the RAINBOW study.

- On the other hand, the primary efficacy analysis in Japan for Study 20090 was not comparison of aflibercept vs. laser photocoagulation, and it should also be noted that the number of subjects in the laser group was limited compared with that in the aflibercept group. However, the response rates [95% CI] in the aflibercept and laser groups of Study 20090 were 82.7 [72.2, 90.4]% and 84.2 [68.7, 94.0]%, respectively, showing no trend towards aflibercept being clearly less efficacious than laser treatment, and the observed response rate in the aflibercept group indicates that aflibercept is expected to be clinically meaningful in the treatment of ROP. In addition, the results of a secondary endpoint of Study 20090, "requirement for intervention with a second treatment modality from baseline to Week 24" and the provisional results as of the data cutoff date concerning "the proportion of subjects with absence of active ROP and unfavorable structural outcomes[14)] at 1 year of age" in Study 20275 also showed a similar trend in the aflibercept and laser groups. Based on the above, taking account of the overall results of Study 20090 etc., the efficacy of aflibercept in the treatment of ROP is expected.
- There were no major differences in the results of the primary endpoint for Study 20090 between the overall population and the Japanese subgroup, and the efficacy of aflibercept is expected also in Japanese patients with ROP. Regarding the results of subgroup analysis of the primary endpoint of Study 20090 by patient characteristics (Table 7), though especially, the number of subjects with a gestational age at birth of ≤24 weeks was limited, the applicant's explanation that there were no major problems with the efficacy of aflibercept by patient characteristics is acceptable.
- The primary efficacy analysis in the countries or regions other than Japan for Study 20090 failed to demonstrate the non-inferiority of aflibercept to laser photocoagulation. The applicant's explanation (this

is attributable to an observed laser response rate that was higher than expected, resulting in the insufficient power) is understandable to some extent.

- The applicant's explanation about the long-term efficacy of aflibercept in the treatment of ROP (the ongoing Study 20275 will be continued as a post-marketing clinical study, and visual function will be evaluated until subjects are 5 years of age) is appropriate.

7.R.2.3 Proportion of subjects with recurrence of ROP

The applicant's explanation about the proportion of subjects with recurrence of ROP:

A secondary endpoint of Study 20090, "the proportion of subjects with recurrence of ROP[27)] from baseline to Week 24" is shown in Table 10. Although the proportion of subjects with recurrence of ROP was higher in the aflibercept group than in the laser group in the overall population, generally, the recurrence rate after treatment of ROP is known to be higher in the anti-VEGF therapy group than in the laser group (*Acta Ophthalmol*. 2016; 94: e744-52). Based on the above, since appropriate treatment needs to be performed promptly after the recurrence of ROP, the information on the proportion of subjects with recurrence of ROP in Study 20090 will be provided using information materials for healthcare professionals etc., and then the need for regular funduscopic examination etc. after treatment with aflibercept in ROP patients will be advised.

The proportion of subjects with recurrence of ROP in the aflibercept group tended to be higher in the Japanese subgroup than in the non-Japanese subgroup (Table 10). Though the interpretation of the results has limitations due to the limited number of subjects in the Japanese subgroup, one of its contributing factors is considered lower birth weights in the Japanese subgroup than in the non-Japanese subgroup.[28)] In all of 7 Japanese subjects with recurrence of ROP[29)] in the aflibercept group, each study eye with recurrence received 1 retreatment, and 6 of the 7 subjects were considered responders with respect to the primary endpoint at 24 weeks after starting study treatment.

Table 10. Proportion of subjects with recurrence of ROP from baseline to Week 24 in the overall population and Japanese and non-Japanese subgroups (Study 20090, FAS)

	Aflibercept	Laser
Overall population	26.7 (20/75)	10.5 (4/38)
Japanese subgroup	70.0 (7/10)	16.7 (1/6)
Non-Japanese subgroup	20.0 (13/65)	9.4 (3/32)

Proportion (%) (n/N)

PMDA's view:

The applicant's explanation (the information on the proportion of subjects with recurrence of ROP in Study 20090 will be provided using information materials for healthcare professionals etc., and then the need for regular funduscopic examination etc. after treatment with aflibercept in ROP patients will be advised.) is acceptable. Though the number of subjects in the Japanese subgroup was limited, as the proportion of subjects

27) Recurrence of ROP was defined as the need for retreatment or rescue treatment in cases where the question "presence of active ROP requiring treatment" (with or without the retinal findings listed in 5)) had been previously answered by investigators with "no."

28) Birth weights (mean ± SD) were 694.7 ± 169.8 g (672.2 ± 170.4 g in the aflibercept group, 732.2 ± 177.5 g in the laser group) in the Japanese subgroup and 889.7 ± 288.8 g (913.3 ± 309.9 g, 841.9 ± 237.8 g) in the non-Japanese subgroup.

29) In Study 20090, all of 10 Japanese subjects in the aflibercept group had 2 study eyes, and among the 7 subjects with recurrence of ROP, 4 had recurrence in both eyes, and 3 had recurrence in 1 eye.

with recurrence of ROP in the aflibercept group tended to be higher in the Japanese subgroup than in the non-Japanese subgroup, the information on the proportion of subjects with recurrence of ROP in the Japanese subgroup should also be provided using information materials etc.

A final conclusion on the appropriateness of the above conclusion by PMDA in Section 7.R.2 will be made, taking account of comments from the Expert Discussion.

7.R.3 Safety

PMDA's conclusion:

Based on the clinical study data submitted and the considerations in Sections 7.R.3.1 to 7.R.3.5, although particular attention should be paid to the possible occurrence of intraocular inflammation, increased intraocular pressure, retinal tear or detachment, traumatic cataract, and arterial thromboembolic events following administration of aflibercept in ROP patients as in the previously approved adult indications, aflibercept has acceptable safety in ROP patients, provided that the package insert includes appropriate warnings and precautions regarding these events, etc. However, post-marketing information on the safety of aflibercept in ROP patients, including effects on neurodevelopment and growth, should be collected.

A final conclusion on the appropriateness of the above conclusion will be made, taking account of comments from the Expert Discussion.

7.R.3.1 Safety profile of aflibercept

PMDA asked the applicant to explain the safety profile of aflibercept in ROP patients, including its differences between ROP and the adult indications, taking account of the incidence of adverse events in global phase III studies (CTD 5.3.5.1.1, Study 20090; CTD 5.3.5.1.2, Study 20275).

The applicant's explanation:

- Table 11 shows the incidence of adverse events in the study eyes in Studies 20090 and 20275 in ROP patients or clinical studies in the adult indications for aflibercept.[30)] In Studies 20090 and 20275, the incidences of all adverse events and adverse events leading to study discontinuation were similar between the aflibercept and laser groups. Although the incidence of serious adverse events other than deaths tended to be higher in the aflibercept group than in the laser group, those events reported by ≥2 subjects in the aflibercept group were retinal detachment (5 subjects) and retinal haemorrhage (2 subjects) in Study 20090 and retinal detachment (2 subjects) in Study 20275, and a causal relationship to study treatment was denied for all those events except for retinal detachment (2 subjects) (1 subject each in Studies 20090 and 20275). In addition, although the incidences of myopia, retinal detachment, etc. as specific adverse events following administration of aflibercept, were higher in ROP patients than in the adult indications, as those

30) A foreign phase III study (the VIEW1 study) and a global phase III study (the VIEW2 study) in patients with exudative AMD, a foreign phase III study (the VISTA-DME study), a global phase III study (the VIVID-DME study), and a Japanese phase III study (the VIVID-Japan study) in DME patients, a foreign phase III study (the COPERNICUS study) and a global phase III study (the GALILEO study) in CRVO patients, a global phase III study in BRVO patients (the VIBRANT study), a global phase III study in mCNV patients (the MYRROR study), and Japanese phase III studies in patients with neovascular glaucoma (the VEGA study, the VENERA study)

events were observed also in the laser group of Studies 20090 and 20275, and retinal detachment can result from the progression of ROP, those events were likely to be attributed to the primary disease of ROP. The incidences of other events including retinal haemorrhage observed in ROP patients largely fell within the incidence ranges in the adult indications.

Table 11. Incidence of adverse events [a)] in study eyes in clinical studies in ROP patients or adult indications (Safety analysis set)

	20090		20275		Adult indications
	Aflibercept	Laser	Aflibercept	Laser	Pooled aflibercept population[b)]
N	75	38	60	29	2917
All adverse events	42 (56.0)	20 (52.6)	14 (23.3)	6 (20.7)	2050 (70.3)
Serious adverse events other than deaths	10 (13.3)	3 (7.9)	5 (8.3)	0	100 (3.4)
Adverse events leading to study discontinuation	3 (4.0)	1 (2.6)	0	0	34 (1.2)
Main adverse events (Among events reported in Study 20090, those reported by ≥5% of subjects in either group or population)					
Myopia	8 (10.7)	3 (7.9)	2 (3.3)	2 (6.9)	1 (<0.1)
Retinal haemorrhage	6 (8.0)	6 (15.8)	1 (1.7)	0	323 (11.1)
Retinal detachment	5 (6.7)	2 (5.3)	2 (3.3)	0	8 (0.3)
Astigmatism	5 (6.7)	3 (7.9)	2 (3.3)	4 (13.8)	3 (0.1)
Conjunctival haemorrhage	4 (5.3)	0	0	0	729 (25.0)
Intraocular pressure increased	3 (4.0)	0	0	0	199 (6.8)
Conjunctivitis	3 (4.0)	4 (10.5)	0	1 (3.4)	44 (1.5)
Eyelid oedema	2 (2.7)	3 (7.9)	0	0	13 (0.4)
Strabismus	0	3 (7.9)	2 (3.3)	2 (6.9)	1 (<0.1)
Nystagmus	0	2 (5.3)	0	0	0
Cataract	0	1 (2.6)	0	0	188 (6.4)

n (Incidence [%])

a) Adverse events that occurred during study period for Study 20090, adverse events that occurred during Study 20090 and remained unresolved at the start of Study 20275 or adverse events that occurred after the start of Study 20275 for Study 20275, and treatment-emergent (reported after the first and not later than 30 days after the last administration of study treatment) adverse events for adult indications were counted.

b) Pooled aflibercept group from studies in adult indications (Footnote 30))

- Table 12 shows the incidence of non-ocular adverse events in Studies 20090 and 20275 in ROP patients or the clinical studies of aflibercept in the adult indications.[30)] In Studies 20090 and 20275, the incidences of all adverse events and adverse events leading to study discontinuation were similar between the aflibercept and laser groups, and the incidence of serious adverse events other than deaths tended to be lower in the aflibercept group than in the laser group. Although there were 3 deaths only in the aflibercept group of Study 20090, a causal relationship to study treatment was denied for all those cases. Although bronchopulmonary dysplasia, etc., were observed as specific adverse events following administration of aflibercept in ROP patients, unlike in the adult indications, those events are the ones expected in ROP patients or preterm infants.

Table 12. Incidence of non-ocular adverse events[a)] in clinical studies in ROP patients or adult indications (Safety analysis set)

	20090		20275		Adult indications
	Aflibercept	Laser	Aflibercept	Laser	Pooled aflibercept population[b)]
N	75	38	60	29	2917
All adverse events	59 (78.7)	30 (78.9)	21 (35.0)	10 (34.5)	2311 (79.2)
Deaths	3 (4.0)	0	0	0	48 (1.6)
Serious adverse events other than deaths	15 (20.0)	14 (36.8)	3 (5.0)	2 (6.9)	604 (20.7)
Adverse events leading to study discontinuation	0	0	0	0	89 (3.1)
Main adverse events (Among events reported in Study 20090, those reported by ≥5% of subjects in either group or population)					
Pyrexia	9 (12.0)	2 (5.3)	4 (6.7)	2 (6.9)	67 (2.3)
Bronchiolitis	7 (9.3)	2 (5.3)	1 (1.7)	0	0
Bronchopulmonary dysplasia	4 (5.3)	0	0	0	0
Nasopharyngitis	4 (5.3)	0	5 (8.3)	0	337 (11.6)
Apnoea	3 (4.0)	3 (7.9)	0	0	0
Bronchitis	3 (4.0)	0	0	0	153 (5.2)
Inguinal hernia	3 (4.0)	2 (5.3)	0	0	11 (0.4)
Umbilical hernia	1 (1.3)	4 (10.5)	0	0	3 (0.1)
Anaemia	1 (1.3)	2 (5.3)	0	0	100 (3.4)
Haemorrhage subcutaneous	0	3 (7.9)	0	0	0
Anaemia neonatal	0	2 (5.3)	0	0	0
Bacterial disease carrier	0	2 (5.3)	0	0	0
Infantile apnoea	0	2 (5.3)	0	0	0
Urinary tract infection	0	1 (2.6)	0	0	147 (5.0)

n (Incidence [%])

a) Adverse events that occurred during study period for Study 20090, adverse events that occurred during Study 20090 and remained unresolved at the start of Study 20275 or adverse events that occurred after the start of Study 20275 for Study 20275, and treatment-emergent (reported after the first and not later than 30 days after the last administration of study treatment) adverse events for adult indications were counted.

b) Pooled aflibercept group from studies in adult indications (Footnote 30))

- Table 13 shows the incidences of adverse events in the Japanese and non-Japanese subgroups in Studies 20090 and 20275. Although the interpretation of the results has limitations due to the limited number of subjects in the Japanese subgroup, there were no major differences in the incidences of all adverse events, deaths, serious adverse events other than deaths, and adverse events leading to study discontinuation in the aflibercept group between the Japanese and non-Japanese subgroups.

Table 13. Incidences of adverse events in the overall population and Japanese and non-Japanese subgroups (Studies 20090 and 20275, Safety analysis set)

		20090		20275[a)]	
		Aflibercept	Laser	Aflibercept	Laser
N	Overall population	75	38	60	29
	Japanese subgroup	10	6	8	3
	Non-Japanese subgroup	65	32	52	26
Study eyes					
All adverse events	Overall population	42 (56.0)	20 (52.6)	14 (23.3)	6 (20.7)
	Japanese subgroup	2 (20.0)	5 (83.3)	2 (25.0)	0
	Non-Japanese subgroup	40 (61.5)	15 (46.9)	12 (23.1)	6 (23.1)
Serious adverse events other than deaths	Overall population	10 (13.3)	3 (7.9)	5 (8.3)	0
	Japanese subgroup	0	0	0	0
	Non-Japanese subgroup	10 (15.4)	3 (9.4)	5 (9.6)	0
Adverse events leading to study discontinuation	Overall population	3 (4.0)	1 (2.6)	0	0
	Japanese subgroup	0	0	0	0
	Non-Japanese subgroup	3 (4.6)	1 (3.1)	0	0
Non-ocular					
All adverse events	Overall population	59 (78.7)	30 (78.9)	21 (35.0)	10 (34.5)
	Japanese subgroup	10 (100.0)	6 (100.0)	5 (62.5)	2 (66.7)
	Non-Japanese subgroup	49 (75.4)	24 (75.0)	16 (30.8)	8 (30.8)
Deaths	Overall population	3 (4.0)	0	0	0
	Japanese subgroup	1 (10.0)	0	0	0
	Non-Japanese subgroup	2 (3.1)	0	0	0
Serious adverse events other than deaths	Overall population	15 (20.0)	14 (36.8)	3 (5.0)	2 (6.9)
	Japanese subgroup	0	2 (33.3)	1 (12.5)	0
	Non-Japanese subgroup	15 (23.1)	12 (37.5)	2 (3.8)	2 (7.7)
Adverse events leading to study discontinuation	Overall population	0	0	0	0
	Japanese subgroup	0	0	0	0
	Non-Japanese subgroup	0	0	0	0

n (Incidence [%])

a) Adverse events that occurred during Study 20090 and remained unresolved at the start of Study 20275 or adverse events that occurred after the start of Study 20275 were counted.

- Based on the above, there were no major safety problems in the aflibercept group of Studies 20090 and 20275, and taking also account of differences in patient characteristics, the ocular and non-ocular safety profile of aflibercept is similar between ROP patients and the adult indications. No new safety concerns unique to ROP patients have been identified. There are also no safety concerns unique to Japanese ROP patients compared with non-Japanese ROP patients.

PMDA's view:

With respect to the incidences of adverse events in the study eyes and non-ocular adverse events in Studies 20090 and 20275 in ROP patients, there were no clinically relevant safety concerns in the aflibercept group compared with the laser group. The applicant's explanation (Although the incidences of retinal detachment, bronchopulmonary dysplasia, etc., were higher in ROP patients than in the adult indications, those events were likely to be attributed to the primary disease of ROP or preterm birth) is understandable, and no safety concerns that are clearly different from those in the adult indications, were suggested in ROP patients. Furthermore, there were no serious safety concerns in Japanese ROP patients in Studies 20090 and 20275. Based on the above, given the currently available data from Studies 20090 and 20275, the safety risk of aflibercept in ROP patients is acceptable, provided that the package insert includes appropriate warnings and precautions

regarding known events in the approved adult indications, etc. However, given that the population of patients with ROP is clearly different from the population of adult patients with the approved indications, and that there is limited clinical experience with aflibercept in Japanese patients in Studies 20090 and 20275, it is necessary to collect post-marketing information on the safety of aflibercept in Japanese patients with ROP.

In the following Sections 7.R.3.2 to 7.R.3.5, the impact of laser photocoagulation on the safety of aflibercept, systemic adverse events related to VEGF inhibition, the risk of neurodevelopmental delay, and growth effect will be discussed.

7.R.3.2 Impact of laser photocoagulation on the safety of aflibercept

PMDA asked the applicant to explain the potential impact of laser photocoagulation on the safety of aflibercept.

The applicant's explanation:

- Table 14 shows the incidence of adverse events by use of rescue treatment in a global phase III study (CTD 5.3.5.1.1, Study 20090).[31)] Events reported by ≥2 subjects who received rescue treatment in each treatment group were conjunctival oedema in 2 subjects, which were adverse events in the study eyes in the aflibercept group. The interpretation of the results has limitations due to the limited number of subjects who received rescue treatment. Though the incidence of adverse events tended to be higher in subjects who received rescue treatment, there was no trend towards a higher incidence of specific adverse events or clearly higher incidences of serious adverse events other than deaths or adverse events leading to study discontinuation.
- Based on the above, as there was no clinically relevant safety concern among subjects who received rescue treatment, no precautionary statement regarding the use of laser photocoagulation after administration of aflibercept or the use of aflibercept after administration of laser photocoagulation in the package insert is necessary.

Table 14. Incidences of adverse events in study eyes and non-ocular adverse events by use of rescue treatment (Study 20090, Safety analysis set)

	Subjects who received rescue treatment		Subjects who did not receive rescue treatment	
	Aflibercept	Laser	Aflibercept	Laser
N	5	4	70	34
Study eyes				
All adverse events	4 (80.0)	2 (50.0)	38 (54.3)	18 (52.9)
Serious adverse events other than deaths	1 (20.0)	1 (25.0)	9 (12.9)	2 (5.9)
Adverse events leading to study discontinuation	1 (20.0)	0	2 (2.9)	1 (2.9)
Non-ocular				
All adverse events	4 (80.0)	4 (100.0)	55 (78.6)	26 (76.5)
Serious adverse events other than deaths	1 (20.0)	0	14 (20.0)	14 (41.2)
Adverse events leading to study discontinuation	0	0	0	0

n (Incidence [%])

31) Regarding efficacy in subjects who received rescue treatment, 5 subjects in the aflibercept group received rescue treatment with laser. When eyes that received rescue treatment were not considered non-responders, the response rate was 80.0% (4 of 5 subjects). Four subjects in the laser group received rescue treatment with aflibercept, and the response rate was 100% (4 of 4 subjects).

PMDA's view:

At present, the applicant's explanation that no precautionary statement in the package insert is necessary is acceptable. Due to the limited number of subjects who received rescue treatment, it is necessary to collect post-marketing information on the impact of laser photocoagulation on the safety of aflibercept.

7.R.3.3 Systemic adverse events related to VEGF inhibition

PMDA asked the applicant to explain if the incidence of systemic adverse events related to VEGF inhibition in global phase III studies (CTD 5.3.5.1.1, Study 20090; CTD 5.3.5.1.2, Study 20075) tended to be different from that in the clinical studies of aflibercept in the adult indications.

The applicant's explanation:

- The incidences of systemic adverse events related to VEGF inhibition[32)] were 26.7% (20 of 75 subjects) in the aflibercept group and 28.9% (11 of 38 subjects) in the laser group in Study 20090 and 1.7% (1 of 60 subjects) in the aflibercept group and 3.4% (1 of 29 subjects) in the laser group in Study 20275. Those reported in the aflibercept group of Study 20090 were retinal haemorrhage (7 subjects [9.3%]); conjunctival haemorrhage (4 subjects [5.3%]); injection site haemorrhage (3 subjects [4.0%]); vitreous haemorrhage (2 subjects [2.7%]); and cardiac failure; retinal artery occlusion; gastric haemorrhage; contusion; neonatal intraventricular haemorrhage; intraventricular haemorrhage; thalamus haemorrhage; and proteinuria (1 subject each [1.3%]). Those reported in the aflibercept group of Study 20275 were retinal haemorrhage; and subdural haematoma (1 subject each [1.7%]). The incidences of serious adverse events other than deaths were 2.7% (2 of 75 subjects) in the aflibercept group and 0% in the laser group in Study 20090 and 1.7% (1 of 60 subjects) in the aflibercept group and 0% in the laser group in Study 20275. Those reported in the aflibercept group were retinal haemorrhage and vitreous haemorrhage; and retinal haemorrhage (1 subject each) in Study 20090 and subdural haematoma (1 subject) in Study 20275, and a causal relationship to study treatment was denied for all those events.
- On the other hand, the incidence of systemic adverse events related to VEGF inhibition[33)] in the pooled aflibercept population from the clinical studies in the adult indications[30)] was 56.3% (1642 of 2917 subjects), and the incidence of serious adverse events other than deaths was 7.4% (216 of 2917 subjects).
- Although the results should be interpreted with care due to differences in the number of aflibercept administrations etc. between Studies 20090 and 20275 and the clinical studies in the adult indications,

32) MedDRA SMQs "cardiomyopathy," "arterial embolic and thrombotic events," "venous embolic and thrombotic events," "gastrointestinal perforation," "haemorrhages," "hypertension," and "proteinuria" and MedDRA PTs "accelerated hypertension," "hypertensive crisis," "hypertensive emergency," "hypertensive encephalopathy," "hypertensive end-organ damage," "hypertensive urgency," "leukoencephalopathy," "malignant hypertension," "malignant hypertensive heart disease," "malignant renal hypertension," "posterior reversible encephalopathy syndrome," "toxic leukoencephalopathy," "tyramine reaction," "abdominal wall wound," "abdominal wound dehiscence," "anastomotic complication," "anastomotic fistula," "anastomotic leak," "debridement," "drain placement," "drain site complication," "drainage," "electrocoagulation," "eschar," "failure to anastomose," "gastrointestinal anastomotic complication," "gastrointestinal anastomotic leak," "impaired healing," "implant site dehiscence," "incarcerated incisional hernia," "incision site complication," "incision site discharge," "incision site erosion," "incision site fibrosis," "incision site impaired healing," "incision site inflammation," "incision site oedema," "incision site ulcer," "incisional hernia," "incisional hernia gangrenous," "incisional hernia repair," "incisional hernia, obstructive," "inflammation of wound," "intestinal anastomosis complication," "pharyngeal anastomotic leak," "post procedural fistula," "post procedural persistent drain fluid," "post procedural urine leak," "postoperative wound complication," "procedural haemorrhage," "promotion of wound healing," "reproductive tract anastomotic leak," "stomal hernia," "strangulated incisional hernia," "suture related complication," "suture rupture," "wound," "wound closure," "wound complication," "wound contamination," "wound decomposition," "wound dehiscence," "wound drainage," "wound evisceration," "wound haematoma," "wound haemorrhage," "wound necrosis," "wound secretion," and "wound treatment"

33) Treatment-emergent (reported after the first and not later than 30 days after the last administration of study treatment) events

there was no trend towards a higher incidence of systemic adverse events related to VEGF inhibition in ROP patients than in the adult indications. Long-term continued treatment with aflibercept is not expected in ROP patients. Given these points, the risk of these events in ROP patients is unlikely to exceed that in the adult indications.

PMDA accepts the above explanation by the applicant. but considers that it is necessary to collect post-marketing information on systemic adverse events related to VEGF inhibition.

7.R.3.4 Risk of neurodevelopmental delay

PMDA asked the applicant to explain the effect of aflibercept on neurodevelopment in ROP patients.

The applicant's explanation:

- Children born preterm remain at high risk for brain injury and long-term neurodevelopmental deficits including abnormal muscle tone or movements, cognitive deficits, language impairments, and behavioral problems (*Clin Perinatol*. 2018; 45: 377-92). At 8 years, approximately a third of children with ROP treated with cryotherapy needed special education services, and almost half had below-grade-level academic performance (*Pediatrics.* 2004; 113: 790-9), etc. These reports suggest that preterm birth, which is also associated with ROP, is likely to affect the neurodevelopment of infants.
- VEGF is critical in the developing and adult nervous system and is involved in the generation of neural circuits such as retinal ganglionic cells and central nervous system by modulating processes such as neuronal differentiation, survival, and migration, and axon outgrowth (*Cell Mol Life Sci*. 2013; 70: 1763-78). In 4[34)] of 14 publications that investigated the potential influence of intravitreal VEGF inhibitor on neurodevelopmental outcomes of preterm infants with ROP, an association between anti-VEGF therapy and neurodevelopmental outcomes was observed in ROP patients. ROP patients treated with intravitreal bevacizumab versus laser had higher odds of neurodevelopmental disabilities (*Pediatrics*. 2016; 137: e20153218). Administration of intravitreal bevacizumab may introduce a risk of developmental impairment of verbal abilities, interpersonal relationships, and/or socializations (*PLoS One*. 2020; 15: e0230678), etc. On the other hand, in 10[35)] of the 14 publications, there was no association between anti-VEGF therapy and neurodevelopmental outcomes in ROP patients. In an extension study of the RAINBOW study, i.e., a randomized trial that compared ranibizumab with laser therapy, as 2-year outcomes of ranibizumab, neurodevelopment scores etc. were similar between the ranibizumab and laser groups, and intravitreal ranibizumab did not appear to affect non-ocular infant development (*Lancet Child Adolesc Health*. 2021; 5: 698-707). Based on the above, the effect of intravitreal VEGF inhibitor on neurodevelopment in ROP patients is unclear at present.

34) *PLoS One*. 2019; 4: e0223972, *Pediatrics*. 2019; 144: e20183537, *Pediatrics.* 2016; 137: e20153218, *PLoS One*. 2020; 15: e0230678

35) *Am J Perinatol*. 2021; 38: 1158-66, *PLoS One*. 2016; 11: e0148019, *J AAPOS*. 2018; 22: 61-5, *Ophthalmology*. 2019; 126: 1567-77, *J Matern Fetal Neonatal Med*. 2022; 35: 415-22, *Cir Cir*. 2017; 85: 478-84, *Ophthalmic Surg Lasers Imaging Retina*. 2020; 51: 220-4, *Curr Eye Res.* 2015; 40: 585-91, *Ophthalmic Surg Lasers Imaging Retina.* 2019; 50: 337-43, *J Perinatol*. 2019; 39: 1300-8

- Table 15 shows the incidence of adverse events related to neurodevelopmental delay[36)] in global phase III studies (CTD 5.3.5.1.1, Study 20090; CTD 5.3.5.1.2, Study 20275), and a causal relationship to study treatment was denied for all those events. The prevalence of cognitive and motor delays in very preterm and very-low-birthweight infants were estimated at 16.9% and 20.6%, respectively (*Dev Med Child Neurol*. 2018; 60: 342-55), etc. The incidences of adverse events related to neurodevelopmental delay in Studies 20090 and 20275 did not exceed the reported prevalence.

Table 15. Incidence of adverse events related to neurodevelopmental delay (Studies 20090 and 20275, Safety analysis set)

	20090		20275	
	Aflibercept	Laser	Aflibercept	Laser
N	75	38	60	29
Any adverse event	2 (2.7)	3 (7.9)	5 (8.3)	4 (13.8)
Auditory disorder	0	1 (2.6)	0	0
Deafness unilateral	0	1 (2.6)	1 (1.7)	0
Nystagmus	0	2 (5.3)	0	0
Developmental coordination disorder	1 (1.3)	0	0	0
Tremor	1 (1.3)	0	0	0
Deafness neurosensory	0	0	1 (1.7)	1 (3.4)
Hypoacusis	0	0	0	1 (3.4)
Speech disorder developmental	0	0	0	2 (6.9)
Dystonia	0	0	0	1 (3.4)
Intellectual disability	0	0	0	1 (3.4)
Motor developmental delay	0	0	1 (1.7)	0
Movement disorder	0	0	0	1 (3.4)
Neurodevelopmental disorder	0	0	2 (3.3)	0

n (Incidence [%])

- Based on the above, according to the currently available clinical data, there is no definitive evidence for the risk of neurodevelopmental delay associated with aflibercept in ROP patients, and this risk is unlikely to become a problem in the clinical use of aflibercept. However, the risk of neurodevelopmental deficits due to VEGF inhibition by aflibercept cannot be ruled out, and the information on its potential long-term effect on neurodevelopment is important. Thus, the ongoing Study 20275 will be continued as a post-marketing clinical study, and its effect on neurodevelopment will be evaluated in more details by collecting information on neurodevelopment (hearing function, cognitive function, motor function, etc.) until subjects are 5 years of age.

PMDA's view:

Given the above explanation by the applicant, the currently available information including the data from Studies 20090 and 20275 has shown no clear risk of neurodevelopmental delay associated with aflibercept. Since the data from Study 20275 are limited, i.e., up to approximately 1 year of age,[19)] it is necessary to collect post-marketing information on its effect on neurodevelopment, including a post-marketing clinical study to follow subjects to 5 years of age, which is planned to be conducted by the applicant.

7.R.3.5 Growth effect

PMDA asked the applicant to explain the effect of aflibercept on growth in ROP patients.

36) MedDRA High Level Group Terms (HLGTs): hearing disorders, mental impairment disorders, neurological disorders NEC, movement disorders (incl parkinsonism), cognitive and attention disorders and disturbances, communication disorders and disturbances, developmental disorders NEC

The applicant's explanation:

- Table 16 shows changes from baseline in body length, weight, and head circumference in global phase III studies (CTD 5.3.5.1.1, Study 20090; CTD 5.3.5.1.2, Study 20275). Those changes were similar between the aflibercept and laser groups in both studies, and were not substantially different from the reported body length, weight, and head circumference in very-low-birthweight infants and preterm infants (1992 MHW psychosomatic disorder study, "Study on comprehensive care system for high-risk infants" [in Japanese]: 96-106,[37] *BMC Pediatrics*. 2013; 13:59[38]).

Table 16. Changes from baseline in body length, weight, and head circumference (Studies 20090 and 20275, Safety analysis set)

		20090		20275	
		Aflibercept	Laser	Aflibercept	Laser
N		75	38	60	29
Chronological age at baseline[a]		10.4 ± 2.8	10.2 ± 2.3	8.8 ± 1.4	8.8 ± 1.5
Body length (cm)	Baseline	41.84 ± 4.97 (68)	40.95 ± 4.63 (37)	64.52 ± 4.29 (59)	63.09 ± 4.53 (28)
	Time point[b]	62.07 ± 3.50 (68)	60.24 ± 3.69 (36)	69.61 ± 3.42 (31)	70.44 ± 5.66 (16)
	Change[d]	20.05 ± 3.13 (61)	19.61 ± 3.69 (35)	26.95 ± 3.52 (26)	28.00 ± 5.96 (15)
Weight[c]	Baseline	2022.4 ± 682.2 (73)	1850.9 ± 546.1 (38)	6.59 ± 1.13 (59)	6.45 ± 1.21 (28)
	Time point[b]	6147.8 ± 926.1 (68)	5764.8 ± 1039.4 (36)	7.86 ± 1.20 (31)	7.62 ± 0.78 (16)
	Change[d]	4117.2 ± 754.6 (66)	3940.8 ± 911.2 (36)	5.66 ± 1.12 (30)	5.57 ± 0.90 (16)
Head circumference (cm)	Baseline	30.09 ± 3.28 (71)	29.73 ± 2.42 (36)	41.09 ± 2.34 (59)	41.85 ± 2.30 (27)
	Time point[b]	40.34 ± 3.52 (68)	40.51 ± 2.17 (35)	43.30 ± 2.15 (31)	44.03 ± 2.37 (16)
	Change[d]	10.05 ± 4.12 (64)	10.98 ± 2.49 (34)	12.65 ± 3.24 (28)	13.84 ± 2.85 (14)

Mean ± SD (Number of evaluable subjects)
a) Unit: weeks in Study 20090, months in Study 20275
b) Week 24 in Study 20090, 1 year of chronological age in Study 20275
c) Unit: g in Study 20090, kg in Study 20275
d) Change from baseline of Study 20090

- Based on the above, according to the currently available data from Studies 20090 and 20275, there was no clear effect of aflibercept on growth in ROP patients, and this risk is unlikely to become a problem in the clinical use of aflibercept. Since the information on the long-term effect of aflibercept on growth is important, the ongoing Study 20275 will be continued as a post-marketing clinical study, and its effect on growth will be evaluated in more details by collecting data until subjects are 5 years of age.

PMDA's view:

Taking account of the above explanation by the applicant, according to the currently available data from Studies20090 and 20275, there was no clear effect of aflibercept on growth. However, as the data from Study 20275 are limited, i.e. up to approximately 1 year of age,[19] it is necessary to collect post-marketing information on its effect on growth, including a post-marketing clinical study to follow subjects to 5 years of age, which is planned to be conducted by the applicant.

37) The applicant's explanation:
According to this report, body length, weight, and head circumference in Japanese very-low-birthweight infants (<1500 g) were predicted to be approximately 37-47 cm, approximately 1100-2700 g, and approximately 27-35 cm, respectively, at approximately 72 days after birth (close to age at baseline in Study 20090), approximately 58-66 cm, approximately 5.0-7.0 kg, and approximately 40-44 cm, respectively, at 240 days after birth (close to age at 24 weeks after starting study treatment in Study 20090), and approximately 65-71 cm, approximately 6.5-8.5 kg, and approximately 42-46 cm, respectively, at 1 year after birth.

38) The applicant's explanation:
According to this report, body length, weight, and head circumference in preterm infants from Germany, the US, Italy, Australia, Scotland, and Canada were predicted to be approximately 43-52 cm, approximately 1.8-3.5 kg, and approximately 29-36 cm, respectively, at 36 weeks of gestational age (close to age at baseline in Study 20090) and approximately 55-65 cm, approximately 4.2-7.2 kg, and 36-42 cm, respectively, at 50 weeks of gestational age (close to age at Week 24 in Study 20090).

7.R.4 Clinical positioning and indication

PMDA asked the applicant to explain the clinical positioning of aflibercept in the treatment of ROP.

The applicant's explanation:

- ROP is classified according to the International Classification of ROP. Each eye is classified based on the location of ROP lesion (Three concentric retinal zones centered on the optic disc: Zone I, central zone; Zone II, intermediate zone; and Zone III, peripheral zone), stage (Stage is defined by the appearance of a structure [Stages 1-5]: Stage 1, demarcation line; Stage 2, ridge; Stage 3, extraretinal fibrovascular proliferation; Stage 4, partial retinal detachment; Stage 5, total retinal detachment), plus disease (the appearance of retinal venous dilation and arterial tortuosity), AP-ROP (a severe, rapidly progressive form of ROP without progression being observed through the typical stages of ROP), etc. (*Arch Ophthalmol*. 2005; 123: 991-9).
- The current treatment options for ROP include laser photocoagulation, anti-VEGF therapy, and vitreoretinal surgery. The majority of cases of mild ROP resolves spontaneously, and those patients are watched without intervention. If there is progression to Type 1 ROP[23)] or AP-ROP, laser photocoagulation or anti-VEGF therapy is indicated upon diagnosis (*Pediatrics*. 2018; 142: e20183061, *Journal of Japanese Ophthalmological Society*. 2020; 124: 1013-9, etc.). In the case of progression to retinal detachment (Stage 4) or above, vitreoretinal surgery is often performed (*Journal of Japanese Ophthalmological Society*. 2012; 116: 683-702).
- Laser photocoagulation is a standard of care for ROP, and its procedure and prognosis have been established. Laser photocoagulation has the following disadvantages: Long-term ocular complications such as increased high myopia and reduced peripheral vision occur frequently due to the destruction and scarring of the retinal tissue caused by retinal ablation; laser treatment often requires general anesthesia and sedation, and patients with systemic complications of prematurity cannot tolerate laser photocoagulation; and laser photocoagulation cannot be performed in patients with local ocular findings such as pupil ankylosis, corneal opacity, and vitreous opacities (*Journal of Japanese Ophthalmological Society*. 2020; 124: 1013-9).
- As anti-VEGF therapy, ranibizumab was approved for the indication of ROP in November 2019 and became a new treatment option for patients with ROP in Japan. Anti-VEGF therapy has the following advantages: Severe patients can be treated with anti-VEGF therapy easily; less time consuming and less burden on the infant; and the potential extension of retinal vessels. On the other hand, anti-VEGF therapy cannot be used if highly active and congestive fibroplasia is present extensively or an ocular infection is present, and anti-VEGF therapy has the following disadvantages: injection-related endophthalmitis or lenticular injury may occur rarely; it causes contraction of fibrous membranes; the recurrence rate is high, and frequent fundus examination is needed over a long period of time after treatment; and its long-term safety has not been established. As to the population to be treated with ranibizumab, since Type 1 Zone II Stage 2 plus disease was not included in the RAINBOW study of ranibizumab, the assessment of whether

to treat these patients with ranibizumab has not been established at present (*Journal of Japanese Ophthalmological Society*. 2020; 124: 1013-9).

- Although the population to be treated according to ROP classification is almost the same for laser photocoagulation and anti-VEGF therapy, when to use laser photocoagulation and when to use anti-VEGF therapy are unclear at present, and it is recommended that laser or anti-VEGF therapy should be chosen, taking account of their respective advantages and disadvantages (*Journal of Japanese Ophthalmological Society*. 2020; 124: 1013-9). Given the above-mentioned advantages and disadvantages of the two therapies, anti-VEGF therapy will be chosen for patients who cannot tolerate or receive laser treatment, or anti-VEGF therapy may be chosen due to concerns about long-term ocular complications or patient burden of laser therapy.
- Since Studies 20090 and 20275 showed the efficacy of aflibercept in the treatment of ROP [see Section 7.R.2], and there were no major safety issues [see Section 7.R.3], as with ranibizumab, aflibercept as an anti-VEGF therapy can become a new treatment option for patients with ROP.

Among ROP patients, those with Type 1 ROP[23)] or AP-ROP were included in Study 20090. PMDA asked the applicant to explain if aflibercept is recommended in patient populations that were not included in this study, and then the appropriateness of the indication and precautionary statements in the package insert for aflibercept.

The applicant's explanation:

- The foreign guidelines (*Pediatrics*. 2018; 142: e20183061, *Paediatr Child Health*. 2016; 21: 101-4, *Eye*. 2009; 23: 2137-9) recommended laser photocoagulation for the treatment of Type 1 ROP and AP-ROP, and the preceding randomized clinical studies of other VEGF inhibitors, i.e., the BEAT-ROP study of bevacizumab (*N Engl J Med*. 2011; 364: 603-15) and the RAINBOW study of ranibizumab (*Lancet*. 2019; 394: 1551-9), suggested the efficacy of anti-VEGF therapy in patients with ROP: Zone I Stage 1 plus disease, Stage 2 plus disease, and Stage 3 and Stage 3 plus disease, Zone II Stage 3 plus disease, and AP-ROP, etc. Thus, Type 1 ROP and AP-ROP were included in Study 20090. Zone II Stage 2 plus disease was not included in the RAINBOW study, and the guidelines in some countries or regions recommend that these eyes should be watched closely and treatment should be considered carefully when the disease worsens. However, given that treatment is recommended in multiple countries or regions including Japan (*Ophthalmologe*. 2020; 117: 873-85, *Journal of Japanese Ophthalmological Society*. 2012; 116: 683-702) etc., Zone II Stage 2 plus disease was included in Study 20090.[39)] Based on the results of Study 20090 etc., patients with Type 1 ROP including Zone II Stage 2 plus disease or AP-ROP can be treated with aflibercept.
- On the other hand, patients with mild ROP that is expected to resolve spontaneously and patients with severe ROP for whom surgery is indicated (Zone I Stage 1, Stage 2, and Stage 4, Zone II Stage 1, Stage 1 plus disease, Stage 2, Stage 3, and Stage 4, Zone III with any ROP Stages [excluding Stage 5]) were not included in Study 20090, and the efficacy and safety of aflibercept in these patients were not investigated. Thus, the use of aflibercept in these patients is not recommended as a rule.

39) In Study 20090, 2 patients with Zone II Stage 2 plus disease each were enrolled in the aflibercept and laser groups, all of whom were responders.

- Based on the above, as with approved ranibizumab, the proposed indication is "retinopathy of prematurity," and then the package insert will advise that since the significance of treatment with aflibercept in patients with mild ROP that is expected to resolve spontaneously and patients with severe ROP for whom surgery is indicated is unclear, prior to initiating treatment with aflibercept, the need for aflibercept should be determined, taking account of the patient's condition, the location of ROP lesion, stage, etc. The information on the characteristics of patients enrolled in Study 20090 (the location of ROP lesion, stage, etc.) will be provided.

PMDA's view:

- With regard to the clinical positioning of aflibercept, given the applicant's explanation and the considerations in Sections 7.R.2 and 7.R.3, aflibercept as an anti-VEGF therapy, can become a new treatment option for patients with Type 1 ROP or AP-ROP.
- As to the target population for aflibercept, there is no problem with the proposed indication of "retinopathy of prematurity" as that for approved ranibizumab, and the package insert should advise that prior to initiating treatment with aflibercept, the need for aflibercept should be determined, taking account of the patient's condition, the location of ROP lesion, stage, etc., and the information on the characteristics of patients enrolled in Study 20090 should be provided. The significance of treatment with aflibercept in mild cases etc. is unclear, and aflibercept is not generally recommended in these cases. After the market launch, if aflibercept is used in such patients based on their condition etc., the information on its reason, safety, efficacy, etc., should be collected.

A final conclusion on the appropriateness of the above conclusion will be made, taking account of comments from the Expert Discussion.

7.R.5 Dosage and administration

PMDA asked the applicant to explain the rationale for the dosage regimen of aflibercept in a global phase III study in ROP patients (CTD 5.3.5.1.1, Study 20090) and the appropriateness of the proposed dosage and administration and precautionary statements in the package insert for ROP, taking account of the results of this study etc.

First, the applicant explained the rationale for the dosage regimen of aflibercept in Study 20090 as follows:

- <u>The dose of aflibercept</u>

According to reported studies of aflibercept in ROP patients,[40)] the rate of ROP regression was 96.2% to 100% in infants who received aflibercept 0.4 to 1 mg/eye, i.e., one half to one fifth of the approved adult dose (aflibercept 2.0 mg/eye), showing efficacy at all dose levels, and there were no serious safety concerns during approximately 1 year of follow-up, etc. In Study 20090, taking also account of concerns about the long-term safety of aflibercept, a VEGF inhibitor, in premature infants, the lowest dose of 0.4 mg/eye among the above doses suggesting efficacy and safety in ROP was selected as the dose of aflibercept.

40) https://www.ncchd.go.jp/center/information/kaihatsu/pdf/h28/26-23.pdf (as of September 21, 2021), *Ophthalmic Res*. 2015; 53: 15-20, *Graefes Arch Clin Exp Ophthalmol.* 2018; 256: 479-87, *Eur J Ophthalmol.* 2017; 27: 751-5

- Treatment regimen of aflibercept

In a clinical trial of ranibizumab in ROP patients, reinjections were allowed after at least 28 days. The efficacy of retreatment was suggested, and there was no particular problem with its safety (*JAMA Pediatr*. 2018; 172: 278-86). Recurrences of ROP activity after anti-VEGF treatment have been reported (*JAMA Pediatr*. 2018; 172: 278-86). According to the dosage and administration of aflibercept for the approved adult indications, the dosing interval is ≥1 month. Given these points etc., in Study 20090, up to 2 additional IVT injections of aflibercept could be administered in each eye (a total of 3 doses including the first injection) if there was presence of ROP requiring treatment, and the interval since the last dose of aflibercept was ≥28 days.

Then, the applicant explained the appropriateness of the proposed dosage and administration and precautionary statements in the package insert for ROP, taking account of the results of Study 20090 etc., as follows:

- The dose of aflibercept

Since Studies 20090 and 20275 showed the efficacy of aflibercept 0.4 mg/eye in the treatment of ROP [see Section 7.R.2], and there were no major safety issues [see Section 7.R.3], the recommended clinical dose of aflibercept for ROP should be 0.4 mg/eye.

- Treatment regimen of aflibercept

Given the following points, the dosage and administration for ROP should allow retreatment with aflibercept after ≥1 month, if necessary, and the package insert should advise that retreatment with aflibercept should be considered if findings suggestive of recurrence of ROP activity are observed after an initial response to treatment with aflibercept.

- Since ROP regresses spontaneously after the active phase of ROP, long-term, continued treatment is not expected. On the other hand, after anti-VEGF therapy for ROP, resolution of ROP activity such as plus disease and neovascularization is observed, and the disease improves to a stage not requiring retreatment in many patients, but some patients have worsening of ROP again and require additional treatment (*JAMA Pediatr*. 2018; 172: 278-86). Actually, also in Study 20090, there were subjects who had worsening of ROP again after aflibercept injection and received retreatment with aflibercept according to the retreatment criteria.[8)] The number of administrations per study eye in the aflibercept group of Study 20090 was 1 (the first dose only) in 82.2% (120 of 146 eyes) and 2 (the first dose and 1 additional dose) in 17.8% (26 of 146 eyes). Based on the above, retreatment with aflibercept according to ROP activity is needed.
- Regarding the efficacy of retreatment, among 26 study eyes retreated in the aflibercept group of Study 20090, the proportion of eyes with absence of active ROP and unfavorable structural outcomes was 38.5% (10 of 26 eyes) before retreatment, 80.8% (21 of 26 eyes) at 1 week after retreatment, and 73.1% (19 of 26 eyes) at 4 weeks after retreatment. The proportion of study eyes that did not show improvement following retreatment and received rescue treatment at 5 weeks after retreatment was small, i.e., 7.7% (2 of 26 eyes). Thus, the efficacy of retreatment with aflibercept was suggested.
- Regarding the safety of retreatment, Table 17 shows the incidences of adverse events in study eyes and non-ocular adverse events by the number of administrations per subject in the aflibercept group of Study 20090. At least one eye received retreatment with aflibercept in subjects who received ≥3 doses. The interpretation of the results has limitations due to the limited number of subjects who received

retreatment with aflibercept. Although the incidence of all adverse events in study eyes tended to be slightly higher in subjects who received 4 doses, there was no trend towards increasing incidences of serious adverse events other than deaths, adverse events leading to study discontinuation, and adverse events related to aflibercept or injection procedure with increasing number of administrations. Based on the above, there was no major problem with the safety of retreatment with aflibercept.

Table 17. Incidences of adverse events in study eyes and non-ocular adverse events by number of aflibercept administrations (Aflibercept group of Study 20090, Safety analysis set)

Number of aflibercept administrations per subject[a)]	1	2	3	4	Total
N	4	55	6	10	75
Study eyes					
All adverse events	0	32 (58.2)	3 (50.0)	7 (70.0)	42 (56.0)
Serious adverse events other than deaths	0	7 (12.7)	2 (33.3)	1 (10.0)	10 (13.3)
Adverse events leading to study discontinuation	0	2 (3.6)	1 (16.7)	0	3 (4.0)
Adverse events related to aflibercept or injection procedure	0	13 (23.6)	0	2 (20.0)	15 (20.0)
Non-ocular					
All adverse events	3 (75.0)	43 (78.2)	5 (83.3)	8 (80.0)	59 (78.7)
Deaths	0	1 (1.8)	1 (16.7)	1 (10.0)	3 (4.0)
Serious adverse events other than deaths	1 (25.0)	12 (21.8)	0	2 (20.0)	15 (20.0)
Adverse events leading to study discontinuation	0	0	0	0	0
Adverse events related to aflibercept or injection procedure	0	1 (1.8)	0	0	1 (1.3)

n (Incidence [%])

a) The first dose in one eye for subjects who received 1 dose; the first dose in both eyes for subjects who received 2 doses; the first dose in one eye and the first dose and 1 additional dose in the other eye for subjects who received 3 doses; and the first dose and 1 additional dose in both eyes for subjects who received 4 doses

- With respect to the interval between treatments, the median time to retreatment [range] in the aflibercept group of Study 20090 was 79.5 [29, 121] days. According to the dosage and administration of aflibercept for the approved adult indications, the dosing interval is ≥1 month. Given these points, the treatment interval between doses for ROP should be ≥1 month.
- As to the maximum number of reinjections, although up to 2 additional injections of aflibercept could be administered in each study eye in Study 20090, no subjects received 2 additional injections in the same study eye (a total of 3 doses including the first injection), and its efficacy and safety have not been shown. Thus, ≥2 additional injections per eye are not recommended. However, as the possibility that ≥2 additional injections per eye (a total of ≥3 doses) are needed according to each patient's condition such as disease progression and treatment response, in clinical practice, cannot be ruled out, the package insert should provide information on additional injections given in Study 20090, instead of specifying the maximum number of reinjections in the DOSAGE AND ADMINISTRATION section.

The applicant's explanation about switching from aflibercept to other treatments:

Given the following points, the package insert should advise that switching to other treatments should be considered if no response is obtained early after treatment with aflibercept.

- ROP may progress rapidly and can lead to blindness. If no response is obtained early after treatment with aflibercept, switching to other treatments should be considered.
- In Study 20090, rescue treatment with laser was allowed if the eyes did not respond to aflibercept, and the rescue treatment criteria[9)] were met. Actually, 5 of 75 subjects in the aflibercept group received rescue treatment with laser, and there were no clinically relevant safety concerns [see Section 7.R.3.2].

PMDA's view:

- The dose of aflibercept

Though it is difficult to say that the doses of aflibercept were fully evaluated to determine the recommended clinical dose for ROP, given that ROP is a rare disease, and that Study 20090 showed the efficacy and safety of aflibercept 0.4 mg/eye [see Sections 7.R.2 and 7.R.3], etc., the recommended clinical dose of aflibercept 0.4 mg/eye for ROP is acceptable.

- Treatment regimen of aflibercept

Given the results from Study 20090 etc., the dosage and administration for ROP allowing aflibercept reinjections after ≥1 month, if necessary, is acceptable. The package insert should advise that retreatment with aflibercept should be considered if findings suggestive of recurrence of ROP activity are observed after an initial response to treatment with aflibercept. On the premise that the package insert appropriately provides information on reinjections given in Study 20090, it is acceptable not to specify the maximum number of reinjections in the DOSAGE AND ADMINISTRATION section.

- Given that ROP may progress rapidly etc., the package insert should advise that switching to other treatments should be considered if no response is obtained early after treatment with aflibercept.

A final conclusion on the appropriateness of the above conclusion will be made, taking account of comments from the Expert Discussion.

7.R.6 Post-marketing investigations

The applicant's explanation:

A use-results survey with an observation period of 6 months and a planned sample size of 75 patients is planned to be conducted as post-marketing surveillance of aflibercept. The main objective of the survey is to collect and assess safety information from ROP patients treated with aflibercept in clinical practice. In order to evaluate the long-term safety and efficacy of aflibercept in ROP patients, the ongoing global phase III study (CTD 5.3.5.1.2, Study 20275) will be reclassified as a post-marketing clinical study after the market launch to follow subjects to 5 years of age. Information on neurodevelopment (hearing function, cognitive function, motor function, etc.), physical development, visual function, etc., will be collected and evaluated.

PMDA's view:

Regarding the safety of aflibercept in ROP patients, although the results from Studies 20090 and 20275 submitted in the present application suggest no safety concerns that are clearly different from those in the approved adult indications [see Section 7.R.3], given that the population of patients with ROP is clearly different from the population of adult patients with the approved indications, and that there is limited clinical experience with aflibercept in Japanese patients in Studies 20090 and 20275, post-marketing surveillance should be conducted to evaluate the safety etc. of aflibercept in Japanese patients with ROP, including determination of the incidences of intraocular inflammation, increased intraocular pressure, and retinal detachment or tear. It is necessary to appropriately collect information on the long-term effects of aflibercept

on neurodevelopment, physical development, visual function, etc., in the post-marketing clinical study being planned by the applicant (Study 20275 will be reclassified).

A final conclusion on the appropriateness of the above conclusion will be made, taking account of 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 compliance 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 5.3.5.1.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that the efficacy of aflibercept in the treatment of ROP is promising, and that aflibercept has acceptable safety in view of its benefits. Aflibercept is clinically meaningful because it offers a new treatment option for ROP patients. PMDA considers that efficacy, safety, clinical positioning and indication, dosage and administration, and the appropriateness of the specifications in post-marketing investigations, etc., are subject to further discussion at the Expert Discussion.

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

Review Report (2)

August 4, 2022

Product Submitted for Approval

Brand Name	Eylea Intravitreal Injection 40 mg/mL
Non-proprietary Name	Aflibercept (Genetical Recombination)
Applicant	Bayer Yakuhin, Ltd.
Date of Application	October 20, 2021

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

PMDA's conclusion:

Based on the discussion in Section "7.R.2.1 Design of Study 20090" in the Review Report (1), from the viewpoint of comparability, the primary efficacy analysis in Japan for Study 20090 could have been more appropriate to be performed in a way that allowed the comparison with laser photocoagulation as control. However, given the limited number of ROP patients and restricted study design options for efficacy assessment, the planned efficacy assessment of aflibercept based on comparison with the pre-specified threshold, which was chosen referring to the result in the laser group of the RAINBOW study of ranibizumab, is understandable. There is no particular problem with the primary endpoint chosen for Study 20090, i.e., "the proportion of subjects with absence of active ROP and unfavorable structural outcomes at 24 weeks after starting study treatment."

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

Based on the considerations in Sections "7.R.2.2 Efficacy taking account of the results from Study 20090" and "7.R.2.3 Proportion of subjects with recurrence of ROP" in the Review Report (1), PMDA made the following conclusions on the efficacy of aflibercept.

- In Study 20090, the success criterion for the primary efficacy analysis in Japan was met because the lower limit of the two-sided 95% confidence interval for the primary endpoint in the aflibercept group was greater than the pre-specified threshold of 66%. However, given that the response rate in the laser group of Study 20090 was higher than the treatment success rate in the laser group of the RAINBOW study, which was used as a reference to choose the threshold value, etc., efficacy evaluation based on the results of the primary analysis has limitations, and it is difficult to conclude that the efficacy of aflibercept in the treatment of ROP was demonstrated just because the Japanese success criterion was met.
- Although the efficacy analysis in Japan for Study 20090 did not primarily focus on the comparison of aflibercept with laser photocoagulation, there was no trend towards a clearly lower response rate in the aflibercept group than in the laser group in Study 20090, and aflibercept is expected to be clinically meaningful in the treatment of ROP. Also, taking account of the results of a secondary endpoint of Study 20090, "requirement for intervention with a second treatment modality from baseline to Week 24" and the provisional results as of the data cutoff date concerning a secondary endpoint of Study 20275, "the proportion of subjects with absence of active ROP and unfavorable structural outcomes at 1 year of age," the efficacy of aflibercept in the treatment of ROP is promising.
- There were no major differences in the results of the primary endpoint for Study 20090 between the overall population and the Japanese subgroup, and aflibercept is also expected to have efficacy in Japanese patients with ROP. There were no major problems with the results of subgroup analysis of the primary endpoint of Study 20090 by patient characteristics.
- A secondary endpoint of Study 20090, i.e., "the proportion of subjects with recurrence of ROP from baseline to Week 24" was higher in the aflibercept group than in the laser group, and the recurrence rate of ROP in the aflibercept group tended to be higher in the Japanese subgroup than in the non-Japanese subgroup. Thus, the information on the proportion of subjects with recurrence of ROP in Study 20090, including the results in the Japanese subgroup, should be provided using information materials for healthcare professionals etc., and the need for regular funduscopic examination etc. after treatment with aflibercept in ROP patients should be advised.
- To elucidate the long-term efficacy of aflibercept in the treatment of ROP, the ongoing Study 20275 should be continued as a post-marketing clinical study, and visual function should be evaluated until subjects are 5 years of age.

At the Expert Discussion, the expert advisors made the following comments.

- Although the success criterion for the primary efficacy analysis in Japan was met for the response rate in the aflibercept group of Study 20090, the point estimate of the response rate was 82.7% in the aflibercept group, which was lower than 84.2% in the laser group. According to the results of an exploratory analysis, the lower limit of asymptotic two-sided 95% confidence interval for the difference between the corresponding response proportions (aflibercept group − laser group) was −16.0%. The primary efficacy analysis in the countries or regions other than Japan for Study 20090 failed to demonstrate the non-inferiority of aflibercept to laser photocoagulation. Thus, caution is needed for efficacy evaluation taking account of the results from Study 20090 etc. other than evaluation results based

on the success criterion for the primary efficacy analysis in Japan. The basis for the conclusion regarding no evident trend towards inferior efficacy of aflibercept as compared to laser photocoagulation in the treatment of ROP needs to be explained based on the data.

- Although laser photocoagulation for ROP is thought to have been performed by specialists, there are difficulties in performing the treatment for some patients, and there is a concern about the risks of long-term ocular complications associated with the characteristics of the procedure, such as increased high myopia and reduced peripheral vision. In Study 20090, there seemed to be no trend towards a substantially lower response rate in the aflibercept group than in the laser group. Taking account of the above-mentioned observations, offering aflibercept as an anti-VEGF therapy for ROP to medical practice has its high significance.

Given the above comments, PMDA made the following final conclusion on the efficacy of aflibercept in the treatment of ROP, in view of the results from Study 20090, etc. other than the success criterion-based evaluation results for the primary efficacy analysis in Japan.

- According to the results of an exploratory efficacy analysis in Japan for Study 20090, the difference in the response rate between the aflibercept and laser groups, etc., failed to demonstrate the non-inferiority of aflibercept to laser photocoagulation. However, the response rates in the aflibercept and laser groups of this study [95% CI] (responders/evaluable subjects) were 82.7% [72.2, 90.4] (62 of 75 subjects) and 84.2% [68.7, 94.0] (32 of 38 subjects), respectively, and the point estimate of the treatment difference (aflibercept group − laser group) [asymptotic two-sided 95% CI] was −1.5 [−16.0, 12.9]%. The obtained point estimate of the treatment difference and its 95% confidence interval showed no trend towards a substantially lower response rate in the aflibercept group than in the laser group.
- With respect to a secondary endpoint of Study 20090 of "requirement for intervention with a second treatment modality[26)] from baseline to Week 24," the proportions of subjects who required intervention with a second treatment modality in the aflibercept and laser groups were 10.7% (8 of 75 subjects) and 13.2% (5 of 38 subjects), respectively. The provisional results as of the data cutoff date concerning "the proportion of subjects with absence of active ROP and unfavorable structural outcomes[14)] at 1 year of age" in Study 20275 are shown in Table 5. The results of these endpoints also showed no trend towards major differences in efficacy between the aflibercept and laser groups.
- Laser photocoagulation is associated with the risk of long-term ocular complications such as increased high myopia and reduced peripheral vision. Laser treatment often requires general anesthesia, etc., and it may be difficult to perform laser photocoagulation in patients with systemic complications of prematurity. Given these points, etc., the observed response rate in the aflibercept group of Study 20090 indicates that aflibercept is expected to be clinically meaningful in the treatment of ROP.

Based on the above, PMDA concluded that the clinical efficacy of aflibercept in the treatment of ROP is expected, and that offering aflibercept as an anti-VEGF therapy to medical practice has its significance. The expert advisors supported the above conclusion by PMDA.

1.2 Safety

PMDA's conclusion:

Based on the considerations in Section "7.R.3 Safety" in the Review Report (1), particular attention should be paid to the possible occurrence of intraocular inflammation, increased intraocular pressure, retinal tear or detachment, traumatic cataract, and arterial thromboembolic events following the administration of aflibercept in ROP patients as in the previously approved adult indications. Nevertheless, aflibercept has acceptable safety in ROP patients, provided that appropriate warnings and precautions regarding these events are given. However, the patient population with ROP is clearly different from the that of adults with the approved indications, and there is limited clinical experience with aflibercept in Japanese patients with ROP in Studies 20090 and 20275. Given these, it is necessary to collect post-marketing information on the safety of aflibercept in Japanese patients with ROP. Also, due to limited available data from Study 20275, i.e., up to approximately 1 year of age, information on long-term safety of aflibercept in ROP patients, including its effects on neurodevelopment and growth needs to be further collected in the post-marketing settings.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

1.3 Clinical positioning and indication

PMDA's conclusion:

Based on the considerations in Section "7.R.4 Clinical positioning and indication" in the Review Report (1), aflibercept as an anti-VEGF therapy, is a potential new treatment option for patients with ROP, and there is no problem with the proposed indication of "retinopathy of prematurity" as that for approved ranibizumab. The significance of aflibercept remains unclear for the treatment of mild and severe ROP, the former is expected to resolve spontaneously while a surgery is indicated for the latter. The package insert should advise that the necessity of the treatment with aflibercept should be judged based on the patient's condition, the location of ROP lesion, stage, etc., and communicate the characteristics of patients enrolled in Study 20090.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

1.4 Dosage and administration

PMDA's conclusion:

Based on the considerations in Section "7.R.5 Dosage and administration" in the Review Report (1), the recommended clinical dose of aflibercept 0.4 mg/eye for ROP is acceptable, and the reinjection of aflibercept after ≥1 month, if necessary, is also acceptable. The package insert should advise that retreatment with aflibercept should be considered if any findings suggestive of the recurrence of ROP activity are observed after the initial response to aflibercept, and that switching to other treatments should be considered if no response is obtained early after treatment with aflibercept.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

1.5 Risk management plan (draft)

Based on the reviews in Sections "7.R.2 Efficacy," "7.R.3 Safety," and "7.R.6 Post-marketing investigations" in the Review Report (1) and the comments from the expert advisors at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for aflibercept should include the safety and efficacy specifications presented in Table 18, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 19.

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

Safety specification		
Important identified risks	Important potential risks	Important missing information
· Intraocular inflammation · Increased intraocular pressure · Retinal tear or detachment · Traumatic cataract	· Arterial thromboembolic events · Neurodevelopmental delay in ROP patients	· Long-term safety in ROP patients
Efficacy specification		
· Long-term efficacy in ROP patients		

a) The safety and efficacy specifications related to ROP only are listed.

Table 19. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)[a)]

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
· Early post-marketing phase vigilance · Specified use-results survey · Post-marketing clinical study (Study 20275)[b)]	· Post-marketing clinical study (Study 20275)[b)]	· Disseminate data gathered during early post-marketing phase vigilance

a) Additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities related to ROP only are listed.
b) The ongoing Study 20275 will be reclassified as a post-marketing clinical study after approval.

Based on the above, PMDA requested the applicant to conduct post-marketing surveillance to investigate the above issues.

The applicant explained that they will conduct a specified use-results survey presented in Table 20.

Table 20. Outline of specified use-results survey (draft)

Objective	To evaluate the safety etc. of aflibercept in clinical use.
Survey method	Central registry system
Population	ROP patients
Observation period	6 months
Planned sample size	75 patients
Main survey items	· Patient characteristics (sex, gestational age in weeks at birth, birth weight, chronological age in weeks at the start of treatment with aflibercept, corrected age in weeks and body weight, prior treatment for ROP, medical history, complications, etc.) · Use of aflibercept (day of treatment, treated eye, the reason for retreatment, etc.) · Concomitant medications/therapies (including laser photocoagulation) · Incidence of adverse events · Ophthalmic evaluation before and after start of treatment with aflibercept (ROP grading, unfavorable structural outcomes, etc.)

PMDA accepted the above.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indications and dosage and administration shown below, with the following approval condition. The present application is intended for a new indication and a new dosage, thus the re-examination period for the indication and dosage and administration claimed in the present application is 4 years.

Indications

Age-related macular degeneration with subfoveal choroidal neovascularization
Macular edema secondary to retinal vein occlusion
Choroidal neovascularization in pathologic myopia
Diabetic macular edema
Neovascular glaucoma
Retinopathy of prematurity

(Underline denotes additions.)

Dosage and Administration

● Age-related macular degeneration with subfoveal choroidal neovascularization

The initial dosage of Aflibercept (Genetical Recombination) is 2 mg (0.05 mL) administered by intravitreal injection once every month for 3 times consecutively (initial phase). In the subsequent maintenance phase, it is usually administered intravitreally once every 2 months. The dosing interval may be adjusted according to the patient's symptoms, but it should be ≥1 month.

● Macular edema secondary to retinal vein occlusion and choroidal neovascularization in pathologic myopia

The dosage of Aflibercept (Genetical Recombination) is 2 mg (0.05 mL) administered by intravitreal injection. The dosing interval should be ≥1 month.

● Diabetic macular edema

The dosage of Aflibercept (Genetical Recombination) is 2 mg (0.05 mL) administered by intravitreal injection once every month for 5 times consecutively. Then, it is usually administered intravitreally once every 2 months. The dosing interval may be adjusted according to the patient's symptoms, but it should be ≥1 month.

● Neovascular glaucoma

The dosage of Aflibercept (Genetical Recombination) is 2 mg (0.05 mL) administered by intravitreal injection. Retreatment with Aflibercept may be performed if necessary, with a dosing interval of ≥1 month.

● Retinopathy of prematurity

The dosage of Aflibercept (Genetical Recombination) is 0.4 mg (0.01 mL) administered by intravitreal injection. Retreatment with Aflibercept may be performed if necessary, with a dosing interval of ≥1 month.

(Underline denotes additions.)

Approval Condition

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

Appendix

List of Abbreviations

aflibercept	Aflibercept (Genetical Recombination)
AMD	Age-related Macular Degeneration
AP-ROP	Aggressive Posterior - Retinopathy of Prematurity
bevacizumab	Bevacizumab (Genetical Recombination)
BRVO	Branch Retinal Vein Occlusion
CI	Confidence Interval
C_{max}	Maximum Concentration
CNV	Choroidal neovascularization
COVID-19	Coronavirus disease 2019
CRVO	Central Retinal Vein Occlusion
CTD	Common Technical Document
DME	Diabetic Macular Edema
ELISA	Enzyme-linked Immunosorbent Assay
FAS	Full Analysis Set
mCNV	myopic Choroidal Neovascularization
MedDRA	Medical Dictionary for Regulatory Activities
PMDA	Pharmaceuticals and Medical Devices Agency
ranibizumab	Ranibizumab (Genetical Recombination)
ROP	Retinopathy of Prematurity
The product	Eylea Intravitreal Injection 40 mg/mL
VEGF	Vascular Endothelial Growth Factor